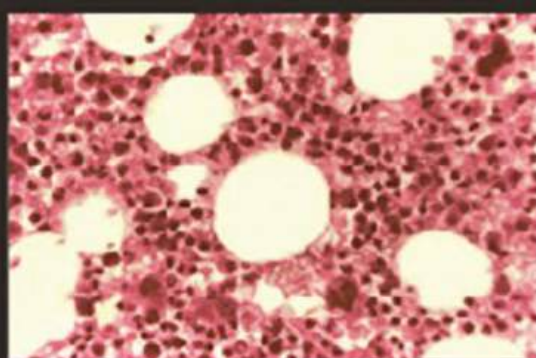


Textbook of Medicine

5th Edition



JAYPEE

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Textbook of MEDICINE

Textbook of MEDICINE

5th Edition

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Textbook of Medicine

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This book is dedicated to my alma mater –
Medical College and Hospital, Thiruvananthapuram –
where I started learning the first principles of medicine and
thereafter; had the honour to serve as its staff and
continue my close association with the college
even several years after my retirement

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Preface to the Fifth Edition

This volume has evolved through four editions, the fourth one was published in 2002. The first edition was introduced as 'A Short Textbook of Medicine', now it has increased in the volume of contents and improved in its quality, commensurate with the quantitative and qualitative advancements in medical information.

Six years is too long a gap for a textbook to be up-to-date and useful, but the demand among students and teachers were the guidelines to continue with the fourth edition until 2008.

As mentioned earlier, the book has been given a new direction, both in its get up and format, so as to include the latest information and present it in a student-friendly manner. This book has been designed to include the up-to-date information obtainable from print material and electronic data and has been presented in a simple language in form of direct statements, so as to make the matter more vivid and comprehensible to the medical students and doctors in India and the neighbouring countries coming from different social and language backgrounds. In areas where more detailed information is desirable for the practitioners and the postgraduate students, authentic reviews and original works are referred to.

Several new figures, many of them taken personally by the contributors from their own clinical practice and flow charts and tables have been added.

Along with several chapters a short summary is given to serve as a ready-reckoner for the students preparing for the examination or the busy practitioners who have only limited time at their disposal.

This volume is intended for the use of undergraduate and postgraduate students of medicine, dental sciences and other allied subjects, students preparing for entrance examinations and practitioners working in India and the neighbouring countries.

All the sections have been thoroughly revised. The number of contributors has also increased including teachers in specialities who have made their mark in their respective specialisation.

The first edition of the "Short Textbook" was produced in 1986 to fulfil a long-felt and widespread need among the undergraduate and postgraduate students, majority of whom relied on class notes or handbooks written on the various subjects by several authors. Many had no access to textbooks and the big volumes available were beyond their understanding. Comprehensive textbooks catering to the needs of the undergraduate medical students written by Indian authors were only a handful. Books published in other countries are quite freely available to our students, but naturally their emphasis is on the conditions prevailing in those countries.

The medical problems of India are unique as the peculiar disease-spectrum here is a blend of what is seen in the affluent countries with what is seen in most developing countries. This Textbook of Medicine has been written with this picture in mind. The section on tropical diseases, which usually gets a separate deal in most of the western textbooks, has been dovetailed into the other sections such as infections, physical agents, nutrition and others to improve the understanding of these subjects. Almost the whole of India is in tropical belt and therefore diseases rampant in tropical countries with a few exceptions like trypanosomiasis, onchocerciasis and others are present in all parts of the country.

This book has its companion volume "Clinical Medicine" third edition edited by me and published by the same publishers in 2005. It gives in detail the clinical aspects of medical practice and investigations. The reader is referred to "Clinical Medicine" for further details on physical examination, clinical symptoms, signs and investigation procedures.

Obsession with the printed matter is the habit of the mediocre; the wise go beyond it and use their common-sense, experience and creativity to form their own decisions.

My contributors have strived hard to collect the material and present it the way it has been done. All of them are veteran teachers and their presentations will be helpful to the entire readership. This book is the collective effort of the whole team, laying emphasis on several aspects of Internal Medicine with special emphasis on conditions prevailing in India and the neighbouring countries.

Human efforts by themselves are lifeless "*karma tat jadam*" (Ramana Maharshi in his Upadesa Sara). They get life and effect only when blessed by the Almighty to achieve the desired effect. This is especially so in medicine, in that both the patient and his physician have to be lucky to get the best results of investigation and treatment. I wish and pray to Almighty, the first physician in the universe to bless all and alleviate suffering. Yajurveda proclaims "*prathamam daivam bhishak*" meaning the "first physician is God". I would consider the work of my teammates and myself fulfilled, if the young entrants into the medical profession in India and the neighbouring countries find this book useful in his studies and career.

K.V. Krishna Das

Preface to the First Edition

This book is written to fulfil a long-felt and widespread need among the undergraduate students. A questionnaire sent to several hundreds of clinical students revealed that majority of them rely on class notes, and handbooks written in the subject by several authors. Many had no access to textbooks in the subject and the big volumes available were beyond their understanding. Comprehensive textbooks catering to the need of undergraduates written by Indian authors are only a few. Books published in other countries are quite freely available to our students, but naturally their emphasis is on conditions prevailing in their lands.

The medical problems of India are unique in that the disease-spectrum is a blend of what is seen in the affluent countries with what is seen in developing countries. This book has been written with this picture in mind. The section on “tropical diseases” which usually gets a separate deal in most of the textbooks has been dovetailed into the other sections such as infections, physical agents, nutrition, etc. It is my feeling that with modern jet travel and the rapidly changing life-styles of Indian subjects, all diseases—the most modern and the most ancient are likely to be encountered by the clinical student in this country. Moreover, the so-called tropical diseases which used to be confined to the tropical belt, are now seen widely all over the world as a result of free and fast migration of population.

I consider my purpose fulfilled if the undergraduates in this country find this book useful.

K.V. Krishna Das

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Introduction to Medicine

K.V. Krishna Das

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History of Medicine

The practice of medicine existed even in the earliest periods of recorded human history.

Medical knowledge always existed in folklore, local health traditions, verbal testimony and other sources. It is their periodic systematization and improvement that led to medical progress.

The fifth century BC was the golden age of Greek medicine and it was during this period that *Asclepid Hippocrates* (born around 460 BC), introduced scientific system of administering medicine which till then was dominated by religious and mystic practices.

Hippocrates embodied the ideal virtues of a physician such as knowledge, readiness to help, purity of life, compassion, skill and patriotism. Hippocratic medicine was based on practice as well as theory with little emphasis on anatomy.

The history of Indian medicine dates back to 3000 BC and excavations of *Mohanjodaro* and *Harappa* throw light on medical practices that flourished at that age, which consisted mainly of religious, magical and empirical procedures.

Ayurveda (the science of life) arose as an offshoot of Atharva Veda which is the fourth Veda. Atharva veda is dated to belong to 1500 BC. It consists of 6000 verses and 1000 prose lines. There are several pieces of evidence and statements that it is very closely associated with

Atharva veda. In any case the science of life (*Ayurveda* means knowledge of life sciences) originated in India along with the vedas. It laid emphasis not only on healing, but also on the prolongation of life, preservation and promotion of health and prevention of illness. The ancient sages recognized health as the very basis of virtue, wealth, enjoyment and salvation. From very early times Ayurveda had developed independent of religious precepts. *Agnivesa* has been credited with the authorship of Ayurveda. Agnivesa composed *Agnivesa tantra* a few centuries before Charaka. The latter produced *Charaka Samhita* between the 2nd century BC and 1st century AD (post Buddhist period) during the reign of the Kusanas. *Charaka samhita* is a creative revision of *Agnivesa tantra* *Charaka samhita* is still in vogue as a basic text used by practitioners of Ayurveda. *Charaka* edited his encyclopedic text, *Charaka Samhita*. *Susruta*, who was a medical teacher of Varanasi during the Buddhist period, practised surgery. *Vagbhata*, another Buddhist physician living in the Indus region (second century AD) wrote two classics in Ayurveda—*Astanga Sangraha* and *Astanga Hridaya*. *Vagbhata* emphasized the principles of medicine, *Susruta* dealt mainly with surgery and anatomy, while *Charaka* emphasized therapeutics. The Yoga concept of physical and mental culture to preserve the health of body and the mind developed in India. Even when the Aryan influx into India brought in Ayurveda, other systems of medicine such as *Siddha* and *Chintamani* existed in this subcontinent, especially in the South from pre-Aryan times. The *Buddha* (sixth century BC) and his disciples practised medicine and consequently healing of the sick was given great importance.

Arabic and middle eastern countries share the tradition of Arabic folk medicine and the *Unani* or adopted *Greek medicine*. It was essentially taken from Galenic teachings during the early Islamic period. Several names stand out prominently among those who developed this system; *Ibn Sina* of Andolasia in Spain, *Al Mansur* of Baghdad, *Avicenna*, *Razi*, *Rhazes* and others. The backbone of the theoretical instruction was the *Alexandrian canons* which summarized a few books compiled by Galen. The

major works in *Unani* were *Al qnanun-Fi-Tibh* by Ibn Sina, *Continend* by Rhazes, *Kitab-Al-Shifa* by Avicenna *Al-Tarsiff* by Abu-Quasim-Az-Zuhra-Wi and several others. Hospitals were established from the tenth century AD in several towns. Surgery and ophthalmology were practised during this period and the works of Unani surgeons paved the way for development of surgery in Europe. In India the Muslim rulers popularized the *Unani* system side by side with *Ayurveda*.

The golden age of Unani Medicine was possibly the twelfth century AD. The Chinese system of medicine had great sway over the far East from very ancient times. Several of its tenets and the herbal pharmacopia have percolated into other systems of medicine far and wide. Though all these systems of medicine flourished during various periods in their countries of origin and the neighbouring regions, many of them suffered from want of continuing research. The homeopathic system of Medicine which was founded by Dr SCF Hahnemann in 1796 in Philadelphia grew into a very popular therapeutic system which continues to grow and attract large sections of people all over the world.

In modern times it is common to include all these traditional systems of medicine as the “alternate systems”. These flourish along with the system of allopathic medicine in almost all the countries and they provide health care services to large sections of the population. The government of India has accepted many of these systems as part of the health care delivery agencies. There are also several institutions imparting teaching in these various systems.

The growth and development of the allopathic system (modern medicine) have been much more rapid and prolific compared to the other systems. Whereas the alternate systems are most accepted in their countries of origin, the allopathic system has gained global acceptance. The term allopathy literally means “treatment of disease by measures which contrast the effect of the disease, in contrast to homeopathy which literally means “treatment of disease by drugs that produce symptoms like those of the disease”. In homeopathy the doses of drugs are minute.

The sixteenth and seventeenth centuries witnessed the growth of modern physical sciences and its scientific methods of study and analysis. Andreas Vesalius, born in 1514, in Brussels made extensive dissections of the human body and produced his classic in anatomy “*De Humani Corporis Fabrica Libri*” on September 1, 1543. William Harvey, a British physician, published his monumental work on circulation of blood, *De mortu cordis* in 1628. It was Harvey who established the scientific basis of medicine. Harvey is often credited with the invention of medical research, (ie) the search for factual evidence about bodily functions and structure.

Starting in the late eighteenth century and developing with a great rapidity in the nineteenth century, the modern medical theory and practice made great progress. Discovery of the microscope by *Leewenhoek* three hundred years ago led to the identification of the cell as the basis of biological existence. Koch’s postulates laid firm basis for establishing the etiology of microbial diseases. *Gregor Mendel* published his observations in 1865 and laid the foundations of modern genetics. Molecular diseases also were identified in the early part of the nineteenth century. From the middle of this century the development of knowledge has been explosive. The discovery of the structure of DNA and the advances in the study of chromosomes and the study of genetic loci which confer susceptibility to disease were of great help in understanding the nature of molecular diseases. Studies of genes, availability of techniques such as polymerase chain reaction (PCR) which helps to identify the presence of nucleic acids (DNA and RNA) enabled great advances in genetic medicine. Completion of the human genome mapping project made available the blueprint of the human genome. Further genomic studies which aim at identification of the effect of different genes in causing and preventing diseases have helped to understand the genetic basis of several diseases including prediction of diseases such as cancer.

Availability of monoclonal antibodies have enabled specific diagnosis of heterogenous diseases such as lymphomas and breast cancers. They are also used in targeted therapy of malignancies, immune mediated diseases and several others for which treatment used to be unsatisfactory.

Though earlier medicine was practised as an art, at present it is a harmonious blend of scientific practices generously tempered with human warmth, kindness and above all, sound commonsense. What is spoken of as a clinical picture is not just the photograph of a man sick in bed, it is the sum total of the patient’s condition, his home, his work, his relations, friends, joys, sorrows, hopes and fears. A good physician honours his patient and his time; sympathy and understanding are lavishly dispensed, and the reward is to be found in that joy of personal bond which forms the source of the greatest satisfaction in the practice of medicine.

Medicine as a Profession

The word ‘doctor’ is derived from the Latin word “docere” which means to teach, since the doctor has the function of instructing the patient and his relatives regarding treatment. Medicine moreover is a technique (an art or a craft of a special kind) with a broad philosophy. The medical profession is supported by a plethora of scientific knowledge which is continuously growing. It is also

guided by the norm of conduct termed “ethics”. Ethics deal with the principles of morality, of right and wrong. Over the centuries the *Hippocratic oath* has been handed down from one to the next generation of practitioners of medical science. Though generally, the code of ethics has been attributed to Hippocrates, it is quite likely that in its present form it came into existence much later. The ethics were laid down to be followed by the students and practitioners so as to command veneration from the public and to prevent misuse of the medical knowledge and exploitation of the society. In modern times of high cost of patient care, availability of invasive investigations and treatment, organ transplantation, prenatal diagnosis of the gender of the fetus and the several others have contributed to unethical use of medical knowledge. This has led to the creation of *ethical committees* in all institutions for controlling research on humans and animals, and ensuring proper treatment to all types of patients.

The progress and achievements in the field of medical sciences have been phenomenal. But in comparison to several other fields such as engineering or technology the safety margin and success rate in techniques requiring precision and skill are considerably less. For example, a failure rate of 1-2% in a major surgical procedure is still acceptable whereas in modern industrial process this would not be so. The relatively higher margin of failure rates are accepted due to the fact that the physician has to deal with subjects whose internal environment and biological processes are not fully available to him before he starts treatment. This leads to unexpected problems such as adverse drug reactions, surgical failures, immunological complications, secondary infections and several others.

The position of the doctor in society was an exalted one from the early stages of human civilization. It continues to be so even in modern times, since his role in relieving human suffering has been accepted in all cultures, especially in India. To perform his task ideally, the physician should combine knowledge, skills, empathy and a readiness to serve his fellow men at all times.

In India, the medical profession has come under the Consumer Protection Act which made the doctor accountable to the public for his actions. This law empowers them to exert their right to receive proper care and consideration from the physician. The patients and their relatives can implicate the doctor for malpractice and negligence. The law requires of the doctor to use the appropriate skills and care in discharging his duties to the public.

The Final Diagnosis

The physician approaches the patient with the total picture of the patient in mind, and with the determination and skill of a detective to unravel the disease and its cause.

While ascertaining the history and conducting the physical examination, an experienced observer forms an impression about the probable diagnosis and the immediate differential diagnosis. The clinical diagnosis should always be supported by investigations. The purpose of investigations may be summarized as: (1) confirmation of the clinical diagnosis, e.g. sputum for acid fast bacilli in tuberculosis or blood culture in typhoid fever, (2) assessment of the severity of affection or damage to organs, e.g. liver function, renal function, etc., (3) assessment of prognosis, e.g. biopsy in malignancy, (4) differentiation of the condition from the closely resembling diseases, e.g. liver biopsy in hepatomegaly or rheumatoid factor in subacute arthritis, (5) planning the therapeutic modality; e.g. determination of acetylase status to decide on the dose of INH therapy, and (6) follow-up of the treatment and to detect early recurrence.

While appropriate investigations are essential to establish the diagnosis and to institute therapy and follow-up, the availability of different types of investigative procedures and the over-dependence on them have led to unnecessary, and sometimes even invasive investigations which may jeopardize the patient's health and life.

In general, invasive procedures include biopsies of vital organs, catheterization of vital structures, angiography, contrast radiography and endoscopies. These may cause temporary or permanent morbidity and even mortality in a small number. Hence the decision to employ them should be taken after evaluating non-invasive methods and only if the risks involved are justifiable. Over-investigation should be avoided and this is possible only if the interrogation and physical examination are properly done. Moreover, results of the investigations should be interpreted in the light of the clinical findings, otherwise they may be misleading and may result in administering inappropriate therapy.

Concept of Millennium Development Goals (MDGs)

In 2000 AD, The United Nations (UN) adopted the *millennium development goals* and made the UN'S *millennium declaration* signed by 189 countries which aimed at achieving the MDGs by the year 2015. Three of the MDGs aims are related to health. These include:

1. Reduction of child mortality by two-thirds compared to 1990
2. Reduction of maternal mortality by 75% compared to 1990 and
3. Prevention of spread of HIV/AIDS, malaria, tuberculosis and other diseases.

The burden of *chronic diseases* comprise mainly of cardiovascular diseases including strokes, cancer, chronic respiratory disease and diabetes. The predicted global deaths from the major diseases projected for 2005 AD are given in Table 1.1.

TABLE 1.1

The projected number of deaths in 2005 AD

Diseases	Approximate figures (millions)
Cardiovascular diseases	17.53
Cancer	7.57
Chronic respiratory diseases	4.1
HIV/AIDS	2.8
Tuberculosis	1.6
Diabetes	1.13
Malaria	0.8

TABLE 1.2

Global distribution of total deaths in an year

Cardiovascular causes	30%
Communicable diseases, maternal and perinatal diseases, and malnutrition	30%
Cancer	13%
Other chronic diseases	9%
Injuries	9%
Chronic respiratory diseases	7%
Diabetes mellitus	2%

Chronic diseases burden affects both developing and developed countries. In India 35% of all cardiovascular disease deaths occurred in persons aged 35-64 years. The trend is for these diseases to affect a greater proportion of younger persons in developing countries compared to those in developed nations.

The global distribution of total deaths (58 million) by major causes in 2005 is given in Table 1.2.

The Concept of Global Burden of Disease

Prevalence of selected major risk factors in different regions of the world has been studied by international agencies such as the World Health Organization (WHO) and others, both governmental and non-governmental. This information has been utilized to estimate the global prevalence of disease and Disability Adjusted Life Years (DALY). Maternal and childhood underweight, tobacco smoking, alcoholism, unsafe sex practices and hypertension account for the majority of the leading causes of global burden of disease. In the poor regions of the world maternal and childhood underweight, unsafe sex practices, unsafe drinking water, poor sanitation and hygiene, indoor air pollution by smoke from burning solid bio-fuels and various micronutrient deficiencies were the main contributory factors.

In both the developed and poor countries alcohol, tobacco, hypertension and high cholesterol levels were equally prevalent.

Recording of Medical Data

Recording of data is important and the method of recording has been considerably improved in recent years. The *problem-oriented medical record (POMR)* is a generally accepted form which greatly helps data retrieval and also helps the physician to make decisions on the spot.

Flow charts giving the design of management have been constructed for many of the common ailments. These help the physician to plan investigations and institute sequential therapy. Customized computer softwares designed for use in doctors' clinics and hospitals are available commercially. The doctor of the future will have to use them in order to keep up with modern progress and to guide him in his day to day work.

Many professional associations have produced consensus statements for the diagnosis, management, and prognosis of several common diseases. These have to be strictly complied with by the doctors of the future, since such consensus statements are based on evidence based information. Though the doctor has freedom to decide on management strategies in individual cases under special circumstances, in general consensus statements come up as ready and reliable data sources. This also will help as safeguards against litigations which may come up.

Evidence Based Medicine

This branch of medicine has developed during the past three decades. Several modern investigative and therapeutic modalities are very expensive, invasive and are liable to legal scrutiny. The ethical responsibility of the doctor in recommending such procedures is also great.

Evidence based medicine gives the status report on

- 1. The efficiency of the modality
- 2. Risks involved regarding mortality and morbidity
- 3. Cost-benefit analysis and
- 4. The improvement in the quality of life

Collection and regular updating of objective evidence of the efficacy and safety of invasive investigations, therapeutic modalities such as drugs, surgery, invasive interventions, implanted equipment like coronary stents, organ transplantations and several others are systematically done by the process of meta-analysis of published data, multi-centre and international prospective studies, reviews, seminars, international consensus conferences and other communications through the Internet. There are several accepted bodies such as the Medline, Pubmed, Cochrane library, Embase and others which collect, analyse and store data for reference by scientists. This data is available in the Internet. Decisions taken by the doctor have to be supported by such evidence based consensus.

Availability of the evidence based consensus is a firm basis for doctors to take decisions in complex and difficult situations and to defend themselves in legal matters. All

modern medical men have to follow the guidelines based on evidence and justify their action if it is at variance from evidence based norms.

Computers in Medicine

Computers are integral equipment for the physician’s profession. Patient’s data, investigations, prescriptions, consultations, referrals, can all be stored by the computer and readily retrieved. Modern information available through the internet, textbooks, prescription guides, and abstracts from journals can be stored in the computer and readily accessed. There are different software designed for assisting the doctor in his clinic and office, including

financial matters, drug information, drug interactions and incompatibilities, safety information on drugs and several other facilities. Many libraries have computerized their procedures and knowledge of computer methods is absolutely essential to retrieve information from libraries and other data sources.

Transplant associations, matching of donor and recipient for transplantation, cancer registries, blood banking data, population data, epidemiological studies, genetic information of population and multicentric and multinational clinical studies have all to depend on computing methodology for performing their tasks. It will not be an exaggeration to state that computer incompetence is even more serious a handicap than total illiteracy.

2

Medical Genetics

K.V. Krishna Das

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General Considerations

6 Many diseases develop as a result of the interaction between the genetic and environmental factors. Some

diseases are predominantly genetic, e.g. achondroplasia and Turner’s syndrome, other cases are predominantly environmental, e.g. typhoid fever and tuberculosis, while in many others genetic and environmental factors play similar roles, e.g. diabetes and hypertension.

The observations in genetics in modern biological sciences are credited to Gregor Mendel, an Augustinian monk and a naturalist at the monastery at Bronn, Bohemia. He observed the results of breeding experiments on peas planted in his garden, for over eight years and published his paper in 1865, on inheritance patterns. He also postulated mathematical laws of inheritance, generally known as Mendel’s laws. Cytogenetics is the genetic analysis of cells using chromosome banding techniques, designed to demonstrate the number and structural integrity of the chromosomes. Several genes are contained in each chromosome and some of them have been mapped. The adult human cell nucleus contains 23 autosomes and one pair of sex chromosomes. The latter contains either two X-chromosomes (female) or X- and Y-chromosomes (male) respectively. Chromosomes can be studied by karyotyping rapidly dividing tissues like the bone marrow or by growing the cells in culture media and examining them during mitosis.

Gene is that length of deoxyribonucleic acid (DNA) which acts as a functional unit. It is also termed as cistron. One gene produces one polypeptide, which may combine with other polypeptides produced by other genes to form biologically active proteins like hormones or enzymes.

The size of fragments of double-stranded DNA is indicated by their length in base pairs (bp) or nucleotides. Each chromosome carries several thousand genes. The DNA from all the human chromosomes exceed 3 billion nucleotide base pairs.

Genetic disorders may be classified as:

1. Single gene disorders
2. Polygenic disorders
3. Chromosomal disorders

Single gene disorders are those involving a mutation or change in a single gene, e.g. achondroplasia, thalassemia, sickle cell disease, hemophilia and others. In these the genetic change is sub-microscopic and hence these have to be demonstrated by other methods. Polygenic disorders are those which arise from the combined influence of multiple small genetic defects. Chromosomal disorders are those in which a change or alteration of the chromosomal number or pattern can be demonstrated, e.g. Down's syndrome, Klinefelter's syndrome or Turner's syndrome. In these the genetic alteration involves large portions of the chromosomal structures so as to become demonstrable microscopically.

Genetic information is contained in deoxyribonucleic acid (DNA). It has a double stranded structure, twisted in the form of a helix, and distributed along the chromosomes. The strand consists of deoxyribose residues linked by phosphate (covalent phosphate diester) bonds. Each strand is connected with one of the four bases—adenine, thymine, cytosine or guanine. The bases on the opposite sides in the two strands are aligned together as base pairs by hydrogen bonds. Adenine always pairs with thymine and cytosine with guanine.

The role of the DNA is to contain and transmit genetic information. That information is encoded by the sequence of bases. DNA transmits this genetic information by unraveling its two strands and exposing previously paired bases, thus forming a template for assembly of a new strand of nucleic acid. If the information is to be propagated to daughter cells, the new strand of nucleic acid synthesized is more DNA. This process of propagation is called *replication*. If the information is to be used by the cell, the new strand is ribonucleic acid (RNA). This process is called *transcription*.

RNA differs from DNA in having ribose as its sugar, and the base uracil instead of thymine. Uracil, like thymine forms base pair with adenine.

The "transcribed" RNA acts as a *messenger* RNA (mRNA), which travels from the chromosome on which it is synthesized to the cytoplasmic ribosomes, where it directs the assembly of amino acids into proteins. This

process is called *translation*. The amino acids are carried to the ribosomes by small RNA molecules called transfer RNAs (tRNAs). Each of the 20 amino acids has one or more specific tRNAs.

Common Terms used in Genetic Studies

Diploid cells: These are somatic cells having two sets of chromosomes, each set derived from either parent, totalling 23 pairs in each cell.

Haploid cells: These are cells containing only half the number of chromosomes that are seen in somatic or body cells. These are germ cells of the ova and sperms.

Autosomes: These are the chromosomes other than sex chromosomes. X and Y are the sex chromosomes; the female pattern being X-X and male pattern being X-Y.

Alleles: These are one of two or more different genes containing specific inheritable characteristics, that occupy corresponding portions (loci) on paired chromosomes. If the alleles are identical, either dominant or recessive, such an individual is termed homozygous for that particular gene. If one of the alleles is abnormal and the other is normal, such an individual is heterozygous for that particular characteristic.

Aneuploidy: This is the condition in which the chromosomal number is abnormal for the particular species.

If one of the pair of genes is altered in such a fashion that it manifests itself in a clinical disorder even when present in a single dose, it is called a dominant gene. If the mutant gene has to be present in double dose to express itself as a disorder it is termed as recessive gene. Thus, both the genes of that pair are abnormal, one derived from each parent.

In general, it is seen that single gene disorders occur with a frequency of 10 per 1000 births. Of these, six are autosomal dominant, three autosomal recessive and one is X-linked recessive. Autosomal dominant disorders are mild and variable in manifestation due to the presence of the other gene (allele) which may be normal. On the other hand autosomal recessive disorders are more severe and uniform in pattern since both the genes are abnormal. The X-linked recessive disorders are intermediate in severity.

Human Genome Project

A highly ambitious project to map the genes present in the human cell nucleus undertaken by the National Institute of Health (NIH), Bethesda (USA) with active participation from many other laboratories internationally, was completed ahead of schedule.

The human genome contains about 80000 genes with about 3 billion base pairs. About 35000 were identified till the end of 2004. Further studies are progressing. About 50% of these genes code for unknown proteins, which

are being studied continuously and fresh information is being added on. Unrelated persons have 99.9% of their DNA in common.

Genomics is the study of molecular abnormalities involving the genes, gene-gene interactions, gene-environment interactions and their phenotypic expression. These involve the study of the proteins they produce. Genomic research has improved our understanding of molecular pathology and pathogenesis of complex diseases.

98% of the genome does not code for any protein. Genes which code for proteins control metabolic functions. Several genes may code for the same protein or the same protein may be controlled by different genes. Study of the effects of the protein products is called **proteomics** and this branch is wider than genomics. While the genes are responsible for determining the inherited characteristics, the environment is equally important in determining their expression.

Identification of genetic variations will help clinicians to subclassify diseases and tailor therapy to fit in with the genetic pattern. On an average one boy in every 100 and one girl in every 150 has a major congenital abnormality, some of which are genetically related. The prevalence of lesser causes of disadvantage caused by congenital abnormalities is at least ten times higher.

Note: The mapping of the genes has been completed ahead of schedule and the information is available from several sources including web sites.

The next step is to correlate diseases patterns with the genetic abnormalities and workout the practical application of the new information.

Types of Inheritance

1. Autosomal recessive
2. Autosomal dominant
3. X-linked recessive
4. X-linked dominant

The pattern of inheritance is determined by taking a family history to cover three generations in full and constructing a pedigree.

Autosomal Recessive Inheritance (Fig. 2.1)

1. The affected individuals are in one generation. This is, therefore, called the horizontal transmission.
2. Males and females are equally affected.
3. There is a 25% chance of recurrence in siblings. In other words, on an average, one-fourth of the children are affected.
4. Both parents are carriers of the disease. In the affected offspring one mutant gene comes from one parent, the other mutant gene in the pair is from the other parent.
5. There is often consanguinity in the parents. The more rare the disorder in question, the more likely it is that

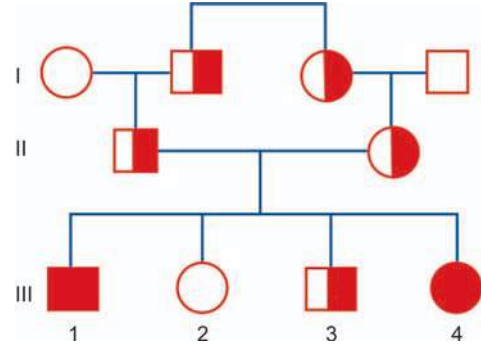


Fig. 2.1: Pedigree of a disorder with autosomal recessive inheritance (horizontal transmission). Roman numerals I-III indicate generations. The nos. 1-4 indicate siblings. Blacked out symbol means an affected individual. Those with one-half blackened indicate carriers

the parents are consanguineous. Each individual is the carrier of 6-8 harmful autosomal recessive genes. In a consanguineous marriage, there is a greater likelihood that the offspring would inherit the same mutant gene from the parents, as a proportion of the genes are common in consanguineous parents, e.g. Friedrich's ataxia, phenylketonuria, Fanconi's syndrome.

Autosomal Dominant Inheritance (Fig. 2.2)

1. The affected individuals are in more than one generation and if, in the pedigree one draws a line through the affected individuals, it will be a vertical line. Hence, it is also called 'vertical transmission'.
2. Males and females are equally affected.
3. There is a 50% chance of recurrence in siblings, irrespective of sex. In other words, on an average, one-half of the children are affected.
4. A male-to-male transmission provides evidence that the disease is not X-linked but is autosomal dominant.
5. Occasionally, both parents of an affected child are normal. In such cases, it is presumed that the offspring has acquired the disease by a new mutation in the gametes of one of the parents. The more an autosomal disorder limits reproduction, the higher is the rate of

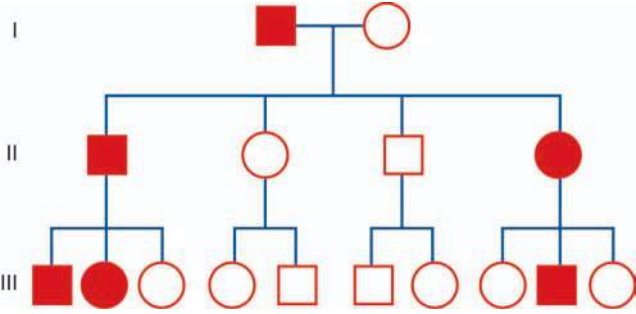


Fig. 2.2: Pedigree of a disorder with autosomal dominant inheritance (vertical transmission). Normal persons do not pass on the trait to their offspring

new mutation for that disorder. Where the disorder arises by a new mutation, the risk of recurrence in future siblings is negligible.

6. Occasionally, an offspring affected by an autosomal dominant disorder is born to normal parents, while one of the grandparents is affected. In such cases it is presumed that the parent on the side of the affected grandparent has the gene but is not manifesting the disease. Such genes are considered *nonpenetrant*.
7. The clinical manifestations in an autosomal dominant disorder vary considerably in the same family. This is partly explained by the fact that only one of the genes of a particular pair is abnormal, while the other gene is normal. The degree to which the presence of a gene is expressed clinically is termed as the *expressivity*. If the expressivity is reduced to an extreme extent so that there is no clinical manifestation, such a gene is called *nonpenetrant*, e.g. achondroplasia, Huntington's chorea, Marfan's syndrome.

Sex Chromosome Related Disorders

In all females one of the 'X' chromosome derived from either parent undergoes inactivation at the early period of gestation, in a random manner governed by the laws of probability Lyon's hypothesis (1961). Females, therefore contain a mosaic of tissue cells containing either the maternal or the paternal X-chromosome. Inactivation of the X-chromosome is effected by the action of a gene called the X-inactivation specific transcript which is located in the long arm of the X-chromosomes. Since 50% of the X-chromosomes in carrier females are normal, they do not manifest signs of the disease, but male offsprings suffer from the disease.

X-linked Recessive Inheritance (Fig. 2.3)

1. There is 'oblique' transmission, i.e., in the pedigree a line drawn through the affected persons is oblique.
2. Only males are affected, females are only carriers.

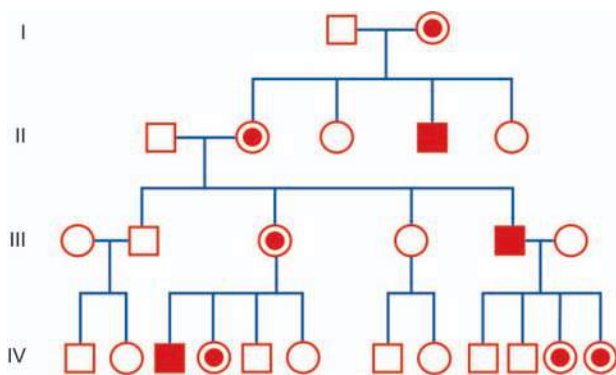


Fig. 2.3: Pedigree of a disorder with X-linked recessive inheritance (oblique transmission). Circles with dots in the centre represent carrier females

3. For the offsprings of a carrier female there is a 50% chance of sons being affected and a 50% chance of daughters being carriers.
4. Among offsprings of an affected male, none of the sons will carry the trait, while all the daughters will be carriers.

A female may manifest an X-linked trait if the normal X-chromosome is inactivated during early fetal life or if she is the offspring of a carrier female and affected male, or if the unaffected X-chromosome is structurally abnormal, as in Turner's syndrome, e.g., hemophilia, Christmas disease, pseudohypertrophic muscular dystrophy.

X-linked Dominant Inheritance (Fig. 2.4)

1. The number of females affected is double the number of affected males.
2. The affected male passes Y-chromosome to his sons (and not the X-chromosome). Therefore, all sons of an affected male are normal, whereas all daughters of an affected male are abnormal.
3. The affected female passes the mutant X-chromosome to half her daughters and to half her sons and, therefore, half the daughters and half the sons are affected.

The disease is usually milder in the female, because of the normal gene on the other X-chromosome, e.g. hypophosphatemic type of vitamin D resistant rickets.

Polygenic Disorders

Polygenic disorders (or disorders due to multifactorial inheritance) are caused by the additive effect of several minor abnormal genes and environmental factors. These are some of the commonest disorders encountered in clinical practice, e.g. anencephaly, spina bifida, talipes equinovarus, congenital dislocation of the hip, diabetes mellitus, essential hypertension, coronary artery disease, and asthma, etc.

In such disorders the environmental factors also play a major part in the development of clinical abnormality.

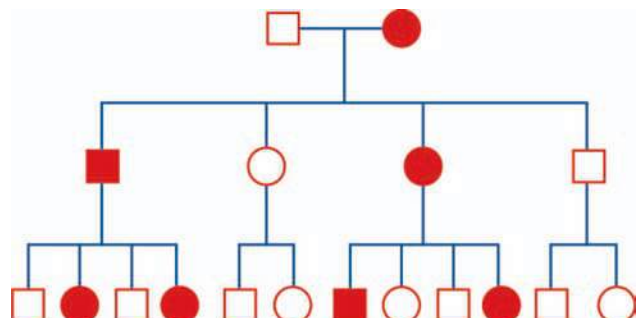


Fig. 2.4: Pedigree of a disorder with X-linked dominant inheritance. Double the number of females than males are affected

Chromosomal Disorders

These are disorders in which abnormalities in the number or pattern of chromosomes are demonstrable. The abnormality may involve the autosomes or sex chromosomes. Characteristics of autosomal disorders are:

1. Mental retardation,
2. Retardation of physical growth,
3. Congenital malformations, and
4. Dysmorphic features.

Sex chromosome disorders are characterized by:

1. Abnormalities of body configuration,
2. Gonadal abnormalities,
3. Abnormalities of the genitalia and secondary sexual characters, and
4. Disturbances of sexual and reproductive function.

Several of the chromosomal disorders are associated with higher incidence of other congenital abnormalities or neoplasms, e.g. congenital heart disease in Turner's syndrome, acute leukemia in mongolism.

Autosomal Disorders

DOWN'S SYNDROME

Syn: Trisomy 21: This occurs with a frequency of 1 per 1000 live births. Chromosome No. 21 is present in triplicate, making the total number of chromosomes to 47. The clinical features include (i) marked hypotonia, easily appreciated by lifting the infant up in one's arms, (ii) poor Moro's reflex, (iii) flat facies, (iv) upward slant of eyes, (v) small circular and dysplastic ears, (vi) loose folds of skin near the neck, (vii) clinodactyly of little finger (short and incurved), (viii) dysplastic middle phalanx of little finger, and (ix) dysplastic pelvis.

Radiologically the iliac bones appear wide and flat with absence of projection of the posterior superior iliac spine.

Diagnosis in the older child is fairly easy. The flat facies, the upward slant of the eyes, the flat occiput, the rough and dry skin, mental and physical retardation, clinodactyly, short and broad hands with simian crease (transverse creases), and wide gap between the big toe and other toes are some of the common features. About 40% have associated congenital heart disease, most commonly ventricular septal defect, endocardial cushion defects or Fallot's tetralogy, and these may prove fatal in the third or fourth decades.

Maternal serum markers are available for diagnosis of pregnancy with a Down's syndrome fetus. The alpha-fetoprotein level at 9-12 weeks of gestation is lower than normal. Other markers include maternal human chorionic gonadotropin, free beta subunit of human chorionic gonadotropin and pregnancy-associated protein A.

The incidence of Down's syndrome increases with increasing maternal age, being 1-2% in the age group of 38-45 years and 5% above this age. There is a twenty-fold increase in the incidence of acute leukemia (both ALL and ANLL) in Down's syndrome.

Other common trisomy syndromes involve chromosomes 18, 13 and 8 and show characteristic morphological abnormalities. Deletion syndromes are those in which a part of a chromosome is lost. Common deletion syndromes involve chromosomes 4, 5 and 13.

Sex Chromosomal Disorders

These constitute 50% of the chromosomal disorders seen at birth. Acquisition of extra X-chromosomes in the male leads to Klinefelter's syndrome. Deletion of one of the X-chromosomes gives rise to Turner's syndrome. The latter commonly affects females, but males also may be affected.

KLINEFELTER'S SYNDROME: It accounts for 1-3% of infertile males. It is characterized by tall stature and small atrophic testes (less than 2 cm in length or 6 ml in volume), scanty facial, pubic and axillary hair, X-chromatin positive buccal smear and XXY chromosomal constitution. The span (the distance between finger tips of outstretched hands) is greater than the height, and lower segment greater than upper segment (lower segment is the distance from heels to the upper end of pubic bone and upper segment from top of the skull to the upper end of pubic bone). The testosterone level in the blood is low or low normal and FSH and LH levels are increased. Almost half the patients have gynecomastia. The testes show atrophic and hyalinized seminiferous tubules and hypertrophic Leydig cells on biopsy.

In some cases the number of extra X-chromosomes may be more than one, i.e. more than two X-chromosomes. Increase in the number of X-chromosomes increases the chance of mental retardation, as well as skeletal and somatic defects.

Treatment consists of administration of long acting testosterone to induce male secondary sexual characteristics during puberty. The dose has to be varied from 25 to 250 mg given IM once in three weeks. Azoospermia does not improve, though the physical features of the patient may change, if treatment is given early.

TURNER'S SYNDROME: This condition was first described in 1938. It occurs with a frequency of 1/2500 to 1/1500 live born female infants. One of the X-chromosome is deleted. The remaining X-chromosome is of maternal origin in 2/3 and paternal origin in 1/3 cases. In Turner's syndrome the sex chromosome pattern is XO. In normal females, the epithelial cells obtained by buccal smear show sex chromatin consisting of inactivated X-

chromosomes. These are called Barr bodies. These are present in all cells. A proportion of neutrophils in peripheral blood shows the X-chromosomes as a knob like projection. In Turner's syndrome these sex chromatin bodies are absent.

Mosaic patterns such as XO/XX and others are sometimes seen. Structural abnormalities such as deletion of parts of the X-chromosome may occur.

Turner's syndrome is characterized by short stature (height below 141 cm), short neck with webbing, undeveloped breasts, scanty pubic hair, hypoplastic uterus and the presence of fibrous streaks instead of ovaries. Often there is edema of the dorsum of the hands and feet at birth due to hypoplasia of lymphatic vessels. The face is triangular with depressed nose, large mouth, small chin and loose folds of skin below the eyelids. Epicanthic folds and high arched palate may be seen. The chest is shield shaped with widely separated nipples and pectus excavatum. Large pigmented naevi, hyperconvex or hypoplastic nails, cubitus valgus, clinodactyly, short metacarpals and increased dermatoglyphic ridges on fingers may occur. 17-40% of patients with Turner's syndrome have congenital heart defects. Coarctation of the aorta, bicuspid aortic valves and left sided cardiac defects occur in the order of frequency. Hypertension, mitral valve prolapse and conduction defects are also more common. Echocardiography is mandatory in the initial work-up of cases of Turner's syndrome, so as to identify the cardiac abnormalities. Other concomitant abnormalities include hypothyroidism (15-30%), strabismus, cataracts, nystagmus, sensorineural deafness and recurrent otitis media.

Other stigmata include renal anomalies such as horse-shoe kidney. There is no mental retardation. Verbal IQ is lower than the performance IQ. The carrying angle of the elbow is increased.

Most patients are amenorrheic though some may show scanty periods. Replacement therapy with estrogens and progesterone after the age of 15 helps to maintain secondary sexual characters, though the height does not improve.

Therapy with human growth hormone initiated at about 5 years of age when growth retardation becomes manifest helps to restore the height partially. Supplementation of estrogens helps to retard osteoporosis. Assistance for pregnancy may be needed.

Patients with Turner's syndrome have a higher prevalence of diabetes mellitus.

XXX SYNDROME: Presence of an extra Y-chromosome confers mental subnormality and a violent or criminal behaviour. The majority have the karyotype XXX. They are generally taller, but are otherwise not distinguishable from normal individuals. Radioulnar synostosis and cubitus varus may be seen in some.

Methods Employed in Studying Genetic Disorders

Genetic studies are undertaken in all cases of morphological and biochemical abnormalities which may be prenatal, perinatal, postnatal or undetermined. Several techniques are employed in genetic analysis.

1. Karyotyping: Humans have 22 pairs of autosomes and one pair of sex chromosomes. Each chromosome has a constriction along its length, called the centromere which divides the chromosomes into two arms of equal or unequal length. The short arm is called 'p' and the long arm is called 'q' for descriptive purposes. During gametogenesis the chromosome number is halved, and therefore, gametes are said to be haploid, whereas the somatic cells are called diploid. In the laboratory, chromosomal pattern is studied by arresting mitosis in a dividing cell, separating the chromosomes by suitable methods, arranging them in order, and photographing them. Study of this pattern (karyotype) helps to identify deletion, addition, translocation, etc (Fig. 2.5).

Chromosomes are present in pairs. One chromosome of each pair comes from the mother and one from the father. As genes are located on chromosomes, it follows, therefore, that genes are also present in pairs.

2. Banding techniques: By special staining techniques subtle abnormalities in individual chromosomes can be detected. The stained preparations take the form of alternate dark and light bands and the patterns are highly diagnostic. Fluorescent quinacrine (Q banding) Giemsa (G banding) or (R banding) are generally used.

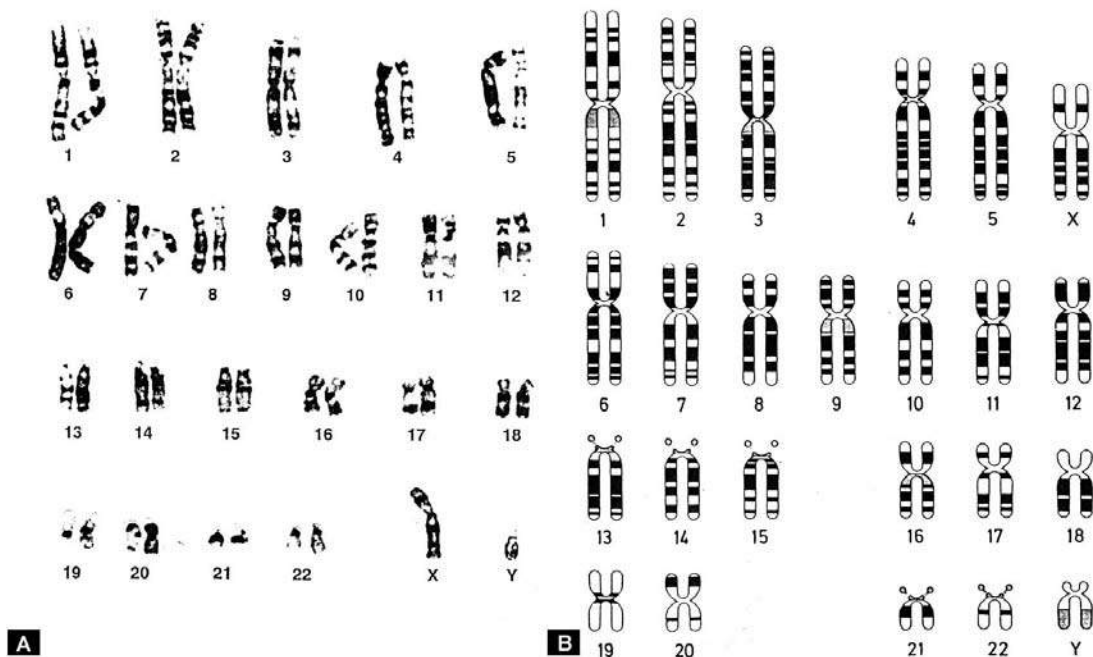
3. Gene mapping: For gene mapping, hybrids between human and mouse cells are created *in vitro*. These hybrids progressively lose human chromosomes, until at last only one human chromosome persists. The genes on this chromosome can be identified by studying the protein synthesis pattern of such a cell.

4. Fluorescence *in situ* hybridization (FISH) is employed to analyse chromosomes.

5. Microarray analysis is a means to probe the expression of thousands of genes simultaneously. This method was introduced into clinical practice in the mid 1990s and it has gained wide popularity for the analysis of several genetic problems.

Newer Developments in Genetics

Human genes were first cloned and sequenced about the end of the seventies. From then, newer knowledge and techniques have developed explosively. The human genome has been almost completely mapped and it is likely that the blueprint of the human genome may soon



Figs 2.5A and B: (A) Normal karyotype of human chromosomes—male G banding
(B) An idiogram showing the G banding pattern

become available. Prenatal diagnosis of genetic diseases is available for many diseases. Normal genes can be introduced into the cells of patients with genetic disorders in an attempt to correct the metabolic abnormality.

Diseases such as severe combined immunodeficiency, phenylketonuria, galactosemia, hemophilia, and diabetes mellitus, may lend themselves to such therapy.

Diagnostic techniques have reached an advanced stage of development at present. Some common terms used in genetic methodology are given below:

Restriction endonuclease: Several enzymes are used for cutting the double stranded DNA at specific nucleotide sequences. These enzymes are highly specific and give rise to predictable and uniform end products. Such enzymes are called restriction endonucleases. They are commonly used to identify the presence of the particular nucleotide sequence and to produce DNA fragments for the polymerase chain reaction (PCR).

DNA polymorphism: This is the inherited condition in which one or two different but normal nucleotide sequences can exist at a particular site in the DNA. Identification of DNA polymorphism can be made use of to identify the inheritance of abnormal genes that produce the disease.

Restriction site polymorphism: This is a specific type of DNA polymorphism in which the sequence of one form of polymorphism contains a recognition site for a

particular endonuclease while the sequence in the other form is devoid of such a site.

Study of DNA polymorphisms is particularly useful to identify the genetic cause for metabolic defects which do not show chromosomal abnormalities. Particular DNA sequences can be identified using DNA probes. DNA probes are fragments of DNA that contain nucleotide sequences specific for the gene or chromosomal region near the region of interest.

The process by which specific DNA probes are made to bind to complementary DNA sequences is called hybridization. Isolation and identification of DNA and RNA are done by blotting studies. If the material being isolated and identified is DNA, the method is called Southern blotting, in honour of EM Southern who developed the method. If the material being identified is RNA, the method is called Northern blotting. Correspondingly the method used for isolation and identification of proteins is called Western blotting, e.g. HIV proteins.

Polymerase chain reaction: A common procedure employed in genetic analysis is the polymerase chain reaction (PCR) by which portions of DNA that carry a particular gene are made to replicate and provide large quantities of the particular gene which is then identified by using biochemical methods. By this technique a particular portion of the genetic material can be multiplied several million folds within a short-time and this can be further submitted for analysis. This method is widely used in genetic studies to analyse genes.

Other non-genetic uses of PCR are in the diagnosis of microbial infection. The nuclear material (DNA or RNA) of the microbe can be detected and quantified. In addition to perfect specificity, PCR studies can detect the infective organism early in the disease even before antibodies develop, thereby helping in early diagnosis.

Prenatal Diagnosis

Many genetic and other disorders can be diagnosed *in utero*. Biochemical tests in pregnant women provide evidence for abnormal pregnancy, e.g., rise in serum alpha-fetoprotein in spina bifida and anencephaly, reduction in urinary estriol in fetal malformations. Direct evidence of fetal abnormality can be provided by imaging techniques such as ultrasonography or genetic analysis of fetal tissues. Materials for prenatal genetic diagnosis include fetal blood cells obtained by amniocentesis and fetoscopy done at 15-16 weeks of pregnancy under ultrasonographic control, and chorionic villus biopsy done towards the end of first trimester by the cervical route. Such procedures are widely undertaken in many parts of the world including a few centres in India. Establishment of major genetic disorder gives the chance for parents to accept abortion. With the availability of assisted reproduction techniques like *in vitro* embryo transfer, pre-implantation genetic investigations are done in order to eliminate genetically defective embryos.

Mitochondria and Mitochondrial Genetics

Mitochondria (MC) are the only organelles in the cell besides the nucleus, that contain their own DNA called mt DNA and their own machinery for synthesizing RNA and proteins. There are hundreds or thousands of mitochondria per cell and each contains approximately five mitochondrial genomes. The total number of genes in the mitochondria is 37. Most of the approximately 900 gene products in the organelles are encoded by nuclear DNA (n DNA) and are imported from the cytoplasm. Structurally MC have four compartments—the outer membrane, the inner membrane, the inter membrane space and the matrix (the region inside the inner membrane). MC perform numerous tasks such as pyruvate oxidation, Krebs's cycle and metabolism of amino acids, fatty acids and steroids. The most crucial function is the production of energy as ATP by means of electron transport chain and the oxidative phosphorylation system the respiratory chain.

The MC is a 16569-base pair double stranded circular molecule containing 37 genes. 24 genes are needed for mt DNA translation and 13 genes code subunits of the respiratory chain.

In MC diseases, some MC may have pathogenic mutations of mt DNA, others may be normal. This situation is known as heteroplasmy. The random distribution of organelles at the time of cell division can change the proportions of mutant mt DNA obtained by daughter cells and when the pathogenic threshold in a previously unaffected tissue is surpassed, the phenotype may also change.

Mitochondrial DNA Related Respiratory Chain Diseases

These share 2 features:

1. Lactic acidosis and 2. massive MC proliferation in muscle giving rise to ragged-red fibre in muscles, MC being present in all cells, many of the MC disorders produce widespread multisystem effects. Several distinct syndromes have been described depending upon the genetic alterations.

Clinical features include symptoms pertaining to all systems.

Nervous system: seizures, ataxia, myoclonus, psychomotor retardation, hemiparesis, cortical blindness, headache, dystonias, peripheral neuropathy and muscle weakness.

Eyes: ptosis, retinopathy, optic atrophy

Blood: sideroblastic anemia

Endocrinology: diabetes mellitus short stature, hypoparathyroidism

Heart: conduction defects, cardiomyopathy

Gastrointestinal system: exocrine pancreatic dysfunction

Kidney: Fanconi's syndrome

Ear: sensorineural deafness.

Genetic Counselling

Genetic counselling is the process of communication which deals with the human problems associated with the birth of an abnormal child or possibility of similar incident, to the concerned parents.

The steps involved are:

1. Making a precise diagnosis and administering appropriate treatment.
2. Reducing anxiety and guilt in the patient or parents and helping them to cope realistically with the affliction.
3. Explaining the relevant genetic facts, informing them about diagnostic facilities, and risk of recurrence in subsequent children, and
4. Helping the couple to make rational decisions regarding further children.

Conclusions: From the days of Charles Darwin 140 years ago, genetics has made great progress so as to become a

major subspeciality in medicine. It is likely to play a major role in the prediction, prevention, diagnosis, and treatment of several major diseases:

1. Study of common diseases help to understand their mechanisms better and provide better care.	Alzheimer's disease, asthma, breast cancer, heart disease, migraine, etc.
2. Re-defining disease mechanism	This helps to identify the geno-type in addition to the pheno-type which will ultimately help to classify more objectively and manage more effectively.
3. Targeting treatment	Genetic studies help to reveal genetic make up predisposing to disease, drug metabolism, effectiveness of drugs, etc. This helps to plan treatment more effectively.
4. Discovering newer targets and effective treatment	Present day treatment, in many cases is the management of the final effect of the disease, e.g. diabetes, asthma, cardiac failure. Understanding the genetic pattern will help to target therapy to the basic abnormality and tackle the cause more effectively.
5. Providing effective preventive care	

Gene Therapy

The first successful attempt at transferring the normal gene for adenosine deaminase to a girl suffering from deficiency of this enzyme was performed on 14th September, 1990. Subsequently several persons have been given normal genes in order to replace defective genes with a view to cure the metabolic defect. The procedure involves isolation of the healthy gene along with the sequences controlling its expression, incorporation of the gene on a carrier or vector as an expression cassette and finally the delivery of the same to the target cells. Gene therapy may be positive or negative. The former is the introduction of a gene whose protein product is necessary for the curative effect. Negative gene therapy implies the inhibition of the 'sick' or over expressed gene function. Gene therapy is likely to become more popular in the near future. Though gene therapy is largely beneficial, insertion of a defective gene may lead to adverse effects in future, e.g. lymphatic leukemia in children treated with single gene therapy for severe combined immunodeficiency.

The other modality of treatment which has been successful in some of the genetically determined diseases is bone marrow transplantation, e.g. thalassemia, hemoglobinopathies.

GENETIC EPIDEMIOLOGY

Genetic epidemiology which is a developing discipline is closely related to traditional epidemiology. It particularly focusses on the familial and in particular, the genetic determinants of diseases and the joint effects of genetic and non-genetic determinants.

The fusion of epidemiology and genetics provides the foundation for genetic epidemiology. Genetic epidemiology can contribute to establishing the causative role of environmentally modifiable risk factors and help in planning preventive measures in future. Pharmacogenomics is that branch of genetic study in which the appropriate dosing with maximum cost effectiveness can be selected, based on genetic information.

Glossary of Terms Used in Genetics

- Allele**—An alternative form of a gene.
- Alternative splicing**—A regulatory mechanism by which variations in the incorporation of a gene's exons or coding regions, into messenger RNA lead to the production of more than one related protein, or isoform.
- Autosomes**—All of the chromosomes except for the sex chromosomes and the mitochondrial chromosome.
- Centromere**—The constricted region near the centre of a chromosome that has a critical role in cell division.
- Codon**—A three-base sequence of DNA or RNA that specifies a single amino acid.
- Conservative mutation**—A change in a DNA or RNA sequence that leads to the replacement of one amino acid with a biochemically similar one.
- Epigenetic**—A term describing non-mutational phenomena, such as methylation and histone modification, that modify the expression of a gene.
- Exon**—A region of a gene that codes for a protein.
- Frame-shift mutation**—The addition or deletion of a number of DNA bases that is not a multiple of three, thus causing a shift in the reading frame of the gene. This shift leads to a change in the reading frame of all parts of the gene that are downstream from the mutation, often leading to a premature stop codon and ultimately, to a truncated protein.
- Gain-of-function mutation**—A mutation that produces a protein that takes on a new or enhanced function.
- Genomics**—The study of the functions and interactions of all the genes in the genome, including their interactions with environmental factors.

Genotype—A person's genetic makeup, as reflected by his or her DNA sequence.

Haplotype—A group of nearby alleles that are inherited together.

Heterozygous—Having two different alleles at a specific autosomal (or X-chromosome in a female) gene locus.

Homozygous—Having two identical alleles at a specific autosomal (or X-chromosome in a female) gene locus.

Intron—A region of a gene that does not code for a protein.

Linkage disequilibrium—The nonrandom association in a population of alleles at nearby loci.

Loss-of-function mutation—A mutation that decreases the production or function of a protein (or does both).

Missense mutation—Substitution of a single DNA base that results in a codon that specifies an alternative amino acid.

Monogenic—Caused by a mutation in a single gene.

Motif—A DNA sequence pattern within a gene that, because of its similarity to sequences in other known genes, suggests a possible function of the gene, its protein product, or both.

Multifactorial—Caused by the interaction of multiple genetic and environmental factors.

Nonconservative mutation—A change in the DNA or RNA sequence that leads to the replacement of one amino acid with a very dissimilar one.

Nonsense mutation—Substitution of a single DNA base that results in a stop codon, thus leading to the truncation of a protein.

Penetrance—The likelihood that a person carrying a particular mutant gene will have an altered phenotype.

Phenotype—The clinical presentation or expression of a specific gene or genes, which may be influenced by environmental factors, or both.

Point mutation—The substitution of a single DNA base in the normal DNA sequence.

Regulatory mutation—A mutation in a region of the genome that does not encode a protein but affects the expression of a gene.

Repeat sequence—A stretch of DNA bases that occurs in the genome in multiple identical or closely related copies.

Silent mutation—Substitution of a single DNA base that produces no change in the amino acid sequence of the encoded protein.

Single-nucleotide polymorphism (SNP)—A common variant in the genome sequence; the human genome contains about 10 million SNPs.

Stop codon—A codon that leads to the termination of a protein rather than to the addition of an amino acid. The three stop codons are TGA, TAA, and TAG.

Translation—This is the production of protein via mRNA
Most genes contain alternating regions called exons and introns.

3

Defence Mechanisms of the Host and Clinical Immunology

K.V. Krishna Das, Aswini Kumar

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Immunology has developed and reached a high level of achievement in the past few decades. Immunological principles have helped in understanding the mechanisms of several disease processes and their management. Man has several defence mechanisms to protect him against microbial invasion. These may be nonspecific and specific.

Nonspecific Defence Mechanisms

1. The skin and mucous membranes form protective barriers against bacteria. The stratum corneum which is a desiccated layer of the epidermis is impermeable to microbes. If microbes enter through wounds, the organisms are killed by neutrophils and macrophages through the mechanism of oxygen intermediates. Antimicrobial substances such as defensins and cathepsidins act against bacteria, viruses and fungi. In atopic dermatitis these antimicrobial peptides may be deficient and this predisposes to bacterial infections, especially *S. aureus*.
2. Lactic acid in the sweat and fatty acids in the sebaceous secretions inhibit growth of pathogenic flora. Fungal infections are common in parts devoid of sebaceous glands, e.g., interspaces between toes, the soles and the sides of the feet.
3. Ciliary movement helps to carry away bacteria through mucous secretions in the respiratory tract. Organisms such as *Pseudomonas aeruginosa* colonize in the lungs, especially in cystic fibrosis. They form biofilms in the respiratory tract and thrive within the biofilm in a free-living planktonic state (a free-living drifting state) which resists all defense forces of the host.

In the normal state, inhaled pathogens are cleared by mucociliary action and natural defenses. If the bacterial population exceeds a threshold number they produce sensors which monitor the defenses forces of the host and in turn, develop virulence genes which protect them against phagocytosis.
4. Mucus of respiratory and urogenital tracts possesses bactericidal properties due to the enzyme lysozyme which lyses the cell wall of the invading bacteria. Moreover, the neuraminic acid content of the mucus competitively inhibits the myxoviruses.
5. Normal commensals of the skin and gastrointestinal tract inhibit the proliferation of pathogenic bacteria.
6. Phagocytosis is the most important nonspecific mechanism by which body tries to eliminate invading organisms. Cells with phagocytic properties are:
 - a. Neutrophil leukocytes,
 - b. Eosinophils,
 - c. Monocytes,
 - d. Histiocytes in tissues,
 - e. Sinus lining cells in the liver (Kupffer's cells), spleen and bone marrow,

- f. Reticulum cells in lymph nodes, and
- g. Microglia in the central nervous system.

Foreign materials are ingested by the phagocytes and later digested intracellularly. The myeloperoxidase present inside the phagocytes also destroys viable bacteria. When the phagocytic function is reduced, generalized infections like septicemia develop leading to high mortality. Several processes aid in phagocytosis. These are:

- i. Chemotaxis by complement breakdown products,
- ii. Opsonization by specific antibodies which neutralise the negative surface charges of bacteria, and
- iii. Cytokines such as macrophage activating factors and macrophage migration inhibition factors released by the T-lymphocytes which lead to local accumulation of active macrophages (Table 3.1).

Colloidal substances, high molecular weight substances and dyes may saturate phagocytic capacity and increase the susceptibility to infection, e.g., carbon particles in heavy smokers, silica particles in mine workers, etc. Some organisms (e.g., *M. leprae*) are not destroyed by the macrophages. On the other hand they multiply in the protected environment of the cell.

Specific Mechanisms

The Immune Response

Any substance which evokes an immunological reaction is an *antigen*. Certain components of the cell membranes act as *specific antigens*. They differ from person to person in their chemical composition and three dimensional structure. The immunocompetent cells can recognize the self from the non-self. Moreover, the body can recognize one antigen from another leading to specificity of immunological reaction. Some substances are strongly antigenic, e.g., dinitrochlorobenzene, while others are weakly antigenic, e.g., bacterial capsular antigen. *Antibody response* is usually selective against certain important regions of the antigen which are termed the antigenic determinant sites. A *hapten* is a small molecule which by itself cannot elicit antibody production, but when combined with a carrier molecule, can do so. The antibodies can combine with the hapten directly, without the help of the carrier. The presence of haptens in tissue proteins is one of the reasons for the development of autoimmunity.

The main cells involved in immune reactions are the lymphocytes. They originate from the totipotent cells of the bone marrow. Some of them pass through the thymus from where they develop to become T-lymphocytes with their specific antigens and functional capacities. They are then specialized for cell mediated immune reactions and are recognizable by thymus specific antigens on their surface. These T-lymphocytes are found mainly in the

TABLE 3.1

Cytokines of importance				
Cytokine	Primary source	Other	Target	Effects
Interleukins Tumour necrosis factor (TNF)	Macrophages Lymphocytes		Macrophages Granulocytes Tissue cells	Activation of cytotoxic cell activity, cachexia, adherence of leukocytes to endothelium
Interferons	Leukocytes T-lymphocytes NK cells	Fibroblast Epithelium	Tissue cells Leukocytes	Antiviral, macrophage activation
Macrophage (M) Colony stimulating factor (CSF)	Monocytes	Endothelium Fibroblast	Stem cells	Stimulation to divide and differentiate
Granulocyte (G) CSF	Macrophages	Fibroblast	Stem cells	-Do-
Migration inhibition factors (MIF)	T-lymphocytes	—	Macrophages	Migration inhibition
Chemotactic factors	Lymphocytes Macrophages Granulocytes	Tissue cells and their components	Leukocytes	Attract to site of infection or tissue damage

paracortical areas of lymph nodes and periarteriolar sheaths in the spleen. On the other hand, the stem cells passing through gut and lung associated lymph nodes (bursa equivalent) are transformed into B-lymphocytes. They eventually occupy germinal centres of lymph nodes and spleen. Upon antigenic stimulation, they transform into plasma cells which synthesize the immunoglobulins and form mediators of humoral immunity. In peripheral blood, 80% of lymphocytes are T-cells, 15% are B-cells and 5% are K-cells (killer).

T-lymphocytes form spontaneous rosettes with sheep erythrocytes (*E. rosette*) at 4°C. These receptors are identified as the CD2 molecules on T-cells. They are also recognised by the presence of specific antigens on their cell surfaces, identified by monoclonal antibodies. CD3 marker is present on T-cells. T-cells include many subsets, most important ones are TH (T helper or CD4 +ve) cells carrying CD4 antigen and TS (T suppressor or CD8 +ve) cells carrying CD8 antigen. (CD stands for cluster determinant).

All T-cells have the T-cell antigen receptor (TCR) on their surface. TCR-2 contains alpha and beta chains; TCR-1 consists of gamma and delta polypeptides. Both are further associated with a set of 5 polypeptides, to form the CD3 complex or TCR complex. In human peripheral blood 90% T cells are TCR-2 and the remaining are TCR-1. TCR-2 cells are further divided into two groups, depending on the presence of CD4 or CD8 markers on their cell surface. The subset, which carries the CD4 marker, helps the B cells to divide, differentiate and make antibody response; these are therefore called T helper (TH) cells. CD4 T cells recognise their specific antigens in association with MHC class II molecules. CD4 positive T helper cells also carry CD 29 antigen.

The CD4 positive cells are further subdivided into two subsets, depending on their capacity to produce cytokines. The TH-1 subset secretes interleukin-2 (IL-2) and interferon-gamma; induces cytotoxic T-cells; enhances delayed hypersensitivity; and activates macrophages. On the other hand TH-2 subset produces IL-4, IL-5 and IL-6; stimulates B-cells; enhances humoral immunity, and activates eosinophils. A small number of CD4 cells belong to a third group, they are the memory cells (TH-M).

The second TCR-2 subset, which carries the CD8 marker, is responsible for suppressing antibody response and so they are termed as T suppressor (TS) cells. CD8 T-cells recognise antigens in association with MHC class I molecules.

The CD8 positive cells are also subdivided into 2 subclasses. The subset that expresses CD28 molecule secretes IL-2 and is mainly suppressor in function. The other subset that carries CD18 antigen does not produce IL-2, but responds to IL-2, and is mainly cytotoxic. This group is responsible for the destruction of host cells that are infected by viruses or intracellular pathogens; they are therefore also called as T cytotoxic (TC) cells.

B-lymphocytes are identified either by the rosette formation with sheep erythrocytes coated with antibodies and complement (*EAC rosette*) or by demonstration of surface immunoglobulins by fluorescent antibody technique. Immunoglobulins are classified into G, M, A, D and E (Table 3.2). All B-cells carry CD 19 and 20 markers and MHC II marker. Pre-B-cells (immature B-cells) carry CD9 and 10 markers. CD5 carrying B-cells are responsible for autoantibody production.

Once the antigens enter the body, they are processed by macrophages and then recognized by the antigen sensitive lymphocytes. Antigens synthesized within a cell,

TABLE 3.2

Characteristics of immunoglobulins					
Class	IgG	IgA	IgM	IgD	IgE
Heavy chain	gamma	alpha	mu	delta	eta
Molecular weight	150,000	400,000	900,000	180,000	200,000
Ultracentrifuge value [S. value (Svedberg's units)]	7	11	19	7	8
Mean serum concentration (mg/dl)	1250	250	125	3	0.03
Antibody activity	+	+	+	–	+
Primary response	–	–	+	–	–
Secondary response	+	+	–	–	–
Placental crossing	+	–	–	–	–

such as viral polypeptides are externalised and associated with MHC (major histocompatibility) Class I molecules and beta-2 microglobulin. Class I molecules are present on all nucleated cells. The complexed antigen is then presented to the CD8 T cells. By contrast, antigens that have been endocytosed are associated with MHC Class II molecules, and these are then presented to the CD4 T cells. The lymphocytes recognise the antigen by means of the receptors present on their surface. The T-cell antigen receptor (TCR) is part of the CD3 complex. Antigen recognition receptors on B-cells are made up of partly by surface immunoglobulins. When the antigen is recognised by receptor, the lymphocytes undergo morphological alterations (blast transformation) and after a series of divisions form a clone of cells which react against the specific antigen. These committed cells differentiate into plasma cells which secrete specific antibodies. Some of the remaining cells are responsible for *immunological memory*. Many infections and vaccinations lead to prolonged immunity due to persistence of immunological memory.

Most animals start producing specific antibodies within 10 days of injection of antigen. Initially these antibodies are mainly of IgM variety. This is the *primary response*. When the same antigen is again introduced, the *secondary immune response* is elicited. The reaction occurs at a faster and augmented rate and lasts longer. This time IgG antibodies predominate. Sometimes even large quantities of antigen may not produce immune response. This is called *tolerance*, which again will be specific to that particular antigen. Tolerance acquired in postnatal life usually fades away with the passage of time. However, tolerance induced *in utero* tends to be permanent.

The effector mechanisms involved in the immune response are as follows:

1. Cell-mediated immunity,
2. Humoral immunity,
3. Antibody dependent cell mediated immunity,
4. NK cells-Natural killer cells mediated immunity, and
5. Macrophage-mediated immunity.

Cell-mediated immunity: This is mediated by the *T-lymphocytes* which form *T-helper cells*, *T-suppressor cells* and *natural killer cells*.

(A) **Immunity against infections** Effective immunity against bacteria such as mycobacteria and listeria, certain viruses and almost all parasites is mediated by T-cells. T-cells from sensitised individuals lyse the target cells bearing the viruses.

(B) **The rejection of allograft and destruction of tumour cells** These are also mediated mainly by T-cells, although other mechanisms are also involved.

(C) **Helper function** Some of the T-cells express CD4 antigen on their cell surface. These are called CD4 positive cells or T-helper (TH) cells. They also carry receptors for the Fc portion of IgM. They form about 50% of the T cells of peripheral blood. They are necessary for the optimal antibody production by plasma cells and for generation of cytotoxic T-cells. Moreover, they produce cytokines needed to stimulate immune response. These cytokines act in an autocrine manner on the CD4 cells themselves and in a paracrine manner on other cells. Human immunodeficiency virus (HIV) specially infects CD4+ cells with consequent destruction of these cells leading to acquired immunodeficiency syndrome (AIDS).

(D) **Suppressor function** The suppressor cell (TS) subgroup which constitutes 10% of the total can be distinguished by the presence of surface receptors for Fc portion of IgG (Tr). They carry CD8 antigens. They regulate the activities of both T- and B-cells. The TS activity is depressed in many autoimmune diseases and in some of the human malignancies.

(E) **Production of soluble mediators** Cytokines are biologically active molecules released by specific cells that elicit a particular response from other cells on which they act. Several lymphokines and monokines (products of monocytes) are known. T-cells stimulated by antigens liberate certain soluble substances called *lymphokines*.

These molecules produced in an antigen specific manner can act in an antigen nonspecific manner to recruit, activate and regulate effector cells with the potential to combat infectious agents.

Lymphokines include *macrophage migration inhibition factor* (MIF), *macrophage activation factor* (MAF), *leukocyte migration inhibition factor* (LMIF), *leukocyte adherence inhibition factor* (LAIF), *chemotactic factor*, *interferons* (IF) and *interleukins* (IL). The MIF and MAF help in accumulation of macrophages at the site of reaction. The resulting erythema and induration form the basis of skin tests. Administration of transfer factor to nonsensitized individuals leads to specific sensitisation.

Chemokines (chemotactic cytokines) mediate inflammatory reaction. The attraction of leukocytes to the site of inflammation is central to the process. More than 40 cytokines have been identified. These are grouped mainly into 4 families. Alpha chemokines attract neutrophils, while beta chemokines act on monocytes, eosinophils and lymphocytes with variable selectivity. C5a (complement activation product) and leukotriene (LTB₄) are generated at the site of bacterial infection and they attract macrophages and mast cells. Chemokines induce cell migration by attachment to specific G-protein controlled cell surface receptors on target cells. These chemokine receptors also act as co-receptors for infective agents such as *Plasmodium vivax* and HIV to get entry into host cells.

Interferons (IF) inhibit viral multiplication in host cells, modulate cell differentiation and inhibit oncogene expression.

The major types of IF are alpha, beta and gamma derived from leukocytes, fibroblasts and activated T lymphocytes respectively. Gamma interferon is antiviral in activity. It also increases cytotoxic activity of T-cells, enhances B-cell differentiation and induces respiratory burst in macrophages. Interferon is useful in the treatment of hairy cell leukemia and chronic myeloid leukemia in addition to several viral infections.

Interleukins (IL) are growth factors secreted by lymphocytes, monocytes and macrophages. There are 15 different interleukins described so far. They are biological mediators which control the amplitude and duration of immune response. IL-1 stimulates production of receptors for IL-2 on lymphocytes. Moreover IL-1 induces production of acute phase proteins, such as C-reactive protein from liver, which in turn produce fever and leukocytosis. IL-2 stimulates T-cells and NK cells so as to become lymphokine-activated killer (LAK) cells. Such specific LAK cells are being used for immunotherapy in cancer patients with promising results. IL-3 is colony stimulating factor for T- and B-cells. IL-4, 5, 6 and 7 are produced by T-helper cells; all of them help in B-cell differentiation. IL-5 stimulates eosinophils; IL-6 enhances myeloid cells

and IL-7 increases platelet production. IL-8 is produced by monocytes and is chemotactic for neutrophils. IL-9 and 10 are general growth factors for lymphocytes.

Leukotrienes (LTs) are derivatives of arachidonic acid. The arachidonic acid may be converted to (A) cyclooxygenase products (prostaglandins and prostacyclin), and (B) 5-Lipoxygenase products (leukotrienes and lipoxins). In myeloid cells leukotrienes A₄, B₄, C₄, D₄ are formed; the last mentioned two are components of the slow reacting substance (SRS) of anaphylaxis. LTs are chemical mediators of allergy and inflammation. LTs play important role in increasing vascular permeability and diapedesis of leukocytes. They produce bronchoconstriction, bronchial mucosal edema and mucous secretion in asthma. They have a role in pathogenesis of acute respiratory distress syndrome (ARDS) and ulcerative colitis.

(F) **Delayed hypersensitivity:** When tuberculin or a similar antigen is injected intradermally in a sensitised individual, an erythematous indurated lesion develops slowly, reaching its maximum within 48-72 hours. This is called delayed type of hypersensitivity. Hypersensitivity is the abnormal over-reaction of the immune system and it usually results in unwanted tissue destruction. This is responsible for caseation in tuberculosis, granulomatous skin lesions in tuberculoid leprosy, rashes in smallpox and measles, skin lesions in herpes simplex and contact hypersensitivity to chemicals and plants. Hypersensitivity reaction mediated by T-cells is called Type IV reaction.

Humoral immunity: Antibodies are produced by plasma cells. These are immunoglobulins, belonging to the class IgG, IgA, IgM, IgD, and IgE. All except IgA are present in plasma mainly. IgA is also present in body secretions and hence present in mucosal surfaces as well. The immunoglobulins consist of specific heavy chain and light chains. IgG is present in maximal amounts in plasma. It is mainly responsible for humoral immunity against microbial infection. Primary response produces antibodies of IgM type, while IgG antibodies predominate in secondary response. IgG can cross placental barrier. Natural antibodies (e.g., antibodies against ABO system of RBC) are of IgM variety; they cannot cross placental barrier, and so the fetus is protected. Anti-Rh antibodies, being IgG type, can cross the placenta, leading to Rh isoimmunization and consequent fetal distress.

The characteristics of immunoglobulins are given in Table 3.2.

Complement system: This consists of plasma and membrane proteins (globulins) that play a major role in host defence against microbes and in several other immunological processes such as hemolysis. They function in two major ways. (1) Opsonization of microbes and alteration in their surface membrane leading to disruption. (2) Promotion of inflammatory response by

TABLE 3.3

Characteristics of complement components

	Serum concentration (µg/mL)	Thermal reaction	Site of synthesis
C1q	100-200	labile	Epithelial cells of small intestine
C1r	—	labile	-Do-
C1s	20-120	labile	-Do-
C2	20-40	labile	Reticuloendothelial cells (RE cells)
C3	1200	stable	Hepatocytes
C4	250-400	stable	RE cells
C5	75-100	labile	Macrophages
C6	20	stable	Hepatocytes
C7	—	stable	-Do-
C8	10	labile	-Do-
C9	2	labile	-Do-

altering vascular permeability and attracting inflammatory cells to the site of injury. Several of them have been named. These are C1q, C1r, C1s, and C2 to C9. Their properties are given in Table 3.3.

Acquired and inherited abnormalities of the complement system predispose to microbial infections and autoimmune disorders. For example, when antigen-antibody complexes are deposited in kidney glomeruli, complement components are activated, inflammatory cells are attracted and immune mediated glomerulonephritis develops. Complement components are used up differentially in several immune mediated diseases and, therefore, measurement of serum levels of complement components gives diagnostic and prognostic information.

The complement system is activated sequentially when antibody attaches to antigen components on the cell surface. The final products create microscopic holes on

the cell membrane. Osmotic entry of water through these holes results in lysis of the target cells. The complement products also activate phagocytosis, chemotaxis and immune adherence. Capillary permeability is also increased. Inhibitors of the complement are present naturally, which check the uncontrolled activity of the complement.

Apart from the classical sequential complement pathway, some microbial polysaccharides can activate an alternate system (properdin system), thereby bypassing the initial complement components. Since this does not require specific antibodies, the alternate pathway acts as a first line of defence against invading micro-organisms. However, the nonspecific nature may sometimes prove disadvantageous as in the case of complement activation by immune complexes leading to widespread tissue destruction as in type III hypersensitivity reaction.

Humoral immunity plays a great role in conferring resistance to bacterial infection. The antibodies destroy the target cells by several mechanisms.

1. Classical complement pathway,
2. Antibody dependent cell-mediated cytotoxicity,
3. Agglutination, and
4. Opsonization of target cells, thereby making them more susceptible to phagocytosis. Characteristic features of various immunological effector arms are shown in Table 3.4.

Antibody dependent immunity: Hypersensitivity reactions mediated by antibodies fall into different types which are described below:

Type I. Anaphylactic reaction Introduction of the antigen (e.g., penicillin) leads to the production of cytophilic antibodies (mainly IgE) in sensitive persons. These are attached to the surface of mast cells. Unlike the other

TABLE 3.4

Characteristic features of various immunological arms

	T-cells	B-cells	K-cells	NK-cells	Macrophages
Cell surface marker	Sheep RBC receptor	Complement receptor and surface Ig	Fc receptor	Fc receptor	Fc receptor and complement receptor
Identification	E-rosette	EAC rosette or surface immuno-globulins	EA rosette	K 562 rosette	Adherence to glass surface
Mechanism of action	Direct cell mediated lysis; lymphokine production	Antibody dependent complement mediated cytotoxicity; agglutination	Antibody dependent cell mediated cytotoxicity	Direct cell mediated cytotoxicity	Phagocytosis
Activity against debris	Virus, parasites, bacteria, cancers, transplanted organs	Bacteria, viruses	Cancers, parasites	Cancer cells	Bacteria, tissue
Hypersensitivity reaction	Type IV	Types I, II, III and V	Type VI		Type III

immunoglobulins which circulate in the plasma, IgE is bound to receptors especially to FC ϵ R which is a distinctive receptor for ϵ chain, present more on basophils and mast cells, and probably on eosinophils as well. Cross linking of cell-bound IgE with the multivalent antigen excites cellular processes which culminate in the liberation of chemical mediators such as histamine and serine proteins into the circulation. This brings on the anaphylactic reaction.

On subsequent exposure the antigen reacts with the preformed antibodies, causing mast cell degranulation and release of histamine, serotonin, and slow reacting substance of anaphylaxis (SRS-A). This may lead to asthma due to bronchoconstriction, or anaphylactic shock due to widespread capillary dilatation.

Allergens such as pollens, house dust and fungi react with cell bound IgE of the respiratory tract leading to bronchial asthma or hay fever. Allergens from food may cause urticaria.

Type I hypersensitivity reaction occurs within 30 minutes of exposure to the allergen. Such reaction can be abolished by drugs like adrenaline and disodium cromoglycate which prevent the release of histamine. Antihistamines compete with the released histamine for effector sites. Repeated introduction of the allergen in small doses results in hyposensitization.

Type II. Cytotoxic hypersensitivity Certain drugs may complex with membrane proteins of blood cells leading to production of autoantibodies. These antibodies can lyse the blood cells through the action of complement. Hemolytic anemia caused by alpha-methyldopa, agranulocytosis produced by amidopyrine and thrombocytopenia induced by chlorothiazides are examples of this mechanism.

Type III. Immune complex mediated tissue damage The continued presence of antigen causes persistent antibody production. Antigen-antibody complexes form and circulate in the blood. These heavy molecules are entrapped in blood vessels, renal glomeruli, lungs, skin and joints. Complement system is activated through the alternate pathway. The complement degradation products attract polymorphs and macrophages and an inflammatory reaction sets in with resultant damage to the tissues.

Platelet aggregation occurs and these microthrombi lead to vascular occlusion and ischemia.

If the antibody is in excess, the complexes are rapidly precipitated and tend to be localized at the site of entry of antigen. This leads to Arthus type reaction. If an antigen is injected intradermally into a hyperimmunized animal, erythema and edema occur at the site of injection. This reaction reaches a peak in 3-8 hours, and is referred to as intermediate type skin reaction. Farmer's lung is the classical example of localized type III reaction. On the

other hand, if antigen is excess, soluble complexes are formed which precipitate in all tissues giving rise to the serum sickness type of reaction. The lumpy granule precipitates seen in renal glomeruli in post-streptococcal glomerulonephritis are due to systemic type III reaction.

Type IV. T-cell-mediated hypersensitivity reaction: This is mediated by T-lymphocytes and it has been described earlier.

Type V. Stimulatory hypersensitivity Thyroid cells are normally stimulated by TSH through a membrane associated receptor. The *long acting thyroid stimulator* (LATS), otherwise known as *thyroid stimulating immunoglobulin* (TSI) is an antibody against some components of the receptor for TSH. The LATS produces TSH like activity, but the action is more prolonged. The continued stimulation by LATS leads to hyperthyroidism. Similarly, antilymphocyte globulin (ALG) is stimulatory to lymphocytes in appropriate conditions. It is used therapeutically in immune mediated aplastic anemia.

Type VI. Antibody dependent cell-mediated cytotoxic mechanism (ADCC) This mechanism does not require complement activity. The effector cells are neither T- or B-cells but are called K-cells. The specificity of this reaction resides in the antibody molecule. Only very small amounts of antibody are required to produce this reaction and, therefore, this mechanism is effective in areas where antibody concentration may be minimal, e.g. at the site of solid tumours. The full significance of this mechanism is not known.

In certain circumstances, more than one mechanism may be operating. Thus in autoimmune damage to endocrine glands, e.g. type I diabetes mellitus, type II and IV hypersensitivity reactions are involved. Autoantibodies against insulin secreting cells, insulin molecules and insulin receptors were described. The clinical features of the hypersensitivity reactions are shown in Table 3.5.

AUTOIMMUNE DISEASES

The autoimmune diseases result from immunologically mediated tissue destruction where the antigens involved are autologous. These are broadly classified into two:

(A) **Organ specific diseases:** The antibodies associated with Hashimoto's thyroiditis react only with thyroid tissue, so the lesion is highly localized. Other examples of organ specific diseases include those of stomach (pernicious anemia).

(B) **Non-organ specific diseases:** In contrast, the serum from patient with systemic lupus erythematosus (SLE) reacts with many tissues in the body; the dominant antibody is directed against cellular double stranded DNA. Although non-organ specific, some autoimmune diseases

TABLE 3.5

Common hypersensitivity disorders

	<i>Skin diseases</i>	<i>Kidney diseases</i>	<i>Lung diseases</i>	<i>Diseases of other sites</i>	<i>Skin test</i>
Type I Anaphylactic, IgE mediated, histamine dependent	Urticaria and rashes due to bacteria, viruses, parasites, food and drugs, atopic dermatitis		Rhinitis and asthma due to pollen dust, feathers, etc.	Penicillin reaction food allergy	Wheal and flare reaction within 30 minutes, immediate type
Type II Cytotoxic antibody mediated complement dependent	Bullous pemphigoid (basement membrane), pemphigus vulgaris (desmosomes)	Goodpasture's (anti GBM) syndrome	Goodpasture's syndrome	Transfusion reactions, isoimmunization (Rh), drug-induced hemolytic anemia, thrombocytopenia, leukopenia	
Type III Immune complex mediated complement and phagocyte dependent	SLE	Post-streptococcal glomerulonephritis, nephrosis of quartan malaria	Farmer's lung due to dusts from hay, bagassosis, cereal grains, etc.	Arthus reaction serum sickness SLE	Erythema and edema, polymorphs predominate, maximum at 3-8 hr intermediate group reaction
Type IV T cell mediated cytotoxic	Contact allergy to chemicals, granuloma in leprosy	Chronic and membranoproliferative glomerulonephritis	Granuloma and caseation in tuberculosis	Hashimoto's thyroiditis	Erythema and induration, lymphocytes predominate maximum at 72 hr, delayed type
Type V Stimulatory antibody mediated				Thyrotoxicosis due to long acting thyroid stimulator	

preferentially involve certain organs; examples are rheumatoid arthritis (joints), scleroderma (skin) and dermatomyositis (skin and muscle). Removal of preformed antibody by plasmapheresis is a therapeutic tool in the management of some of these disorders.

Several mechanisms have been proposed to explain the pathogenesis of autoimmune diseases.

a. Forbidden clone theory: All the clones which react with self antigens are destroyed during intrauterine life, but such a clone may be generated by somatic mutation in later life.

b. Sequestered antigen theory: Antigens exposed to lymphoid system during intrauterine life are recognized as self. But some tissues (e.g., lens, thyroid, CNS) are anatomically sequestered or guarded from the lymphocytes. In adult life, when such antigens are exposed, the immune system reacts against them.

c. Suppressor cell deficiency: Small quantities of thyroglobulin (and other antigens) are seen in circulation even in normal persons, but they are below the threshold level

for immunostimulation. The suppressor cells also inhibit sensitization. In persons with deficient T-cell activity, inappropriate immune reactions are produced.

d. Genetic effect: Autoimmune diseases show familial distribution and female preponderance. Many of them are associated with particular HLA types. These suggest that genetic predisposition may play a role in their pathogenesis.

e. Cross reacting antibodies: Antibodies produced against exogenous antigens can cross react with tissue proteins, e.g. post-rabies vaccine encephalitis, and post-streptococcal rheumatic fever. In any given instance one or more of the above mechanisms may be operative. Some of the immune-mediated disorders are listed in Table 3.6.

Diagnostic Procedures

The tests used in immunology range from simple tests such as agglutination, flocculation, precipitation,

TABLE 3.6

Some important immune-mediated disorders

Diseases	Auto-antigen	Diagnostic test
I. <i>Organ specific diseases</i>		
Pernicious anemia	Parietal cells of stomach, intrinsic factor	IFT
Ulcerative colitis	Lipopolysaccharides of mucous membrane of colon	Neutralization
Acute post-streptococcal nephritis	Streptococcal antigen	IFT
Sympathetic ophthalmia	Uveal protein	CFT and IFT
Bullous pemphigoid	Basement membrane	Skin test
Pemphigus vulgaris	Desmosomes	IFT
Hashimoto's thyroiditis	Thyroglobulin microsomes	IFT
Thyrotoxicosis by LATS	Cell surface receptor proteins	CFT
		Bioassay
II. <i>Affecting two or more organ systems</i>		
Goodpasture's syndrome	Glomerular and lung basement membranes	IFT
Autoimmune hemolytic anemia	Membrane proteins of RBC	Coombs' test
Immune thrombocytopenia	Platelet components	Demonstration of antibody
Myasthenia gravis	Acetylcholine receptors in nerve endings	IFT
Primary biliary cirrhosis	Liver and kidney mitochondria	IFT
Rheumatic fever	Streptococcal antigen cross reacting with heart and joint tissues	IFT
III. <i>Systemic or generalized diseases</i>		
Rheumatoid arthritis	Immunoglobulins, especially IgG	Latex agglutination
Sjögren's disease	Ducts, mitochondria of glands	IFT
Systemic lupus erythematosus	Nuclear DNA and nucleoproteins	IFT
Systemic sclerosis (scleroderma)	Nuclear proteins	IFT

IFT = Immunofluorescence test; CFT = Complement fixation test.

hemagglutination, reverse passive hemagglutination, complement fixation and immunofluorescence to the more advanced tests such as immunoelectrophoresis, enzyme-linked immunosorbent assay (ELISA), immunoblotting, e.g., Western blot, and the use of specific monoclonal antibodies.

Enzyme-Linked Immunosorbent Assay (ELISA) Test

This is one of the most frequently performed immunological tests in most of the laboratories in India to detect antigens and antibodies. The test is useful even when they are present only in minute quantities. Specific pre-prepared antibody or antigen is employed to fix the corresponding antigen or antibody, respectively, present in the patient's serum. The antigen-antibody complex is detected by appropriate colour developing techniques. Though the original test was a complicated one, at present test kits are available for most of these estimations. Therefore ELISA tests are available even in laboratories which do not undertake high level work, e.g.

detection of antibody—hepatitis B and C, HIV

detection of antigens—alphafetoprotein, carcino-embryonic antigen.

Serum Sickness

Syn: Systemic immune complex disease

This is produced as a result of circulating immune complexes. The biological and inflammatory potential of circulating immune complexes depend on the nature of the antibodies and antigens as well as the molar ratio of the two reactants. The magnitude and duration of antigen exposure is also important. The manifestations are transient if the exposure to the antigen is short, but if supply of the antigen is continued, immune complexes are continuously formed and serum sickness like reaction follows. Main lesions are in the glomeruli, choroid plexus, synovium, skin and uveal tract, which are the sites of inflammation due to deposition of immune complexes.

Apart from the introduction of external protein antigens and viral infections, drugs like penicillin and other drugs are more often responsible for this condition in man.

The antibodies are initially of IgG type and a Type III reaction occurs. Later IgE antibodies are formed and a Type I reaction may also occur.

Clinical features: About 7-14 days after the injection of serum or exposure to the offending drug, the disease starts

with fever, arthralgia, peri-arthritis, urticarial or morbilliform rashes and lymphadenopathy. Myocarditis may occur rarely. Glomerulonephritis is rare in humans. Peripheral neuropathy is a late sequel. The condition generally is self-limiting.

Treatment: Withdrawal of the offending agent gives relief in mild cases. Prednisolone in a dose of 1 mg/kg body weight may be required in severe cases. Prednisone or other corticosteroids are indicated if there is myocarditis and peripheral neuropathy.

Serum sickness may be partially prevented by giving large doses of cyproheptadine (0.7 mg/kg per day) or hydroxyzine (5 mg/kg/day) along with the serum.

Immunodeficiency States

Immunodeficiency may be congenital or acquired. In many of these cases, the defect may differ and the susceptibility to get infection also varies.

Severe forms of immunodeficiency states are so incompatible with life that they are rarely seen in clinical practice. The disorders are classified as:

1. Combined immunodeficiency states,
2. Deficiency of humoral immunity,
3. Deficiency of cellular immunity,
4. Deficiency of phagocytes,
5. Deficiency of complement system, and
6. Secondary immunodeficiency states.

1. Combined immunodeficiency: There is deficiency of both cellular and humoral immunity. This is produced as a result of block of maturation of the stem cells which give rise to immunocytes. Severely affected children are incapable of limiting bacterial, viral and fungal infections and they die in childhood.

Several subtypes have been described, e.g., sex-linked recessive types (thymic type) and autosomal recessive (Swiss) types. Relatively benign types are the Wiskott-Aldrich syndrome (sex-linked) and ataxia telangiectasia (autosomal recessive). In both, lymphoreticular malignancies are more common. *Adenosine deaminase* (purine catabolizing enzyme) deficiency, an autosomal recessive disorder leads to severe combined immunodeficiency. Gene transfer therapy has been tried recently with promising results in a few of such cases. Adenosine deaminase gene from normal lymphocytes was introduced by gene splicing and recombinant technology into the defective lymphocytes. The cells are grown in culture and reintroduced into the patient.

2. Humoral immunodeficiency: This may be a selective primary deficiency affecting only one of the G, M or A classes of immunoglobulins. In IgG deficiency the affected persons suffer from repeated pyogenic

infections, especially by encapsulated organisms such as *H. influenzae* and *Strep. pyogenes*.

In IgA deficiency, respiratory and atopic allergies are also common. IgA deficiency also lowers the resistance to gut commensals leading to malabsorption syndrome.

Congenital hypogammaglobulinemia may be sex linked (Bruton type) or autosomal dominant. In these cases, severe depletion of B-cells and circulating immunoglobulins are noticed with consequent severe bacterial infections. Incidence of autoimmune diseases such as hemolytic anemia are high in primary agammaglobulinemia. Immunodeficiency may occur in presence of normal quantity, but functionally deficient immunoglobulins, e.g., *Job's syndrome*.

3. Cellular immunodeficiency: Primary deficiency of T-cells leads to severe viral and monilial infections and affected children usually succumb within the first few years of life. The lymphocytes of the patients are unable to respond to mitogens *in vitro*. The thymus may be almost absent (*Nezelof's syndrome*), or aplastic (*Di George syndrome*) or in some cases it may be normal, e.g., chronic mucocutaneous candidiasis.

4. Defect of phagocytosis: *Chronic granulomatous disease* is a sex-linked inherited condition where hydrogen peroxidase is deficient inside the phagocytes, leading to decreased microbicidal activity. Recurrent suppurative granulomas due to catalase positive and peroxidase negative organisms (*Staph. aureus* and *Proteus*) are common in this condition. In myeloperoxidase deficiency, infections by peroxidase positive bacteria such as hemophilus are common. In *Chédiak-Higashi syndrome*, the neutrophils show defective degranulation and sluggish motility with consequent predisposition to pyogenic infections.

5. Deficiencies in complement system: *Hereditary angioneurotic edema* is inherited as an autosomal dominant disease. It is characterized by absence of the enzyme which normally inhibits the activity of C₁ esterase. This results in unrestrained C₁ esterase activity which activates the complement cascade reactions leading to liberation of kinins and vasoactive peptides. Recurrent attacks of edema of skin and mucosa are very common and edema of glottis may sometimes be life-threatening.

Deficiency of C₃ is inherited as an autosomal recessive character. Deficiencies of other complement components, though reported, are very rare. Generally, the clinical conditions mimic immunoglobulin deficiency states.

6. Secondary immunodeficiency: The transplacental transfer of immunoglobulins takes place mostly in the last few weeks of pregnancy. Premature infants, therefore, may suffer from mild hypoglobulinemia. Secondary defects in lymphocyte functions are seen in many conditions such

TABLE 3.7

Immunocompromised hosts

Predisposing cause	Effect on immune system	Types of infections
Immunosuppression by drugs Viral infections; measles, EB virus, HIV	Humoral and cellular immunity diminished Impaired T-helper activity	Infections of lung, urinary tract, bacteremias, fungal infections Secondary bacterial infections, opportunistic infections
Tumours of immune system e.g., lymphomas, myeloma, leukemias	Replacement of immune competent cells	Bacteremia, pneumonia, urinary tract infections
Malnutrition	Lymphoid hypoplasia, decreased lymphocyte and phagocyte activity	Measles, TB, respiratory infections, GI infection
Breakdown of tissue barriers, burns, wounds, injury, foreign body, etc.	Local effect	Local and systemic infections

as burns, malnutrition, leukemias, lymphomas and uremia. In multiple myeloma, though total immunoglobulins are increased, the biologically active ones are depressed, leading to functional deficiency. Acquired immunodeficiency may be due to primary causes such as infections (especially HIV), drugs or malignancies. These are listed in Table 3.7.

Treatment of immunodeficiency states as a whole is unsatisfactory. Immunoglobulin injection (0.25 g/kg/week) may abort recurrent pyogenic infections in hypogammaglobulinemia. Treatment of cell-mediated immune deficiency states is still more difficult.

Immunocompetent cells can be restored by bone marrow transplantation.

Immunization

Immunity in the human body against disease can be induced by several methods.

1. **Active induced immunity:** This is induced by immunization with toxoid, or killed or attenuated organisms. Table 3.10 for immunization schedule.
2. **Active natural immunity:** This is the immunity produced by exposure to clinical or subclinical infections.
3. **Passive induced immunity** Temporary protection against the infecting organism can be conferred on the susceptible host by giving preformed antibodies obtained by immunizing heterologous or homologous hosts. Such passive immunization is recommended for the post-exposure prophylaxis in the following conditions:

Along with the induction of passive immunity to tide over the incubation period, active immunization using vaccine should also be started simultaneously for conferring lasting immunity.

Passive immunization by preformed antibodies

Hepatitis A	Human hyperimmune serum 0.2 ml/kg IM
Hepatitis B	Hepatitis B immunoglobulin (HBIG) 0.5 ml IM
Varicella	Varicella zoster immunoglobulin (VZIG) 125-625 units IM
Tetanus	Tetanus immunoglobulin human 500-3000 units IM
Rabies	Rabies immunoglobulin-human (HRIG) 20 IU/kg. 50% IM and the rest infiltrated around the wound
Measles	Human immunoglobulin 0.25 ml/kg IM

Therapeutic use of preformed antibodies

Infective conditions	Non-infective conditions
Tetanus	Myasthenia gravis
Botulism	Guillain-Barré syndrome
Diphtheria	Immune thrombocytopenia
Anthrax	Some cases of aplastic anemia
The dose of IgG given is moderate	The dose of IgG in these conditions is very large.

4. **Passive natural immunity** Transfer of immunoglobulins (especially IgG) to fetus takes place *in utero*. These antibodies remain in the circulation of the child for 3-6 months of postnatal life.

Immunization for Indian subjects is given in Table 3.10.

HLA System in Humans

Several diseases are known to have intimate association with disease susceptibility shown by distinctive HLA types (Tables 3.8 and 3.9). HLA system stands for human leukocyte antigen system which is the human version of the major histocompatibility complex (MHC).

TABLE 3.8

Association of HLA system with diseases—global data					
Diseases	Associated HLA type	Relative risk	Diseases	Associated HLA type	Relative risk
Ankylosing spondylitis	B-27	81	Multiple sclerosis	DW2	5
Reiter's syndrome	B-27	48	Psoriasis	B-13	4.3
Coeliac disease	B-8	9.5	Pemphigus	A-10	4.3
Rheumatoid arthritis	DW4	8	Sjögren's syndrome	B-8	3.2
Addison's disease	B-8	6.4	Graves' disease	B-8	2.5
Chronic active hepatitis	B-8	6	Hodgkin's disease	B-18	2
Myasthenia gravis	B-8	5	Diabetes mellitus (insulin dependent)	B-8	1-9

Note: Relative risk is the chance of developing the disease compared to controls who do not possess the particular HLA types.

TABLE 3.9

HLA association with diseases commonly seen in India	
Ankylosing spondylitis	HLA B-27
Reiter's disease	HLA B-27
Acute anterior uveitis	HLA B-27
Rheumatoid arthritis	HLA DR4
Juvenile RA	HLA DR5, DR8
Insulin dependent diabetes	HLA B-8, B-21, DR3
Graves' disease	HLA DR2, DQ2
Rheumatic heart disease	HLA DR3
Myasthenia gravis	HLA B-21, B-8
Tuberculoid leprosy	HLA DR2, DR6
Lepromatous leprosy	HLA DQW1
Pulmonary tuberculosis	HLA DR2, DR6

HLA system plays a role in very different situations such as:

1. Transplant rejection,
2. Chronic inflammatory diseases such as rheumatoid arthritis and ankylosing spondylitis,
3. Coma in cerebral malaria,
4. Immunodeficiency states, and
5. Advanced hepatic cirrhosis with iron overload.

HLA complex is mainly represented on chromosomes 6 and it contains over 200 genes. More than 40 of them encode leukocyte antigens. The HLA genes that are involved in the immune response fall into classes—I and II which are structurally and functionally different. The class I genes code for the alpha polypeptides of the class I molecule. The beta chain of class I molecule is encoded by a gene on chromosome 15—the beta 2 microglobulin gene. There are about 20 class I genes in the HLA region. Three of them—HLA-A, B and C are the main actors in the immune response. These are called the classic or class I genes.

The class I genes code for both the alpha and beta polypeptide chains of the class II molecules.

Their position on chromosomes 6 is identified by the three letters given below:

D—this indicates the class

M,O,P,Q or R—this represents the family

A or B—the chain that is affected.

The three main class II molecules are HLA, DP, DQ and DR. The individual genes of the HLA system are represented by Arabic numerals.

Class I genes are expressed by most somatic cells. In contrast class II genes are expressed selectively on a subgroup on cells concerned with immunity such as B cells, activated T cells, macrophages, dendritic cells and epithelial cells of the thymus.

The A, B and C loci can be identified by serologic tests. The D locus which controls lymphocyte antigens is detectable by mixed lymphocyte culture. The products of HLA genes are proteins which are found on all tissues including leukocytes and platelets but not on erythrocytes. HLA molecules are dimers of two different polypeptide chains, designated as alpha and beta. The variable amino acid sequences in these chains produce distinct three dimensional structures which will allow the identification of foreign cells. HLA typing of A, B and C loci is done by *complement mediated cytotoxic test* utilizing a panel of reference antisera. The D locus is typed by the mitogenic effect using a panel of lymphocytes. Inheritance of certain alleles confer susceptibility to particular diseases when exposed to suitable environment. Table 3.8 gives the association of HLA system with some of them.

The HLA antigens play a central role in cell-to-cell interaction in the immune process. The MHC molecule interacts with antigens and presents them to T-cell receptors for recognition and further action.

The HLA antigens play a great role in identifying self from non-self and in giving rise to rejection, when HLA incompatible tissues are transplanted into an individual. Histocompatibility is defined as the similarity between tissues of two different individuals. Organ transplantation

TABLE 3.10

Immunization schedule for Indian conditions

Vaccine	Description
A. OBLIGATORY	
1. DPT	1st dose - 6-12 weeks 2nd dose - 17-21 weeks 3rd dose - 36-38 weeks Tetanus toxoid IM or SC Diphtheria toxoid Pertussis-killed organisms
BOOSTER DT	1st dose - 18-24 months 2nd dose - 5-6 years Purified components of B. pertussis (acellular vaccine) is available either singly or in combination as DTaP. The DTaP is safer in children who have febrile convulsions.
2. POLIO	
a. ORAL POLIO VACCINE (OPV-Sabin)	1st dose - 3rd month Thereafter 3-4 doses at 2-6 wk. intervals. Fifth dose later Live attenuated human diploid cell vaccine oral
BOOSTER	Booster doses in the 2nd and 5 years
b. INACTIVATED POLIO VACCINE (IPV Salk)	1st dose 3-4 months The next two at 4-6 weeks interval Killed organisms SC This is rarely used in selected situations
BOOSTER	4th dose 6-12 months later At 4-6 years
3. MEASLES (Solid immunity occurs when vaccine is given after the 1st birthday. If the vaccination is done earlier, booster dose is necessary)	12-15 months Live attenuated SC
B. ADVISABLE	
BCG	During neonatal period or any time during childhood. Live attenuated Intradermal
MUMPS RUBELLA	Along with measles vaccine. Booster not required if given after first birthday. Live attenuated SC
Rota virus (Note: Combined MMR vaccines are available)	2, 3, 4 months Live attenuated Oral
C. VACCINATION NECESSARY UNDER SPECIAL CIRCUMSTANCES	
HEPATITIS-B VACCINE VACCINE (rDNA)	Pre-exposure prophylaxis: Special health care professionals, hemodialysis patients, hemophiliacs Travellers going to endemic areas, homosexual individuals, contacts of HBV carriers. Dose: 1 mL IM over deltoid 3 doses—2nd dose one month and 3rd dose six months after the 1st dose
	Post-exposure prophylaxis: -infants of HBV carrier women, contacts of HBV hepatitis, -victims of needle stick injuries from HBsAg positive patients or recipients of blood products. Give Hepatitis B Vaccine and Hepatitis B immunoglobulin at birth
RABIES VACCINE HUMAN OR OTHERS DIPLOID CELL VACCINES (Killed vaccine)	Pre-exposure prophylaxis: lab workers, veterinarians, etc. 1 mL IM over deltoid on days 0,7,28. Booster depending on serology
	Post-exposure prophylaxis: (a) those previously immunized 2 doses 1 mL over deltoid (IM) on days 0 and 3. Rabies immunoglobulin (RIG) should not be administered.

Contd...

Contd...		
Vaccine		Description
	(b) those not immunised	1 mL over deltoid (IM) on days 0,3,7,14 and 28. RIG 20 IU/Kg body wt half infiltrated at bite site and rest IM if the risk is severe
JAPANESE ENCEPHALITIS (Killed vaccine)	To be given to communities exposed to risk of encephalitis	0.5-1 mL SC. Two doses at 7-14 days interval, and booster within 12 months Revaccination at 3 yearly intervals
VACCINATIONS DESIRABLE UNDER SPECIAL CIRCUMSTANCES		
(For detail see appropriate sections)		
ENTERIC FEVER	:	Phenol and heat killed. 2 doses 0.5 mL SC. 4 weeks apart, or live oral vaccine, 4 oral doses, boosters every 4 years.
CHOLERA	:	0.5 mL IM or SC. Phenol killed vibrio vaccine, 2 doses 1 week to 1 month apart, at least 10 days before travel.
YELLOW FEVER	:	Immunized before going to endemic areas of Africa and South America.
TETANUS	:	In immunized persons, 2 doses of 0.5 mL toxoid, boosters every 10 years.
INFLUENZA	:	<i>H. Influenzae</i> type B polysaccharide conjugated to diphtheria toxin, primary 1 dose 0.5 mL.
MENINGITIS	:	Meningococcal polysaccharide vaccine, tetravalent, primary 0.5 mL SC given before going to endemic area.
PNEUMOCOCCUS	:	Polyvalent vaccine
VARICELLA	:	Live attenuated.
H. INFLUENZAE	:	a b c d e f strains.
HEPATITIS A	:	rDNA vaccine
JAP ENCEPHALITIS	:	During epidemics.

can be successfully carried out only if the donor and recipient are at least partially, if not completely matched. Since identical twins have identical HLA loci, they are the most suitable for tissue transplantation. Next in order of compatibility are parents and siblings, near blood relatives and others. Since exact HLA matching is not available in the vast majority of cases, one has to satisfy with as close a match as possible.

The difference in HLA constitution between a donor and recipient results in immunological reactions against the graft (*host vs graft disease—HVG*D) or the graft against the host (*graft vs host disease—GVH*D). This can be suppressed to a great deal by continuous use of immunosuppressants like corticosteroids, cyclophosphamide, cyclosporine and antilymphocytic serum.

Modulation of Cellular Behaviour

Chaperones in cells: The term chaperon denotes a person who modulates behaviours properly. All cells in the human body maintain a complete set of functionally competent

proteins, even in the presence of stress and injury, by the action of various mechanisms, including systems of proteins called molecular chaperons. The function of a chaperon is to assist a nascent polypeptide chain to attain functional information as a new protein and to assist its arrival at the site of its action in the cell. Chaperones also assist damaged protein molecules to regain their functional conformation. In the absence of chaperon function protein molecules become denatured, insoluble and functionless. They precipitate and appear as inclusion bodies within cells. e.g. Parkinson’s disease, Huntington’s disease, Alzheimer’s and others. Stresses which damage a cell include physical agents like heat, oxygen free radicals, changes in pH, osmotic changes, nutritional disorders, drugs, mechanical injury, infections and inflammation. Diseases such as Alzheimer’s dementia, inclusion body myositis, cataracts, von Hippel-Lindaus’ disease and others are considered to be due to dysfunction of molecular chaperones. Chaperonopathies may impair immunological function. It is likely that genetic disease may cause abnormalities of chaperones.

4

Principles of Drug Administration

1

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Chapter Summary

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Drugs are generally employed as replacement therapy, as agonists, or as antagonists. Drugs are used as replacement for conditions in which there is deficiency of a natural substance-endogenous, e.g., hormones, or exogenous, e.g., nutrients.

Agonist drugs produce a pharmacological effect, e.g., hypotensives, analgesics.

Antagonist drugs prevent the action of natural substances like anticholinergics or counteract the action of other drugs, e.g., nalorphine.

Drugs produce their effect by interacting with specific receptor sites on the cell membrane. At the receptor sites the action may be positive (e.g., agonists) or opposite to those of agonists (e.g., antagonists). Initially there is physical interaction between the drug and the receptor and this drug receptor complex *produces the therapeutic response*.

Routes of drug administration This may be oral, sublingual, topical or parenteral. Parenteral routes are subcutaneous, intramuscular, intravenous, intra-arterial, intrathecal, intraventricular (cerebral ventricles), intra-articular, intracavitary (into viscera like pleura or peritoneum or abscess cavities), and intra-amniotic.

Drug Metabolism**Absorption of Drugs**

The amount of drug that reaches the systemic circulation intact and is available to the target tissues for effective function is called the “*bioavailability*” of a drug. The rate of absorption, and the metabolic processes which tend to

eliminate or inactivate the drug determine the bioavailability of the ingested drugs. Absorption from the gastrointestinal tract depends upon lipid solubility, degree of ionization, and molecular weight of the drug. Low molecular weight substances and alcohol are absorbed passively, while other drugs are absorbed by active processes requiring energy, e.g., alpha methyl dopa. Lipid-soluble drugs are absorbed easily. Since drugs have to be in solution to facilitate absorption, formulations which disintegrate rapidly, are more easily absorbed. Due to the variability of physical properties, bioavailability of the same drug may vary when administered in different formulations and therefore it is important to avoid frequent changes in formulations from time-to-time. Other factors influencing gastrointestinal absorption are the availability of surface area for absorption, motility of the gut, pH within the gut, local blood flow, and presence of other substances in the gut lumen.

Drug interactions in the gut may alter absorbability. For example, antacids reduce the absorption of iron by changing the pH and anticholinergics reduce the absorption of other drugs due to delay in gastric emptying. Absorption of drugs may be altered by the presence of food in the stomach. In many instances the absorption is delayed, whereas it is facilitated in the case of others. It is important to know this aspect in order to optimise the timing of drug administration. For several drugs, administration with water on an empty stomach ensures maximum absorption. In malabsorption states drug absorption is erratic. In congestive heart failure venous stasis occurring in the intestines impairs absorption. Drug absorption is unpredictable in the elderly.

Drugs which are better absorbed from the buccal mucosa are preferably given sublingually. Some drugs like nitroglycerine and isoprenaline are destroyed by the gastric acid and hence sublingual administration is ideal. Usually, the clinical effect is evident within minutes. Another advantage of sublingual administration is that drug toxicity can be avoided by removing the drug from the mouth or swallowing it as soon as the desired effect is achieved.

Topical routes include the skin and the mucous membranes of the nose, rectum and lungs. Preparations for topical application include inunctions (e.g., nitroglycerine), suppositories into the rectum (e.g., pitressin) and aerosols which are inhaled. Rate of absorption of topically applied drugs depends on the concentration, lipid solubility and local blood flow. Absorption is lower from keratinized epithelium. The size of the particle is important when drugs are applied as aerosols. Only particles below 2 nm in size reach the alveoli. Absorption from the respiratory epithelium is rapid and the effect is immediate. The portion deposited in the oropharynx is later swallowed and absorbed to produce mild and delayed effect. Considerable attention to details is necessary for ensuring proper administration of the aerosol.

Parenteral administration is resorted to when more rapid action is desired and when patient's cooperation cannot be relied upon. Local vascularity influences absorption from sites of intramuscular or subcutaneous injections. Aqueous formulations are absorbed rapidly whereas oily preparations are absorbed only slowly. Local warmth and massage favour absorption.

Intramuscular injections are usually given into the deltoid, rectus abdominis or gluteal muscles. Certain drugs like diazepam and phenytoin may be erratically absorbed, so that oral administration may be more reliable than intramuscular doses.

The subcutaneous route is to be preferred when the volume of drug is small and the drug is non-irritant. The rate of absorption is slightly lower than the intramuscular route. When the peripheral circulation is insufficient, as is seen in shock, subcutaneous and intramuscular routes are unreliable. Intravenous route should be resorted to when the drug action has to be immediate, or large volumes of drugs have to be given. Since the onset of action is immediate, the pharmacological effect can be adjusted by controlling the rate of intravenous infusion. At present several devices such as programmable infusion pumps which can deliver the required quantity over prolonged periods are available, and these are employed in critical care departments and intensive care areas. For management of conditions like diabetes where insulin has to be administered round the clock at varying rates, implantable devices are available. Certain drugs like digoxin take several minutes to exert their full effect even after intravenous administration. Even highly irritant drugs like nitrogen mustards can be given into a rapidly flowing drip since the drug is diluted and the venous walls are relatively resistant. Local damage to vein can be avoided by releasing the drug into more central portions of the circulation, e.g., inferior vena cava. Intra-arterial infusions are indicated when a large dose of drug has to be given in a high concentration to a particular organ.

At present the pharmaceutical industry is bringing newer forms of drug presentation and delivery systems

in order to reduce the toxic effects, acceptability, absorbability and timed release in the body. Encapsulation within a lipid vesicle (liposome) or attachment to a polymer greatly increases safety profile and permits the use of higher dosage. Newer degradable materials which act as vehicles for drugs, intelligent drug delivery systems and newer routes of drug administration are all being actively pursued.

Drugs are transported with the aid of transport proteins and they exert their effects through specific receptors. Genetic factors modify the absorption, transport, receptor mechanisms, distribution, therapeutic effects, toxicity and the elimination of drugs. At the blood-brain barrier, P-glycoprotein in the choroid plexus limits the accumulation of several drugs in the brain.

Drug distribution In the circulation, the drugs are reversibly bound to plasma proteins. Entry into the tissues depends upon the blood flow and the ability of the drug to enter the tissues. Easy entry into the tissues depends upon lipid solubility, and the concentration gradient across the cell membranes. Major proportion of any drug is distributed to the tissues where it has no pharmacological action. In conditions like 'shock' when tissue perfusion is poor, the drug remains in the plasma in high concentrations without entering the tissues and this leads to toxicity. Specialized tissues take up drugs selectively. Most tissues of the central nervous system restrict the entry of polar (ionized) compounds. Lipid soluble substances enter easily down a concentration gradient, while sugars and amino acids are actively transported. This blood-brain barrier breaks down when there is meningeal inflammation. At conditions of equilibrium the drug is distributed among the plasma water, plasma proteins and tissues. Since lipid soluble drugs enter cells more readily, their concentration in the plasma is lower compared to water soluble drugs. By hemodialysis water-soluble compounds can be removed from circulation, but this is not effective for lipid-soluble drugs. Magnitude of response of any drug depends on the level of free drug available at the receptor site. The level of free drug in the plasma depends upon two factors: plasma protein binding and ease of distribution to other tissues.

Plasma protein binding Plasma proteins, especially albumin forms reversible complexes with drugs in circulation. The degree of absorption depends upon the plasma pH and affinity of the drug to the protein. When many drugs compete for absorption, the high affinity drug displaces the ones with weak affinity. Acidic drugs will be displaced from protein complex when acidosis develops.

Liver Since most of the absorbed drugs pass through the liver, they are either bound, metabolized or excreted in the bile. Hepatic metabolism of drugs occurs in two stages; stage I reactions include oxidation, reduction, and hydrolysis; and stage II reactions involve conjugation of

the original compound or its metabolites by acetylation, sulphation, O-methylation, and glycine-conjugation. These products are water-soluble and hence are excreted.

The metabolism of drugs in the body is governed by enzymes belonging to the class cytochrome P-450 (CYPs) cyp1, cyp2 and cyp3) which play important roles in the biosynthesis and degradation of endogenous compounds such as steroids, lipids and vitamins. There are more than 30 families of drug metabolizing enzymes in humans. All have several genetic variants which determine the functions of the proteins encoded. They metabolize drugs and several chemicals found in foods and environment. They also participate in their elimination. In humans more than 57 cytochrome P-450 enzymes have been identified, each with substrate specificity. Liver is the major site of cytochrome P-450 metabolism, next in importance is the enterocytes lining the small intestine. Enzyme Cy p3 A7 is an important enzyme present at both these sites. It is involved in the metabolism of more than 50% of the drugs administered.

Lungs Basic compounds are selectively taken up and sequestered from the general circulation.

Transplacental transfer The placenta behaves like a selective barrier. Lipid soluble drugs of molecular weight lower than 1000 diffuse freely from the maternal to fetal circulation, while water soluble drugs diffuse only slowly. Since the drug elimination systems of the fetus are immature, serious toxicity will ensue. The mechanism to remove the drug from the fetal circulation is diffusion back to the maternal side. Direct approach to the fetus by surgical techniques is feasible in a few hospitals.

Elimination of drugs: Drugs are eliminated from the body by (1) metabolism in the liver and kidney, and (2) excretion as the parent drug as such or its metabolites by the kidneys predominantly, but also by the gut, skin, lungs, sweat glands, breasts, and salivary glands. Urinary excretion depends upon the processes of: (1) glomerular filtration, (2) active tubular secretion and reabsorption, and (3) passive diffusion.

Pharmacogenetics

The influence of genetic factors in drug effects was recognized as early as the 1950s. Enzyme defects may give rise to arrested metabolism of drugs, thereby leading to unexpected drug effects.

For example, Cytochrome P 450 2D6 (CYP2D6) influences the metabolism of codeine, dextromethorphan, metoprolol and nor-typtaline.

Deficiency of the enzyme N-acetyl transferase leads to slow acetylation of INH, hydralazine and procainamide. At present genetic tools are available for identifying such genetic alterations.

Pharmacogenomics is the study of genes encoding the drug metabolizing enzymes and genome-based approaches to drug-behaviour in different persons.

Molecular diagnostic methods to determine the genotypes of individuals are becoming more freely available. At present it is possible to get genotype analysis from single blood samples and about 5000 genes and 20000 single nucleotide polymorphisms can be studied in a single assay. It can help more individualised selection of drugs with better efficiency and safety.

General Principles of Drug Administration

The effective and safe dose of any drug should be determined by considering the body mass or surface area. Though general instructions regarding dose are available, each dose should be tailored to the individual patient, based on his weight, status of vital organs like kidneys and liver, the severity of the infection and the immune status of the host. Though a long course of therapy is ideal for effecting cure, yet chances for toxicity limits the total dose.

Seriously ill patients should be treated by injection since this ensures predictable serum levels. Intravenous injection is more effective in giving peak serum levels and is less painful than intramuscular or other routes. This is the route of choice when large volumes of drugs have to be given and that too continuously. Though polyethylene cannulas are handy and convenient for use, steel needles are better to avoid infection. Ideally, the needles have to be re-sited at least every 48 hours to avoid venous thrombosis and infections.

Parenteral preparations are more likely to produce anaphylactic reactions than oral preparations. Topical application of drugs for general antibacterial action except to the eye and ear should be discouraged, since they produce local reactions and also give rise to emergence of resistant strains. Intrathecal injection of antibiotics is potentially hazardous and is often unnecessary except in the case of resistant meningitis, unresponsive to systemic therapy.

Chemoprophylaxis: Use of antibiotics for chemoprophylaxis is controversial. Bacteria resistant to the antibiotics may be selected out to multiply, and the possible toxicity of drugs may also occur. Chemoprophylaxis does not guarantee prevention of infection. The aim of chemoprophylaxis is to prevent a known organism from reaching a target tissue and if it reaches, to abort infection. Chemoprophylaxis is employed in special situations such as prevention of active tuberculosis in special groups, prophylaxis against *Pneumocystis carinii* in AIDS patients, accidental needle stick injuries in laboratory workers, newborns of HIV positive mothers and other similar circumstances. If an antibiotic is

intended to give coverage during a surgical procedure, it should be given intramuscularly 30 minutes before operation, or intravenously during the surgery and for a short period thereafter.

Severe infections Life-threatening infections such as septicemia, pneumonia, peritonitis, meningitis, etc. have to be treated even before microbiological results are available, especially so, if the patient is neutropenic. Helpful investigations include microbial identification, determination of antibiotic sensitivity and serum levels of the drug.

DRUG ADMINISTRATION IN SPECIAL GROUPS

1. Children The action of drugs differs quantitatively and qualitatively in children compared to that in adults. Before embarking on therapy it is absolutely essential to take into consideration the following points:

- Is the drug absolutely essential?
- Is it safe for the age group?
- Which preparation is best, most palatable and convenient for administration?
- Which is the best drug with least side effects?

The absorption, distribution, breakdown and elimination of drugs depends upon the maturity and relative size of body tissues. Other than age and size, genetic constitution, maturity of the kidneys, enzyme development in the liver, protein binding of the drug, organ sensitivity, distribution of the drug in the body and development of the central nervous system affect drug response and toxicity in infants and children. Changes in body composition, development of blood-brain barrier with increasing age, and metabolic disturbances such as acidosis affect the distribution of drugs. The rate of drug elimination is greatly diminished in neonates, especially premature infants. Topically applied drugs are significantly more absorbed in infants and children, particularly in prematures. Drugs excreted in breast milk during the early postnatal period may influence the baby. Proper education of the parent and child is important to ensure drug compliance.

2. Drug administration during pregnancy: The fact that the drugs may harm the mother, fetus or both should be borne in mind. The main dangers to the growing fetus include:

- Destruction of the embryo and abortion, e.g., quinine, cytotoxic drugs.
- Congenital defects and disorders of organ development are particularly common with drugs like thalidomide, radioactive drugs, anticonvulsants and anticancer drugs. Almost all drugs including large doses of some vitamins are associated with embryotoxicity in varying degrees at specific periods of gestation.

3. Incorporation into the tissues of the fetus, e.g., tetracycline into the teeth.

4. Pharmacological effects on the fetus by drugs which cross the placenta, e.g., antithyroid drugs may cause thyroid dysfunction in the newborn. Hormone administered to the mother may affect the fetus.

Apart from the damage caused to the embryo, the mother is more susceptible to the toxic effects of several drugs during pregnancy, e.g., tetracyclines are more likely to produce hepatic damage during pregnancy.

In general it is a golden rule to withhold medication to a pregnant woman unless absolutely indicated.

3. Drug administration in the elderly: Old subjects are likely to have multiple pathological lesions and hence they are susceptible to the cumulative adverse effects of several drugs which are concurrently administered. Elderly persons behave erratically to drugs. Since their weight is low, the ordinary doses may prove to be toxic. Absorption from the alimentary tract may not be predictable. Moreover, impairment of functions of the liver and kidney lead to their accumulation in the body. In addition, the organ systems may also show increased sensitivity, e.g., aged persons are more prone to develop cardiotoxicity of digitalis and ototoxicity of the aminoglycosides. Adverse effects of drugs constitute a major cause for morbidity in old persons and, therefore, great care is required for prescribing drugs to them. Aged women with history of allergic diathesis are particularly susceptible to develop drug toxicity. An early sign of drug toxicity is mental confusion and disorderly behaviour which should not be ignored.

Drug compliance is generally poor in the older age groups due to their physical disability, mental confusion and economic dependence. Particular care, therefore, is to be taken to ensure that drug schedules are followed.

Hospitalization should be avoided as far as possible since older persons cannot adapt to the hospital environment. As a consequence they develop confusion and disorientation. Moreover, hospitalization and immobilization lead to complications like respiratory infection, urinary retention, fecal and urinary incontinence, falls, venous thrombosis, embolism, and strokes. Confinement to bed should be kept to the minimum and the patient should be ambulated as early as possible.

Drug Related Adverse Effects

Adverse drug reactions are extremely common in present day medical practice. There are two types of adverse drug reactions, A and B. Type A is the result of an augmented or exaggerated pharmacological action of a drug given in the therapeutic doses (Table 4.1). These are primarily dependent upon the intrinsic biodynamic properties of the

TABLE 4.1

Types of adverse drug reactions

	Type A	Type B
Drug response	Augmented	Bizarre
Pharmacologically predictable	Yes	Bizarre
Dose-dependent	Yes	No
Dependence on host	Often independent	Usually dependent
Incidence	High	Low
Morbidity	High	Low
Mortality	Low	High
Treatment	Dose adjustment	Stop and antidotes

drug, often host-independent, dose-dependent and usually reproducible in animals. They are sometimes called predictable reactions which include overdosage, side effects, drug-caused disease and drug interactions.

e.g., Beta-adrenergic blockers produce bradycardia.
Ephedrine causes tachycardia and insomnia.

Type B reactions are totally bizarre unpredictable or aberrant effects that are not to be expected from the known pharmacological effects of a drug when given in usual therapeutic doses and with no alteration in pharmacokinetic processes. They are “idiosyncratic”, host-dependent, often apparently dose-independent and difficult to reproduce in animals.

Type A reactions: The factors involved in Type A reactions are divided into pharmaceutical, pharmacokinetic or pharmacodynamic causes.

Pharmaceutical causes	factors that affect drug dose and release from the formulation.
Pharmacokinetic causes	factors which alter absorption, distribution, metabolism and elimination.
Pharmacodynamic causes	factors which depend on dose-response relationship, drug receptor status, homeostatic mechanisms and disease state of the individual.

Type B reactions : Type B reactions, which are characterized by the existence of some qualitative difference either in the drug or in the patient or possibly in both, are classified as intolerance, idiosyncrasy and allergy. The causes of Type B reactions could be pharmaceutical, pharmacokinetic or may lie in a target organ response.

Table 4.1 shows the salient differentiating features between the two types of adverse drug reactions.

Rational therapeutics is defined as the use of the least number of drugs to obtain the best possible effect in the

shortest time, and at a reasonable cost. In general about 25% of hospitalized patients suffer from DRAs which may prove fatal. Risk of adverse events increases at the rate of 6% for every additional day of hospitalization. It is likely that about 5 million persons may suffer from serious ADRs. Aggressive drug therapy, particularly poly-pharmacy (concurrent use of several different classes of drugs) increases the risk, 50% of these are preventable if the physician and his staff are careful to avoid DRAs and to take early remedial steps.

Medical errors include the following:

Adverse event (AE): A definable injury caused at least in part by medical management, the injury must have prolonged the hospital stay or caused disability at the time of discharge.

Adverse drug event (ADE): AE related to the administration of drugs.

Negligent adverse event: An injury caused by failure on the part of the doctor to meet standards expected of an average doctor in his settings.

Drug related problem (DRP): An event or circumstance that involves patient’s drug treatment that actually or potentially interferes with achievement of an optimal outcome.

The spectrum of ADEs include following types:

1. Wrong choice of drug,
2. Wrong dose, frequency and route of administration,
3. Drug-drug interaction,
4. Inadequate instruction to nursing staff,
5. Allergic reactions.

Failure to use a life-saving drug when indicated does also amount to negligence on the part of the doctor.

While prescribing antimicrobial agents the full duration of therapy should be insisted upon even though symptomatic relief is achieved early. In India the most common causes of medical errors arise from inadequate information for the doctor (29%), wrong diagnosis (18%), wrong administration, and failure to recognize ADEs early.

The need to monitor ADRs and to prevent them has been realized by the medical fraternity in India. The common defects in prescription detected by limited surveys included:

1. No mention of the dose of the drug	-60%
2. Absence of information on the route and method of administration	-99%
3. Administration of antibiotic for inadequate duration	-60%
4. Information of the dose was given only partly	-11%

Some of the State Governments in India including the Govt. of Kerala supply drug formularies to their doctors which provide factual data on drugs.

Suggestions to Reduce the Frequency of ADEs

- 1. Use of check lists, protocols and computerized aids for writing prescriptions.
- 2. Improved access to information using computerized programmes.
- 3. Error proofing using customised computer software so that overdose, suboptimal drug doses, improper duration and allergic reactions can be avoided.
- 4. Training of doctors, nurses and other staff on safe prescribing practice.
- 5. Informing the public on adverse drug reaction and their remedy.

It is a golden rule to use a limited number of drugs, about which the doctor has full information as far as possible. The Government of India has accepted an essential drug list containing 279 drugs which are adequate to manage most of the common ailments.

The adage “*there are no biologically safe drugs; there are only safe physicians*” holds good even now; and it will continue to be so forever.

Prescription of Drugs

- 1. Medicines should be prescribed only when absolutely indicated. Once prescribed, the dose, route of administration, relationship with food and duration of therapy should be clearly specified. The total quantity of each drug to be dispensed should be separately specified.
- 2. As far as possible generic names should be specified. Proprietary names should be used only when it is unavoidable.
- 3. Avoid decimal points as far as possible, e.g. 3 mg instead of 0.03 g or 3.0 mg.
- 4. Quantities below 1 mg should be given as micrograms (mcg or µg) or smaller units, e.g. instead of 0.1 mg write as 100 mcg.
- 5. When decimals are unavoidable, use the format as 0.5 mL and not as 5 mL.

- 6. The prescription should be authenticated by legible signature of the prescriber, and his address.

The legal responsibility of a prescription rests on the prescriber.

The *drugs and cosmetics* ACT of 1945 has included drugs into different schedules.

- 1. Drugs in schedule G should be administered only under the supervision of a Registered Medical Practitioner (RMP).
- 2. Drugs in schedule H should be dispensed only on the prescription of RMP.
- 3. Drugs included in schedule X include psychotropic drugs and all prescriptions should be made in duplicate and authenticated by the full signature, address and registration number of the practitioners.

Patient education which is a very important responsibility of the prescribing doctor should include information on the following aspects.

- drug
- time
- dose
- intervals
- duration of treatment
- and cost

The patient should be instructed to report adverse reactions promptly after stopping the drug. On no account should the doctor shy away from the responsibility of having prescribed the drug. He should view the situation with empathy and confidence. Almost all the adverse drug reactions (ADRs) are remediable if detected early. Prompt handling of the situation will increase the confidence of the patient. Irresponsible behaviour on the part of the prescriber often leads to legal complications.

The availability of a vast number of antimicrobial drugs with specific actions, the problems in diagnosis and management created by the changing nature of the microbial flora, development of resistance by organisms and the emergence immunosuppressed hosts have necessitated the creation of the subspeciality of Infectious Diseases.

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Introduction

The initial specific antibacterial drugs, sulphonamides were introduced in the early part of the 20th century. Discovery of penicillin and its introduction into therapeutics in the first half of the 20th century leading to dramatic cure of infections, acted as a stimulus for intense research to discover further antimicrobial drugs. As a result many types of antibiotics were introduced in succession.

Table 5.1 gives the site of action of the commonly used classes of antibacterial drugs.

Antibacterial Agents**Penicillins**

Penicillin discovered by Alexander Fleming in 1928 was the first effective antibiotic to be produced commercially, marketed widely and accepted with great zeal all over the world on account of its efficacy, safety and affordable cost. Introduction of penicillin ushered in the “antibiotic” era in the therapy of infective diseases.

The basic nucleus is 6 amino penicillanic acid which contains a thiazolidine ring linked to beta lactam ring. Further derivatives of penicillin contain the beta lactam ring and all such members are included under the term beta lactam antibiotics. Many bacteria develop resistance by producing beta lactamase. Penicillin and its derivatives block the synthesis of the bacterial cell wall peptidoglycan. Penicillin and its derivatives hold their pride of place among the most powerful antibiotics against susceptible bacteria. They are the drugs of choice in the appropriate

TABLE 5.1

Principal types of antibacterial drugs with their main site of action

Drug	Site of action	Mechanisms
Penicillin	Cell wall	Inhibits cell wall synthesis
Cephalosporins	Cell wall	"
Other beta lactams	Cell wall	"
Glycopeptides		"
e.g., Vancomycin	Cell wall	"
Tetracyclines	Ribosomes	Inhibit protein synthesis
Chloramphenicol	Ribosomes	"
Aminoglycosides	Ribosomes	"
Macrolides	Ribosome	"
Lincosamides		"
e.g., clindamycin		"
lincomycin	Ribosomes	"
Fusidic acid	Ribosomes	"
Rifamycin		"
e.g., rifampicin	RNA synthesis	Inhibit DNA or RNA synthesis as the case may be
Sulphonamides	Folate metabolism	"
Diimidopyrimidines		"
e.g., Trimethoprim, pyrimethamine	Folate metabolism	"
Quinolones	DNA synthesis	"
Nitrofurans	DNA synthesis	"
e.g., nitrofurantoin, nifurtimox		"
Nitroimidazoles	DNA synthesis	"
e.g., metronidazole, tinidazole		"

situations on account of their proven bactericidal activity, wide availability, safety profile and relatively lower cost.

Susceptible organisms: *Strep. pyogenes*, *pneumococci*, *susceptible gonococci* and *meningococci*, *spirochetes* such as *T. pallidum*, *T. pertenuis* and *leptospira*, *anaerobes* such as *Cl. tetani*, *Cl. botulinum*, *Cl. perfringens*, *peptococci*, *peptostreptococci*, *bacteroides*, *B. anthracis* and *Staphylococci* which are sensitive, respond well to penicillin. *Strep. viridans*, the organism causing infective endocarditis is susceptible in many cases.

Safety: Penicillins are generally safe. Most important adverse side effects are allergy and Jarisch-Herxheimer reaction. Anaphylactic shock and cardiac arrest may occur in unexpected situations. So any history of allergy to penicillin, however mild it is, is an absolute contraindication to even testing for drug sensitivity. In the absence of any history of allergy, allergy can be tested by a scratch test on the forearm using a weak solution (1000 units/mL) of penicillin.

Antacids reduce the absorption of orally administered penicillin. Penicillins are mainly eliminated in the urine. Probenecid reduces the urinary excretion when given in a dose of 250-500 mg bd orally along with penicillins. It helps to keep the blood levels of penicillin higher for longer periods.

Resistance to penicillins: Several microbes such as staphylococci, gonococci, meningococci, pneumococci and others have developed resistance in a big way and this has posed major problems in the management of life-threatening infections.

Mechanisms of Resistance

1. *Production of beta lactamases:* e.g. staphylococci, gonococci. This can be overcome by the concurrent use of beta lactamase inhibitors such as clavulanic acid, sulbactam or tazobactam.
2. *Reduction in the permeability of the outer membrane,* e.g. gram-negative bacteria.
3. *Alteration in the binding sites for betalactams,* e.g. methicillin resistant staphylococci.

Dosage of benzyl penicillin congeners

	dose
Benzyl penicillin-penicillin G	4-6 lac units 6 h
Phenoxymethyl penicillin-penicillin V	4-6 lac units 6 h oral tablets
Procaine penicillin	6-12 lac units once or twice a day IM injection
Benzathine penicillin	12-24 lac units IM (1.2-2.4 mega units once in 3 weeks)

Beta lactamase resistant penicillins: These are less potent than benzyl penicillin, but they are effective against penicillinase producing staphylococci and other mixed infections.

Cloxacillin

It is available as capsules of 250 and 500 mg and as injections of 0.5 and 1.0 g.

Dose: Oral-500 mg-1 g 6 h; later maintenance dose of 250-500 mg 6 h, given one hour before or 2 hours after food.

Parenteral: IV or IM injections 250-500 mg 6 h.

Cloxacillin is available as combination preparations along with ampicillin or amoxycillin.

Other members of this group are methicillin and nafcillin which are not freely available in India.

Broad Spectrum Penicillins

The antimicrobial activity covers gram-negative organisms such as *H. influenzae*, *E. coli* and *Proteus* in addition to the spectrum of penicillin. These are also inactivated by beta lactamase.

Ampicillin

Preparations available include capsules of 250 and 500 mg; injections containing 250 mg to 1 g and pediatric syrup and drops.

Dose: 250-500 mg 6 h.

Parenteral: 0.5 to 2 g IM or IV 6 h, depending upon the severity of the infection.

Cross sensitivity with penicillin may occur, but allergic reactions are generally milder. In patients with infectious mononucleosis, ampicillin worsens the clinical condition. Administration of probenecid helps to maintain blood levels higher for longer periods.

Amoxycillin

This drug resembles ampicillin in actions and antimicrobial spectrum. When given orally the blood levels are twice as high as that of ampicillin.

Preparations available: Capsules 125, 250 and 500 mg and injections containing 250 and 500 mg.

Dose: 250-500 mg oral or IM or IV 8 h.

Other members of this group include bacampicillin, pivampicillin and talampicillin. These are not freely available in India.

Extended spectrum penicillins: The additional spectrum includes pseudomonas, enterobacteriaceae and proteus. Carbenicillin, ticarcillin, azlocillin, piperacillin and mezlocillin come under this group. Piperacillin and mezlocillin are active against *Klebsiella* also.

Carbenicillin

Preparations available include injections of 1g and 5 g.

Dose: 2-6 g 6h IM or slow IV infusion.

Mixed infections including *Pseudomonas* and *Proteus* especially in immunocompromised hosts are special indications for carbenicillin.

Special risk: Due to the high sodium content it may precipitate cardiac failure in susceptible subjects.

OTHER BETA LACTAM ANTIBIOTICS

Imipenam (Carbapenam)

This is a very powerful bactericidal antibiotic with a very broad spectrum including gram-positive and gram-negative aerobic and anaerobic organisms. It is enzymically inactivated in the kidney and therefore concurrent administration of cilastin which inhibits the enzyme helps to potentiate the antibacterial activity.

Dose: 500-700 mg 8 h IM or IV up to 2 g/day in divided doses.

Meropenam: 500 mg IV or IM 3-4 times a day.

Aztreonam

This is a monocyclic beta lactam antibiotic. It is active against gram-negative aerobic bacteria including *Pseudomonas aeruginosa*.

Cephalosporins

These are among the most popular and widespread antibiotics at present. They contain 7-aminocephalosporanic acid nucleus, which bears structural resemblance to 6-amino penicillanic acid and the beta lactam ring. They are listed arbitrarily as first, second, third and fourth generation mainly on the basis of their antimicrobial activity and also on the period of their introduction as well as structure.

The first generation members resemble penicillin in antibacterial activity. Successive inclusion in the second, third and fourth generations depends upon their wider antimicrobial coverage and effectiveness on resistant strains.

The list is very long and several newer drugs are being added from time to time. The important and easily available members are listed here (Table 5.2).

First Generation

They resist beta lactamase. They do not penetrate into CSF. This group includes:

Cephalexin	oral	250-500 mg	6 h	Tab or cap 150, 250, 500 mg
Cephadroxyl	oral	1-2 g	12 h	Tab or cap 125, 250, 500 mg
Cephadrine	IV or oral	1-2 g	4-6 h	vials 1, 2 g
Cephazolin	IV or IM	0.5-2 g	8 h	vials 125, 250, 500 mg
Cephalothin	IV	1-2 g	4-6 h	vials 1 g, 2 g
Cephaloridine	IV	0.5 g	6 h	vials 0.5, 1 g

TABLE 5.2	
List of cephalosporins and their route of administration	
Oral	Parenteral
First generation	
Cephalexin	Cephazolin
Cephadroxyl	Cephalothin
Cephadrine	Cepharin
	Cephaloridine
Second generation	
Cefaclor	Cefuroxime
Cefuroxime axetil	Cofoxitime
	Cefhamandole
	Cefotetan
Third generation	
Cefixime	Ceftizoxime
	Cefoperazone
	Ceftazidime
	Cefotaxime
	Caltriaxone
	Cefsulodin
Fourth generation	
	Cefipime

Second Generation

They have expanded spectrum of activity against gram-negative bacilli, especially ampicillin resistant *H. influenzae*. Penetration into CSF is poor. Activity against gram-positive cocci is less than that of the first generation.

Cefaclor	oral	150-500 mg	8 h	275 or 350 mg tablets
Cefuroxime axetil	oral	250 mg	12 h	125, 250, 500 mg tablets
Cefuroxime	IM or IV	750 mg- to 1.5 g	8 h	250, 750 or 1500 mg vial
Cefoxitime	IM or IV	1-2 g	4-8 h	1 g, 2 g vial
Cephamandole	IM or IV	1-2 g	4-6 h	1 g, 2 g vial
Cefotetan	IM or IV	1-3 g	12 h	1, 2 and 10 g vial

Third Generation

These are effective against most of the gram-negative beta-lactamase producing bacteria, especially enterobacteriaceae and pseudomonas for gram-positive cocci is less compared to the first generation. Except cefoperozone, penetration into CSF is good.

Cefixime	200-400 mg	oral	12-24 h	Tablet of 200 and 400 mg
Ceftizoxime	1-2 g	IM or IV	8-12 h	0.5 and 1 g vial

Cefoperazone	1-2 g	IM or IV	8-12 h	0.5 and 2 g vial
Ceftazidime	1-2 g	IM or IV	8-12 h	0.5 and 1 g vial
Cefotaxime	1-2 g	IM or IV	8 h	0.5 and 1 g vial
Ceftriaxone	1-2 g	IM or IV	12-24 h	0.5 and 1 g vial
Cefsulodine	0.5-1 g	IM or IV	6 h	0.5 and 1 g vial

Fourth Generation

This includes drugs which have got extended spectrum of activity compared to the third generation drugs. They are also more resistant to the action of beta-lactamase. Their special use is in the treatment of aerobic gram-negative bacilli resistant to the other drugs.

Cefepime	2 g	IV	12 h
Cefepirome	1-2 g	IV	12 h

Aminoglycosides

These are bactericidal antibiotics. They derive their name on account of the presence of aminosugars in glycoside linkage in their structures. They have to be given parenterally, since they are not absorbed from the gut. Their distribution is mainly in the extracellular fluid, higher concentrations in renal cortex and endolymph and perilymph of the internal ear. These organs are more liable to suffer from toxic effects, especially in the elderly. At both extremes of age and in the presence of renal insufficiency the dose has to be modified to avoid toxicity. Diffusion into CSF and ocular structures is poor. Bacteria develop resistance rapidly, especially if administered singly. Administration along with other antibacterial agents reduces the chances for development of resistance. When combined with betalactam antibiotics such as penicillins or cephalosporins the action is synergistic. The important members in this group are streptomycin, gentamicin, amikacin, kanamycin, tobramycin, netilmycin, neomycin, framycetin and paromomycin (Table 5.3).

Antibacterial Spectrum

Streptomycin: Gram-negative bacteria, *Str. viridans*, *Y. postis*, *F. tularensis*, *brucella*, *M. tuberculosis*. Until two decades ago this was among the first line drugs for the treatment of tuberculosis. With the availability of rifampicin, streptomycin has been moved down to be a second line drug.

Gentamicin: Gram-negative bacteria esp *E. coli* and *proteus*, *Ps. aeruginosa*, *Klebsiella*, *acinobacter*, *mycoplasma*, Group A *Streptococcus* and *Staphylococcus* are susceptible. It is very effective in mixed infections such as peritonitis, empyema, urinary tract infection and others.

TABLE 5.3

Therapeutic details of aminoglycoside

Drug	Dose	Route	Preparation
Streptomycin	15-25 mg/kg/day	IM single dose	1 g or 0.75 g vials
Gentamicin	2-5 mg/kg/day	IM or IV divided doses 8 h	80 mg or 60 mg vials
Amikacin	15 mg/kg/day	IM or IV 8 h	50 mg to 500 mg vials
Kanamycin	15 mg/kg/day	IM 8 h	500 mg to 1 g vials
Tobramycin	3 mg/kg/day	IM 8 h	40 mg and 80 mg vials
Netilmycin	5 mg/kg bw	IV/IM 8 h	vials of 10-200 mg/mL

It is one of the very reliable and powerful bactericidal antibiotics to be used in combination in serious life-threatening infections, even before the microbiological results are available. Preparation for topical use are available, e.g. eyedrops. In view of the risk of development of resistance it is advisable to minimise their use.

Amikacin: *Serratia*, *proteus*, *pseudomonas*, *Klebsiella*, *enterobacteriaceae*, *E. coli* nonsocomial *Gram negative infections* and *atypical mycobacteria* are susceptible. This is one of the very powerful antibiotics available for use in life-threatening conditions.

Kanamycin: Gram-positive and gram-negative organisms causing urinary tract infections, septicemia, meningitis, bacterial endocarditis and pelvic infections respond to the drug. It is an “add-on” drug with other broad spectrum antibiotics.

Tobramycin: It is more active against *pseudomonas*. It is usually given along with ampicillin or ceftazidime.

Netilmycin- This drug is effective in serious infections of the respiratory tract and other locations such as intra-abdominal infections. It is also used as a prophylaxis for bacteremias in a dose 5 mg /kg bw 8 h. It is available as IV injection vials in strengths ranging from 10 mg-200 mg/mL.

TETRACYCLINES

These are in existence for over six decades. They are bacteriostatic. They act by inhibiting protein synthesis in the microbe. Though they are not considered as the first line of drugs for the common bacterial infections, they retain their pride of place for several infections such as *rickettsiae*, *mycoplasma chlamydia* and others. They are active against a wide range of microorganism.

Antimicrobial Spectrum

They are the drugs of choice for *rickettsiae*, *mycoplasma*, *ureaplasma*, and *chlamydia*.

They are effective against gram-positive cocci, gram-negative bacteria, *H. influenzae*, *Klebsiella*, *E.coli*, *brucella*, *Y. pestis*, *F. tularensis*, *B. recurrentis*, *C. jejuni* and *H. pylori*. Their adverse side effects include diarrhea, drug rashes, photosensitisation and hepatic and renal damage in susceptible individuals. Tetracycline orthophosphate gets deposited in the developing teeth of fetuses and young children and also in bones. The teeth may become permanently discoloured yellow. In patients on marginal nutritional status, destruction of the colonic bacterial flora may give rise to overt deficiency of the B. complex vitamins. It has therefore been a practice to prescribe B. complex vitamins along with tetracyclines. Tetracyclines can be given orally on an outpatient basis. Absorption is better if given on an empty stomach. Parenterally they can be given IM or IV. The popular preparations in this group are tetracycline, oxytetracycline, and colortetracycline which are short acting (6 hours) and doxycycline and minocycline which are long acting (up to 24 hours).

Dose	Oral	Parenteral	Preparations
Tetracycline	250-500 mg 6h	250-500 mg IM or IV 8-12 h	Tablets and capsules 250 mg and 500 mg injections 100-500 mg vials

Chlortetracycline and oxytetracycline resemble tetracycline in dose, efficacy and toxicity.

Doxycycline: 200 mg oral on first day followed by 100 mg once or twice a day for 5-10 days. Capsules and tablets of 100 mg are available.

Minocycline Dose: 100 mg bd.

MACROLIDES

These antibiotics derive their name due to the presence of many numbered lactone ring in the nucleus. They are very popular and safe drugs which can be given orally. Side effects include gastrointestinal upsets, allergy, hepatic damage and Stevens Johnson syndrome. Antimicrobial spectrum includes *Gram positive cocci*, *Gram negative bacilli*, *C. diphtheria*, *campylobacter*, *Legionella*, *leptospira*, *borrelia*, *nocardia*, *mycoplasma* and *Chlamydia (trachoma)*. Macrolides interact with several drugs and therefore great care has to be taken when prescribing them along with other drugs. The important members in this group are erythromycin, roxithromycin, azithromycin, clarithromycin, oleandomycin and spiramycin (Table 5.4).

Ketolides- e.g. Telithromycin. These are drugs with spectrum of action similar to macrolides. They inhibit

TABLE 5.4 Dosage of macrolides			
	Dose	Route	Preparation
Erythromycin	250-500 mg 6 h	oral	Tablets and capsules of 100 and 500 mg
Roxithromycin	150 mg bd or 300 mg od	oral	150 and 300 mg tab, capsules
Azithromycin	250-500 mg od	oral on empty stomach	100 and 250 mg tablets, capsules
Clarithromycin	250-500 mg bd or tds	oral	250 and 500 mg tablets
Spiramycin	3 miU bd	oral	tablets 3 miU
Note: Clarithromycin is useful for the prophylaxis and treatment of atypical mycobacteria, eradication of <i>H. pylori</i> and as an add-on drug for treating resistant malaria.			

protein synthesis in the microbe. Though the antibacterial spectrum resembles that of other macrolides, it is more potent than erythromycin. It is active against multi-drug resistant *Pneumococcus*, *H. influenzae*, *M. catarrhalis*, *N. gonorrhea*, and *N. meningitides*. It is not active against enterobacteracea, acinitobacter and *Ps. aeruginosia*.

Dose 800 mg oral od for 7-10 days for community acquired pneumococcus. The course is for 5 days for other respiratory pathogens. Adverse effects include gastrointestinal upsets, elevation of liver enzymes and prolongation of QT interval in the ECG. Mitochondrial damage has been reported.

Chloramphenicol

It is a bacteriostatic drug active against gram-positive and Gram-negative organisms, rickettsiae, chlamydia and *mycoplasma*. Since it diffuses into CSF it is an excellent drug for the treatment of meningitis especially due to meningococci, pneumococci and *H. influenzae*. It held its pride of place as the antibiotic of choice for treatment of enteric fevers till three decades ago. Development of resistance by salmonella against chloramphenicol and other drugs has been rapid and widespread and therefore at present it is used as a second line drug for the treatment of enteric fevers only under special circumstances. Major toxic effects include allergy, peripheral neuropathy, optic neuritis, dose related reversible anemia, fatal bone marrow depression, and permanent aplastic anemia (in 1/30000). When chloramphenicol is given to newborn infants whose hepatic and renal functions are still immature a toxic state may develop in which the baby becomes listless, pale and grey in colour. This is called 'grey baby syndrome'. Continuation of the drug may lead to death due to circulatory failure.

Dose of chloramphenicol	Tablets or capsules
250-500 mg oral 6 h	125 to 500 mg
Parenteral IV or IM same as oral dose vials	500 mg and 1 g

Due to the possibility of fatal bone marrow depression, chloramphenicol should be used with caution.

SULPHONAMIDES

These were the first group of antibacterial drugs introduced for the therapy of infections. The commonly used sulphadugs, in vogue from time to time include sulphadiazine, sulphaguanidine, sulfamethoxazole, sulphasoxazole, sulphadoxin, sulphacetamide, silver sulphadiazine and salicyclazosulpha pyridine (salazopyrin). Sulphonamides are bacteriostatic. Sulphamethoxazole in combination with trimethoprim (co-trimoxazole), salazopyrin, sulphadoxin and silver sulphadiazine are currently in wide use. The other members in this group have been largely replaced by newer drugs, on account of the greater efficacy and safety of the latter.

Co-trimoxazole

This is a combination of 1 part of trimethoprim with 5 parts of sulphamethoxazole 80 mg and 400 mg respectively. The action is bactericidal. The antimicrobial spectrum includes *gram-positive cocci*, *proteus*, *brucella*, *yersinia*, *E. coli*, *klebsiella*, *H.influenzae*, *shigella*, *salmonella*, *pneumocystis carinii* and others. Adverse side effects include allergy, leukopenia, megaloblastic anemia and bone marrow suppression.

Dose: 160 mg trimethoprim with 800 mg sulphamethoxazole twice a day orally for the usual infections.

For the treatment of *Pneumocystis carinii* pneumonia and its prevention in immunocompromised hosts larger doses have to be employed. Intravenous preparation is available. This may be combined with carbenicillin for the management of infections in neutropenic patients.

Trimethoprim

This has antibacterial property on its own. It is active against *E. coli*, *proteus*, *klebsiella*, *enterobacter* and *staphylococci*.

Dose: 100 mg oral bd or 200 mg od.

Toxic effects include rashes, gastrointestinal upsets and bone marrow suppression.

Sulphadoxine

This has a serum half-life of six days. It is used as an antimalarial against resistant *P. falciparum* infections. The

compound Fansidar tablets containing sulfadoxin 0.5 g and pyrimethamine 25 mg are given in a dose of 3 tablets orally as a single dose.

Salazopyrin

This is used as an antiinflammatory and immunomodulatory drug in ulcerative colitis, rheumatoid disease and reactive arthritis. It is not used as an antimicrobial drug.

Silver sulphadiazine: Is used as 1% drops or cream for topical use, especially in burns to prevent bacterial colonization.

OTHER ANTIBIOTICS

Vancomycin

It is a glycopeptide antibiotic used for the treatment of multidrug resistant *Staph. aureus* (MRSA) and pseudomembraneous colitis caused by *Cl. defficile*. It is bactericidal. It can be given orally or parenterally.

Dose: Oral—125-500 mg 6 h (7 mg/kg bw) for pseudomembraneous colitis.

Parenteral: Intravenous infusion of 500 mg to 1.0 g over one hour at intervals. It is available as 50 mg tablets and vials of 0.5 and 1 g.

Teicoplanin

It is a related antibiotic similar to vancomycin in action, but with a longer duration of activity. This drug is active against potentially serious gram + infections including *Staph aureus*, especially MRSA. The drug is available as Targacid (Aventis) as vials containing 200 and 400 mg. The dose is 400 mg IM or IV single dose on the first day followed by 200 mg daily. In severe infections the dose is 400 mg IM/IV 12 hourly for the first 3 days followed by 400 mg daily.

Lincomycin

It is a lincosamide antibiotic active against organisms which are penicillin resistant. Its use is limited to acute and chronic osteomyelitis, respiratory infections, septic arthritis and endocarditis.

Dose: Oral—500 mg 6-8 h or 600 mg IV or IM 12 h.

Preparations available: Capsules of 500 mg and injections of 600 mg in 2 mL.

Clindamycin

It is a derivative of lincomycin useful in infections caused by mixed bacterial flora, malaria and toxoplasmosis. It can be given orally or parenterally.

Dose: Oral—150-300 mg 6 h.

Parenteral: 600 mg to 2.7 g as IV infusion or IM over 24 hours in divided doses. This drug is available as 150 mg capsules and vials containing 150 mg/mL.

Oxazolidinones: e.g. Linezolid. These are newer synthetic antibacterial antibiotics which inhibit protein synthesis in the microbes. Linezolid is 100% bioavailable on oral administration. The antibacterial spectrum is wide against gram positive bacteria. It is especially useful against MRSA, and vancomycin resistant *Enterococcus faecium*.

Dose: oral- 600 mg 12 h or IV 600 mg 12 h for 10-14 days. When giving IV, linezolid should not be mixed with other drugs. Adverse side effects include pain at the site injection, elevation of liver enzymes, renal impairment and thrombocytopenia.

Daptomycin is a cyclic lipopeptide antibiotic that is rapidly bactericidal for most of the gram positive bacteria including *S. aureus*.

Dose: 6 mg/kg bw given IV once a day. It has been tried to treat MRSA bacteremia with encouraging results.

Fusidic Acid

Sodium Fusidate (Fucidin) is obtained from the parasite fungus *Fusicidium coccinimum*. It has a steroid structure and it is active against gram+ organisms. All strains of staphylococci are sensitive. Streptococci and pneumococci are relatively resistant.

Dose: 500-1000 mg oral 8 h. Milk reduces the absorption of this drug. The available parenteral preparation is diethanolamine fusidate 580 mg IV 8 h. Sodium fusidate is also a general purpose local antiseptic, available as ointment. Fucidin shows bactericidal synergism with penicillin and erythromycin.

Spectinomycin

This is effective in gonococcal urethritis.

Dose: IM or IV 2-4 g single dose or 2 g bd for 3-5 days.

Quinespristin-Dalfopristin

This group of drugs which belongs to the class streptogramins is active against gram+ organisms, vancomycin resistant MRSA, resistant enterococci and atypical organisms.

Dose: Quinpristin/dalfopristin mixture (30/70%) is given IV 8 h at 7.5 mg/kg bw.

Nitrofurantoin

This is a synthetic nitrofuran with activity against gram-negative bacteria of the urinary tract. It is used for the

prophylaxis and long-term treatment of urinary tract infections.

Dose: Oral—for prophylactic use 50-100 mg at hs.

For therapy of established infection 200-400 mg/day is divided doses.

The drug has to be used with caution in the presence of renal impairment.

QUINOLONES

The fluoroquinolones are synthetic bactericidal agents related to the parent drug nalidixic acid. The popular drugs in this group are norfloxacin, ciprofloxacin, pefloxacin, ofloxacin, lomefloxacin and sparfloxacin. The parent drug nalidixic acid is still in use. The antimicrobial spectrum is wide including gram-negative cocci and bacilli such as *enterobacteriaceae*, *H. influenzae*, *shigella*, *campylobacter*, *neisseria*, *gonococcus*, *pseudomonas* and others.

Ciprofloxacin one of the most potent among the quinolones is bactericidal for salmonellae and at present this is the drug of choice for enteric fevers. It is also used to eradicate the carrier state for *meningococci* and *S. typhi*. It is particularly active against *pseudomonas*.

Ofloxacin has action against multidrug resistant staphylococci, chlamydia and legionella.

Lomefloxacin has action similar to ciprofloxacin.

Sparfloxacin has action against anaerobic organisms. Lomefloxacin and sparfloxacin are long acting and therefore once a day dosage is adequate. Some of quinolones are available for local application such as eyedrops. Quinolones are generally contraindicated during pregnancy and lactations.

Levofloxacin: This is available as tablets of 250 and 500 mg to be given orally once or twice a day for up to 14 days. It is also available as an IV infusion containing 5 mg/mL, 100 mL vials, to be given as a slow infusion over 60 minutes, once or twice a day for up to 14 days. Side effects include QT prolongation in ECG, cardiac arrhythmias, hepatic impairment, tendon inflammation, and polyneuropathy. The drug is contraindicated in children and pregnant and lactating women.

Gatifloxacin and **moxifloxacin** are newer fluoroquinolones are powerful antibacterial drugs. They act by inhibiting the enzyme DNA gyrase (topoisomerase: II and IV) which are required for DNA replication, transcription, repair and recombination. Both are active against a wide spectrum of gram + and gram- bacteria, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae* and penicillin resistant pneumococcus. They are less effective than ciprofloxacin against *Pseudomonas aeruginosa*.

Adverse effects include dizziness, nervousness, precipitation of seizures, erosion of cartilage in weight

TABLE 5.5

Dosage of quinolones

<i>Norfloxacin</i>	400 mg bd	oral	Tablets 100 to 800 mg
<i>Ciprofloxacin</i>	250-750 mg bd 200-400 mg bd	oral IV infusion	Tablets 100-750 mg
<i>Pefloxacin</i>	400 mg bd 400 mg	oral IV infusion 1 hour	Tablets 400 mg IV infusion 4 mg/mL 100 mL
<i>Ofloxacin</i>	200-400 mg/bd 200-mg infusion	oral IV in 30 minutes	Tab 100 and 200 mg infusion 2 mg/mL 100 mL
<i>Lomefloxacin</i>	400 mg o.d	oral	Tab 400 mg
<i>Sparfloxacin</i>	400 mg first day Then 200 mg/day	oral	Tab 200 and 400 mg
<i>Levofloxacin</i>	250-500 mg	oral IV infusion	Tab 250 and 500 mg 500 mg vials
<i>Gatifloxacin</i>			
<i>Moxifloxacin</i>	400 mg od	oral	400 mg tablets
<i>Nalidixic acid</i>	1 g qid	oral	Tab 250 mg to 1 g

bearing joints in young subjects and prolongation of QT interval in the ECG. Gatifloxacin may produce hypoglycemia and at times, hyperglycemia with symptoms requiring urgent attention.

Dose: 400 mg daily po for 5-10 days. The drug has to be given with caution in diabetes (Table 5.5).

The Imidazole Derivatives

Two drugs, **metronidazole** and **tinidazole**, originally developed as antiamebic drugs have potent antibacterial properties and therefore they are used widely for that purpose as well.

Metronidazole: This drug has anti-protozoal activity against amebae, giardia and trichomonas. It has wide antibacterial activity against the anaerobic organisms bacteroids, clostridium, fusobacterium, peptococcus, peptostreptococcus and eubacteriaceae. In combination with clarithromycin and a proton pump inhibitor it is bactericidal to *Helicobacter pylori*. Metronidazole is available as tablets of 200 and 400 mg, suspensions containing 200 mg/ 5 mL and vials of 100 mL containing 500 mg of the drug for IV use.

Dose: Amebiasis 400-800 mg tds po × 5-10 days.

For trichomoniasis, giardiasis and others 400 mg tds × 5 days.

For anaerobic infections, loading dose of 15 mg/kg bw IV infusion over 30-60 minutes followed by maintenance dose of 7.5 mg/kg bw 6 h for 7-10 days.

Metronidazole can be used as a primary drug for *Clostridium difficile* in dose of 400 mg tds oral for 5-7 days.

Tinidazole is available as tablets containing 500 mg and 1 g. It is effective against protozoa such as ameba, giardia and trichomonas.

Dose: Amebic dysentery-2 g/day/po in single or divided doses for 3-5 days.

Amebic liver abscess – 2 g/day in divided doses for 5 days or more.

Giardiasis and trichomoniasis – 2 g/day for 1 day as single or divided doses.

Anaerobic infections-treatment and prophylaxis -2 g initially, followed by 500 mg bd po for 5-7 days.

For preoperative sterilization - 2 g single dose po 12 hours prior to surgery.

Ulcerative gingivitis and bacterial vaginosis 2 g po single dose.

Rifampicin

This is a bactericidal antibiotic with a wide antibacterial spectrum. It is very effective against *M. tuberculosis* and *M. leprae* and therefore almost exclusively used for treating them.

Dose: 10 mg/kg bw orally daily as a single dose.

Capsules of 150-600 mg and tablet of 450 and 600 mg are available.

Absorption is best when given an empty stomach. Any food or drink should be given only an hour later. Resistance develops very rapidly if given alone. All forms of tuberculosis respond. The course of treatment should continue uninterrupted for six months or more.

For the treatment of leprosy supervised monthly doses of 450-600 mg are given depending upon the clinical status.

Other indications include infections by staphylococcus, legionella and gram-negative bacilli. It is effective as a prophylactic agent against *H. influenzae* and meningococcal meningitis in contacts.

Rifabutin

It is an antimycobacterial antibiotic, used for the prophylaxis and treatment of *M. avium complex*.

Dose: 150 mg/day oral for 6 months. In AIDS patients the dose is 300 mg/day to be given indefinitely. For multidrug resistant tuberculosis, rifabutin is effective in a dose of 300-450 mg day.

Rifapentine: This is a rifamycin derivative with excellent activity against *M. tuberculosis*. Compared to rifampicin its half-life is longer (10-15 hours vs 2-3 hours). Therefore it can be given at longer intervals. Regimens such as rifapentin 600 mg once a week with INH 900 mg weekly have been tried in non-cavitating pulmonary tuberculosis in HIV negative persons, with success.

POLYENE ANTIBIOTICS

These are all polypeptide antibiotics. These include bacitracin, polymyxin B, and colistin. They are less widely used for systemic diseases due to their non-availability, higher toxicity and higher cost.

Bacitracin

The antimicrobial spectrum includes *Gram-positive organisms meningococcus, gonococcus, treponemes* and *H.influenzae*. For systemic use it has to be given IM or IV.

Dose: 1000 units/kg/day in divided doses.

For local use it is available as eye ointment of 500 units/g, and powder in combination with polymyxin-B and neomycin.

Polymyxin-B

This is active against gram-negative organisms, especially *Ps. aeruginosa*. It is used systemically as well as for topical use in the eye and skin. It is available as injections (500,000 units vials), eyedrops (5000 u/mL) and ointment (5000 u/g).

Dose: IM injection 15-20000 units/kg bw/day in divided doses.

Colistin

The antimicrobial spectrum resembles that of polymyxin B, but the action is weaker. It is available for oral use as syrup containing 2.5 mg/mL (i.e.) 50,000 units/mL.

Dose: 3-5 mg/kg/day in divided doses.

Table 5.6 for choice of antibiotics.

Antiviral Drugs

Antiviral drugs are available at present for specific treatment and prophylaxis of many viral infections although several others have to be managed only symptomatically. From time-to-time antiretroviral drugs for the prophylaxis and treatment of acquired immunodeficiency syndrome (AIDS) are being introduced. Some of them have activity against other viruses as well. Availability of specific antiviral drugs has necessitated virological diagnosis of infections, in order to get best results (Tables 5.8 to 5.10). Antiviral drugs may be broadly classified based on their clinical effectiveness.

1. **Drugs for herpes group viruses:** acyclovir, valacyclovir, gancyclovir, famciclovir, pancyclovir, foscarnet, vidarabin and idoxuridine.
2. **For influenza A virus and other respiratory viruses:** amantadine, rimantadine, ribavirin, zanamivir, ostelamivir.
3. **Anti-retroviral drugs:** At present several drugs are available for the treatment of Human Immunodeficiency virus (HIV). Mainly they belong to four classes, based on their pharmacological effects. These include:
 - A. *Nucleoside Reverse Transcriptase Inhibitors (NRTI) and Nucleotide Reverse Transcriptase Inhibitors- NtRTI*
 - B. *Non-Nucleotide Reverse Transcriptase Inhibitors (NNRTI)*
 - C. *Protease Inhibitors- PI and*
 - D. *Entry inhibitors (EI)*
4. **Nonselective Human alpha interferons.** antiviral agents (Table 5.7)

Acyclovir (Acycloguanosin): This is a potent drug which inhibits the multiplication of herpes simplex types 1 and 2, varicella zoster and EB virus. Acyclovir is given intravenously in a dose of 5 mg/kg as an infusion running over 1 hour and repeated every 8 h for 5 days. Side effects include allergy, renal impairment, local necrosis of tissues, and hepatic dysfunction. The dose should be reduced in patients with impaired renal function. This is one among the most effective and widely used antiviral drugs. It inhibits replication of herpes viruses. Infected cells concentrate the drug 40-100 times higher than uninfected cells. It is the most active agent in HSV₁, HSV₂ and varicella zoster virus. Preparations for topical use are also available for herpes simplex and herpes zoster lesions.

TABLE 5.6

Choice of antibiotics for common infections

Disease	Proven value (conventional antibiotics)	Cephalosporins group
Respiratory tract infections		
Pharyngitis	Benzylpenicillin	Cephadrine
Otitis media	Amoxycillin	Cefaclor
Necrotising otitis	Ticarcillin	Cefsulodin, ceftazidime
Sinusitis	Amoxycillin	
Pneumonia		
<i>Strep. pneumoniae</i>	Benzylpenicillin	First generation cephalosporins
<i>H. influenzae</i>	Ampicillin	Cefuroxime, cefotaxime, cephamandole
<i>Staph. aureus</i>	Nafcillin, cloxacillin	Cephalothin, cefazolin
Klebsiella	Cefazolin	Cefotaxime, moxalactam
Pseudomonas	Ticarcillin	Ceftazidime
Anaerobic organisms	Penicillin, clindamycin metronidazole	Cefoxitin, moxalactam
Urinary tract infections		
Domiciliary	Ampicillin	
Hospital-acquired enterobacteriaceae	Aminoglycosides	Cefotaxime, moxalactam
Pseudomonas	Aminoglycosides	Ceftazidime
Meningitis		
Neonatal	Ampicillin, gentamicin	Cefotaxime, moxalactam + ampicillin
<i>Strep. pneumoniae</i>	Benzyl penicillin	Cefotaxime
<i>N. meningitidis</i>	Benzyl penicillin	Cefotaxime
<i>H. influenzae</i>	Ampicillin, chloramphenicol	Cefotaxime, moxalactam
Enterobacteriaceae	Aminoglycosides	Cefotaxime, moxalactam
Bone and joint infections		
<i>Staph. aureus</i>	Nafcillin, cloxacillin	Cefazolin
Enterobacteriaceae	Aminoglycosides	Cefotaxime, moxalactam
Pseudomonas	Ticarcillin + aminoglycosides	Cefsulodin, ceftazidime
Diarrheal disease		
Shigella		
Salmonella	Ampicillin	None
Campylobacter		
Gynecological infections		
Endometritis, salpingitis	Clindamycin + gentamicin	Cefoxitin, cefotaxime, moxalactam
Sexually transmitted disease		
Gonorrhea	Penicillin	Cefoxitin, cefotaxime
Intra-abdominal infections		
Septicemia	Clindamycin + gentamicin Ampicillin + aminoglycosides Ticarcillin + aminoglycosides	Cefoxitin, cefotaxime, septicemia Cefotaxime Moxalactam
Leptospirosis	Penicillin, tetracycline, doxycycline	

Dose:

Genital herpes	200 mg oral 5 times a day—
curative	10-12 days
	or IV 5 mg/kg 8 h for 5 days
suppression	400 mg bd for long periods.
HSV encephalitis	10 mg/kg IV 8 h for 10-14 days
Neonatal HSV	IV 10 mg/kg 8 h for 10-14 days
Varicella zoster	800 mg qid or tds for 10-14 days

Gancyclovir: This drug is effective against cytomegalovirus (CMV) and is indicated for the treatment of life-threatening lesions such as colitis and pneumonias in immunocompromised host and for retinitis which may lead to blindness. The dose is 5 mg/kg given as intravenous infusion within one hour, repeated twice daily. The initial course extends for three weeks after which the maintenance dose is 5 mg/kg/day for several weeks. Drug

TABLE 5.7			
Antiretrovirals approved for use			
NRTI	NNRTI	PI	Entry inhibitor
Zidovudine (ZDV)	Nevirapine (NVP)	Saquinavir (SQV)	Enfuvirtide* (T-20)
Stavudine (d4T)	Efavirenz (EFV)	Indinavir (IDV)	
Lamivudine (3TC)	Delavairidine* (DLV)	Ritonavir (RTV)	
Didanosine (ddI)		Nelfinavir (NFV)	
Zalcitabine* (ddC)		Lopinavir (LPV/r)	
Abacavir (ABC)		Atazanavir* (ATV)	
Emtricitabine* (FTC)		Amprenavir* (APV)	
Tenofovir (TDF)		Fos-amprenavir* (FPV)	
(Nucleotide RTI)		Tipranavir (TPV)*	
*Drugs not available in India. Several newer drugs which are in the process of development are likely to be introduced from time to time in the near future.			

toxicity includes neutropenia and thrombocytopenia. It is available in vials of 500 mg.

Phosphonoformate (Foscarnet): This is a pyrophosphate analogue that inhibits DNA polymerase of all herpes viruses and RNA polymerase of influenza viruses. Topical application is found to be beneficial in herpes labialis and herpes genitalis. It is being used parenterally in AIDS and CMV infections.

Vidarabine: This is a derivative of adenine arabinoside. It inhibits DNA synthesis and is active against several herpes group viruses. It is used therapeutically in herpes simplex, varicella zoster and cytomegalovirus infections. The drug has to be given intravenously as a 12 hr infusion in a dose of 5-15 mg/ kg/day for 10 days. Toxicity occurs in a few cases and this includes nausea, vomiting, diarrhea and tremors. For the treatment of herpes simplex encephalitis and neonatal herpes simplex infections, vidarabine has to be given intravenously. Adenine arabinoside is available as a 3% ointment for topical use in herpetic keratoconjunctivitis.

Idoxuridine: This is effective against herpes simplex infections, although the organisms develop resistance rapidly. The drug is given as local application to the eye as 0.1% drops and as 0.5% ointment. Toxic effect include irritation and local allergy.

TABLE 5.8	
Mode of action of antiviral agents	
Acyclovir	Nucleoside analogue
Amantidine and rimantadine	Viral uncoating and assembling
Foscarnet	Inhibition of polymerase
Ganciclovir	Nucleoside analogue
Idoxuridine	-Do-
Ribavirin	-Do-
Trifluridine	-Do-
Vidarabin	-Do-
Zidovudine	-Do-
Inosine pranobex (Inosiplex)	Immunomodulator
	Nucleoside analogues interrupt viral nucleic acid synthesis

TABLE 5.9	
Site of action of antiviral drugs	
Stage of viral replication	Effective drug
Attachment	Antibody to virion-binding Antibody to cell receptors
Penetration/uncoating	Amantadine
Viral macromolecular synthesis	Nucleoside analogues Vidarabine, acyclovir, ganciclovir, ribavirin, zidovudine, foscarnet, Interferons

Note: The details of anti-retroviral drugs is given in Table 5.10

Amantadine hydrochloride (Symmetrel): It is active against RNA viruses such as myxoviruses, paramyxoviruses and togaviruses. The drug is effective particularly against influenza A virus, but not against influenza B. The drug is mainly used for the prophylaxis against influenza A in vulnerable groups. There is a 50-60% reduction in attack rates. For prophylaxis after exposure it should be given within 24-48 hours. It is given orally 100 mg twice a day. Toxic effects include confusion, hallucinations, anxiety and insomnia. It may produce embryopathy when given in pregnancy. This drug is also used in parkinsonism. Rimantadine is an analogue.

Ribavarin: It is a synthetic triazole nucleoside with wide spectrum of activity both against DNA and RNA viruses. It is useful in the treatment of influenza and respiratory syncytial virus (RSV) when given as an aerosol. When given orally or intravenously the drug is effective against Lassa fever, hepatitis B and C, viral hemorrhagic fevers caused by hantan virus and Argentinian and Congo-cremean hemorrhagic fevres.

Lamivudine has also suppressive action on hepatitis B virus (in a dose of 100 mg oral daily). Several others anti-retroviral drugs have also been produced and they are under different stages of trial.

TABLE 5.10

Antiviral drugs, their antiviral activity, preparations and toxicity

Name	Antiviral activity	Preparation	Indication	Main toxicity
Idoxuridine	Herpes virus (HSV), Superficial lesions	0.1% solution or 0.5% ointment for eye	HSV keratitis	Local irritation
Trifluridine	HSV keratitis	1% eyedrops	-do-	
Vidarabin	DNA viruses esp. Herpes group, HSV, VZV, CMV	eye ointment, IV infusion 5-15 mg/kg/day for 10 days	HSV keratitis, HSV encephalitis, disseminated varicella zoster, CMV infections	GI toxicity, tremors
Acyclovir (Zovirax)	HSV, VZV, BB virus	Local cream 5% IV 15-30 mg/kg/day oral tablets 800 mg 4 h	Herpes labialis, Herpes encephalitis EB virus infection	Allergy, renal and hepatic damage
Ganciclovir (Cymevene)	CMV infections	IV 7.5 mg/kg/day	Systemic congenital or acquired CMV infections	
Zidovudine (Azidothymidine)	HIV	250 mg oral 6 h	AIDS and AIDS related disorders	Bone marrow suppression
Ribavirin	Lower resp. tract viruses esp. syncytial virus, Lassa fever virus hepatitis B and C virus	Aerosolized ribavirin, oral tablets 600-1200 mg/day	Influenza, Resp. syncytial virus, Lassa fever HBV, hepatitis C virus	Hemolytic anemia Neoplasia
Amantadine and Rimantadine	Influenza A virus	200 mg/tab. orally	Prevention of Influenza A	Neurotoxicity
Zanamivir and Ostelamivir	Influenza A and B	Zanamivir 5 mg inhalation Ostelamivir 75-100 mg bd oral	Do treatment	—
Phosphonoformate (Foscarnet)	Herpes viruses and influenza virus	Topical	Recurrent herpes labialis	
Alpha interferon	Rhinoviruses HBV, non A non B hepatitis, delta virus hepatitis	Nasal spray parenteral preparation up to 20 mega units/day	Prevent rhinovirus infections Hepatitis B,C,D	Fever

Note: Several newer anti-retroviral drugs are being developed with a view to improve the results in AIDS. Many of these are given along with the chapter on AIDS

Neuroaminidase inhibitors: They inhibit the growth and release of influenza virus from the infected cell. The available drugs are zanamivir and ostelamivir. They inhibit both influenza types A and B. They are used for chemoprophylaxis and curative treatment.

INTERFERONS

Interferons are cytokines produced by host cells in response to viral infection or other stimuli. They are glycoproteins in structure.

Three types of interferons are available-*alpha* interferon produced by lymphocytes and monocytes, *beta* interferon produced by fibroblasts, and *gamma* interferon produced by sensitized T-helper (TH1) lymphocytes. Alpha interferon has two subtypes 2a and 2b which slightly differ in activity. Interferons are commercially produced by rDNA technology, and they are widely used for a large variety of unrelated conditions. Alpha interferon is the most widely used. The antiviral spectrum

includes *hepatitis B, C and D, herpes zoster, EB virus* and *juvenile laryngeal papillomatosis*. Interferon exerts its action possibly by interfering with the translation function in the host cell.

Neoplastic conditions such as chronic myeloid leukemia, hairy cell leukemia and multiple myeloma respond well to alpha interferon.

Alpha interferon is given SC, IM or IV in doses of 5 million units daily or on alternative days for prolonged periods depending upon the indications. Adverse side effects include flu-like symptoms, somnolence, confusion, paresthesia, motor neuropathy, alopecia, leukopenia and thrombocytopenia. *Pegylated interferon* is available. Adverse side effects are less and the preparation is more acceptable. It is more expensive too.

A single dose costs Rs. 1500-2000 and therefore the treatment becomes very expensive.

Beta interferon is used to reduce the frequency and severity of relapses in multiple sclerosis. Gamma

interferon is immunomodulatory in action. It takes part at different stages of the immune mechanisms of the host, including activation of macrophages and NK cells and regulation of antibody production by lymphocytes.

Inosiplex (Inosine pranobex): This drug stimulates B-lymphocytes to produce antibodies, promotes the differentiation of T-lymphocytes and increases macrophage and interleukin activity. Its use is beneficial in hepatitis, subacute sclerosing panencephalitis (SSPE) and herpes simplex virus infections.

At present specific antiviral drugs should be considered for the treatment of the following conditions:

- 1. Herpes simplex infections-severe mucocutaneous or generalized forms in an immunocompromised host, ophthalmic forms, genital herpes, lesions in neonate, meningitis and encephalitis,
- 2. Varicella-zoster infections in immunocompromised host,
- 3. Cytomegalovirus,
- 4. EB virus,
- 5. Hepatitis B, C and delta virus,
- 6. Respiratory viruses—influenza A, RSV, rhinoviruses, corona virus,
- 7. AIDS and HIV infection,
- 8. Lassa fever and other viral hemorrhagic fevers.

Antifungal Drugs

Fungal infections may take the form of superficial or deep systemic infections. With the increase in number of immunocompromised individuals as a result of disease or its treatment, systemic fungal infections have assumed more serious proportions. Several drugs are available for their treatment.

Refer Table 5.11.

Systemic Antifungal Drugs

Several groups of drugs have antifungal properties. These include:

- 1. Antibiotics, e.g: amphotericin B, nystatin, hamacin, griseofulvin.
- 2. Antimetabolites, e.g: flucytosine which impairs synthesis of fungal DNA.
- 3. Azoles, e.g: clotrimazole, econazole, miconazole, ketoconazole, fluconazole.
Voriconazole: This is a broad spectrum triazole compound active against aspergillus species. Dose is 4-6 mg/ kg bw IV bd for 7 days followed by 200 mg oral bd for maintenance.
Compared to amphoterecin B the results are superior.
- 4. Other topical agents, e.g: tolnaftate, terbinafine.

TABLE 5.11		
Antifungal drugs		
Drug	Dose	Main toxicity
Amphotericin B	0.5 mg/kg/day intravenous infusion daily or 0.8-1 mg/kg intravenous infusion in 5% glucose over 4-6 h	Phlebitis, vomiting, nephrotoxicity, anaphylaxis, hypomagnesemia, hypokalemia
Flucytosine	150 mg/kg/day in 4 divided doses orally for 6 weeks 200 mg/kg IV infusion daily	Nausea, vomiting, leukopenia, thrombocytopenia, hepatic dysfunction
Griseofulvin	125-250 mg qid oral with meals for 2 weeks-1 year	Photosensitivity, urticaria, gastrointestinal disturbance, hepatotoxicity
Itraconazole	100-200 mg oral/day	"
Ketoconazole	200-400 mg orally daily	Rashes, hepatotoxicity, gynecomastia
Miconazole	Oral gel 125-250 mg 6 h Parenteral intravenous 8 h; intrathecal 20 mg; topical 2% cream or 100 mg pessary	Mild local reaction, anaphylaxis, nephrotoxicity, hyponatremia, hyperlipidemia, acute psychosis
Fluconazole	50-200 mg/day oral or 200-400 mg/IV day	"
Voriconazole	4-6 mg/kg bw IV bd oral 200 mg bd	
Nystatin	Oral 50,000 U 6 h; topical 10,000 U/g ointment or vaginal tablet	Rash, lymphadenopathy, parotitis, lacrimation, dermatitis
Clotrimazole	1% cream or 100 mg vaginal tablet for 6 days	Mild local effects
Econazole	1% cream or powder	Nil
Miconazole		
Terbinafine	Oral 250 mg daily Cream for local use 10 mg/g	

Most important among them are amphotericin B and the azole drugs.

Mechanism of action: Antifungal drugs, especially the azoles are targeted against ergosterol which is the main sterol in the fungal cell membrane. The synthesis of ergosterol is inhibited. Ergosterol is required for the membrane integrity and growth of fungi. Respiration of the fungi is also inhibited in body tissues.

Spectrum of Activity

Amphotericin B: This is active against cryptococci, aspergillus, histoplasma, coccidioides, blastomyces and Candida. This drug is indicated in systemic infections by these fungi. The drug is contraindicated in renal failure.

Liposomal formulations are available. These permit higher dosage. Toxicity is less-but cost is higher.

Azoles: They are active against most of the organisms that cause systemic and deep-seated fungal infections. The sensitive spectrum includes:

Cryptococcus neoformans,
Candida albicans,
Coccidioides immitis,
Histoplasma capsulatum,
Blastomyces dermatitidis (miconazole is not effective against this organism),
Paracoccidioides brasiliensis, and
Sporothrix schenckii.

Voriconazole is active against aspergillus species.

Action against *Candida* and related yeasts and *Torulopsis glabrata* is weaker.

Ketoconazole inhibits cytochrome p-450 enzyme which is necessary for adrenal and gonadal steroids synthesis, thereby leading to inhibition of these glands in experimental animals, though this action is very weak.

Terbinafine is an orally and topically effective fungicidal agent. Its spectrum of activity includes mainly dermatophytes, and to a lesser extent, candida and pityriasis ovale. The drug is lipophilic and keratinophilic. Adult dose is 250 mg orally daily given for periods varying from 2-6 weeks depending upon the indication.

Echinocandins

Over 50% of candida species isolated from blood stream is formed by *Candida albicans*. Echinocandins are a new class of antifungal agents. They inhibit the cell wall synthesis of candida species. Candida species which are resistant to azoles may be susceptible to echinocandins. Drugs in this class include

Capsofungin (candide Merck) dose 70 mg IV 1st day thereafter 50 mg IV daily.

Micafungin (mycanine- Funguard, Fijisawa) dose 100 mg IV/daily.

Anidulafungin (Eraxis, Pfizer)

dose 200 mg IV initially, followed by 100 mg IV daily.

These drugs are not absorbed orally in effective doses. Adverse side effects include histamine like reactions, thrombophlebitis. These drugs are expensive. The dose for 20 days costs \$ 7000-8000. These drugs should be considered in candida bacteremia not susceptible to amphotericin B or fluconazole.

Further reading: J.E Bennet. Echinocandins for candidemia in adults without neutropenia N. Eng JI. Med. 2006. 355. 1154-1159.

Treatment of Specific Fungal Infections

Systemic candidiasis: Amphotericin B is the drug of choice. Combination of amphotericin B with flucytosine may be synergistic. Fluconazole given orally is almost as effective as amphotericin B.

Cryptococcosis: For cryptococcal meningitis, the conventional treatment is to give amphotericin B. Fluconazole is an attractive alternative, since it penetrates into CSF. Both the drugs are equally effective in cryptococcal meningitis complicating AIDS. Due to the chance of recurrence such patients should receive life-long maintenance therapy. A common regimen is to give amphotericin B in a dose of 1 mg/kg IV once a week and 200 mg fluconazole orally once everyday.

Endemic mycosis: Blastomycosis, coccidioidomycosis and histoplasmosis. Amphotericin B is very effective. Azole drugs are effective alternatives. Itraconazole is the drug of choice due to ease of administration and effectiveness, in these infections.

Invasive aspergillosis: Amphotericin B, itraconazole, echinocandins are effective.

Antifungal prophylaxis: This may become necessary under special situations like neutropenia, organ transplantation and others. The orally administered antifungal drugs are being tried for this purpose.

Antifungal drugs used for superficial mycoses: Superficial mycoses are treated generally by surface applications of the drug. These are described in Chapter 204.

Drug Resistance of Microbes

Failure to attain optimum response to a drug may be:

1. Due to wrong diagnosis of the disease and choice of the antimicrobial agent.
2. Inadequate dose and inappropriate route of administration.
3. Impotency of the drug due to several factors.
4. Resistance developed by the microbes against the therapeutic agent.

Drug resistance is a major problem encountered in present day clinical practice and at present several microbes are highly resistant to drugs which were very effective, when

they were introduced. Though some degree of development of resistance is an inescapable biological process evolved by the microbes, a great deal of this problem has been brought about by the widespread and often inappropriate use of the drug over prolonged periods.

The magnitude of drug resistance is given in table:

Staph aureus—80% of strains resistant to betalactam antibiotics

N.gonococci—more than 50% resistant to penicillin

S. typhi—more than 50% resistant to chloramphenicol

S. shigae—more than 80% resistant to tetracyclines

P. falciparum—more than 50% resistant to chloroquine.

Microorganisms develop drug resistance by several mechanisms. Important ones include:

1. Development of alternate metabolic pathways by enzymatic process. e.g. *Staph aureus*.
2. Mechanisms which inactivate the antimicrobial drug. e.g. beta lactamase.

The resistance developed in the microbe may be due to mutation of the microbial genome or acquisition of resistant genetic material from another organism. Four processes are important.

1. Transformation—The DNA of one organism is released during bacterial lysis and this is acquired by another.
2. Transduction—Gene transfer occurs between two organisms through the medium of bacteriophage.
3. Conjugation—Two organisms come close together and develop a bridge between them. Through this bridge genetic material is exchanged.
4. Plasmids—These are extra-chromosomal double stranded DNA occurring in circular form. These can replicate spontaneously. Gram negative bacteria contain plasmids. In gram-negative bacteria plasmids can be transmitted by conjugation between bacteria, whereas in gram+ve bacteria this does not happen.

Superinfection occurs when resistant strains proliferate and overgrow.

Other causes for resistance include.

- a. Absence of the target of action of the antimicrobial drug on the organism, e.g. chlamydia which lack cell wall are resistant to penicillin which acts on the cell wall.
- b. Inaccessibility of the drug to the target of action, e.g. penicillin cannot penetrate the outer membrane of gram-bacilli and reach the peptidoglycans, to exert its action.
- c. Efflux pumps develop, which remove the drug from the microbe e.g. gram -ve bacilli resist the action of tetracyclines.
- d. Modification of the target to resist drug action, e.g. resistance to quinolones is brought about by the point

mutation in DNA gyrase which prevents the binding of the drug to the target.

It is absolutely essential for the doctor to know about the prevalence of resistance in his area. Simple and most effective methods to prevent drug resistance are:

1. Use the antibiotic only if definitely indicated, thereby reducing widespread and unnecessary use.
2. Use the full dose at the recommended intervals and route for the full period, so that relatively drug resistant mutants are not left behind to proliferate.
3. Whenever possible, try to get the drug sensitivity of the microbes before launching therapy. Avoid unduly prolonged use of the same drug, unless definitely indicated.
4. Wherever necessary, use synergistic combination of antibiotics which will also prevent the chance for developing drug resistance.

At present several newer antimicrobial agents are being used as the first line drugs on an empirical basis to treat possibly resistant infections, e.g. ciprofloxacin for *S. typhi* infection.

The Compromised Host

A compromised host is defined as a patient with a defect in the normal defence mechanisms, which makes him vulnerable to infection. He is not only liable to get severe or recurrent infections with the usual pathogens, but also liable to attack by "opportunistic" microbes which otherwise have minimal pathogenic potential. Particular infections are common in each of the live categories of defects in the normal immune and inflammatory response.

i. **B-cell defect:** *Str. pneumoniae*, *Staph. aureus*, *N. meningitidis*, *H. influenzae*, *E. coli*, *Giardia lamblia*.

ii. **T-cell defect:** *Listeria monocytogenes*, *Mycobacterium sp*, *Candida sp*, *Aspergillus sp*, *Cryptococcus neoformans*, cytomegalovirus (CMV), herpes simplex, herpes zoster.

iii. **Combined B- and T-cell defect:** Combination of (i) and (ii).

iv. **Neutrophil defects:** This includes, neutropenias, defects of adhesion, defects in signalling, defects of intracellular killing and defects in the formation of cytoplasmic granules—gram negative bacilli, candida, *Staph. aureus*, *Streptococcus pyogenes*.

v. **Complement defects:** *Staph. aureus*, *Str. pneumoniae*, *Pseudomonas sp*, *Proteus sp*, *Neisseria sp*, *Salmonella sp*.

vi. Present day chemotherapy for cancer with anti-cancer drugs and several immune mediated diseases with immunosuppressants, monoclonal antibodies and others lead to severe immunodeficiency and susceptibility to opportunistic infections. They also increase the risk of development of secondary

neoplasms such as lymphomas. Infection with human immunodeficiency virus (HIV) leads to gradual depletion of CD4 T-lymphocytes and profound immunodeficiency when the patient develops acquired immunodeficiency syndrome-AIDS. Several opportunistic infections and specific neoplasms like Kaposi's sarcoma and lymphomas may develop.

In addition to systemic chemotherapy, an alteration or breach in the skin or mucosal defence barriers that permit micrograms to cause a local or systemic infection also makes the patient immunocompromised, e.g. burns, indwelling catheters, intravenous lines and others.

The type of immunosuppression and the duration of immunodeficiency partly determine the type of nosocomial or superinfection they acquire. Among the acquired causes of immunocompromise, cancer chemotherapy, use of corticosteroids and immunosuppressants, organ transplantations (both solid organ and bone marrow) splenectomy and AIDS from the major bulk.

Fever in Immunocompromised Host

At times fever may be the principal or even the only manifestation in the immunocompromised patient. The pattern of fever in such patients is nonspecific despite different pathogenic agents. In severely immunocompromised state fever may even be absent. Fever is the result of the release of proinflammatory cytokines, such as interleukins 1-alpha, 1-beta, 4,6, and tumour necrosis factor. Endogenous pyrogens are known to arise from polymorphonuclear leukocytes. These are also produced by macrophages, lymphocytes, fibroblasts, epithelial cells, and endothelial cells, as a consequence of infection or inflammation. Even in severe neutropenia fever may occur, the pyrogens arising from alternate sources.

Immunosuppressed patients rapidly deteriorate and die if infection is allowed to establish. Therefore empirical antimicrobial therapy may have to be started depending on the clinical state. In general neutrophil counts below 500/cmm predispose the patient to life-threatening infections. The clinical signs of infections may be minimal and therefore, misleading. Presence of multiple factors such as breaches in the epithelium, neutropenia, reduction in CD4+ lymphocytes and concurrent cytotoxic or immunosuppressant drugs worsen the condition. Neutropenia occurring after cytotoxic chemotherapy is much more dangerous compared to neutropenia occurring in aplastic anemia or following viral infection. Prolongation of neutropenia beyond 10 days adds to the risk of infection.

Severe depression of CD4 cell counts also predispose to infection. Reduction of CD4 cells to < 1500/cmm in the first year of life, < 750/cmm in children between 2 and 6 years of age and < 200/cmm in children above

6 years is associated with risk of life-threatening infection with *Pneumocystis carinii*, *Toxoplasma gondii* and cytomegalovirus. Patients with AIDS are susceptible to *tuberculosis* irrespective of the CD4 counts, whereas *M.avium complex* affects those with CD4 count < 50/cmm. The infective agents affecting the immunocompromised host vary widely. Virtually all organisms including avirulent ones can become pathogenic.

Acute infections are commonly due to *staphylococci*, *Ps. aeruginosa*, *E.coli* and *klebsiella*. Infections lower the immunity further. Infections such as *respiratory syncytial virus*, *adenovirus*, *parainfluenza virus* and *cytomegalovirus* are common. Multiple infections by bacteria, fungi, viruses and protozoa may occur. Fungal infection by *Pneumocystis carinii*, *cryptococcus*, *aspergillus*, *candida* and *mucor* are common. Protozoal infections include *toxoplasmosis*, *amebiasis* *cryptosporidiosis* and others.

Patients who had splenectomy or *autosplenectomy* in sickle cell disease are susceptible to develop infection by capsulated organisms such as *pneumococcus*, *H. influenzae* or *N. meningitidis*.

Management: Fever and infection in the immunocompromised host are managed based upon the nature of the hosts disability such as neutropenia, defective cellular immunity, or mucosal disruption. The guiding principle has been to treat severely immunocompromised febrile patients empirically for the major pathogens to which they are susceptible. Broad spectrum antibiotic therapy is given with a view to cover gram-positive and gram-negative aerobic organisms. Combination antibiotic therapy or monotherapy with third generation cephalosporins or carbapenams is given.

Rational Use of Antibiotics

Selection of Antibiotics

The drug has to be tailored to the need of the individual patient, site of infection and organism causing the infection. The following points are important:

1. Efficacy – to be given top priority.
2. Cost – must be affordable to the patient
3. Toxicity – potentially toxic drugs like aminoglycosides, chloramphenicol and others are to be used only when definitely indicated.
4. Availability.
5. Least disturbance to normal flora whenever possible.
6. Prevent development of drug resistance and super infections.
7. As far as possible try to get culture and sensitivity results to select the appropriate antibiotic. However, in special situations the laboratory results should not be the only criteria for deciding the treatment, clinical judgment may also have to play its role. If the

specimens are obtained from closed sites that are normally sterile, e.g. CSF, blood and pleural, peritoneal and joint fluids, isolation of a microorganism is definitely pathological. Isolation of a pathogen from areas such as skin, mucosa and the respiratory, alimentary and lower genito-urinary tract should be interpreted on the basis of the clinical picture as well.

Overuse of Antibiotics – is common in the following situations

1. Higher specialities – all branches
2. General specialists
3. General practitioners
4. Quacks
5. Chemists who dispense ‘over the counter drugs
6. Patients who resort to self medication

Misuse of Antibiotics

1. Use without evidence of bacterial infection.
2. Prophylactic antibiotics without indication.
3. Combination of drugs when single agent is sufficient.
4. Use of unscientific combinations.
5. Use of parenteral agents when oral medication is sufficient.
6. Use of expensive and newer drug - when simple and cheaper agents are equally effective.
7. Improper selection of antibiotics.
8. Duration and dose - not conforming to the standard recommendation.
9. Using single drugs when combinations have to be used e.g. Tuberculosis.

Overuse and misuse of antibiotics are commonly seen in the treatment of fever, upper respiratory tract infections, viral infections, poisonings, asthma, chronic respiratory diseases, amebic liver abscess, indwelling urinary catheters and the like.

Antibiotics are employed empirically without evidence of bacterial infection.

More than 75% of antibiotic prescriptions are without indication.

1. *Fever* - Short febrile illness is most commonly produced by self-limiting viral infections with no indication for antibiotics, but extensively used.
2. *Upper Respiratory Tract Infections (URTI)* – Almost always they are viral in etiology and there is no role for the routine use of antibiotics. The common adage “*If common colds are left alone they clear over the course of a week, whereas if treated vigorously they disappear within 7 days*” holds true even now.
3. *Influenza* - Routine antibacterial drugs are not indicated, but they have to be used in selected patients with severe COPD or heart disease.
4. *Poisoning* – Routine use of prophylactic antibiotics is not recommended, but extensively overused.

Appropriate antibacterial drugs are indicated only in selective situations.

5. *Asthma* – Usually the precipitating factor is viral infection. Para influenza and RSV in young children and rhinovirus and influenza virus in older children and adults. Bacterial infection may supervene and then the sputum becomes purulent. Rarely yellow sputum may be due to the presence of eosinophils even without secondary infection. Therefore the routine use of antibiotics is not indicated.
6. *Indwelling catheter* – Prophylactic antibiotic during the first 4 or 5 days reduces the risk of infection. Beyond 5 days there is no benefit, and hence antibiotic prophylaxis fails when the catheter is kept for longer periods. Infections have to be treated when they occur.

Prophylactic Antibiotics

Indications for Chemoprophylaxis

1. When there is a high risk of infection, e.g. wound infection after colonic surgery.
2. Risk is low, but consequences are severe if infection results e.g. insertion of prosthetic heart valves and prosthetic joints.

Observe the following principles

1. Risk of severe infection should be greater than the adverse effects of antimicrobials.
2. Antibacterials should be given only for the minimum period necessary to prevent infections.
3. The drug should be given before the onset of risk such as before starting surgery or as soon as possible after exposure to infection.

Common clinical situations requiring prophylactic antibiotics

1. Rheumatic fever
2. Infective endocarditis
3. Meningococcal meningitis
4. Recurrent cystitis
5. Surgical prophylaxis in selected situations
6. Recurrent cellulitis in conjunction with lymphedema
7. Severely neutropenic patients

Improper Selection of Antibiotics

This leads to poor clinical response, increased cost of treatment and adverse side effects.

Use of parenteral route when oral administration is effective

The route of administration should be preferably oral if the drug is suitable for oral use and the patient can tolerate oral medication. Since parenteral administration ensures

quicker and more reliable bioavailability, parenteral route should be preferred in severe infections such as meningitis, infective endocarditis or severe pneumonias. Intravenous route is preferable in patients with hypotension and circulatory depression. In those in whom repeated large doses are required for prolonged periods, an intravenous line or central venous line is the ideal route. When the patient improves, change to the oral route. Parenteral therapy is inherently more expensive, inconvenient and predisposing to the risk of nosocomial infection. Drugs which are effective when administered orally as single daily doses have better patient acceptance and compliance.

Use of combination drugs when single agent is effective, and using unscientific combinations

Infections are to be treated with single drugs if they are definitely effective. Combinations are definitely indicated in some situations.

- a. *When antimicrobial synergy is clearly advantageous:*
e.g. *Pseudomonas aeruginosa* – aminoglycoside + beta lactam (ceftazidime/piperacillin) more effective.
Enterococci – ampicillin + aminoglycoside like (gentamicin)
Brucellosis – aminoglycoside + doxycycline or doxycycline + rifampicin
Mycobacteria – Combination of 3 or more anti tuberculosis drugs – for preventing the development of drug resistance.
- b. *To broaden the spectrum of antibacterial action*
e.g. – *peritonitis following perforation* – Mixed infection is common. This may require a combination of β lactam antibiotics + aminoglycoside + metronidazole
- c. *Neutropenic patients with sepsis*

Combination therapy may lead to increased cost, change in microbial ecology and chances of superinfection.

Combination of amoxycillin/ampicillin with cloxacillin is marketed by many pharmaceuticals and extensively prescribed. Such fixed drug combination should be avoided as far as possible.

Use of costly and newer agents when cheaper conventional agents are effective

When many drugs with equal efficacy and toxicity are available, one should choose the least expensive drug. When an expensive drug is more effective and absolutely indicated, its use is justified. Newer agents generally cost more and they are promoted more vigorously. Older agents like penicillin G, amoxycillin, co-trimoxazole and doxycycline are relatively cheap, but quite effective against several organisms.

Duration of Therapy

Therapy has to be continued until cure is achieved as assessed by clinical and laboratory parameters. Most acute infections require treatment for 5-10 days. The key factors include – type of infection, location of infection and immunocompetence of the patient. The duration may vary from single oral dose for gonococcal cervicitis to 4-6 weeks of IV therapy for infective endocarditis. Most acute infections of the respiratory tract, ear, paranasal sinuses and GIT should be treated for 5-10 days.

For streptococcal pharyngitis/tonsillitis, 10 days treatment is indicated to ensure eradication.

Prolonged therapy is not only more expensive, it can also lead to adverse side effects and emergence of bacterial resistance.

Consequences of overuse and misuse

1. Emergence of drug resistance
2. Increased cost of treatment
3. Unwanted side effects
4. Disturbance of the normal flora and risk of superinfection.

6

Therapeutics of
Glucocorticoids

1

S. Bhasi

Chapter Summary

General Considerations 53

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Inhibition of Hypothalamo-Pituitary Adrenal Axis 55

General Considerations

The initial therapeutic use of glucocorticoids in 1948 resulted in dramatic clinical improvement in a patient with severe rheumatoid arthritis. Today, glucocorticoids are extensively used in therapeutics to manage a wide variety of conditions. Presently available corticosteroid preparations are all synthetic.

Cortisol (hydrocortisone) is the natural glucocorticoid produced from adrenal cortex. The normal rate of endogenous cortisol production as evidenced by recent studies is only 8 to 15 mg/day. ACTH controls normal secretion. In healthy unstressed persons normal secretion shows a diurnal pattern – plasma cortisol is highest in the early morning hours and lowest in the evening. Less than 10% is in the free form which is biologically active. In stressful situations like infection, trauma, burns, surgery and others, cortisol secretion is increased 2 to 6 times in proportion to the severity of the stress. The diurnal variation is also lost.

Several formulations of corticosteroids are available for therapeutic use. They differ in their glucocorticoid and mineralocorticoid activities. In addition to cortisone and hydrocortisone other derivatives include prednisolone, methyl prednisolone, betamethasone, dexamethasone and triamcinolone which have increased glucocorticoid activity with less of mineralocorticoid activity. They have the following properties:

1. Higher affinity for glucocorticoid receptors
2. Less binding with cortisol binding globulin and therefore more of the drug remains in the free form
3. Higher potency

4. Longer duration of action and
5. Less salt- retaining property.

Comparison of commonly used Glucocorticoids

Compound	Anti-inflam- matory potency	Mineralo- corticoid potency	Biological half-life (Hours)	Equi- potent dose (mg)
Short acting				
Cortisol	1	1	8-12	20
Intermediate acting				
Prednisolone	4	0.25	12-36	5
Methyl- Prednisolone	5	< 0.01	12-36	4
Triamcinolone	5	< 0.01	12-36	4
Long acting				
Betamethasone	25	< 0.01	36-72	0.75
Dexamethasone	25	< 0.01	36-72	0.75

Therapeutic Effects

1. Anti-inflammatory effect. Glucocorticoid receptors suppress inflammatory activity
2. Immunosuppressive action
3. Membrane stabilizing effect
4. Modulates vascular responsiveness and permeability
5. Surfactant production in the lung.

Common Indications**1. Endocrine disorders - Physiological replacement**

A. *Hypoadrenal-corticism and hypopituitarism.* Hydrocortisone is ideal – 15 to 20 mg/day. Prednisolone is the convenient alternative - dose 5 mg/day – $\frac{2}{3}$ of the dose is given in the morning and $\frac{1}{3}$ in the evening. Doubling the dose is needed during concurrent minor acute illnesses. Further increase is required in severe stressful situations.

B. *Non-endocrine indications* – Steroids are given in pharmacological doses which are larger.

1. *Allergic diseases* – Anaphylactic shock, atopic dermatitis, asthma, drug reaction, urticaria and others.

2. *Autoimmune diseases*—Systemic lupus erythematosus, rheumatoid arthritis, systemic vasculitis, temporal arteritis, myasthenia gravis, mixed connective tissue disease.
3. *Hematological diseases*—Autoimmune hemolytic anemia, immune thrombocytopenia, leukemia, lymphoma, multiple myeloma.
2. *Gastrointestinal disorders* – Ulcerative Colitis Crohn's disease, autoimmune chronic active hepatitis
3. *Ocular conditions* – Acute uveitis, choroiditis, optic neuritis
4. *Respiratory diseases* – Asthma, interstitial lung disease, pleural effusion, chronic obstructive pulmonary disease
5. *Prevention of graft rejection* in organ transplantation
6. *Metabolic homeostasis* – Acute hypercalcemia
7. *Miscellaneous conditions* – Shock, cerebral edema, thyroid storm, myxedema coma and several others.

Unique Advantages of Glucocorticoids

In several life-threatening and serious diseases such as severe asthma, fulminant ulcerative colitis and systemic vasculitis, the relief brought about by glucocorticoids is dramatic. Maintenance dose helps to prevent exacerbation. Glucocorticoids produce mild euphoria and offers better quality of life. They are relatively cheap, widely available and often available even without prescription. Due to all these advantages glucocorticoids have been used extensively for prolonged periods, often empirically, even as self medication.

Glucocorticoids have several adverse effects. Therefore it is necessary to assess the benefits and adverse effects before starting therapy. In medical emergencies, often high doses may have to be administered for short periods even in the presence of minor contraindications, fully aware of the risk, e.g. severe asthma in diabetic patients. However they should never be administered for more than a few days in such patients without full evaluation and review.

ADVERSE SIDE EFFECTS

1. Iatrogenic Cushing's syndrome.
2. Growth retardation in children.
3. Flaring up of infection – especially tuberculosis and fungal infections.
4. Unmasking of latent diabetes and worsening of existing diabetes.
5. Osteoporosis – especially in elderly and post menopausal women, leading to compression fractures.
6. Hypertension.

7. Increased appetite, polyphagia, obesity, dyslipidemia.
8. Delayed wound healing, dehiscence of scars, striae over the skin.
9. Acid Peptic disease –hyperacidity, ulceration of the upper GI tract, exacerbation of peptic ulcer, gastroduodenal hemorrhage and perforation of the upper GI tract.
10. Ocular problems – cataract, glaucoma.
11. Myopathy – mainly proximal muscles.

Timing of Side Effect

Insomnia, euphoria, glucose intolerance and increased appetite may develop within hours. Psychotic symptoms may occur within hours or may develop later. Osteoporosis takes weeks to months to develop.

MANAGEMENT OF GLUCOCORTICOID THERAPY

Evaluation of Patient Prior to Glucocorticoid Therapy

Look for the following

1. Presence of TB or other chronic infections.
2. Evidence of glucose intolerance or frank diabetes mellitus.
3. Evidence of osteoporosis.
4. History of peptic ulcer, esophagitis, or gastritis.
5. Evidence of hypertension or cardiovascular disease
6. History of psychiatric disorder.

Management of patients on steroid therapy

- Diet with calorie restriction to avoid weight gain, high protein, low sodium and rich in potassium.
- Regular exercise to prevent muscle wasting and osteoporosis.
- Patients with acid peptic disease to be given H₂ receptor antagonists or proton pump inhibitors and antacids.
- Growing children should have regular monitoring of growth.
- Investigate for detecting diabetes or impaired glucose intolerance at monthly intervals. If these develop, consider withdrawal or at least substantial reduction of dose of the glucocorticoid. If the glucose does not come to normal start anti-diabetic therapy. If the glucocorticoid cannot be withdrawn, give it with concurrent anti-diabetic therapy – preferably insulin.
- Supplement Vitamin D 400 IU and calcium salts (gluconate, carbonate and others) 500 mg od or bd orally.

Routes of Administration

1. **Oral:** This is the most commonly used route for systemic effects.
Prednisolone is the commonly used drug, though all the others can be employed.
2. **Parenteral:** IM/IV: Acute severe asthma, craniospinal trauma, brain tumour with cerebral edema, transplant rejection, fulminant presentation of autoimmune diseases, septic shock with corticosteroid deficiency, acute adrenal crisis.
3. **Inhalation:** For relief of life-threatening asthma and for its long term prophylaxis.
4. **Intralesional:** Tenosynovitis, enthesitis, keloids, local painful inflammatory lesions and others.
5. **Intra-articular:** Inflammatory joint disease such as oligoarticular rheumatoid arthritis in 1-2 joints
6. **Topical to skin:** Many steroid responsive dermatosis
7. **Retention enema and foam:** ulcerative colitis.
8. **Ophthalmic indications:** Topical application in the form of eye drops or ointment is indicated for conditions like allergic conjunctivitis, and other inflammatory conditions.

Topical preparations of corticosteroids, especially betamethasone and its analogues may be absorbed from normal and inflamed skin, joints and the large intestine to produce systemic adverse effects if continued for long. Aerosol preparations also can give rise to systemic drug effects if used regularly over several months.

INHIBITION OF HYPOTHALAMO-PITUITARY ADRENAL AXIS

Glucocorticoids give rise to suppression of the hypothalamo-pituitary-adrenal axis (HPA) leading to reduction in corticotrophin releasing hormone (CRH) and adrenocorticotrophic hormone (ACTH). The degree of suppression depends on duration of treatment and the dose.

1. When used for long periods HPA suppression occurs at all doses. Pharmacological doses produce more severe suppression. There is individual variation in the suppressibility. Short courses may not produce marked suppression, but if given for more than three weeks the HPA axis is impaired.
2. Timing of dosing influences the suppression. Doses given in the morning are less harmful compared to doses in the afternoon. Alternate day drug administration is clinically effective, at the same time only less suppressive of the HPA axis.

Steroid withdrawal following long-term therapy. The following problems occur:

1. Worsening of underlying disease

2. Slow recovery of HPA axis
3. Secondary adrenal insufficiency

In the early stages of drug withdrawal, though adrenal cortical function may recover to be adequate at ordinary times, it may fail during stress. Complete recovery may take 6 to 9 months or even more. Many patients may remain steroid dependent.

Steroid Withdrawal Syndrome: This develops rarely in persons receiving prolonged glucocorticoid therapy, on rapid withdrawal of the drug. It is characterized by lethargy, anorexia, malaise, weight loss, arthralgia, myalgia, headache and sometimes fever. Since aldosterone secretion is not ACTH dependant, its level is maintained. Therefore blood pressure level and electrolytes remain normal.

Protocol for corticosteroid withdrawal: These should be followed for all cases where steroid therapy is given in doses above the equivalent of 20 mg of prednisolone daily for 2 weeks or more

- Step 1:** Taper steroid dose gradually to physiological level (i.e.) 5 mg/day
- Step 2:** Change to alternate day therapy for prednisolone and single morning dose for cortisone
- Step 3:** Measure serum cortisol level at 8 AM. Procedure to be followed is given below:

- a. Cortisol level below 3 mcg / d L—This indicates adrenal cortical insufficiency. Continue steroid at lower dose and re-test later in 2-6 weeks
- b. Cortisol level 3-20 mcg/d L— Reduce dose of steroid, re-test later.
- c. Cortisol level above 20 mcg/d L—HPA axis has recovered. Steroid can be withdrawn safely.

Stimulation of adrenal cortex by giving ACTH (tetracosactin depot) 1 mg. IM injection daily, prior to, during and following the period of glucocorticoid withdrawal helps to hasten recovery.

In patients who have been on long-term corticosteroid therapy recovery of the adrenal may take several months.

Glucocorticoids are life saving drugs in many serious clinical conditions even though they possess mild and severe, even life threatening, adverse side effects. On no account the fear of side effects should result in withholding in the drug is essential indications.

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Principles of Oncology

K.V. Krishna Das

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General Considerations

The International Union Against Cancer has defined cancer as a disturbance of growth characterized primarily by excessive proliferation of cells without apparent relation to the physiological demands of the organs involved. Oncology deals with the prevention, diagnosis, treatment, and research aspects of cancer. Cancer is a leading cause of death all over the world, 7 million deaths occurred during 2001. Globally 35% of these are attributable to 9 potentially modifiable factors. 1/3 of cancer deaths occur in affluent, and 2/3, in developing countries. Among these 2/3 are men and 1/3 are women. The modifiable risk factors include obesity, low consumption of fresh vegetables and fruits, physical inactivity, tobacco smoking, alcoholism, unsafe sex practices, urban air pollution, indoor air pollution by burning bio-fuels and sharing of contaminated needles.

As the life expectancy increases, the incidence of cancer also increases. Table 7.1 shows the frequency of the common malignant neoplasms in India compared to the West.

The pattern of cancer has changed over the past decade in many parts of India. Figures of the hospital based tumour registry from Regional Cancer Centre, Trivandrum 1996 reveal the following. Oral cancers related to tobacco chewing habit still constitute the single largest group. Among the other leading cancers the frequency is given in Table 7.2.

TABLE 7.1

Comparison of incidence (age-standardised incidence rate per 100,000 persons) of common malignant neoplasms in India and the developed countries. (from Cancer Incidence in Five Continents, Vol. 7, International Agency in Cancer, 1997)

<i>In India*</i>		<i>In developed countries**</i>	
Cancer in male population			
Oral cavity	10.8	Prostate	79.1
Lung	10.6	Lung	62.1
Lymphoma	7.3	Colon	30.4
Cancers in female population			
Breast	18.8	Breast	93.3
Cervix	15.9	Lung	35.2
Oral cavity	5.9	Colon	21.6

*Regional Cancer Center, Trivandrum (data as on 1992)
**Connecticut, USA (data as on 1997)

TABLE 7.2

Frequency of cancer in different sites (Numbers denote the percentage out of total cancers) (Data as on 1996, from Hospital Cancer Registry, Regional Cancer Centre, Trivandrum, 1999)

Males		Females	
Oral cavity	16.3%	Breast	24.8%
Lung	12.6%	Uterine cervix	16.3%
Lymphoma	6.8%	Oral cavity	9.5%
Pharynx	6.2%	Thyroid	9.0%
Esophagus	6.0%	Ovary	7.0%
Leukemia	5.9%	Leukemia	4.2%
Larynx	5.8%	Lymphoma	3.5%
Stomach	3.8%	Brain	2.1%
Liver	2.7%	Esophagus	1.9%
Brain	2.6%	Body uterus	1.8%

This clearly shows that as the health conditions improve there is a change in the pattern of malignancy as well. Moreover, with improved facilities for early cancer detection and the mass education programmes launched by the Regional Cancer Centre, Trivandrum, a considerably higher proportion of cancer patients are seeking treatment at an earlier stage when chance for cure is much higher.

Etiology: Several factors operate to bring about carcinogenesis. These are genetic, hormonal, metabolic, physical, chemical and other environmental factors. During the course of cell division malignant mutants may be formed which proliferate to form tumours. Carcinogens increase the rate of mutation and thereby the possibility of malignancy is also increased. Cancer is more frequent in old age, since the occurrence of aberrant mutation is increased. Many mutants are destroyed by immunological mechanisms of the body.

Chemical carcinogens: These act cumulatively to bring about carcinogenesis. Food additives, coloring agents, aflatoxins and n-nitroso compounds are common carcinogens. The incidence of lung cancer is about 11 times more in cigarette smokers compared with non-smokers. Cancer may be produced: (a) at the site of exposure to the carcinogen, e.g., skin cancers in tar workers and buccal cancer in tobacco chewers; (b) at the site of metabolism, e.g. liver cancer in aflatoxicosis; or (c) at the site of elimination, e.g., bladder cancer in workers using aromatic amines.

Diet: Some dietary factors or aspects of life-styles are significantly associated with certain malignancies. Thus salt-cured and smoked foods are related with cancer of esophagus and stomach; high fat diet with cancer of breast and colon; alcohol with cancer of liver and esophagus; tobacco with cancer of lung and oral cavity. Vegetable fibres in the diet increase the intestinal motility and so reduce the incidence of colon cancers. Fresh vegetables, beans and fruits in the diet will reduce cancer incidence, especially of gastrointestinal tract cancers. Some of the important etiological agents are shown in Table 7.3.

Initiation and progression: It is postulated that a carcinogen produces a mutation, but it remains dormant unless acted upon by a promoter. Benzopyrine or croton oil applied alone will not produce skin cancer. But when benzpyrine is followed by croton oil, tumour develops. The benzpyrine acts as a carcinogen to produce a mutation. But the promoter (croton oil) gives the drive for unchecked cell division, which is the characteristic feature of malignancies.

Antimutagens are substances which will inhibit with tumour promotion. Vitamin A and carotenoids are shown to reverse precancerous conditions, especially oral leukoplakia. Butylated hydroxy anisol (BHA), vitamin E and vitamin C are antioxidants, which prevent the damage made by free radicals and superoxides. Curcumin, the yellow substance in turmeric is known to prevent mutations in experimental systems.

Viruses: Several viruses have been implicated in many cancers. Epstein-Barr virus has been identified as the causative factor for Burkitt's lymphoma in African children and for nasopharyngeal carcinoma in chinese

TABLE 7.3	
Important etiological agents of cancer	
Agent	Associated cancer
<i>Physical agents</i>	
Sunlight (UV)	Skin cancers
<i>Chemical agents</i>	
Tobacco smoking	Lung, mouth, esophagus, larynx, bladder
Tobacco chewing	Oral cavity
Alcohol	Oral, esophagus, liver
Polycyclic aromatic hydrocarbons (produced during deep frying)	Liver colon
N-nitroso compounds	Stomach, esophagus, bladder, liver
Aflatoxins (Fungal contamination)	Liver
<i>Microbial agents</i>	
<i>Helicobacter pylori</i>	Stomach
<i>Schistosoma hematobium</i>	Urinary bladder
<i>Viruses</i>	
Epstein-Barr virus	Burkitt's lymphoma; nasopharyngeal carcinoma
Hepatitis B virus	Hepatocellular carcinoma
Hepatitis C virus	Hepatocellular carcinoma
HTLV-1	T cell leukemia
HPV (human papilloma)	Uterine cancer
HSV-2 (herpes simplex)	Uterine cancer
HHV-6 (human herpes)	Lymphomas
HHV-8	Kaposi's sarcoma

population. Papilloma viruses (different types) and herpes virus type 2 have been shown to be associated with carcinoma cervix, hepatitis B and C viruses with primary carcinoma of liver, herpes virus type 6 with lymphomas and herpes virus type 8 with Kaposi's sarcoma. This virus is also associated with multicentric lymphoma and multicentric Castleman's disease.

Physical agents: Ionizing radiation cause a marked increase in cancer incidence in later life. Exposure to X-rays in fetal life increases the risk of developing leukemia in later life. The risk of developing cancer in a population exposed to ionizing radiation in a dose of 1 rad/year is 40 per million annually. Indiscriminate use of diagnostic X-rays constitutes a health hazard, and has to be avoided. Chronic irritation by heat (*kangri* in Kashmir and lighted cigarettes inside the mouth in Andhra Pradesh) lead to cancer of the abdominal wall and the palate in different populations. Bilharziasis is associated with higher risk of bladder neoplasms.

Genetic factors: Many neoplasms show evidence of genetic predisposition. For example,

1. Retinoblastoma, multiple polyposis of the colon, and carcinoma breast run in families.
2. Mongolism is associated with a ten-fold increase in the risk of leukemia.

3. Blood group A is associated with a higher risk of gastric carcinoma, compared to blood group B and O.
4. Hodgkin's disease is more frequent in subjects with HLA B 18.

Breast cancer shows a strong familial predisposition. Women with BRCA1 or BRCA2 mutations have a 60-85% cumulative lifetime risk of invasive breast cancer up to 70 years of age and 15-65% cumulative life time risk of invasive ovarian cancer. Prophylactic mastectomy reduces the risk of breast cancer. Salpingo- oophorectomy reduces the risk of both breast cancer and tubo-ovarian cancer.

Colonic epithelial cancers all also increased in patients with BRCA 1 and 2 mutations.

Several chromosomal changes have been demonstrated in malignant cells. Many of them are characteristic to be of diagnostic help, while others are not. For example, Ph1 chromosome is diagnostic of chronic myeloid leukemia. When chronic myeloid leukemia transforms into the acute phase diagnostic chromosomal rearrangement occurs. Myelodysplastic syndrome is characterised by specific chromosomal patterns. Several examples of chromosomal abnormalities in cancers are known at present.

Genetic studies have yielded rich dividends in understanding the initiation and progress of cancer. These include the identification of *oncogenes*, *proto-oncogenes*, *onco-suppressor genes*, genetic changes caused by *retroviruses* and several others.

Oncogenes are altered forms of normal genes called proto-oncogenes. More than 80 human proto-oncogenes are known. For example, erb-B is located in chromosome No.7, and it produces the receptor for epidermal growth factor (EGF-R). The sis gene, located in chromosome 22 produces platelet derived growth factor (PDGF). The abl, located in chromosome No. 9 and src, in chromosome No. 20 produce proteins with tyrosine kinase activity. The protein products of proto-oncogenes have essential roles in cell growth and differentiation. But the proto-oncogenes are under the control of other regulatory genes. When proto-oncogenes are activated there will be continuous expression of the gene leading to uncontrolled cell division and malignant transformation. A proto-oncogene may be activated by the following mechanisms:

(A) **Chromosomal translocation:** In all cases of Burkitt's lymphoma, translocation of chromosome 8 to chromosome 14 takes place with consequent activation of C-myc. In Non-Hodgkin's lymphoma, translocation of chromosome 14 to 18 is very common. The breaks on chromosome 18 occur either in major break point region (MBR) or at the major cluster region (MCR), both involving the bcl-2 oncogene. The bcl-2 product suppresses programmed cell death, leading to tumour formation.

(B) **Promoter insertion:** Virus promoter genes may be integrated upstream to the oncogene so that continuous expression of the oncogene takes place.

(C) **Mutation of proto-oncogene:** The ras gene produces a protein termed p-21 (mol. wt. 21,000), which suppresses the activity of adenyl cyclase and thereby, cell division. In human bladder cancers, a mutated p-21 is demonstrable, leading to continuous activity of adenyl cyclase. In many cases particular mutations leading to the formation of oncogenes have been identified.

Oncogenes are generally coded with a combination of three small letters, e.g., myc, L-myc, N-ras, C-abl, etc., while onco-suppressor genes are coded by two capital letters, e.g., RB-1, for retinoblastoma, WT-1 for Wilms' tumour, NE-1 for neurofibromatosis.

Oncosuppressor genes present in normal cells usually prevent cancer formation. For example, when both alleles of the RB gene are deleted, retinoblastoma results. An onco-suppressor gene called p-53 produces a phosphoprotein with molecular weight 53,000. It can complex with proteins generated by other oncogenes.

Most tumours have a complete absence of p-53 while others show mutant nonfunctional p-53.

Several different mechanisms may activate oncogenes. Thus viruses, chemical carcinogens, chromosome translocation, gamma rays and spontaneous mutation may activate oncogenes to produce malignancy.

Growth factors: These are humoural factors which generally cause mitosis or differentiation to target cells. More than 100 such growth factors are described. Epidermal growth factor (EGF) produced by fibroblasts stimulates growth of epidermal and epithelial cells. Platelet derived growth factor (PDGF) produced by platelets, accelerates wound healing and stimulates growth of mesenchymal cells. Nerve growth factor (NGF) produced by salivary glands stimulates growth of sensory and sympathetic neurons. Oncogene activation leads to imbalance in such growth factors.

Apoptosis: Programmed cell death is known as apoptosis. During the normal growth, old cells are to be removed, so that new cells can replace them. Hypoxia, reactive oxygen species, chemicals, irradiation, DNA damage, immune attack, malnutrition, tumour necrosis factor, and many other signals activate the apoptotic pathway. The final effectors of this pathway are a group of enzymes known as caspases (cysteiny peptidases with aspartate specificity). They are named 1 to 14 according to their order of identification. They activate nucleases and cause DNA to be fragmented into small fragments (step ladder pattern of DNA in agar gel electrophoresis). The apoptotic cells show chromatin condensation, shrinking of the cells, and finally disintegration. In normal organs, the number of cells produced by cell division will be equal to the

number of cells undergoing apoptosis. If the regulation of apoptosis is altered the cells in that tissue accumulate leading to neoplasms. Apoptosis promoting (suicidal) genes are c-fos, P53 and Rb: they are oncosuppressor genes. On the other hand, apoptosis inhibiting genes are cancer promoting genes, e.g. Bcl-2.

Clonal origin of neoplasms: It is widely accepted that most of the tumours arise from a single clone of altered cell, the clone having the potential to multiply and form the tumour. The biological history of a tumour shows several steps of progression. In the normal individual the aberrant cells tend to be destroyed by immune mechanism. When this breaks down, cells with malignant potential survive and proliferate. Initial progression of the tumour is very slow and it takes several years for an abnormal clone to multiply and become clinically recognizable. The early changes indicating dysplasia of the cells, can be identified and treatment at this stage can lead to arrest of the neoplasm and cure in many cases.

Immunological changes: Malignant cells show different degrees of de-differentiation. Several functional genes are present which are active in fetal life, but which are repressed in later life leading to the disappearance of several fetal antigens from the surface of the adult cells.

In malignant cells, embryonal antigens reappear on the cell surface due to derepression of these genes, and these are termed onco-fetal antigens, e.g., carcino-embryonic antigen (CEA) in colon cancer and alpha-fetoprotein (AFP) in liver cancer.

TUMOUR MARKERS

Tumour markers or tumour index substances are factors released from the tumour cells; these could be detected in blood and therefore indicate the presence of the tumour. They are useful (A) For follow up of cancer and to monitor the effectiveness of the therapy (B) To detect the recurrence of the tumour (C) For prognosis; serum level of tumour marker usually indicates roughly the tumour load, which in turn indicates whether the disease is advanced or not and (D) To facilitate detection of cancer. The presence of high levels of tumour marker suggests the diagnosis, but caution is to be taken to rule out other nonmalignant conditions. The levels of tumour markers are increased in inflammatory and other conditions as well but drastic elevation is suggestive of malignancies. The following are some of the commonly employed tumour markers:

1. Alpha-fetoprotein (AFP). It is a fetal albumin. It is increased in hepatocellular carcinomas, germ cell tumours, teratocarcinoma of ovary and in pregnancy with fetal malformations of neural tube.
2. Carcino-embryonic antigen (CEA). It is increased in colorectal and other gastrointestinal tumours.

3. CA-125 (ovarian cancer antigen) is a glycoprotein and is increased in ovarian cancers of epithelial origin.
4. CA-199 is another glycoprotein seen in circulation in cancers of stomach and colon.
5. Alkaline phosphatase (ALP) level is increased in bone and liver diseases; high level of heat-labile isoenzyme (bone isoenzyme) is seen in bone secondaries.
6. Placental isoenzyme of ALP (heat stable and inhibited by phenyl alanine) is found in normal pregnancy. It is also seen in certain cases of carcinoma of lung, liver and gut and testicular seminomas, then it is called Regan isoenzyme.
7. Acid phosphatase (tartrate labile isoenzyme) is increased in prostate cancers.
8. Prostate specific antigen (PSA) is produced by secretory epithelium of prostate. It is normally secreted into seminal fluid, where it is useful to liquify the ejaculate. It is a protease, and in serum it is seen complexed with alpha-1 antitrypsin. The PSA level, especially the complexed form is increased in prostate cancers.
9. Neuron specific enolase (NSE) level is raised in nervous system tumours.
10. Beta chain of human chorionic gonadotropin (hCG) is elevated in choriocarcinoma.
11. Big ACTH is seen in pulmonary oat cell carcinomas.
12. Vasoactive intestinal polypeptide (VIP) is elevated in apudomas (amine precursor uptake decarboxylaseomas).
13. Tissue polypeptide specific antigen (TPS) measures an antigenic determinant associated with human cytokeratin. TPS level is elevated in almost all solid tumours. It is a marker of tumour cell activity, in contrast to all other markers related to tumour burden. Although non-specific with reference to the site of origin of tumour, it is very useful in assessing the efficacy of the treatment, and also for early detection of recurrence.
14. Immunoglobulin levels are increased, and are seen as a monoclonal peak in electrophoresis, in multiple myeloma and in Waldenström's macroglobulinemia.
15. Vanillyl mandelic acid (VMA), metabolite of catecholamines, is excreted in increased quantities in urine of patients with pheochromocytoma and neuroblastoma.
16. Hydroxy indole acetic acid (HIAA), metabolite of serotonin, is raised in urine of patients with carcinoid syndrome.
17. Hydroxy proline excretion in urine is elevated in bone metastasis.

Malignant cells show several biochemical abnormalities compared to normal cells. Some of them have **59**

been beneficially exploited in cancer chemotherapy, e.g., use of L-asparaginase for acute lymphatic leukemia.

Paraneoplastic Syndromes

Tumours may produce signs and symptoms distant from the tumour site of metastasis; this is referred to as paraneoplastic syndrome. This is due to the production of hormones or metabolically active factors by tumours arising from non-endocrine tissues. The substances produced by the neoplasms are analogues of the natural hormones or their precursors. Several neurological manifestations may develop, such as neuropathies, myopathies, myasthenic reaction, myositis, and brainstem encephalitis. Antibodies against neuronal proteins may be demonstrable. These lesions may precede the overt manifestations of the tumour in many cases. Some of the important paraneoplastic syndromes are listed below:

1. **Ectopic ACTH syndrome** is seen in small cell carcinoma of lung, medullary cancer of thyroid and cancer of pancreas. These malignant cells may produce ACTH, leading to Cushing's syndrome.
2. **Syndrome with inappropriate antidiuretic hormone** (SIADH), where arginine vasopressin is synthesised by the tumour cells, leading to clinical manifestations of hyponatremia. It is seen in non-small cell lung cancers, lymphomas, leukemias, and head and neck cancers.
3. **Ectopic parathyroid hormone** (PTH) is produced by thoracic and intestinal solid tumours.
4. **Oncogenous osteomalacia** is seen in calcitonin secreting malignancies, usually cancers on thyroid and mediastinum.
5. **Human placental lactogen** (HPL) is commonly elevated in bronchial cancers and thyroid cancers.
6. **Polycythemia** is occasionally noticed in hypernephroma.
7. **Acanthosis nigricans** (brown plaques in neck, axilla and flexor regions) are seen in adenocarcinomas, especially of gastrointestinal origin.
8. **Hyperpigmented palms** are seen in some cases of gastric and lung cancers.
9. **Acrokeratosis** (acral hyperkeratosis) in toes, ears and nose is seen in squamous cell carcinomas.
10. **Hypertrophic osteoarthropathy** (digital clubbing) is noted in non-small cell cancers of lung and metastatic malignancies.
11. Symptoms of **limbic and brainstem encephalitis** may occur at times in testicular tumours.

It should be remembered that many typical or atypical endocrine manifestations can develop as a result of paraneoplastic manifestations of several neoplasms. It should be the endeavour to detect such lesions if the clinical manifestations are not classic.

METASTASIS

Cell membrane of the malignant cells show qualitative and quantitative changes resulting in an increase of the negative charge on the surface. This leads to mutual repulsion of the cells and increases the tendency to disseminate. Another phenomenon noted in malignant cells is loss of contact inhibition. When two normal cells come into contact this inhibits further cell multiplication. This property is lost in malignant cells which continue to multiply and grow. The tissue in which the metastasis develop is also conditioned to favour the growth of the metastatic cells.

Tumour Kinetics

Growth of the tumour depends on the balance between cell proliferation and cell loss. Cellular proliferation depends on: (1) the proliferation coefficient, i.e., the ratio of active to resting cells, and (2) the cell cycle interval.

Cell loss depends upon: (1) cell death by apoptosis aging, lack of oxygen and nutrition; (2) abortion, i.e., incapability of the cells to multiply; (3) escape, detachment of cells from the tumour mass; and (4) specific cell destruction by immunological mechanisms. All these parameters are important in deciding "tumour doubling time" (i.e. the time taken by a tumour to exactly double its mass), which will be constant for a particular growth over a long period. The tumour doubling time in human cancer varies widely between 10 to 450 days, with a median of about 100 days. In the case of a tumour with doubling time of 100 days, the time taken for the growth to reach 1 g from the initial mutation is about 8-10 years. It naturally follows that the tumour is present in the system for a considerable period before clinical detection. The same reason can explain the development of the secondaries several years after the treatment of primary growth. Modern treatment aims at reducing the tumour growth by increasing the cell loss coefficient. When this is achieved, the patient may remain apparently normal for many years. When referring to the management of cancer, the term 'control' is more appropriate than 'cure'. Five-year survival figures are usually taken for comparing the results of different forms of treatment in several neoplasms. It should be remembered that 5-year survival is not synonymous with cure of the lesion.

Precancerous lesions: Precancerous or preinvasive lesion is a stage where individual cells are abnormal but cancer cells have not yet invaded the surrounding normal tissues. About 5-10% of such cases develop invasive tendency within a few years, e.g., leukoplakia of oral cavity, hyperkeratosis of skin, papillomas of the urinary bladder, polyps of bowel, and stage 0 cancer of cervix.

Prognosis in Cancer

(1) The most important factor determining survival is early detection. The earlier the diagnosis, the better is the

curability. Mass screening of susceptible groups of persons by Pap smear and other methods can lead to early diagnosis, (2) Prognosis is better for slow-growing tumours, (3) Well differentiated tumours have a better prognosis than undifferentiated ones, (4) If the host can effectively mount an immunological attack against cancer cells, the outcome is more favorable. Prognosis is better in neoplasms where the immunological status of the individual is not depressed. (5) For several cancers modern treatment protocols are available, which are highly effective. In such lesions early diagnosis and proper therapy are curative.

Therapy

The aim of therapy is to reduce the tumour mass within the shortest possible time and to destroy the remaining cells and prevent them from multiplying and disseminating. This ideal is possibly achieved only in the case of very few cancers but in the majority of cases this is not possible due to: (1) late diagnosis, (2) presence of secondaries early in the disease, (3) surgical risk, and (4) toxic effects of radiation and chemotherapeutic agents. Cancer has emerged as one of the curable diseases among the serious chronic diseases. Modern radiotherapy has reached a high level of effectiveness in eradicating tumours, with minimal damage to normal tissues. In the management of solid tumours, multimodal therapy, combing irradiation with chemotherapy is employed, except in the case of very early tumours.

Surgery and radiotherapy are most effective to reduce the initial tumour load. These are the prime modalities of treatment in solid tumours. In the case of disseminated neoplasms like leukemia and myeloma and in the case of some rapidly growing tumours like trophoblastic tumours, chemotherapy has to be employed as the first line of treatment. The technical perfection and complexity of management of malignant neoplasms have resulted in the achievement of successful results in many case if detected early. Several sub-specialities such as radiation oncology, solid tumour oncology, hemato-oncology and others have developed.

Radiotherapy

Tumour cells are more radiosensitive as they proliferate faster than normal cells. Radiotherapy may be given as the only modality of treatment or combined with surgery and chemotherapy. With the advent of highly sophisticated equipment such as the linear accelerator, large doses may be focused on deep seated tumours with only minimal injury to adjacent tissues. Therapeutic efficacy of radiation is enhanced by exposure to hyperbaric oxygen and radiosensitizing drugs such as metronidazole.

Radiation produces ionization in its path. This causes physical and/or chemical changes. The nucleic acid in the cell is damaged, so as to arrest the next cell division. Radiotherapy mainly affects cells in the dividing phase. X-rays produce breaks in DNA. Break of 2 single strands of DNA lead to disruption of the integrity of the chromosomes and tissue destruction.

Depending on the sources of radiation, the radiotherapy may be (a) unsealed sources, (b) sealed sources or brachytherapy and (c) teletherapy. Unsealed sources are radioactive substances kept in liquid form. The beta rays are the main effective radiation in these sources. For treating primary and metastatic thyroid cancer, ¹³¹I (dose 50-100 mCi) is administered. Since iodine is preferentially concentrated in thyroid cells, the radioactivity is specifically taken up by these cells, and so they are destroyed. ³²P (dose 5 mCi) is given intravenously to treat polycythemia vera. Phosphorus is an essential constituent of DNA and so rapidly dividing cells take up the radioactive phosphorus. The dose may be repeated after 3 months, if necessary. Radioactive gold (¹⁹⁸Au) (75-150 mCi) may be instilled into serous cavities to reduce malignant pleural and peritoneal cavities. Commonly used radioisotopes are listed in Table 7.4.

Brachytherapy: The radioactive source is covered by platinum alloy to absorb alpha and beta radiation, so that only gamma rays are allowed to penetrate into the tissue. Alpha and beta rays if allowed to come out, will produce necrosis of tissue around the source within a short time.

TABLE 7.4 Widely used radioisotopes				
Element	Isotope	Half-life	Major radiation	Important applications
Carbon	¹⁴ C	5600 years	Beta	Research in metabolism
Phosphorus	³² P	14 days	Beta	Polycythemia treatment
Chromium	⁵¹ Cr	28 days	Gamma	RBC kinetic in diagnosis
Iodine	¹²⁵ I	60 days	Gamma	Radioimmunoassay
Iodine	¹³¹ I	8 days	Gamma	Thyroid cancer treatment
Radium	²²⁶ Ra	1600 years	Gamma	Implantation in tumours
Tantalum	¹⁸² Ta	115 days	Gamma	Implantation, bladder cancer
Gold	¹⁹⁸ Au	2.5 days	Beta	Instillation into serous cavities
Cobalt	⁶⁰ Co	5.3 years	Gamma	Teletherapy for cancer
Caesium	¹³⁷ Cs	30 years	Gamma	Teletherapy for cancer.

The sources are packed as needles inside small tubes with a length of about 2 to 5 cm and a diameter of about 2 mm. ^{137}Cs with a half-life of 30 years, is the preferred sealed source. Intracavitary application (for cancer of body of uterus, cancer of cervix uteri, cancer of vagina) and interstitial applications (for buccal cancer, tongue cancer) are very commonly used.

Teletherapy: Here the source of radiation is kept at a distance from the patient. The high penetration power of the gamma rays has an advantage. Maximum dose is received not on the skin, but on the underlying tissues, which reduces unwanted skin reactions.

Gamma rays from ^{137}Cs (Caesium) or ^{60}Co (Cobalt) are used for teletherapy. Here the energy equivalent is in the order of 2 MV (megavolt or million volts). Usual diagnostic X-ray works in the region of 80-150 KV (kilovolt or thousand volts). Since penetration power is dependent on the energy of the ray, better machines, called linear accelerators with energy levels of 5-12 MV are now being used. The present machines are able to provide programmed doses of radiation at specific targets in high doses, with minimal damage to surrounding tissues. The aim of radiotherapy in general, and teletherapy in particular, is to provide maximum destruction of tumour tissue, while retaining the regenerative capacity of surrounding normal tissues. The art of radiotherapy is to decide the most beneficial risk-benefit ratio. Radiation fields can be designed, using shielding blocks, computerized planning and automated tracking techniques.

Radiosensitivity: The effectiveness of radiotherapy varies with different tumours. In general, lymphomas, Hodgkin's disease and neuroblastoma are highly radiosensitive. Epithelioma, cancer of oral cavity, cancer of cervix, cancer of breast and lung cancer are moderately radiosensitive. Poorly radiosensitive tumours are osteosarcoma, and malignant melanoma.

Fractionation of doses: Radiation given in a single dose is not optimally effective, because only 5-10% of cells are in the dividing phase at any one time and the radiation kills only this fraction. If divided doses are given at programmed intervals which coincide with the cell division fresh cells are killed successively. Fractionation also helps to reduce the toxic effects of radiation. In general a total dose for many cancers is 5,000 to 6,000 rads (also called centigray-cGy) given in 15-20 fractions, administered over a period of 25-35 days. Recovery from radiation damage is quicker in normal cells than in cancer cells.

Adverse effects: The adverse effects of radiotherapy are due to the damage caused to normal tissues; some degree of which is inevitable. These are described below:

1. **Skin** Epilation, damage to sweat glands, erythema and blisters. These constitute the syndrome of acute

radiation dermatitis. These reactions are generally mild and acceptable in most cases, but overdosage may produce burn and sloughing of superficial tissues. Long-term effects include minor degrees of ischemia, atrophy, hypopigmentation, fibrosis and loss of elasticity.

2. **Mucous membranes** Mucosal surface cells are replenished very rapidly, about a third being formed everyday. Since radiation damages the dividing cells most, gastrointestinal problems are very common during radiotherapy. Minor manifestations include nausea, vomiting, and diarrhea. In severe cases, ulceration and bleeding may occur. Late sequelae such as adhesions, fibrosis, stenosis and luminal obstruction may develop several months after radiotherapy.
3. **Blood cells** Bone marrow and lymphoid tissues are highly radiosensitive because of the higher rate of cell division in the organs. Cytopenias are the most common adverse effects. Platelets, granulocytes and erythrocytes are frequently reduced. Continuation of the dose may lead to marrow aplasia. Leukopenia leads to infections and thrombocytopenia leads to hemorrhage. It is important to repeat blood counts before each successive dose of irradiation and modify therapy accordingly.
4. **Reproductive organs:** Complete sterility may result if 1000 rads are given over the pelvic region. Smaller doses of radiation may produce genetic effects in the offspring.
5. **Radiation sickness:** This depends on the radiation dose and the tissue volume irradiated. 100-150 rads given as a total body irradiation will cause severe illness which can be fatal, if untreated.

The maximum permissible dose (MPD) of radiation for whole body among radiation workers including doctors, is 5 mRem/year, and for general population is 0.5 mRem/year.

TABLE 7.5

Common malignant conditions in which combination chemotherapy is administered

Acute lymphatic leukemia	:	Vincristine + Prednisone + Adriamycin + L. asparaginase
Acute myeloid leukemia	:	Doxorubicin + 6-Thioguanine + Cytosine arabinoside
Hodgkin's lymphoma	:	Nitrogen mustard + Vincristine + Prednisone + Procarbazine
Non-Hodgkin's lymphoma	:	Cyclophosphamide + Vincristine + Prednisone
Multiple Myeloma	:	Melphalan + Vincristine + Prednisone
Ewing's tumour	:	Vincristine + Actinomycin D + Cyclophosphamide
Embryonal tumours	:	-do-
Breast cancer	:	5-Fluorouracil + Adriamycin + Mitomycin
Oral cancer	:	Mitomycin + Methotrexate + Bleomycin

TABLE 7.6

Commonly used anti-cancer drugs

Group of drug and mechanism of action	Name of drug	Dose and route	Most important side effects	Indications
Alkylating agents				
They form electrophilic lymphatic ions making covalent bonds (alkylation) with guanine residues leading to cross-linking of DNA strands and interference in DNA replication	<i>Cyclophosphamide</i>	100-150 mg oral daily	Cystitis and marrow	Acute and chronic
	<i>Endoxan</i>	or 1 g/m ² every 3 weeks		suppression
	<i>Cytosan</i>			lymphomas Ca. of
	<i>Nitrogen mustard (Mustargen)</i>	6 mg/m ² infusion intravenous	Local inflammation	ovary lungs and cervix
	<i>Phenylalanine mustard (Melphalan)</i>	6 mg/m ² /d oral for 5-10 days every 4-6 weeks	Marrow suppression	Several tumourus
	<i>Chlorambucil (Leukeran)</i>	0.1 mg/kg/day oral	-do-	Multiple myeloma
	<i>Busulfan (Myeleran)</i>	4-12 mg/day oral	Pulmonary fibrosis marrow suppression	CLL, lymphoma
				CML
Antifolates				
Inhibit dihydrofolate reductase; tetrahydro-folate is not produced; one carbon units are not available for DNA synthesis	<i>Amethopterin</i> <i>Methotrexate</i>	5 mg/day oral or 30 mg/m ² intravenous twice weekly	Marrow suppression; hepatic and renal toxicity, painless nodules over fingers	ALL, Ca. of breast, lung, head and neck sarcomas choriocarcinoma
Antipyrimidines				
Inhibit thymidylate synthetase and thus DNA synthesis	<i>5-Fluorouracil</i>	15-20 mg/kg/week intravenous: maximum dose is 1 g	Gastrointestinal disturbance; marrow suppression	Ca of brest, colon, stomach, ovary, head and neck
Inhibit deoxycytidine and DNA synthesis	<i>Cytosine arabinoside</i> <i>Cytosar, Ara-C</i> <i>Cytarabine</i> <i>Gemcitabine (Difluorodeoxy cytidine)</i>	100-200 mg/day intravenous 1000 mg/m ² IV infusion	-do- Hyperuricemia Myelosuppression hepatotoxicity	AML, ALL Advanced adenocarcinoma of pancreas
Antipurines				
Interfere with purine biosynthesis and interconversions	<i>6-Mercaptopurine</i> <i>Purinethol (Hypoxanthine analogue)</i> <i>6-Thioguanine (Guanine analogue)</i>	2.5 mg/kg/day oral 2 mg/kg/day oral	Hepatotoxicity marrow suppression marrow suppression	AML, ALL, CML, AML, ALL
Vinca alkaloids				
Derived from periwinkle (vinca rosea) plant. Interfere with microtubule assembly in mitotic spindle formation	<i>Vinblastine (Velban)</i> <i>Vincristine (Oncovin)</i>	5-15 mg/m ² every 1-2 weeks intravenous 0.5-2 mg/m ² every 1-2 weeks intravenous	Mental depression, local inflammation, marrow suppression. Peripheral and autonomic neuropathy; alopecia.	ALL, neuroblastoma Wilms' tumour lymphomas, Ca lung
Taxene group				
Inhibits microtubule assembly; mitotic block in metaphase/anaphase boundary	<i>Paclitaxel (Taxol)</i> <i>Docetaxel</i>	175/m ² IV infusion repeated every 3 weeks 60 mg/m ² IV infusion	Hypersensitivity Myelosuppression Hypersensitivity fluid retention	Breast cancer Ovarian cancer Advanced Breast carcinoma

Contd...				
Group of drug and mechanism of action	Name of drug	Dose and route	Most important side effects	Indications
Podophyllotoxins				
Semisynthetic drugs	<i>Etoposide (VP-16)</i>	100-200mg/m ²	Marrow suppression	Ca of lung, breast and testis lymphomas, AML, Kaposi's sarcoma
Selective inhibition of DNA topoisomerase, and inhibition of S and G2 phases of cell cycle	<i>Teniposide (VM-26)</i>	I. V. on alternate days 3-4 weeks	Late development of leukemia	
	<i>Irinotecan</i>	125 mg/m ² IV infusion	Diarrhea	Advanced cancers of colon and rectum
	<i>Topotecan</i>	1.5 mg/m ² IV infusion × 5 days	Myelosuppression	Ovarian carcinoma
Antibiotics				
Inhibiting DNA directed RNA synthesis	<i>Actinomycin</i>	12-15 mcg/kg/day	Marrow suppression	Wilms' tumour
	<i>Dactinomycin</i>	5 d for 2-4 weeks	local inflammation	Rhabdomyosarcoma
	<i>Cosmegen</i>	intravenous		
	<i>Bleomycin</i>	1-5 mg/d intravenous or intramuscular. maximum 300 mg/m ²	Pulmonary fibrosis with minimal myelosuppression.	Ca of head and neck, skin, lung, gut, and GIT
Inhibiting DNA synthesis	<i>Daunomycin</i>	60 mg/m ² intravenous	Cardiotoxicity	AML, ALL
	<i>Daunorubicin</i>	3-4 weeks		
	<i>Rubidomycin</i>			
	<i>Adriamycin (Doxorubicin)</i>	60 mg/m ² intravenous once in 5 days for 3-4 weeks. Maximum total dose 500 mg	Cardiotoxicity	Soft tissue tumour, lymphomas, ALL, Ca of breast, GIT, and gut
	<i>Mitomycin-C</i>	20 mg/m ² intravenous every 4-6 weeks	Local inflammation, marrow suppression.	Ca of stomach, cervix, colon, breast
	<i>Mutamycin</i>			
Enzymes				
L. asparaginase depletes L. asparagine availability: inhibits protein synthesis	<i>L. asparaginase</i>	6000 IU/m ² intravenous	Allergy; coagulation defects. Pancreatitis	ALL
Nitrosoureas				
Inhibit nucleic acid synthesis	<i>Cyclohexyl chloroethyl nitrosourea (CCNU)</i>	100 mg/m ² oral every 4-6 weeks	Delayed marrow suppression	
	<i>Bis chloroethyl nitrosourea (BCNU)</i>	200 mg/m ² intravenous every 4-6 weeks	-do-	-do-
Hydrazine derivatives				
Damage DNA through peroxide formation	<i>Procarbazine (Methylhydrazine derivative)</i>	50-100 mg/m ² daily orally for 10-14 days	Myelosuppression	Hodgkin's
Imidazole derivatives				
Mechanism uncertain, probably alkylation	Dimethyl triazenomidazole carboxamide (DTIC <i>Dacarbazine</i>)	150-250 mg/m ² intravenous for 5 days repeated every 3 weeks	Myelosuppression	Malignant melanoma
			Hepatotoxicity	Hodgkin's sarcoma
Platinum complexes				
Inhibit DNA synthesis by intrastand crosslinking	Cis-diamino dichloro platinum. <i>Cis-platin</i>	100 mg in 500 mL intravenous once a week in 3-4 weeks	Renal toxicity, Ototoxicity	Ca of head and neck, lung, cervix, oavary
	<i>Carboplatin</i>	300 mg/m ² IV infusion every 28 days	Peripheral neuropathy	Advanced ovarian carcinoma
	<i>Oxaliplatin</i>	130 mg/m ² IV infusion	Thrombocytopenia	
			GIT toxicity	Colorectal and liver cancers
			Myelosuppression	

Contd...				
Group of drug and mechanism of action	Name of drug	Dose and route	Most important side effects	Indications
Hormones				
Androgens	Testosterone	300 mg weekly deep intramuscular	Virilisation	Ca of breast
Antiandrogen	Flutamide	750 mg oral daily		Advanced prostate cancer
Estrogens	Diethylstilbestrol	5-15 mg oral daily	Feminization	Ca of prostate
Estrogen linked to nitrogen mustard	Estramustine	140 mg oral		Advanced prostate cancer
Progestogens	Medroxy progesterone acetate (Provera)	300 mg daily orally	Withdrawal bleeding	Ca of breast and endometrium
Antiestrogens	Tamoxifen (Nolvadex)	20-30 mg daily orally	Vomiting	Breast cancer
Adrenocorticoids	Prednisone	40-60 mg/m ² orally/ day	Cushingoid features	ALL
Thyroxine	L. thyroxine sodium	0.1-0.3 mg daily orally	Hyperthyroidism	Ca. thyroid
Biological response modifiers				
Interleukin-2		6 lakhs IU/kg, IV every 8 hr × 5 days	Hypotension Fever	Advanced renal cancer, AML
Interferon-Alpha		1-2 million U/day		Hairy cell leukemia CML, Kaposi's sarcoma
GMCSF (Granulocyte Macrophage Colony Stimulating Factor)		250 mcg/m ² IV daily	Fever, bone pain, hypotension	
Adjuvants used in cancer therapy				
Levamisole (immunostimulant)		150 mg/d/oral		Useful in 5-FU treatment
Amifostine (Radioprotector)		900 mg/m ² IV	Hypotension infusion	Prevents hepatotoxicity of cis-platin; reduces mucosal toxicity of radiation
Pamidronate (Bone resorption inhibitor)		60-90 mg IV infusion	Fever	Osteolytic bone lesions; Paget's disease of bone
Dexrazone (Radioprotector)		500 mg/m ²	Myelosuppression IV infusion	Prevents cardiotoxicity of doxorubicin
All trans retinoic acid (ATRA) (Vesanoid)		45 mg/m ² daily oral	Hypervitaminosis	Induced cytodifferentiation; adjuvant in acute promyelocytic leukemia, germ cell tumours
13-cis retinoic acid		1-2 mg/kg daily oral for 3 months		Oral leukoplakia, basal cell carcinoma, T cell lymphomas

In may cases surgery or radiation is used as the first modality to reduce tumour bulk. This can be followed or preceded by chemotherapy (Table 7.5).

Chemotherapy

Chemotherapy is the sheet anchor of therapy in leukemias, advanced lymphomas, choriocarcinoma and other widely disseminated malignancies. It is combined with surgery in embryonal tumours and used as the primary treatment

in advanced cancers not amenable to surgery or radiation. The effectiveness of cytotoxic drugs is directly proportional to the doubling time of the tumours, and is inversely proportional to the number of cancer cells. Prior reduction of tumour mass by surgery or radiotherapy augments the effectiveness of chemotherapy. Cytotoxic drugs are non-selective and affect all cells which are in certain phases of their proliferative activity (Table 7.6).

Cell destruction by a cytotoxic drug follows the first order kinetics, i.e. it reduces a constant percentage and

put in larger values not a constant number of cancer cells. Thus the same dose which reduces the cancer cells from 10^8 – 10^7 is required to reduce them from 10^3 – 10^2 . It is difficult, therefore, to eradicate the last portion of any tumour by chemotherapy alone without serious toxicity. Surgery, radiation and chemotherapy leave residual tumour tissue even after completion of therapy. These cells are generally destroyed by the immunological system of the body, but if the immune mechanism is weak, the residual cancer cells rapidly multiply and produce recurrence. It should be remembered that both radiotherapy and chemotherapy depress the immune status of the individual. From time to time attempts have been made to stimulate the immune status of the individual by nonspecific immunostimulants such as levamisole or specific immunizing agents such as tumour antigens or modified tumour tissue. Tumour infiltrating cells and LAK (lymphokine activated killer cells) specifically active against tumour antigens were used with limited success in advanced solid tumours. Monoclonal antibodies (immunoglobulin of known specificity produced by single clone of hybrid cells) conjugated with toxins or radioactive isotopes were used in hematological malignancies.

Human interferon obtained by recombinant DNA technology has been successfully used in hairy cell leukemia, chronic myeloid leukemia, cutaneous T cell lymphomas and Kaposi's sarcoma. Interleukin-2 has been tried in advanced cancers, especially in renal cell cancers with success. Interferons and interleukins are described in Chapter 3.

Palliative Care and Pain Management

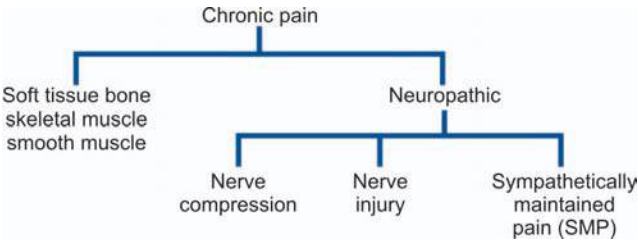
The care for terminally ill cancer patients include (a) control of symptoms, (b) control of pain, (c) treatment of psychological disturbances, (d) maintenance of quality of life, and (e) preparation for a decent death. Moderate to severe pain is associated with 80-90% of advanced cancers. The pain may be somatic (soft tissue origin; dull, aching localised type) in 40% cases; visceral (due to compression of tissues; deep and poorly localised) in 20% cases; neuropathic (due to infiltration of nerve; severe burning type) in 10% cases; or a combination in the rest of the cases.

Palliative care is the active total care of the patient and their families by a multiprofessional team at a time when the patient's disease is no longer responsive to curative treatment and life expectancy is relatively short.

SYMPTOM MANAGEMENT

Pain

‘Pain is what the patient says hurts’.
Pain is an unpleasant *sensory* and *emotional* experience associated with actual or potential tissue damage or



Factors Affecting Pain Threshold	
Threshold lowered	Threshold raised
Discomfort	Relief of other symptoms
Insomnia	Sleep
Fatigue	Sympathy
Anxiety	Understanding
Fear	Companionship
Anger	Creative activity
Sadness	Relaxation
Depression	Reduction in anxiety
Boredom	Elevation of mood
Mental isolation	Analgesics
Social abandonment	Anxiolytics
	Antidepressants

described in terms of such damage. In other words, pain is a somatopsychic phenomenon.

The aim of management of pain in terminal cancer cases is to render freedom from pain. Treatment of cancer pain includes: (a) treatment of the underlying cause, if possible; (b) analgesic drug therapy; (c) anesthetics; (d) neurosurgery and (e) psychiatric consultations. Out of this, analgesic drug therapy is the main choice. Here, the aim is to make adequate pain relief with minimum side effects. Drug dose is to be titrated to individual needs. The basic principle is summarised as “by the clock, by the mouth, by the ladder”. Drug doses are titrated to individual needs, and doses are given every 4-6 hours, by the clock. Administration by mouth is preferred.

The WHO three-step analgesic ladder is briefly shown below (Fig. 7.1 and Table 7.7):

1. Start with non-opioid drugs individually or in combination. If necessary, adjuvant drugs may be added. This form of therapy produces no tolerance or physical dependence. The first step will be sufficient in about 20-40% patients.
2. If pain persists, as the second step, mild opioids are started, along with non-opioid drugs, with or without adjuvant drugs. Taper the opioid dose slowly, reduce by 25% every 2 days, until a suitable dose is reached. This strategy will be useful for another 20-40% patients.
3. If pain still persists, as the third step, strong opioids are used, along with non-opioids and adjuvants. Oral route is preferred, but severe pain may need continuous subcutaneous or intravenous administration.

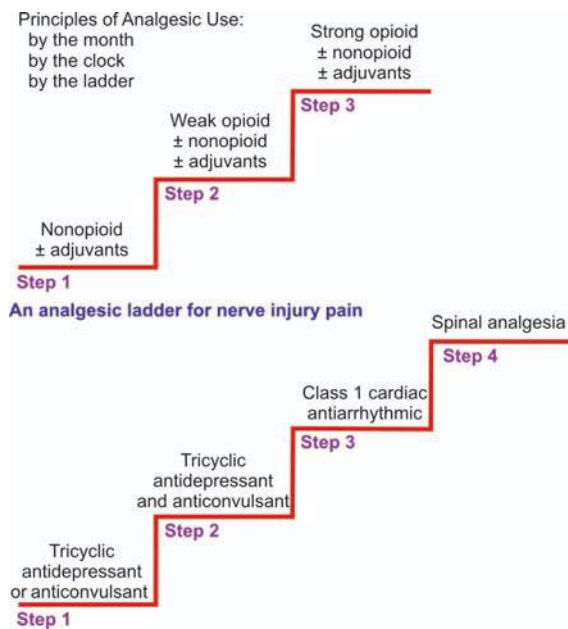


Fig. 7.1: The World Health Organization 3-step analgesic ladder

4. As a last resort, as the step four, anesthetic drugs may be employed. Further, nerve block or even nerve root ablation may be tried. Metastasis in bone may produce severe pain, which may be treated by osteoclast inhibitors such as biphosphonate compounds (etidronate, 60 mg biweekly; pamidronate, alandronate), gallium nitrate, strontium and calcitonin (25 IU per day). Corticosteroids are used especially in pain associated with spinal cord compression.

TABLE 7.7

Drugs used to control pain in palliative care

1. Nonopioid drugs (oral administration)
Paracetamol, up to 4 g/day in divided doses
Naproxen, up to 1 g/day in divided doses
Ibuprofen, maximum 2 g/day in divided doses
Diclofenac, 50 mg 6 hourly
Ketorol, maximum 100 mg/day in divided doses
Aspirin, 500 mg 4 hourly (maximum 4 g/day)
2. Mild opioids (oral administration is preferred)
Codeine, 200 mg 6 hourly
Propoxyphene, 100 mg 6 hourly
Oxycodone, 30 mg 6 hourly
Tramadol, 50 mg 6 hourly
Buprinorphine (sublingual, not freely available)
3. Strong opioids
Morphine 30 mg/day, orally, in divided doses
Methadone, 10 mg orally (useful in morphine dependence)
Fentanyl, 25-100 mcg/hour, transdermal patch
Pethidine (Meperidine) 75 mg intramuscular
4. Adjuvant drugs
 - a. Antidepressants:
Amitriptyline, 50 mg at night
Benzodiazepines, diazepam, 10 mg at night
 - b. Antiemetics:
Domperidone, 30 mg/day
Metaclopramide, 3-5 mg/kg/day
Ondansetron, 8 mg/4 hourly
 - c. Anticonvulsants:
Carbamazepine, 200-400 mg/8 hourly
Sodium valproate, 200 mg/8 hourly
 - d. Corticosteroids, prednisolone, 15-30 mg/day or higher doses
5. Anesthetics:
Local anesthetics
Nerve block (peripheral, epidural, intrathecal)
Lumbar sympathetic/stellate ganglion block
Nerve root ablation (rhizotomy)

8

Organ Imaging Techniques

K.V. Krishna Das

Chapter Summary

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Deeper tissues in the body have been studied by different methods from time-to-time. Visualisation of organs and tissues by imaging techniques have reached a high degree of technical perfection. Production of newer machines and provision of more advanced facilities to help the physician to assess the state of the various organs with further precision and at greater speed with loss of discomfort to the patient, have been taken up by the industry. The subject of imageology has established as a major speciality in all modern medical establishments in India and abroad. The forerunner in this field is the introduction of X-rays and radiological procedures in the early part of the last century.

RADIOLOGY

The most time-honored and well-established method of imaging is radiology, which employs X-rays. Shadows cast on the photosensitive film by different tissues vary in density and this principle is used in interpreting the radiographs. Different techniques like plain radiography, contrast radiography, and tomography are employed. Radiological imaging gives details about anatomical and structural alterations in an organ e.g., foreign bodies in the bronchi, consolidation of the lungs, cardiac enlargement, abnormalities of bones, etc. Both the anatomic abnormalities and physiological functions can be studied by techniques using contrast radiography, e.g., *barium swallow*, *barium meal follow-through*, *cholecystography*, *contrast urography*, etc. Angiography elegantly reveals the vascular supply of an organ. Apart from visualizing occlusion and aneurysms, the vascular pattern gives indirect evidence of tumours, space occupying lesions and also the functional state of the organ. Angiography has been extensively applied in cardiovascular, neurological, renal, hepatic and other disorders. Angiography has been used with other methods like *computerized tomography* to improve the resolution of details further. Angiography has been applied to the arteries, veins and lymphatics.

A new development in the field is interventional radiology in which investigative or therapeutic procedures are done under radiological control. The technique is highly sophisticated, demanding very great skill and perfect team work. A few classical examples of *interventional radiography* are endoscopic retrograde cholangiopancreatography (*ERCP*) with removal of pancreatic or biliary calculi, renal artery dilation through a renal artery catheter, relief of coronary occlusion using a balloon catheter in the coronary artery, and use of devices such as vortablator, stents, and laser procedure.

Radiology is still a standard technique of imaging since this investigation answers many of the questions. Moreover, its universal availability and relatively low cost have helped to make it the most acceptable investigation.

only about 1/100. Repeated exposures lead to cumulative toxicity. Despite this the benefits arising from radiological procedures far outweigh the risk. Still it is prudent to avoid exposure to X-rays during early fetal development.

Chest X-ray remains the primary investigation of pulmonary, cardiovascular and other thoracic lesions involving the soft tissues and skeleton. Plain radiographs of the abdomen in different positions provide reliable evidence of visceral perforation, intestinal ileus, megacolon and abnormalities of solid organs.

Intravenous urography, retrograde urography and cystography have been replaced to some extent by ultrasonography, but still they are employed frequently before surgical procedures. Cholecystography has been almost replaced by ultrasound investigations. Contrast bronchography using iodinated dyes has been replaced to a large extent by computed tomographic and MRI procedures.

Conventional angiography using radiocontrast dyes is still the gold standard for detecting abnormalities of vascular lumen, e.g. coronary angiogram. Digital subtraction angiography (DSA) has modified the procedure to a great extent and made it less invasive and more diagnostic, in some situations. Barium contrast examination as a diagnostic procedure for esophageal gastric, duodenal and upper intestinal lesions has been replaced to large extent by endoscopy. Endoscopy gives direct visualisation and facilities for biopsy and therapeutic interventions. Barium procedures still hold their position where the motility of the gut structures, transit time of ingested material, multiple polyps, diverticulitis, foreign bodies, fistulisation and functional abnormalities are to be demonstrated. Barium enema procedures, especially double contrast enema are done frequently for the diagnosis of colonic lesions.

Though conventional radiography is noninvasive, contrast studies are invasive in varying degrees. X-ray contrast media fall under two categories—ionic and non-ionic, all containing organic compounds of iodine. When dissolved in water, the former dissociates into anions (benzoic acid) and cations (Na^+ , Ca^+ , Mg^+ or methyl glucosamine⁺). Their osmotic activity is 7 times that of plasma. The non-ionic agents do not dissociate in solution and therefore their osmotic activity is only 2.5 to 3 times that of plasma. Ionic contrast media are much more toxic, but less expensive. Toxic complications are caused by osmotic activity and chemotoxic effects. Osmotic effects give rise to feeling of warmth during injection, vasodilation, hypotension and rigidity to the erythrocytes. Chemotoxic effects lead to inhibition of enzymes, hemorrhagic states, neurotoxicity, renal failure and others. Contrast agents such as iodixanol which is a third generation isosmolar non-ionic iodinated dye is safer with less of nephrotoxicity.

The exposure to diagnostic X-rays, though small quantitatively, adds to cumulative irradiation received by the subject. It is well known that irradiation of the fetus *in utero*, especially during early pregnancy can be harmful to the baby. So also repeated radiographic studies can give cumulative toxicity due to X-ray. Though the dose and the field of exposure have been considerably reduced in modern machines, this risk should not be taken lightly and radiological studies should be undertaken only if properly indicated. Many radiological techniques are supplemented by the newer imaging techniques like ultrasonography, isotope scanning, computerised tomography, nuclear magnetic resonance and positron emission tomography.

ULTRASONOGRAPHY

This uses ultrasound which is nonionizing. The advances in this technique over the past two decades have been phenomenal. The earlier machines used '*M*' mode echography subsequent ones employed real time and two dimensional echography. Further improvements in technique such as colour coding, three-dimensional studies, and computerization have been introduced. Ultrasonography has been employed in the imaging of almost all organs, such as heart, abdominal and pelvic organs, retroperitoneal tissues, thyroid, scrotal structures, intracranial structures and others.

Ultrasonography is the method of choice in the diagnosis of jaundice where other diagnostic methods have failed to distinguish between medical and surgical jaundice. In kidney it distinguishes cysts and hydronephrosis from tumours. Abdominal masses can be distinguished with reasonable accuracy, so also the distinction of aortic aneurysm from other masses. Investigation of thyroid lesions employs ultrasonography very often.

Most widespread use of ultrasonics is in cardiological diagnosis. Ultrasound studies are the most valuable noninvasive methods for the study of anatomic abnormalities of pericardium, heart chambers, heart valves, cardiac muscle, and great vessels. Function of the myocardium can be assessed by echocardiography. Doppler ultrasound which uses the principles of reflection or scattering of the ultrasonic waves by moving objects, is used to assess the blood flow in superficial vessels. Advent of ultrasonography has obviated the use of invasive techniques like angiocardiography in many instances.

The practical management of obstetrics has been considerably influenced by the use of diagnostic ultrasound. *In vivo* measurement of fetal head diameter helps in assessing fetal maturity and growth. Diagnosis of early pregnancy and fetal abnormalities and location of the placenta are easily done with this technique.

Several additional facilities and newer probes have been introduced. These include:

1. Use of Doppler studies to assess the hemodynamics in the heart and major blood vessels, peripheral arteries and veins.
2. Use of colour coding to detect and quantify abnormalities of blood flow in the heart and arteries.
3. Use of esophageal probe during echocardiography to visualize the posterior chambers in the heart.
4. Intravascular probes mounted on suitable catheters, which can make direct observations of vascular lumen, thrombi, etc.
5. Vaginal probes which help to delineate abnormalities of the pelvis, tubo-ovarian structures and uterine cavity from different positions.

Ultrasonographic localization of hepatic abscesses, tumours, thyroid nodules, and cystic lesions, help to direct aspiration needles more accurately on to the target and thus get more reliable information.

Newer technological advances include high definition imaging, wide range of transducers, tissue specific imaging, harmonic imaging, integrated image management and use of contrast agents.

ISOTOPE IMAGING—NUCLEAR MEDICINE

Isotope imaging is based on the use of ionizing radiations emitted by radioactive isotopes administered into the system. The metabolic pathways taken up by the isotope are studied. Several isotopes are available, emitting different radiations and the appropriate radioactive source is employed for visualizing different organs e.g., ^{131}I for thyroid, $^{99\text{Tm}}$ technetium for brain, liver and kidney, ^{201}Tl thallium for myocardium, etc. Radioactivity is quantitatively recorded. The procedure is generally non-invasive. The radiation dose is kept small, so as not to produce a health hazard. Isotope images do not depict detailed anatomic structures, they are much more of a functional nature. If purely anatomical information is sought, isotope imaging is not the method of choice, but if the clinical problem requires an answer in terms of evaluation of function, then isotope imaging is the ideal. If demonstration of widespread metastatic lesions is desired isotope imaging is the method of choice, since whole body imaging can be simultaneously done and a total picture obtained. The patient can be followed up with repetition of the tests.

Some important techniques include the detection of pulmonary emboli, ventilation-perfusion studies of the lungs, assessment of thyroid function, studies on erythropoiesis and red cell life span, imaging of the liver, kidneys and brain, and study of the state of the myocardium in ischemic heart disease. Isotopic imaging is more sensitive than radiography in detecting early bone metastases. For brain lesions isotope scanning is less sensitive than computerised tomography. Functional imaging of the brain using isotopes has a clinical role in assessment of suitability for epilepsy surgery.

In the investigation of jaundice, ultrasonography is more rewarding than isotope studies.

The isotopes used in small doses in conjunction with monoclonal antibodies help to locate tumours and other lesions, *Immunoscintigraphy* is an accepted diagnostic tool with a high degree of sensitivity and specificity. Quantitative autoradiography studies can be integrated and correlated with positron emission tomography to study the distribution and function of cellular receptors. These areas are being actively investigated and expanded particularly in the field of tumour diagnosis and management.

COMPUTED TOMOGRAPHY (CT)

Godfray Hounsfield, an English physicist discovered computed axial tomography (CAT) in 1972.

The principle of this technique is that the resistance offered by different tissues such as skull, brain, CSF and blood vessels to the passage of more than thirty thousand, 2-4 mm beams of X-rays directed horizontally at different horizontal planes of the brain are computed and revisualized.

The differing densities caused by different tissues are clearly distinguishable in the resultant picture. The technique is noninvasive. The final picture gives an anatomical reconstruction of the part to be studied. Use of contrast agents such as metrizamide serves to bring out lesions more clearly. This technique has been most frequently used in the investigation of neurological disorders. Hemorrhage, tumour, abscess, softened and edematous areas, and blood vessels can be identified. Precise size and shape of the ventricles can be assessed.

Indications for CT scanning include traumatic lesions, stroke, space occupying lesions, spontaneous intracranial hemorrhage, arteriovenous malformations, hydrocephalus, herpes encephalitis, parasitic cysts, epilepsies, etc. Supratentorial lesions are detected more easily by CT scanning. Being a noninvasive method with high diagnostic efficiency, many invasive investigations like angiography and ventriculography can be avoided if CT scanning is undertaken as a primary investigation.

Machines are available for the examination of all parts of the body (*whole body scan*). This is a very useful non-invasive method to detect intrathoracic, intra-abdominal and pelvic lesions and to detect solid from cystic masses.

CT scanning exposes the patient to ionising radiation. Modern machine use X-ray source which sweeps 360°. Spiral CT is an advancement, which has reduced the imaging time to less than a minute (the earlier machines take several minutes). The requirement of contrast agent is also much less. Magnetic resonance imaging (MRI) is a technique which developed after the introduction of CT. Though it has several advantages over CT, CT still stands out as the investigation of choice in several specific situations.

MAGNETIC RESONANCE IMAGING (MRI)

The production of images depends on magnetic properties of the hydrogen ions (protons) in the nucleus and radiofrequency pulses. Also known as magnetic resonance (MR), this technique utilizes the phenomenon that the nuclei which contain water and other elements behave like magnetic dipoles and possess magnetic fields of their own. Each nucleus is spinning like a top in its magnetic field. The magnetic fields of different nuclei are in different directions. When a strong magnetic field is applied to this system all the nuclei tend to align parallel to the induced magnetic field. If at this stage a burst of radiofrequency is delivered to the tissue, the spinning nuclei are tilted or made to precess to 90° or even 180°, depending on the strength of the radiofrequency. After cessation of the induced magnetic field the precessed nuclei resume their original position. In doing so they emit the absorbed radiofrequency, which can be detected by suitable detectors arranged all around the organs under study. The energy given out in relation to the space is called "*spin-lattice time*" (T1) and that in relation to its own spin is called "*spin-spin time*" (T2). Using these parameters, the computer reconstructs the organ. All parts of the human body can be imaged by magnetic resonance imaging (MRI). Vertebrae, intervertebral discs, eyes, knee joints, upper and lower pelvic regions, and many other tissues can be clearly studied.

In the brain MRI can distinguish between grey and white matter, and thus detect plaques of demyelination in life, which was possible only by biopsy or autopsy. Posterior fossa lesions which are less clearly visualized by CT due to bone artifacts can be seen quite clearly by MRI. Due to this advantage, techniques such as pneumoencephalography and angiography can be avoided. MRI has been very useful in imaging CSF spaces, spinal canal, spinal cord, vertebral column, intervertebral discs, etc. without interference from surrounding bony structures.

In the case of liver, MRI provides detailed informations not available by other noninvasive methods. Various parenchymal liver diseases can be distinguished. The myocardium can be visualized without contrast medium, so also the cortex and the medulla of the kidney can be differentiated. MRI is rapidly enlarging in its scope and usefulness. MRI is capable of imaging the products of conception. No untoward reactions have been reported so far. Still it is used only with caution to delineate maternal parts like the uterus and cervix or the fetal anatomy.

Several newer facilities have been added on to conventional MRI studies. *MRI angiography* can delineate the vasculature in the brain without direct puncture of any major artery. *Chemical imaging* is a technique employed to identify intracytoplasmic lipids within the adrenal

cortex. This helps to distinguish adenomas from cancers. *MRI spectroscopy* gives information about cellular metabolism.

Functional MRI of the blood- oxygen level dependent (BOLD) contrast is increasingly used to lateralize language area before neurosurgery and to predict deficits in the temporal lobe before surgical resection.

MRI is devoid of the risk of exposure to ionizing radiation. Due to the powerful magnetic field, susceptible metal parts may be attracted by the magnetic source. This danger has to be taken care of. Implanted gadgets such as pace makers, metallic prosthesis and others should be taken into account before deciding upon MRI.

MRI machines are now available in India in several centers and in within reach in many towns.

The technology of CT scan is utilized also in MRI scans. The latter gives greater differentiation between tissues, such as the grey and white matter of the brain, renal cortex and medulla and so on. Ionising radiations are not used and therefore the risk to the patient is less. Both CT and MRI can study tissue sections as thin as 1 mm or even less. Pictures in all planes—sagittal, coronal and axial can be obtained. MRI is generally the more rewarding imaging modality for neurological diseases. MRI spectroscopy and diffusion/perfusion imaging are improvement on the parent modality.

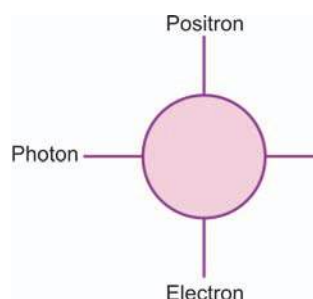
POSITRON EMISSION TOMOGRAPHY

Syn: PET

Substances such as radioactive fluorine, oxygen, rubidium, etc. are positron emitters. Positrons are positively charged electrons. When positrons collide against electrons and annihilation takes place, two photons (or X-ray particles) fly out in opposite directions from this meeting point.

PET which is a sophisticated isotopic technique depends on isotopes with short half-lives and very high release of energy. These have to be prepared fresh in a cyclotron which forms part of the equipment. Commonly used isotopes for PET are ^{11}C (half-life 20 minutes) ^{15}O (2 minutes) and ^{13}N (10 minutes) and ^{18}F .

The principle of PET is to give positron emitters systemically and the photons emitted by the organ under study are detected by an array of detectors. Detection of these rays permits the reconstruction of the tissue



distribution of the tracer radionuclide through the organ, or in the body. By computer techniques the source and pattern of these photons can be reconstructed to give an image which lacks in anatomical details, but gives functional details. ^{18}F -labelled deoxyfluorine or other isotopes are given to the subject and metabolic function of the brain such as glucose utilization can be studied. Metabolic alterations in tumours can be detected. PET can distinguish between viable tumour tissues and necrosis and fibrosis after treatment of cancer. It can detect recurrence of tumour and metastases early. Dynamic changes occurring in brain metabolism can be followed up by serial studies.

Single Photon Emission Computed Tomography (SPECT)

This technique utilizes single gamma rays emitted by other radionuclides such as $^{99\text{m}}\text{Tc}$, ^{123}I and ^{111}In . Photographs are taken by a gamma camera and the distribution of tracer in the organ is visualized.

PET and SPECT can be employed to study the abnormalities or regional blood flow and metabolic derangements in the brain.

PET provides information on the biochemical processes. In addition to studies on cerebral blood flow and metabolism, PET is used for studies on the heart, distribution of receptors and others. PET is to be used complementary to CT scanning and nuclear magnetic resonance imaging, which provide excellent morphological details with pathological information as well. SPECT is useful in identifying epileptic foci in the brain and this may be needed in intractable cases where other methods fail to locate the lesion, especially so if surgery is necessary.

There are only a few PET machines available in India at present.

2

Diseases due to Arthropods Marine Animals and Snakes

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General Considerations

Invasion of tissues or body cavities by the larvae (maggots) of dipterous flies is called myiasis. Myiasis may be of either primary or secondary type.

In primary myiasis the human infection occurs as part of the obligate life-cycle of the parasite and in secondary myiasis the human infection is accidental. Primary myiasis affects persons in good general health, whereas secondary myiasis supervenes on dead or necrotic tissues.

Classification: In general, the infection is of two types:

1. *Ectoparasitic, Auchmeromyia leuteola*,
2. Endoparasitic.
 - a. Cutaneous, e.g., caused by *Dermatobia hominis* and *Cordylobia anthropophaga*,
 - b. Tissues or cavities, e.g., caused by *Sarco-phaga*, *Wohlfartia*, *Fannia*, *Oestrus*, *Chrysomia*, and *Callitroga*.

The maggots are dull white or pink in colour, actively motile and have spines on their body. The body is tapered and segmented, the narrow anterior end bears the mouth parts, the thicker posterior end bears the opening of the spiracles which are dark coloured and useful in identifying the genera. Their length varies from 0.5 to 3 cm. The larvae feed voraciously on tissues or discharges and in 2 to 4 weeks develop and fall off to the ground to pupate.

Final identification of the species can be done by allowing the larvae to complete the life-cycle *in vitro* and examining the adult flies.

Cutaneous Myiasis—Ectoparasitic

***Auchmeromyia leuteola* (Congo maggot fly)** This fly lays eggs on soil and crevices in the floor. The larvae hatch out in 2 days. They can survive drying and starvation upto one month. Once hatched out, they attach themselves to the skin of the humans who sleep on the floor unprotected, suck blood for 20 minutes and drop off leaving maculopapular lesions. This process is repeated several times before the larva pupates in 2-12 weeks. Bites can be prevented by protective clothing or insect repellents like dimethylphthalate or N-N diethyl benzamide.

Localised Cutaneous Myiasis

***Dermatobia hominis* (Human bot fly or warble fly)** The adult fly lays eggs on hematophagous insects like mosquitoes, stomoxys and ticks or others such as housefly (*Musca*). When the latter alights on man, the larvae hatch out and wriggle on to the surface. They enter through the wound, produced by the insect or penetrate the unbroken skin and develop in the subcutaneous tissues.

The initial lesion is papular and pruritic. It becomes furuncle-like and painful later. The posterior end of the actively motile larva may be seen in the lesion through the opening. In 2-3 months the larvae mature and fall off to the ground. Lesions are seen on the exposed parts. The disease is worldwide in distribution.

***Cordylobia anthropophaga* (African tumbu fly)** The adults lay eggs on clothes spread out for drying or in dirty soil.

The larvae develop in 24-48 hours and penetrate the human skin either from the clothes or through the bare feet.

The lesion is initially papular and pruritic and becomes painful in a short time. Secondary infection may occur. Unlike the former, the life-cycle is shorter and is completed in 2-3 weeks.

Treatment The maggots may be extracted surgically. A drop of mineral oil placed on the lesions suffocates the

larvae which wriggle out and can be extricated. Penicillin in usual doses should be used to prevent secondary infection.

Migrating lesions resembling cutaneous larva migrans are produced by the larvae of genus *Gastrophilus* (*horse bot flies*) and *Hypoderma* (*cattle bot flies*), which develop from eggs laid on the hairs. Man is an accidental host and the larvae penetrate the skin, enter the subcutaneous tissues and wander producing eruptions similar to larva migrans of *Ancylostoma braziliense*, but more painful. They survive for a few weeks and die. Application of mineral oil over the lesions helps to visualize the underlying larvae. Tissues of the eye may be affected. In addition to surgical removal, symptomatic relief may be obtained by antihistamines.

Deep Tissue Myiasis

Larvae of the flies belonging to the families *Callitroga* (*Cochliomyia*), *Chrysomya*, *Sarcophaga*, *Wohlfartia*, *Fannia* and *Oestrus* invade tissues extensively when the eggs are laid on open wounds, damaged tissues or discharging surfaces, by the adult flies. The larvae of *Wohlfartia* can penetrate even unbroken skin.

The lesions are commonly seen in the nasal cavities, paranasal sinuses, middle ear and orbit. Cartilage and bone may also be destroyed by the screw-shaped larvae which may extend intracranially leading to fatal meningitis. The lesions are very painful and the larvae may be discharged from these sites.

Treatment is manual removal of larvae or extraction after spraying the area with chloroform. Repeated sessions may be necessary.

Secondary infection has to be treated with broad spectrum antibiotics like ampicillin.

Ophthalmic Myiasis

Flies of the genus *Chrysomya* and *Oestrus* may lay their eggs in the conjunctival sac. The larvae hatch out and produce lesions resembling acute conjunctivitis with severe irritation. Rarely corneal ulceration and loss of sight may occur.

Removal of the maggot after anaesthetising the eye and application of topical antibiotic drops will relieve the condition.

Intestinal Myiasis

The larvae or pupae of *Musca*, *Fannia*, *Sarcophaga* and *Tubifera* may be passed in stools or appear in vomitus. The eggs may be laid by the flies around the lips or anus while sleeping, especially if there are foul smelling discharges around these orifices.

The larvae hatch out from a few hours to two days and are swallowed to reach the upper gastrointestinal tract or they may crawl up into the rectum and large intestine. They develop in the stomach or in the intestines. Sometimes larvae may be swallowed along with infested foodstuffs. The larvae cause symptoms of gastritis or colitis which may persist from weeks to months. If reinfection does not occur, the condition is self-limiting.

Treatment consists of administration of purgatives and reassurance about the self-limiting nature of the illness.

Urinary Myiasis

Larvae of *Muscae*, *Fannia* or *Sarcophaga* may enter the bladder, when the eggs are laid around the external genitalia and produce symptoms of lower urinary tract infection with proteinuria, pyuria and hematuria. The larvae may pass in urine. Rarely urinary system may be involved by maggots eroding their way from the gastrointestinal tract.

Arthropod Bites and Stings and Injuries due to Marine Animals

K.V. Krishna Das

Chapter Summary

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Spider

Nearly 40000 species of spiders have been identified worldwide. A few are poisonous and aggressive. Reliable information can be obtained from local inhabitants. Several species of spiders bite man accidentally. Some species like *Latrodectas mactans* (black widow spider) attack man (Fig. 10.1). Females are more aggressive and venomous compared to males. The venom is generally neurotoxic, sometimes, also hemolytic. The bite is followed by intense local pain and the part becomes tender and spastic. Generalized muscular rigidity especially marked over the abdomen, pupillary constriction, salivation, excessive sweating and cardiovascular collapse



Fig. 10.1: Black widow spider

may follow. Death may occur in children and debilitated subjects. Spiders of the genus *Loxoscelles* seen in the tropical regions of several countries cause necrotic ulcers at the sites of bite.

Treatment consists of washing the area of bite with soap and water. Administration of 20 mL of calcium gluconate intravenously relieves muscle spasm. Muscle relaxants like mephenesin in a dose of 1 g orally and anticholinergics like atropine (0.5 mg given intravenously) give symptomatic relief. Supportive measures are indicated if shock supervenes.

Specific antivenene is available in S. American countries, but not in India.

Scorpion

Scorpions are nocturnal in habits and they come out at night to catch insects as their prey. These are killed by injecting the poison by the sting arising from the poison gland situated at the posterior end of the tail like abdomen. Nearly 1000 species of scorpions belonging to six families are known. Among these some species belonging to the family *buthidae*, especially the red scorpions are capable of inflicting toxic sting which could be fatal. In India the *Mesobuthus tamulus* is one among the dangerous scorpions. Scorpion venom contains short chain peptides that affect the mechanisms of sodium and potassium channels in excitable tissues. The toxins are classified into α and β toxins. By acting on sodium potassium channels they lead to intense persistent depolarization of autonomic nerves with massive release of neurotransmitters from adrenal medulla.

The neurotoxic effects leads to a cholinergic stimulation followed by adrenergic stimulation resulting in tachycardia, hypertension, cardiac failure and pulmonary edema in 1-2%. ECG abnormalities may develop which clear up on recovery. Cerebral and cerebellar infarcts may develop. Other major effects include hemolysis, disseminated intravascular coagulation, myocarditis, motor paralysis and respiratory depression. Left ventricular dysfunction, which is reversible over varying periods is a sequel. At times dilation of the ventricle may persist.

There is intense pain, edema and redness at the site of sting. This is followed by tachycardia, sweating, salivation, and vomiting. In severe cases paralysis of the tongue and abdominal muscles, convulsions, and respiratory depression supervene.

Myocarditis manifesting as tachy or brady arrhythmias and cardiac failure may occur not unusually. Rarely, hemorrhagic states due to disseminated intravascular coagulation (DIC) may develop. Pancreatitis is a rare complication.

Treatment For local treatment the affected part is immersed in ice cold water and washed. In filtration of 5 mL of 2% xylocaine around the sting gives relief to pain.

General treatment consists in the management of anaphylactic shock, ventilatory support and prevention of cardiac death. The use of prazosin, an alpha blocker has revolutionized the management of scorpion stings. Oral prazosin given in a dose of 250 µg at 3 hours intervals for children and 500 µg three hourly for adults is life saving. Scorpion antivenene is available and it may be given in doses of 10-20 mL IV. This neutralizes the circulating venom. Acute pulmonary edema responds to general resuscitative measures and sodium nitroprusside given IV. Another drug which is also reported to be effective is captopril given in doses of 12.5-25 mg thrice daily orally. Physical activity should be permitted only after adequate convalescence and normalization of the ECG.

Ref: 1. Bawaskar HS, PH Bawaskar JAPI. 2007, 55. 14 to 21.
2. Krishnan A et al ibid pp 22-6.

Bees, Wasps and Hornets

These insects abound in many parts of India and other tropical and temperate regions, especially during the flowering season. Multiple stings, especially over the face, are serious. During the sting, the stinger which is the modified ovipositor at the posterior end of the abdomen is inserted into the skin and the venom is discharged. In the case of bees, the stinger is left behind in the skin and injection of the venom continues for a few minutes even after the insect has left. The toxic components include phospholipase A2, histamine, bradykinin, acetylcholine, dopamine, serotonin, mast cell de-granulating peptide, hyaluronidase and mellitins.

The venoms of bees and wasps differ from each other even though the main allergenic components are common. The composition of the venom may vary seasonally. In the case of allergy to bees most of the antibodies are directed towards phospholipase A2.

In the case of wasp venom antigen 5 is the specific component towards which IgE is directed.

Initial symptoms consist of intense local pain, angioneurotic edema, respiratory obstruction, and

anaphylactic shock. Local tissue necrosis, intravascular hemolysis and renal failure may complicate a few cases. Delayed hypersensitivity reactions resembling serum sickness may occur after two or three weeks. Multiple stings, especially over the face are associated with considerable mortality. Wasp stings may cause bilateral ptosis and other upper cranial nerve palsies which respond to neostigmine, suggesting a myasthenia like reaction (RD Singh et al JI Asso Phys. India, 2003;51: 828-9).

Treatment In all cases, the local site should be inspected. The stinger should be removed by gentle scraping. Injection of adrenaline and corticosteroids and other supportive measures may be required to combat the anaphylactic reaction. Maintenance of the airway and ventilatory support are life-saving when the edema obstructs respiration. Specific antisera are available in some countries. Sensitized persons should avoid further exposure to these insects and wear protective clothing when so exposed. Auto-injecting pen syringes loaded with 0.15 or 0.3 mg of epinephrine are available for instant use- Desensitization by repeated injections of the venom can be done in persons likely to be exposed to the risk occupationally.

Centipedes

Syn: Chilopoda

Several species of centipedes are seen in warm climates. They vary in length from a few centimeters up to twenty centimeters, the larger ones can affect painful bites on man. The poison glands are situated at the anterior end and the poison is injected through the claws on the mandibular legs during the bite. Centipedes hide under clothes or bedding and bites are accidental. Bite mark may be visible as a pair of tiny red spots separated by a few millimeters. Symptoms consist of local pain lasting for 2-4 hours, edema, redness and enlargement of the draining lymph node. Headache, vertigo, vomiting and fever may follow. Centipede bites are usually not fatal.

Treatment Treatment consists of antihistamines, analgesics and reassurance. Infiltration of 2% xylocaine locally gives immediate relief of pain.

Ants

Certain species of fire ants belonging to the genus *Solenopsis* inflict bites on the skin and also introduce the poison through the stinger situated at the posterior end of the abdomen. Local irritation and allergic reactions follow.

Ants may colonize in the bed clothes of debilitated patients, newborn babies and comatose subjects and eat away superficial tissues producing shallow ulcers. When large numbers are involved tissue loss may be considerable. This can be avoided by exerting care in nursing

chronically bedridden patients and dusting 10% DDT powder under the cot and beds.

Lice

Lice, belonging to the family *Pediculidae* cause pediculosis in man. Their bodies are flattened and their mouth parts which are retractile are intended for piercing and sucking. The legs are provided with single claws which enable the insect to cling to hairs or clothes. The posterior end of the male is rounded and that of the female is notched. Lice are worldwide in distribution.

Head louse (*Pediculus humanus capitis*) is found on the head, the body louse (*Pediculus humanus corporis*) is found all over the body and clothes; the pubic louse (*Phthirus*) is seen over the pubic hair, eye lashes and sometimes all parts of the body as well. The eggs (nits) are glued to the hairs. The nymphs hatch out within 7-10 days. They reach adulthood after three moultings in two weeks and the fertilized females start laying eggs within a month. Each female lays a total of about 300 eggs. Life span is 4-6 weeks. Pediculosis leads to local irritation, pruritus, secondary infection and local lymphadenopathy of the posterior cervical group. Chronic infestation leads to pigmentation—Vagabond's disease.

Spread from person to person is by close contact, sharing of clothes or sleeping in the same room. Pubic louse may spread through sexual contact.

Lice leave the body when it cools down after death or when there is rise of temperature due to fever or physical exercise, and seek new hosts. By this process the body louse transmits typhus, trench fever and relapsing fever.

Treatment Benzyl benzoate 25% emulsion, applied to the scalp or other infested areas for a period of three hours, followed by a bath serves to kill the lice and the nits. Alternatively DDT 10% powder applied over the surface once a week for 3 weeks eliminates the infestation. Reinfestation from bedding and clothes should be avoided. Lice and nits on clothes can be killed by immersion in boiling water or use of a hot iron. All affected members should be treated simultaneously.

Topical insecticides such as permethrin, synergized pyrethrin and malathion are effective for preventing reinfestation. Resistance to the insecticide may develop. Ivermectin applied as a 0.8% weight to volume solution is highly effective if applied overnight.

The local custom of wet-combing of hair practiced in several communities is an effective and safe method of delousing.

Ticks

Medically important ticks belong to the families ixodidae (hard ticks) and argasidae (soft ticks). *Dermacenter*,

amblyomma, *rhhipicephalus*, *hemaphysalis* and *ixodes* are the hard ticks which are vectors of rickettsiae, borrelia, viruses and bacteria. Among the soft ticks *Ornithodoros* is the most important. It transmits *Borrelia recurrentis* and *Pasteurella tularensis*. Ticks crawl up and attach themselves to skin folds, insert their mouth parts into the skin and feed for 24-48 hours after which they fall off and undergo moulting. The site of bite may develop into an eschar which is an indolent necrotic ulcer.

- *Borrelia recurrentis* and *Coxiella burnetii* can be transmitted transovarially to the subsequent generations of ticks and hence an infected colony can act as reservoir of infection for prolonged periods. Ticks live for two years or more.

Tick Paralysis

This is a neurologic syndrome caused by a potent neurotoxin produced by female ticks which attach themselves to feed, particularly in the upper parts of the body, especially on the scalp, face or neck. *Dermacenter variabilis* and *D. andersoni* have been described from N. America. In Australia the main offender is *Ixodes holocyclus*. The ticks take 4-5 days to engorge fully and drop off. Mating with male may occur during this process and this leads to acceleration of the engorgement of the tick, fertilization of the ova and oviposition after falling off. The toxin of the tick is called ixovotoxin.

The neurotoxic venom causes impairment of nerve conduction, reduction of muscle action potential, inhibition of terminal nerve conduction and acetylcholine release at the presynaptic neuromuscular junction of muscle fibres. It may lead to total blockage of transmission at myoneural junctions.

Clinical Features

Children are more affected mainly on account of their lower body weight and greater susceptibility to tick infestation. Symptoms start with tingling sensations of extremities and weakness of limbs and trunk, ataxia of limbs and trunk and flaccid paralysis closely resembling Guillain-Barré syndrome. If the tick continues to feed this may progress to total flaccid paralysis demanding ventilatory support to maintain life. With the removal of the tick rapid resolution of symptoms occur and recovery may be complete within hours to days. Untreated, the condition can be fatal. Differential diagnosis includes Guillain-Barré syndrome, paralytic poliomyelitis, other forms of paralytic viral diseases, botulism, myasthenic reactions and others. Electrophysiology tests show reduced nerve conduction, reduction in muscle action potentials and neuromuscular block. The CSF is normal unlike as in Guillain-Barré syndrome and encephalomyelitis.



Fig. 10.2: 1. Hard tick 2. Soft tick

Diagnosis Strong clinical suspicion and careful search of the scalp and other parts of the body for attached ticks help to establish the diagnosis (Fig. 10.2). Its removal and supportive care during the period of paralysis are most rewarding. In Australia *Ixodes holocyclus* antitoxin is available for administration before the tick is removed.

Chigoe Flea

***Tunga penetrans*-Jigger** This is found in the feet or other exposed parts of body in people who walk bare-footed and with poor hygiene. The fertilized female burrows into the skin and produces painful itchy lesions. Secondary infection is common. Treatment consists of immersing the part in lysol baths, surgical removal of the fleas and antibiotics to combat secondary infection.

Injuries due to Marine Animals

Seabathers, fishermen or persons working under water may be stung by marine animals. Among these the most important are jellyfish, cone shells and stinging fish.

Jellyfish belonging to the class *Hydrozoa* (*Portuguese men of war*) and *Scyphozoa* are frequently found in coastal water in the sea, backwaters and riverine estuaries in all parts of India especially the eastern coast. They possess tentacles which may be several meters long and these bear nematocysts which contain poison and on contact with the human skin the contents are injected over a period of time. There is intense irritation followed by formation of wheals, vesicles and anaphylactic reaction. Sweating, abdominal pain and vasomotor collapse may occur. Rarely, the stings may be fatal due to cardiac and respiratory

failure. Treatment is to give intravenous calcium gluconate, adrenaline and glucocorticoids to combat the allergic reaction. If tentacles are left on the surface, the nematocysts must be inactivated by the application of dilute acetic acid (vinegar) for 30 seconds, concentrated sugar or salt solution before pulling out the broken tentacles. In some countries (Australia), specific antisera are available. The dose is 20000 IU given IV slowly.

Cone Shells (*Conidae*) are large marine snails found in the bed of lakes, coral reefs, and similar regions. The venom is neurotoxic and in severe cases death results from respiratory paralysis. Treatment is symptomatic. The spines on sea urchins may cause painful injuries.

Stinging Fishes Many species of fishes are capable of inflicting painful stings. Their dorsal fins contain spines connected to poison sacs. The spine may be broken and remain embedded in the victim. Intense local irritation occurs. In a few, neuromuscular symptoms may develop. Rarely respiratory paralysis may lead to death. Treatment is symptomatic and supportive. Immersion of the part in hot water may give relief of pain. In some countries specific antiserum is available.

Sting Rays These are common around the sea coasts and river mouths in tropical countries. Venom secreting tissue is situated in the grooves and sheaths of barbed horny spines seen on the dorsum of the tail. Stings are inflicted when these animals are trodden upon. Treatment is symptomatic.

Several animals inhabiting the sea effect dangerous and painful stings with the injection of poison.

These include the following:

Sting rays	Neurotoxic venom
Scorpion fish	Neurotoxic venom
Coelenterates including hydroids, jellyfish and anemones	Local effects and systemic toxicity
Sponges	Local pruritus
Sea urchins, Starfish	Myotoxicity
Bristle worms	Local pruritus
Molluscs and others	Curare like effect (paralysis)

Chapter Summary

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Snake bite is a common emergency seen in almost all parts of India. Most of the bites occur in persons while engaged in agricultural operations or while walking in darkness. Snakes are found more frequently around dwelling houses, embankments, cultivated fields and in bushes. They tend to frequent places where they get their prey—rodents and frogs. Most of the bites take place in the rural areas though they do occur in towns also. About 15 to 20 thousand deaths occur in India due to snake bite annually. Most of the poisonous bites (80%) are due to *vipers* (*Vipera russelli* and *Echis carinatus*). Cobras (*Naja naja*) cause 10% and kraits (*Bungarus caeruleus*) 4%. Rarely, poisoning due to sea snakes is encountered (1%). Majority of bites are inflicted by non-poisonous snakes. The incidence of snake bites varies with the season in different regions.

Identification of Poisonous Snakes

- 1. They have large ventral scales covering the whole of the ventral aspect.
- 2. The mouth contains only one pair of poison fangs in the upper jaw, placed anteriorly (krait and cobra) or posteriorly (viper).
- 3. Presence of rows of small teeth is characteristic of non-poisonous snake.

Viper: The head is triangular with a narrow neck. The scales on the body and neck are small and of uniform size. *Vipera russelli* is larger, often grows to one meter in length and shows three rows of oval rings on the body, running along the whole length. *Echis carinatus* has overlapping saw-shaped scales covering its body and a broad

arrowmark on its head and two rows of wavy bands running longitudinally.

Pit vipers belonging to the family Crotalidae are less common in India. They show a depression between the nose and the eye, the loreal pit. Vipers have larger fangs which are tunnelled and the bite marks are more prominent. Often the snake hangs on to the limb and it has to be disentangled by violent movements.

Cobra: Cobra has an expandable neck and the head shows a single (monocellate) or double (binocellate) dark ring on the dorsum. The third supralabial shield touches the eye and nostril. When provoked, the head and neck are raised to form the hood. The fangs are small and anteriorly grooved.

Rarely, king cobras (*Naja hanna* or Hamdyard) may be seen in thick forests but bites by these deadly snakes are very uncommon. They grow to large size (often 3-4 meters) and unlike the cobra, they are unhooded.

Krait: Kraits show white bands on the body; those in the posterior part being more definite. The dorsal scales on the body are hexagonal. The head and the sides of the lower jaw are covered with large shields, the fourth shield on the lower jaw being the largest.

Sea snakes: Sea snakes are found in good numbers in the coastal waters of India. They show laterally compressed and flattened tails. The two common genera seen in the Western coast are *Enhydrina* and *Hydrophis* (Fig. 11.1).

Snakes bite when they are inadvertently trodden upon. Rarely, cobras may attack but they usually do so only during the mating season.

The Venom

Venom is modified saliva and 0.25 to 1 mL of it is injected into the victim when the snake bites. Enzymes such as phosphatidases, proteases, cholinesterases, hyaluronidases, ribonucleases, deoxyribonucleases, ophioxidase, lecithinase and erepsins are present in the venom. In addition, the venoms of cobra and krait also contain non-

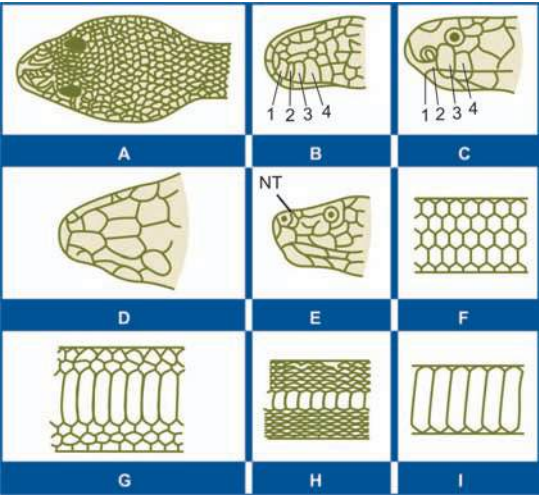


Fig. 11.1: Identification of snakes

- A Small uniform head scale, narrow neck—viper.
- B Undersurface of mouth, the 4th inferolateral shield is largest—krait.
- C 3rd supralabial shield larger than the rest and touches the shields of the nostril and eye—cobra or coral snake.
- D Large head shields.
- E Deep pit midway between the nostril and the eye (Loreal pit)—pit viper.
- F Under surfaces of non-poisonous snakes—small belly & scales and moderately large transverse scales which do not reach the entire length.
- G Hexagonal row of spinal shields on the dorsum of krait.
- I Large ventral shields reaching the entire width of the body—poisonous or non-poisonous.

enzymatic components like basic polypeptides which are highly neurotoxic. These toxins produce neuromuscular block.

The viperine venoms contain hemorrhagic, necrotic, coagulant and hemolytic substances leading to extensive damage to several tissues. Lesions are due to intravascular coagulation, fibrinolysis, damage to the vascular endothelium and extensive necrosis. The venoms of sea snakes are neurotoxic and they also cause extensive necrosis of the muscles.

The speed of action of the venom depends upon the site of injection and the amount of venom injected. If the venom directly enters the bloodstream, the effect may be rapid and lead to sudden death. In most of the cases, the absorption of venom is slower and especially in viperine bites with extensive local reaction, considerable amount of venom may remain locally to be absorbed into circulation in due course.

The severity of envenomation depends upon the circumstances of the bite. Bites sustained during the early part of the night are generally more serious since the poison sacs of the snake are full at this time. Bites through clothes are less dangerous. Children and underweight persons suffer more than normal adults since the

concentration of the venom is relatively higher in them. Violent physical activity helps to disseminate the venom rapidly and this worsens the prognosis.

Clinical Features

Immediate response Severe fright and mental agitation leading to tachycardia, sweating, hypotension and even vascular collapse are prominent features soon after the bite. These nonspecific symptoms may be seen in all snake bites.

Local reactions Local reactions are more prominent in the case of viper bites and less so in others. Intense pain, swelling and violaceous discoloration develop within minutes and often serosanguinous fluid exudes from the fang marks. The edema and discoloration spread proximally and in a few hours vesicles and hemorrhagic blebs may appear. Rarely, gangrene may supervene (Fig. 11.2).

General effects These vary with the type of snake. Cobra and krait venom are predominantly neurotoxic, while those of vipers are histotoxic and hemorrhagic. Some degree of overlap does occur, especially during certain seasons of the year, cobra bites producing moderate or severe tissue necrosis and viperine bites leading to mild neuromuscular paralysis.

Cobra and krait bites Soon after the bite, the patient complains of a sinking feeling, drowsiness, blurring of vision, diplopia, dysphagia and dyspnea. Extraocular palsies and paralysis of palate, pharynx, tongue, and respiratory muscles supervene. The limbs show flaccid paralysis. Coma and death due to respiratory failure or shock may occur within 6-48 hours.

In some cases the clinical features may resemble acute myasthenic crisis. In the cases that survive, recovery starts in 12-24 hours and may be complete in 48-96 hours.



Fig. 11.2: Viper bite. Note gangrene of middle finger right

Viper bites: Within 3-4 hours of the bite, the hemorrhagic manifestations appear in the nature of extensive bruising, bleeding from the bitten part and injection sites, bleeding from the gums, epistaxis, blotchy purpura, hemoptysis, hematuria, hematemesis and melena. Bleeding may exsanguinate the patient and produce shock.

The blood is uncoagulable when taken in a test tube and estimation of coagulation time provides a fairly reliable side room test for the severity of envenomation and requirement of antivenin. Cardiac manifestations include tachycardia, myocarditis and cardiac failure. Electrocardiogram may show abnormal T waves and disturbances of conduction. Pulmonary edema and hemorrhage may develop.

Rarely, optic neuritis may develop leading to partial or complete blindness in 2-7 days. Delayed onset of optic atrophy has also been recorded. Blindness may also result from intraocular bleeding.

Renal changes Proteinuria and hematuria may develop within a few hours after the bite. In the majority of cases these subside with treatment. Acute renal failure may develop in 50-60% of cases with severe envenomation. This manifests in 3-7 days of the bite. The most frequent and dreaded complication is anuric renal failure developing as a result of direct nephrotoxicity of the venom, hypotension, disseminated intravascular coagulation, hemoglobinuria and reactions to the antivenom administered therapeutically. Lesions include acute tubular necrosis, hemorrhagic interstitial nephritis, and even glomerulonephritis. Shock aggravates the renal damage. In 10% anuria may supervene and persist demanding peritoneal or hemodialysis. In survivors renal sequelae are rare but salt losing nephritis, renal parenchymal calcification and membranous glomerulonephritis have been reported.

Death in viperine bite is due to shock, hemorrhages, secondary infection, renal failure or cardiac failure.

Long-term sequelae like panhypopituitarism may manifest 3-5 years after severe viperine envenomation. Pituitary apoplexy has been noted. Myxedema may develop rarely.

Krait venom is the most lethal on weight for weight basis. Manifestations are similar to that of a cobra bite but the local reaction at the site of bite may be minimal.

Since kraits are prone to come into dwelling houses and hide under clothes or other material, bites acquired during sleep and paralysis manifesting on waking up are more likely to be due to krait bites. Careful search of the premises may reveal the offender.

Sea snake bites are identified by the victims as sharp pricks. The local reaction may be insignificant. Signs of envenomation occur within one hour and initial symptoms consist of pain and stiffness of the muscles of the neck,

back and proximal parts of the limbs but rapidly becoming generalised. Trismus, ptosis, external ophthalmoplegia and paralysis leading to respiratory failure may follow. Proteinuria and myoglobinuria are seen 3-6 hours after the onset of symptoms. Death is due to respiratory paralysis or renal failure. If the victim survives, muscle weakness may persist for months.

The overall mortality of the poisonous bites is 10-15%.

Death in snake bites is due to: (1) paralysis of respiratory muscles, (2) upper airway obstruction, (3) cardiac arrest, (4) hypotension and shock, (5) severe bleeding including intracranial bleed, (6) renal failure and (7) septicemia.

Interval between the Bite and Time of Death

	Range	Mean
Cobra	30 minutes-60 hours	8½ hours
Krait	3-68 hours	18 hours
Russels' viper	2 hours - 9 days	2 days
Echis carinatus	1-41 days	5 days
Sea snakes	12-24 hours	variable

Management

The most important step is to start first aid, reassure the victim and to decide upon the need for specific antivenin. *Distinction between poisonous and non-poisonous bites* Information from the local inhabitants is very helpful in identifying the species.

Poisonous	Non-poisonous
1. Only two fang marks	Multiple teeth marks
2. Local reaction present	No local reaction
3. Evidence of systemic envenomation present	Only fright reaction

Proper first aid is vitally important to reduce envenomation and this plays a major role in subsequent treatment. The bitten part should be immobilized using an improvised splint, washed well with soap and water and a tight tourniquet applied nearest to the site of bite where there is only a single bone. This tourniquet should occlude the lymphatics and veins but not the arteries. Chilling the limb in ice reduces the rate of absorption of venom. Immediate hospitalization is required.

General treatment consists of reassurance, sedation with diazepam, treatment of shock, antibiotics to cover the infection, and immunization against tetanus and gas gangrene. Corticosteroids may be necessary to combat shock. Metronidazole in a dose of 500 mg intravenously every 8 hours is very useful in treating anaerobic sepsis which invariably accompanies the snake bite.

Specific Treatment

Specific treatment is to administer anti-snake venom (ASV) which should be given only if signs of envenomation are definite or if the snake is identified to be definitely poisonous. The ASV available in India is made by Haffkine Biopharmaceutical Corporation Ltd, Bombay, and the Central Drug Research Institute, Kasauli. It is polyvalent. 1 mL of reconstituted ASV can neutralize 0.6 mg each of cobra, krait, Russell viper, and saw scaled viper venoms. It is prepared from sera of horses hyperimmunized with the venom and is available as the lyophilized product with the diluent.

Once reconstituted, the ASV has to be used immediately since it rapidly loses its potency. Being made from horse serum, it has to be tested for anaphylaxis by the intradermal and intravenous methods before administration and the product instructions should be carefully followed.

The total dose of ASV depends on the severity of envenomation.

Dose of ASV

Mild envenomation	3-5 vials
Moderate envenomation	5-10 vials
Severe envenomation	10-20 vials
Very severe envenomation	20-40 vials

ASV is given intravenously as a drip or slow push doses.

Children and underweight persons require the same dose of ASV as for the normal adults.

In cases allergic to horse serum, ASV may have to be withheld. In such cases desensitization may be done by injecting small quantities of ASV under cover of corticosteroids, before administering the full dose.

Local treatment The tourniquet should be released after systemic administration of antivenom. Wound toilet and protective dressings must be done. Incisions, suction, drainage and local instillation of ASV which used to be in vogue earlier are not undertaken. With adequate dosage of systemic ASV such aggressive measures can be avoided.

Guidelines for repetition of ASV Clotting and clot retraction can also be employed to assess the adequacy of ASV in viperine bites. Antivenom administration is adequate if the clotting time is within 20 minutes, the clot retraction is complete within 6 hours and the serum is straw coloured. If clotting time is prolonged beyond 20 minutes a further 10 vials may be needed. If clotting time is below 20 minutes but clot retraction is poor after 6 hours, a further 5 vials of ASV are needed. If clotting and retraction are normal, but the serum is red, two vials have to be given further.

For neurotoxic bites, since there is no laboratory parameter to monitor treatment, higher doses are often



Fig. 11.3: Cobra bite with myasthenic reaction

used. ASV should be given if signs of envenomation are present even if the patient is seen 1-2 days after the bite. Trials employing regimen containing higher and moderate doses of ASV have shown that the latter is quite adequate if laboratory monitoring is possible and the clinical condition is stable. Cases which have received smaller doses of ASV have quicker recovery and shorter hospitalization and therefore overdose of ASV should be avoided. The cost of 1 vial of ASV ranges around Rs. 300.00.

Treatment of complications Since cobra and krait bites may lead to acute myasthenic reaction with respiratory paralysis, prompt administration of neostigmine can be life-saving (Fig. 11.3). Intravenous doses of 2.5 mg repeated at suitable intervals brings about prompt relief. Respiratory failure has to be managed with artificial ventilation, if injection of neostigmine does not work. Renal failure has to be anticipated in all cases of viperine bites. Urine volume has to be regularly monitored. Early institution of hemodialysis and careful management of renal failure in an institution with facilities for renal support have helped to save many patients, who would otherwise have died. Extensive local sloughing may demand skin grafting.

Steroid Therapy

In a few cases methyl prednisolone given in a dose of 1 g IV daily for 2-3 days may be life saving. The indications include:

- (1) hypotension persisting after fluid and electrolyte correction before the administration of antivenin
- (2) peri-orbital puffiness,
- (3) chemosis of conjunctiva,
- (4) acute respiratory distress and
- (5) edema due to capillary leak.

Ref: Vimala, Kasi Visweswaran, Georgy K Nainan. In Snake bite: Consensus Statement as the management of common diseases in Kerala (ed) Poulose KP, Sajith S Kumar 2006; 268-9.

Prevention

Snakes should not be indiscriminately destroyed since they play a major role keeping the rodent population under check.

Snake bites can be avoided by:

1. Carrying a torch while walking in the snake infested areas,

2. Wearing shoes and other protective clothing, and
3. Using a stick which, if tapped on the ground, scares away most of the snakes.

Potent antivenin in sufficient quantity should be readily available in all the hospitals situated in snake-infested areas.

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12

Disorders Caused by Heat

3

T.K. Suma, K.V. Krishna Das

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GENERAL CONSIDERATIONS

Man has a remarkable ability to withstand physical stresses and strains and adapt to varying environment. When changes in climate are abrupt, adaptation may not be possible in some individuals and this leads to adverse effects. Ill effects of heat are seen in tropical conditions either among the natives or the new entrants. Heat is dissipated from the human body by conduction, convection and radiation, through breathing and by evaporation of the sweat, which is the most effective way. Radiation accounts for 65% of body heat loss under normal conditions. But at high temperatures evaporation becomes the major mechanism for dissipation of heat. Heat disorders result from the breakdown of heat regulatory mechanisms. The clinical picture may be acute or chronic.

On a very hot day the total loss of water in the form of sweat may reach 5-6 litres with a salt loss of 10-12 g. When acclimatization occurs there is increase in extra-cellular fluid volume, which is accommodated by expanded vascular bed. This results in reduction of the pulse rate, and increase in the cardiac output. The sweat glands start producing more sweat even at lower temperatures. Excretion of salt is reduced by lowering the levels of salt in the sweat (2 g/litre) and urine, mainly due to activation of renin-angiotensin system and increased production of aldosterone. Acclimatization to hot environment by proper training occurs in 10-14 days.

Acclimatized individuals are capable of performing well in hot climates, provided the intake of water and salt are adequate (5-6 litres and 15-20 g/day respectively).

There is evidence that the global temperature is going up steadily due to various factors such as increase in population, burning of fossil fuels, denudation of forest cover, irrigation schemes and the effect of heat-trapping gases which produce a greenhouse effect. The Intergovernmental Panel on Climate Change (IPCC) has predicted that the global temperature may go up by 2.5 °C by 2100 AD. In addition to the direct effects of warming it may also increase the incidence of natural disasters and vector transmitted diseases. It is estimated that the sea level will rise by an additional 19 inches by 2100, flooding coastal areas. Heat waves will be more frequent and more intense. Droughts and wildfires will occur more often. Disease-carrying mosquitoes will expand their range. More than one million species could be committed to extinction by 2050 if global warming pollution is not curtailed.

Despite wide variations in ambient temperatures, humans and other mammals can maintain a constant body temperature by balancing heat gain with heat loss. When heat gain overwhelms the body's mechanisms of heat loss, the body temperature rises, and a major heat illness ensues. Excessive heat denatures proteins, destabilizes phospholipids and lipoproteins, and liquefies membrane lipids, leading to cardiovascular collapse, multiorgan failure, and, ultimately, death. Management of heat related disorders is closely linked with that of fluids and electrolytes.

Heatstroke

Syn: Heat Hyperpyrexia

Definition, etiology and pathogenesis. Heatstroke follows exposure to heat and is characterized by hyperpyrexia owing to deranged heat regulatory mechanism. Heatstroke is defined clinically as a core body temperature that rises above 40°C and that is accompanied by hot, dry skin and central nervous system abnormalities such as delirium, convulsions, or coma. Heatstroke results from exposure

to a high environmental temperature (classic, or non-exertional heatstroke) or from strenuous exercise (exertional heatstroke). Neuropsychiatric disturbances are prominent. Heatstroke generally occurs at temperatures ranging from 40 to 45° C, but may also occur at wet bulb temperatures as low as 30-35° C, especially if the humidity is high. The external temperature at which heatstroke occurs varies between individuals and therefore is not a reliable parameter for diagnosis. Precipitating factors include lack of acclimatization, unaccustomed and sustained heavy work at high temperatures, alcoholism, infections, dehydration, use of drugs like atropine, antihistamines, phenothiazines, antidepressants and diuretics, and obesity.

The systemic and cellular responses to heat stress include thermoregulation, an acute-phase response whereby various cytokines and acute phase proteins are liberated, and the production of heat-shock proteins. Increased levels of heat-shock proteins in a cell induce a transient state of tolerance to heat stress, allowing the cell to survive. Thermoregulatory failure, exaggeration of the acute phase response, and alteration in the expression of heat-shock proteins may contribute to development of heatstroke.

Clinical features: The onset is sudden or even abrupt with a rapid rise of body temperature to 41°C or more with acute neurological features such as confusion, restlessness, delirium, agitation, convulsions and coma. In a few patients there may be prodromata, including headache, giddiness, thirst, irrational behaviour and restlessness, and the onset is gradual.

The cardinal diagnostic features are hyperpyrexia, neuropsychiatric disturbances, and a hot and dry skin (hot dry man). The temperature (oral or rectal) varies from 41.5 to 44°C. It is preferable to take the rectal temperature in these cases. The patient has tachycardia and tachypnea. 25% of patients have hypotension. Electrocardiogram shows T wave changes suggestive of myocardial involvement.

Complications The most serious complication of heatstroke is multi-organ dysfunction. This includes encephalopathy, rhabdomyolysis, acute renal failure, acute respiratory distress syndrome, myocardial injury, hepatocellular injury leading to jaundice, intestinal ischemia or infarction, pancreatic injury, and hemorrhagic complications, especially due to disseminated intravascular coagulation. Untreated, the condition is fatal owing to circulatory, hepatic or renal failure.

Diagnosis: Diagnosis should be suspected in the presence of the three cardinal features, viz. hyperpyrexia, neurologic disturbances, and a hot and dry skin in a subject exposed to high ambient temperature. It is important to rule out falciparum malaria. Malaria may

coexist with heatstroke but in cerebral malaria the peripheral blood will show signs of malaria hyperinfection. Other conditions like septicemia, typhus, pyogenic meningitis, encephalitis, pontine hemorrhage and closed head injuries have to be excluded.

Laboratory features of heatstroke include neutrophil leucocytosis, thrombocytopenia, elevation of blood urea bilirubin, uric acid, and reduction of plasma bicarbonate, potassium, sodium, calcium and phosphorus. None of these are diagnostically specific. Therefore, diagnosis has to be clinical.

Treatment: Heatstroke is a medical emergency. Treatment aims at the reduction of the rectal temperature to 39°C within one hour, restoration of circulating blood volume and support of various organ system functions.

The patient is covered with wet sheets or towels and sprayed with cold water while air is blown or fanned over him to promote evaporative cooling. The patient should preferably be in the lateral recumbent position or hands and knees position to expose as much of skin as possible to the air. As an alternative the patient may be immersed in cold water. Immersion in ice water is not preferred because of the possibility of shivering and hypotension. The limbs are gently massaged to promote circulation. When the rectal temperature falls to 39°C the patient is transferred to a cool room and watched for further rise of temperature. Recurrence is quite common and temperature regulation may remain unstable for weeks.

Rapid cooling to rectal temperatures below 38-39°C may precipitate convulsions, vomiting and hypotension. A mechanical body cooling unit is available in which cold water at 20°C is sprayed over the patient, while a blast of hot air at 50°C is blown from above. This prevents vasoconstriction and also augments evaporation.

Prompt and effective cooling restores neurological functions in the majority of patients. Recovery of central nervous system function is a favorable prognostic sign. Chlorpromazine (25-50 mg) administered intravenously is a useful adjunct during cooling. Antipyretics like acetaminophen and aspirin have no role and are contraindicated also.

If there is suspicion of malaria, antimalarials are given parenterally. Shock and cardiac failure have to be treated appropriately. The patient should also be observed and treated for renal failure due to rhabdomyolysis, disseminated intravascular coagulation and hepatic failure. Maintenance of hydration and electrolyte balance are important to prevent renal failure.

Sequelae include headache, insomnia, giddiness, cerebellar dysfunction and even coma. Most of these clear up in the course of weeks or months.

Prognosis: If left untreated, 50 -70% of subjects die of heatstroke. Early treatment reduces the mortality to

Disorder due to Physical Agents

15-20%. Shock also carries a bad prognosis. Presence of other systemic diseases and extremes of age worsen the prognosis.

Prevention: Heatstroke is a preventable disease. To prevent heatstroke, people should acclimatize themselves to heat, schedule outdoor activities during cooler times of the day, reduce level of physical activity, drink additional water and consume extra amounts of salt – (12 to 15 g/day).

Important points

1. Heatstroke, which is preventable, occurs at temperatures ranging from 40-45°C
2. Heat stroke could be exertional or non-exertional
3. Neuropsychiatric manifestations are prominent
4. Multiorgan dysfunction is the usual cause of death
5. Shock, extremes of age and systemic diseases are bad prognostic features

Anhidrotic Heat Exhaustion

Syn: Tropical Anhidrotic Asthenia, Thermogenic Anhidrosis

This is characterized by depression of sweating, exhaustion, and vesicular skin lesions on the trunk (Miliaria profunda).

Etiology: The condition is probably caused by the blockage of the sweat ducts by swelling of the cells of the stratum corneum and keratotic plugs, with consequent absence of sweating. This leads to retention of fluid and vesicle formation. The syndrome is frequently associated with prickly heat.

CLINICAL FEATURES

The illness can occur in newcomers or even in normal acclimatized persons, on prolonged exposure to heat. Feeling of extreme warmth during the hot part of the day, asthenia even at rest and impairment of working capability are initial symptoms. These symptoms are aggravated by even mild exertion. Tachycardia, tachypnea, and mild pyrexia (38-40.5°C) occur. Anhidrosis may extend all over the body or may be localized. This may persist for several weeks. There may be polyuria, the urine contains diminished amounts of chlorides.

Skin lesions superficially resemble prickly heat, but in miliaria profunda there is no erythema around the lesions and these are seen most commonly in the proximal parts of the limbs and on the trunk.

Diagnosis: Clinical diagnosis is based upon the symptoms. Simple heat exhaustion and malingering are to be ruled out.

Treatment: The patient should be transferred to cool surroundings. Recovery is generally rapid. Resumption of work in hot environment may lead to relapse.

Important points

1. Anhidrotic heat exhaustion is caused by blockage of sweat ducts
2. Frequently associated with prickly heat
3. Asthenia even at rest and impairment of work capacity are early features
4. Diagnosis is based on symptoms

Heat Syncope

Syn: Heat Collapse

Heat syncope may occur in a hot environment in the absence of demonstrable water and salt depletion. Heat syncope may occur in a wide range of temperatures, not necessarily the highest. The condition may affect newcomers or the natives in the locality doing excessive physical exertion.

Syncope results from cutaneous vasodilatation and resultant systemic and cerebral hypotension, pooling of blood in the blood vessels of the muscles and skin, especially of the lower limbs, during or after physical activity.

CLINICAL FEATURES

Syncope or collapse occurs either during or immediately after heat exposure on prolonged standing or sudden change of posture. Giddiness, vertigo, and nausea are common. The patient is pale with shallow breathing and frequent yawning. The blood pressure is low and the pulse is slowed as in vasovagal syncope. The symptoms may pass off in a few minutes after lying down. Rapid recovery occurs if the patient is transferred to cool environment.

Diagnosis

Syncope with postural changes during or immediately after heat exposure, without demonstrable water or salt depletion and the rapid recovery of the patient are diagnostic.

Treatment

The patient should be transported to a cool room and put to bed. Adequate fluids in the form of simple beverages should be given and urine output maintained at 1.5 liters per day. The patient should be encouraged to take adequate amounts of salt (15-20g/day) to avoid recurrence.

Important points

1. Heat syncope occurs in the absence of demonstrable water and salt depletion
2. Syncope is caused by secondary to cutaneous vasodilatation
3. Rapid recovery results when patient is transferred to cool environment
4. Intake of adequate quantity of water and salt are to be ensured for recovery

Water Depletion Heat Exhaustion

This type of dehydration is caused from prolonged strenuous activity in a hot environment with inadequate intake of water and other fluids. This is usually preceded by a period of prolonged sweating which leads to considerable loss of water. Children are more susceptible to this disorder than adults.

Etiology and pathogenesis. The major factor is water deprivation, which may be due to insufficient provision of water at the place of work, or voluntary avoidance of fluids in between meals. Negative water balance develops in persons doing heavy manual work in hot environment due to excessive sweating. From 6 to 8 litres of sweat may be lost in a day. Loss of water leads to reduction in the volume and increase in the osmolarity of the extracellular fluid. Intracellular water moves into the extracellular compartment. Salt depletion does not occur if salt intake is adequate, otherwise hyponatremia also develops. Heat exhaustion is characterized by dehydration, sodium depletion or isotonic fluid loss with associated cardiovascular changes.

CLINICAL FEATURES

Severe thirst is experienced in the early stages. The patient sweats even when the extremities are cold. Other early symptoms are nonspecific such as dryness of the mouth, irritability, restlessness, and weakness. Hyperventilation secondary to heat exhaustion can lead to respiratory alkalosis. In the fully established case dysphagia, hoarseness of voice, tachycardia, hypotension, oliguria, and anuria follow. Untreated, mental changes such as delirium and coma supervene and the condition may end fatally.

Diagnosis: The circumstances under which this syndrome occurs viz. the high environmental temperature and the clinical picture, especially with intense thirst, are diagnostic in a conscious patient. Difficulties arise in comatose patients who are also febrile. Distinction from salt deficiency may be difficult but the high sodium content of urine and plasma help to distinguish pure water depletion state.

Treatment: Patient should be kept at rest in a cool room. In mild cases oral fluids and flavored drinks are adequate. In severe cases the oral intake should be 5-8 liters on the first day with 15-20g sodium chloride. In an unconscious patient 5% dextrose solution is given intravenously in the first 24 hours with close monitoring of urine output. The levels of serum sodium, urinary sodium and chloride should be estimated and deficiencies should be corrected. Increasing urine output, rise of blood pressure and return of weight to normal are indications of clinical recovery.

Salt Depletion Heat Exhaustion

This condition is characterized by asthenic symptoms, because of salt depletion caused by prolonged sweating without sufficient intake. The symptoms are fatigue, nausea, vomiting, giddiness, insomnia, and cramps, but these patients do not complain of thirst.

Etiopathogenesis Unacclimatised subjects engaged in hard work in a hot environment are affected. There is considerable variation in susceptibility. Salt depletion has been proved to play a major role in the pathogenesis. There is a fall in osmolarity of extracellular fluid leading to movement of water intracellularly and consequent reduction in extracellular fluid volume. Plasma sodium and chloride levels fall.

CLINICAL FEATURES

A wide spectrum of symptoms may occur. In many patients there is a prodromal phase with vague symptoms like anorexia, nausea, giddiness and headache. Even at this stage the patient sweats profusely and the urine output is reduced. Diagnosis at this stage may not be very clear in the absence of cramps. The severe illness is characterized by asthenia and painful cramps. As the condition progresses, tachycardia, hypotension, dehydration, oliguria, and even shock ensue. Postural syncope is common. Coma and pulmonary edema precede death.

Laboratory findings Plasma sodium and chloride levels are proportionately reduced. Volume and salt content of urine are low. Severe dehydration leads to pre-renal azotemia.

Diagnosis The salt depletion heat exhaustion has to be differentiated from the water depletion type by the absence of thirst, the presence of muscle cramps, and oliguria with low levels of sodium and chloride in urine.

Treatment In mild cases oral replacement with 4-5 liters of normal saline in 24 hours may be adequate. 10-20 g of salt can be added to food and drinks as supplement. Severe cases require intravenous fluids. Two liters of isotonic saline are given in the first four hours rapidly with monitoring of urine volume and urinary chloride. Intravenous 3% saline may be necessary if sodium depletion is severe. Recovery is rapid. Consumption of extra salt in food and drinks helps to prevent recurrence.

Important points

1. In salt depletion heat exhaustion asthenic symptoms occur due to salt depletion
2. Usually there is a prodromal phase with vague symptoms
3. Asthenia and painful cramps and absence of thirst are characteristic features
4. With severe sodium depletion IV 3% saline infusion may be required

Heat Cramps

This occurs in persons who sweat excessively in hot environment without having normal or supplementary salt intake. This is a milder form of salt deficiency heat exhaustion. Severe cramps develop in the voluntary muscles. These are painful and may last from a few seconds to several minutes. The cramps are precipitated by heavy work, are very painful and commonly involve the extremities. Muscle cramps recur at intervals. Laboratory evaluation may show low serum sodium, hemoconcentration, and elevated urea and creatinine. Oral Supplementation of 10-15 g of salt relieves the cramps in mild cases. In more severe cases, administration of 600 mL normal saline gives dramatic relief. The patient has to take rest for 1-3 days with continued dietary salt supplementation before returning to work.

Skin Lesions Caused by Exposure to Sun and Hot Environment

Direct exposure to sun leads to sunburn and solar keratosis. Prickly heat develops in persons exposed to hot environment even without direct exposure to the sun.

Sunburn: It is caused by direct exposure to ultraviolet light. Fair-skinned persons, especially newcomers are more commonly affected. Symptoms start with erythema and pruritus and proceed to acute painful edema, vesiculation and bullae formation. Prolonged and repeated exposure results in increased pigmentation and improved

tolerance. Local application of calamine lotion containing 0.5% crystal violet or any antihistaminic cream gives relief. Para-amino benzoic acid, which absorbs ultraviolet light, gives some protection and this can be applied as a cream (5%) or lotion. Prevention consists of avoidance of direct exposure and the use of protective clothing and umbrella.

Solar keratosis Repeated exposure to direct sunlight causes patchy hyperkeratosis. The neck, back, dorsum of the hands and forehead are affected maximally. Albinos suffer more. These lesions may predispose carcinoma, especially melanoma.

Miliaria rubra (Prickly Heat) These are papular lesions seen in persons exposed to hot environment, especially if humidity is high. This condition results from blockage of sweat glands by the prickly cell layer of the epidermis, escape of sweat in to the epidermis and further inflammatory changes. Areas covered by clothing are more severely affected. Papular lesions develop which may become vesicular or pustular with surrounding erythema. These may be associated with pruritus and a prickly sensation. Secondary infection may develop later.

Treatment Local application of calamine lotion gives soothing relief. Excessive washing of the skin with strong soap should be avoided. Use of bland soaps and regular use of gingeli oil (sesame oil) over the skin applied for one hour weekly prevents this lesion in the native population. In established cases, stay in a cold environment and use of loose clothing brings about relief in 2-3 weeks.

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Injuries due to Cold

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muscular work occurs when there is abrupt demand to increase heat production. The core temperature will drop if there is failure to maintain thermal balance.

Freezing Cold Injury

Syn: Frost Bite

This is seen in persons exposed to temperature below freezing point such as mountaineers, explorers, war

Humans adapt to cold by peripheral vasoconstriction, which reduces heat loss, and increase in the metabolic rate, which produces more heat. Shivering, which involves



Fig. 13.1: Blisters of fingers due to frostbite

casualties, or victims of natural disasters. There is freezing of extravascular fluid with formation of ice crystals in tissues leading to damage of vascular endothelium, microvascular thrombosis, ischemia and superficial necrosis. In mild cases where only the skin and subcutaneous tissues are involved numbness, prickling and itching are the features. Paraesthesia and stiffness occur with involvement of deeper tissues. The skin loses its elasticity and becomes immobile. Blisters, edema, necrosis and gangrene may set in (Fig. 13.1).

Management Rewarming: Superficial frostbite can be treated by firm pressure with a firm hand, placing fingers in the axilla. General warming of the body to elevate core temperature should be undertaken before local warming of the affected limb. After restoration of the core temperature, the affected limb should be warmed in a moving water bath preheated to 40–42° C. During thawing re-establishment of circulation may result in intense pain. Analgesics and antibiotics are given if indicated. Protection of the affected part by avoiding friction or pressure is important. Tetanus prophylaxis has to be considered as there is increased susceptibility. Antiplatelet agents, haemodilution, peripheral vasodilators and hyperbaric oxygen are other therapies used with varying results. Early sympathetic blockade may reduce symptoms, but use of sympathectomy is controversial. The condition can be prevented by covering the body with proper clothing, protection of the affected part, avoidance of local pressure, frequent changes of position and avoidance of smoking.

Important points

1. Frost bite occurs when exposed to temperature below freezing point
2. Damage to vascular endothelium caused by the ice crystals is the main pathology
3. In mild cases only the skin and subcutaneous tissue are involved

4. Severe cases produce parasthesia, weakness, and gangrene
5. General warming the body followed by local warming of affected limb is important

Nonfreezing Cold Injury

Syn: Trench foot, immersion foot

Exposure to cold damp environment above freezing point for long periods leads to tissue ischemia. This is seen in warfare, persons marooned in floods, cases of shipwreck and other natural calamities. Initially, the limb is cold, numb and pale (pre-hyperemic phase). During the hyperemic phase they become hot with intense pain and burning. The post-hyperemic phase is the vasospastic period where the skin becomes pale or cyanotic. Movements may not be possible. Arterial pulses may be undetectable. The limbs are especially susceptible to trauma and infection leading on to gangrene and maceration. In many cases, permanent sequelae like sensorimotor defects may result. Secondary complications are lymphangitis, cellulitis and thrombophlebitis.

Management The body is gradually warmed by exposure to air at room temperature, keeping the limb elevated and taking care to avoid overheating of the part. Analgesics and antibiotics should be given as indicated. Chilblains result from minor forms of cold injury. This manifestation is reversible if the environment is altered.

Important points

1. Trench foot occurs on exposure to damp environment above freezing point
2. Three phases- prehyperemic, hyperemic and post-hyperemic
3. Permanent sequelae like sensorimotor defects may occur
4. Gradual warming of the part without overheating reverses the lesion

Hypothermia

When the core temperature falls below 35 °C (95 °F), the condition is called hypothermia. Hypothermia may be induced for therapeutic purpose or may be accidental. The later is serious and it affects persons at the extremes of age with disturbed thermoregulatory mechanisms, or may be caused by disease, starvation or injury. It can occur in fit subjects when subjected to extreme cold without protection.

Accidental Hypothermia

This condition develops during cold-water immersion, shipwreck, mountaineering, etc. Hypothermia may be rapid or slow depending upon the rate of cooling. When cooling is slow, compensatory mechanisms set in.

Disorder due to Physical Agents

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Starvation, alcoholism and drugs like phenothiazines aggravate the ill effects of cold environment. Diseases like hypothyroidism, hypopituitarism, hypoadrenalism and cirrhosis of the liver predispose to hypothermia. Physiological functions such as oxygen consumption, myocardial repolarisation, peripheral nerve conduction, gastrointestinal motility and respiration will be slowed down due to systemic hypothermia.

CLINICAL FEATURES

The appearance of a patient with accidental hypothermia is characteristic. The skin is pale, cold and cyanotic. Initial manifestations include lethargy, drowsiness, irritability, confusion and impaired coordination. As the core temperature falls below 35°C, there is progressive slowing down of cerebral functions resulting in mental stupor and subsequently leading to coma.

Shivering may occur if the temperature is above 30 °C but below this level the muscles become spastic and resemble rigor mortis. Respiration is slow and shallow. Tissues suffer from hypoxia since the oxygen dissociation curve of hemoglobin shifts to the left at low temperatures. Cardiovascular signs include bradycardia, hypotension, and cardiac arrhythmias like atrial fibrillation and ventricular fibrillation.

Cardiac arrest is likely to occur when the core temperature drops to 25°C. Electrocardiographic changes such as prolongation of PR and QT intervals and J waves (positive deflection at the end of QRS complex) may occur. Biochemical abnormalities include hypoglycemia, metabolic acidosis, hyperkalemia and mild azotemia. Thyroid function may be depressed.

Complications The core temperature usually continues to drop further for 10-20 minutes even after removing the patient from the cold environment. This phenomenon is called the 'after drop'. Respiratory infections are common in cases of hypothermia.

Differential diagnosis This includes myxedema coma which closely resembles hypothermia, poisoning, starvation, hypoglycemia, and neurological disorders.

Treatment Accidental hypothermia has to be managed as a medical emergency to save life, if possible in an

intensive care room. As in all comatose patients attention should be given to the maintenance of patent airway, proper ventilation, blood volume, and levels of electrolytes.

External re-warming is effective in the mildly hypothermic patient. External re-warming is done in a moving water bath heated to 40-42°C. When the core temperature has reached 34-35°C, the patient is placed on a warm bed and insulated against further heat loss. Antibiotics are required in many patients. In severe cases it is advisable to increase the core temperature by hemodialysis or repeated peritoneal dialysis using 2 L of warm potassium free dialysate warmed to 37°C, wherever facilities are available.

Prognosis The prognosis depends upon the duration and severity of hypothermia and the underlying disorder. Aged patients are at a higher risk. In general, majority of deaths occur within 30 minutes of rescuing the victim. Death is caused by cardiac arrest or ventricular fibrillation. In a few patients with apparent absence of vital signs on admission, these appear when the body is warmed. *Hence, all cases should be resuscitated irrespective of the initial findings and they should not be pronounced dead until they have been observed for at least 30 minutes, after warming to 36°C or above.* In persons who are susceptible to chronic hypothermia, preventive measures like domestic heating and visits by social workers should be arranged. In all cases of hypothermia, underlying medical conditions such as hypothyroidism, hypopituitarism and poisonings should be excluded by early investigation, since specific management for these conditions is absolutely essential to save life.

Important points

1. Accidental hypothermia is more common and more serious in extremes of age
2. Slowing of cerebral function occurs at body temperatures below 35°C leading to stupor and coma
3. Cardiovascular changes include bradycardia, hypotension and atrial or ventricular fibrillation
4. "After drop" is a complication during management
5. Hypothermia is a medical emergency and death is caused by cardiac arrest or ventricular fibrillation

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Disorders due to Alterations in Barometric Pressure

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Caisson Disease 94

EFFECTS OF SUDDEN REDUCTION IN BAROMETRIC PRESSURE**Syn:** Dysbarism

Those who live in high altitudes, passengers in unpressurized aircrafts, divers and workers in pressure chambers who are decompressed without proper supervision are susceptible to the ill-effects of sudden reduction in ambient pressures. Slow and graded decompression allows the gases contained in body cavities and dissolved in the blood and tissue fluids to be liberated gradually without producing untoward effects. Normally eustachian tube functions to equalize middle ear and ambient environment pressures. In persons suffering from upper respiratory infection, sinusitis, or Eustachian blockage, symptoms like ear pain, vertigo, giddiness, or deafness may occur. Expansion of gas in the alimentary tract results in abdominal distention and dental pain which results from increase in the volume of gases within dental cavities. Aseptic necrosis of bone may occur in some cases.

As a result of rapid decompression more serious consequences occur due to formation of bubbles from liberation of nitrogen dissolved in the blood and tissues fluids. Acute decompression sickness follows rapid reduction of environmental pressure sufficient to cause the formation of bubbles from dissolved gases in the tissues. The bubbles act as emboli. This disease is seen in divers and those working under water in harbours, ports, naval installations, offshore oil drilling, and mining industry. In patients with airway obstruction, expansion of air in the lungs leads to pulmonary rupture with resultant pneumothorax or surgical and mediastinal emphysema.

Factors, which influence clinical manifestations are obesity and physical activity during the compression phase and individual susceptibility. Obese subjects suffer more. In addition to the mechanical effects due to the liberated gases, secondary phenomena also develop. These are fat embolism, sludging of erythrocytes in the micro-circulation, platelet activation and disseminated intravascular coagulation. The gas bubbles themselves may be transient, but the effects they induce are

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The standard atmospheric pressure of 760 mm Hg exerted at mean sea level may fluctuate by 15-20 mm Hg under normal weather conditions. Lowering of barometric pressure is generally associated with lowered oxygen content of inspired air. If the oxygen supply is maintained adequately, humans can tolerate lowering of atmospheric pressure for prolonged periods. The volume of gases held in closed body cavities changes inversely with the external pressure.

EXPOSURE TO INCREASED BAROMETRIC PRESSURE**Syn:** Barotrauma

This may occur in deep-sea divers, tunnel workers and patients under hyperbaric therapy chambers. The volume of gases held in the middle ear, paranasal sinuses, lungs, intestines, dental cavities etc., diminishes under the high pressure and transudation occurs into these cavities. Severe rise of pressure leads to distortion and damage to tissues. In the middle ear it may lead to transudation and in severe cases even rupture of the tympanic membrane - *otitic barotrauma*. Changes in the volume of air in the paranasal sinuses leads to headache, nasal discharge, or epistaxis.

Compressed air, used for breathing at depths by sea divers, is generally safe but the increased partial pressure of nitrogen can cause nitrogen narcosis. This is characterized by euphoria, error of judgment and intellectual impairment. Oxygen toxicity may occur if pure oxygen is administered at a pressure of 2.8 bar (equivalent to a depth of 18 m water), especially when the individual is engaged in vigorous activity. Confusion, convulsions and damage to the lungs may result from oxygen toxicity.

prolonged. Increased permeability leads to fluid loss into tissues, hypovolemic shock, hemoconcentration and hyperviscosity states.

The classical form of decompression sickness occurs in Caisson disease. Caisson is pressurized equipment used to take divers under water for work. Safety rules have been laid down for surfacing such workers from depths. Non-compliance with the rules results in development of decompression sickness.

Important points

1. Increase in volume of gases in body cavities produces symptoms when there is sudden reduction in barometric pressure
2. Nitrogen bubbles liberated during decompression result in serious problems like embolism.
3. Pulmonary rupture, pneumothorax and mediastinal emphysema are other complications
4. Fat embolism, disseminated intravascular coagulation, hypovolemic shock and hemoconcentration are secondary phenomena of decompression sickness

Caisson Disease

Syn: Bends, Acute Decompression Sickness, Compressed Air Illness

Caisson is a large water tight chamber open at the bottom in which workers can work under water for long periods. A high air pressure is maintained within the caisson to keep water out. Persons who work in deep under-water surroundings have to follow strict safety precautions to avoid ill effects of rapid changes in barometric pressure. This disorder occurs in divers who have been brought to the surface rapidly without conforming to the safety precautions. Under high barometric pressure more of air dissolves in blood and tissue fluids. Oxygen may be used up but nitrogen is not. When the barometric pressure is lowered the nitrogen comes out of the solution as bubbles which lead to pathological consequences. Some workmen are particularly susceptible. Nitrogen being more lipid soluble, more bubbles are formed in the nervous tissue and hence neurological symptoms predominate. The spinal cord is most commonly affected, the brainstem and cerebral hemispheres are affected to a lesser extent. Autopsy shows hemorrhages in the white matter and micro infarcts. Other tissues involved include the joints, skin and lungs.

CLINICAL FEATURES

Symptoms start within three hours of surfacing, but rarely they may be delayed by several hours. Mild cases show pains and cutaneous lesions. In the severe types neurological and pulmonary lesions are prominent. An apparently mild case may rapidly become severe and

hence the initial presentation may be misleading. Early cutaneous manifestations include pruritus, erythematous skin lesions and cyanotic patches, and these should alert the physician of the impending disease. The commonest presenting symptom is joint pain (bends) felt over the knees, shoulder, hips, and elbows.

More serious features are pulmonary decompression sickness (chokes) presenting with retrosternal pain, cough and dyspnea and neurologic manifestations. Tachypnea, hypotension and shock may follow the onset of chest pain and the patient may die in coma. The neurologic symptoms include paraesthesiae, girdle pains, varying degrees of motor and sensory deficits, headache, blurring of vision, diplopia, pupillary abnormalities, dysarthria and vestibular dysfunction characterized by vertigo, nystagmus, nausea and vomiting (staggers).

Diagnosis The condition is likely to be missed by the unwary physician. History, the circumstance of the case and the physical manifestations should suggest the possibility of decompression sickness. Delay in onset of symptoms should not go against the diagnosis if other features are suggestive.

Course and prognosis The course is unpredictable since mild cases may rapidly become serious and die. Prognosis depends upon the promptness and adequacy of recompression and graded decompression. This measure should be instituted without delay even in hopeless cases. Many a time the recovery is remarkable. Neurological deficit tend to persist if treatment is delayed. Early recompression can prevent the development of neurological lesions. In suggestive cases valuable time should not be wasted by undertaking detailed clinical examination before recompression is instituted.

Treatment Specific treatment is to institute immediate recompression in a pressure chamber, as an emergency measure. Respiratory depressants like morphine should be avoided. The pressure equivalent and the duration of recompression have to be decided by personnel trained in recompression techniques. Usually, a pressure of 2.8 atmospheres (283.7 kPa) is beneficial. *Hyperbaric oxygen* helps to improve oxygenation of ischemic tissues.

In patients with neurological deficits, shock or cerebral edema, corticosteroids are beneficial. Low molecular weight dextran (dextran 40) helps to reduce vascular sludging. Infusion of appropriate fluids helps to restore blood volume, improve the circulatory state, and mobilize trapped bubbles.

After suitable recompression, the patient should be carefully decompressed, allowing sufficient periods at each stage to prevent recurrence of bubble formation. Susceptible persons should refrain from diving till recovery is complete.

Important points

1. In Caisson disease nervous system involvement is more predominant-spinal cord being commonly affected, than the brainstem or cerebral hemispheres

2. Joint pain (bends) involving knee, elbow, hip and shoulder are common
3. Pulmonary symptoms (chokes) are retrosternal pain, cough, dyspnea and tachypnea
4. Immediate recompression in a pressure chamber is the treatment

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Diseases due to High Altitude

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Introduction

Twenty-five percent of the earth's land mass is mountainous, at heights above 2500 m above sea level. 10% of the world's population lives in mountains. More than 80% of them are poor without basic medical facilities. Iodine deficiency is common. Natural calamities such as land slides, avalanches, floods, thunder and lightning and earthquakes are more common in these regions since mountains are sites of continental plate collision in the natural evolution of the planet. Many people from other regions of the world visit the mountainous regions for occupation, sport or adventure. *The term high altitude illness refers to the total clinical picture occurring in unacclimatised entrants into high altitude regions shortly after their entry.*

In India, in the Himalayas alone more than 2 lakh persons undertake trekking annually. Many of the Indian troops are deployed at high altitudes. Constant vigil and unexpected combats have to be performed by our troops to protect our northern borders, were very adverse conditions such as altitude above 3000 m, temperature below 5°C, atmospheric pressures far below normal and

inadequacy of communication are built-in handicaps. Peoples inhabiting heights above 2000 m are smaller in size, have a higher hemoglobin level in health and are adapted to the environment. Features such as koilonychia have been detected in them, even in the absence of iron deficiency anemia. Incidence of tobacco smoking and alcoholism is high among the mountain tribes. Mountaineering and trekking by holiday makers are popular sports in India.

The term "high-altitude illness" describes the cerebral and pulmonary syndromes developing in unacclimatized persons shortly after ascent to high altitude. These include acute mountain sickness, high altitude cerebral edema and high altitude pulmonary edema.

Acute Mountain Sickness (AMS)**Syn: Soroche**

Sudden exposure to heights above 2,400 m may lead to hyperventilation, increased heart rate, palpitation, and headache resulting from lowered oxygen tension and this is known as acute mountain sickness (AMS). The symptoms typically develop within 6 to 10 hours after ascent. In most individuals symptoms subside within 24-48 hours. Cold weather and intense physical activity predispose to this condition. The exact process of acute mountain sickness is not known. Hypoxia elicits neurohumoral and hemodynamic responses in brain and lungs and these result in over perfusion of microvascular beds, elevated hydrostatic capillary pressure, capillary leakage and edema. Newer evidence suggests that all people develop swelling of the brain on ascent to high

altitudes. Those with a greater ratio of cerebrospinal fluid to brain volume are better able to compensate for swelling through displacement of cerebrospinal fluid. These people may not develop acute mountain sickness. So acute mountain sickness might be related to a person's ability to compensate for the swelling of the brain.

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CLINICAL FEATURES

Three clinical patterns are seen

1. The **pulmonary form** is characterized by cough, dyspnea, chest pain, and basal rales. Cheyne-Stokes respiration may be observed. During the apneic phases the patient may be cyanosed. There is peripheral vasoconstriction. Appearance of basal rales may precede the onset of high altitude pulmonary edema.
2. The **cerebral form** presents with headache, giddiness, irritability, forgetfulness, insomnia, drowsiness and convulsions. Vertigo, tinnitus, visual and auditory disturbances can also occur. Papilledema may be observed in severe cases. Headache increases with increase in cerebral edema.
3. The **hypoxic form** is vague in its clinical picture. Symptoms include muscle cramps, anorexia, gastrointestinal disturbances and epistaxis.

In the majority of cases the onset is within 6-24 hours after arrival. Symptoms subside spontaneously, but recur everyday for 3-4 days till acclimatization occurs. A few cases may develop acute pulmonary edema. Altitude proteinuria is a common finding, which tends to disappear with oxygen therapy or on returning to the lower altitudes.

Treatment Definitive treatment is immediate descent to lower altitude. Rest and administration of oxygen 1-2L/min often relieves acute symptoms. If immediate descent is not possible portable hyperbaric chambers may be useful. Other recommended therapies are acetazolamide 125-250 mg every 12 hours and dexamethasone injections 8 mg initially followed by 4 mg every 6 hours.

Prevention Slow ascent and avoidance of physical exertion for 72 hours help to prevent AMS. Acetazolamide in a dose of 250 mg four times a day is beneficial if started a day prior to the travel and continued for 2-3 days. Dexamethasone 4 mg every 12 hours beginning the day of ascent, continued for three days at high altitude and then tapering off over 5 days is another alternative.

Important points

1. Acute mountain sickness occurs on rapid ascent to above 2000 m
2. Symptoms usually start within 6 to 10 hours after ascent and subside within 48 hours
3. Hypoxia and its effects result in edema in brain and lungs
4. Oxygen inhalation, acetazolamide and dexamethasone recommended for treatment
5. Slow ascent and avoidance of physical exertion help to prevent AMS.

High Altitude Pulmonary Edema

This is a more serious complication compared to AMS. Young subjects in apparently good health are more affected. It may manifest in newcomers and also in subjects acclimatized to high altitudes, if they ascend the heights rapidly after long periods of stay at lower altitude. Altitudes above 2500 m can be harmful, but most of the cases occur at heights of 3050 to 4550 m. Heavy meal, physical exertion and too rapid an ascent precipitate the condition. Symptoms start within 6 to 48 hours of reaching the station.

Pathophysiology Though pulmonary hypertension is invariably found as a consequence of hypoxia, only a small proportion of subjects develop acute pulmonary edema. High-altitude pulmonary edema is a non-cardiogenic pulmonary edema associated with pulmonary hypertension and elevated capillary pressure. The pulmonary hypertension is secondary to the exaggerated pulmonary vasoconstriction induced by hypoxia. Sympathetic over activity, endothelial dysfunction, and hypoxemia are the proposed mechanisms. An immunogenetic basis also has been suggested because of higher incidence of HLA-DR6 and HLA-DQ4 antigens in susceptible individuals.

CLINICAL FEATURES

Many cases follow acute mountain sickness, but in some, pulmonary edema develops abruptly. Early symptoms are cough, tachypnea, dyspnea, and chest pain. These are soon followed by hemoptysis, cyanosis, frothy expectoration, and intense chest discomfort. Oliguria may develop.

The course is variable. In some, the pulmonary edema worsens while in others it may become sub acute and persist for a few days. In severe cases right-sided heart failure may follow and this may precede death. Radiographic abnormalities include prominence of the pulmonary arteries, irregular patchy infiltration of one lung or bilateral nodular densities (Fig. 15.1). Electrocardiogram reveals acute right ventricular strain due to pulmonary hypertension.

Diagnosis High altitude pulmonary edema should be anticipated in healthy subjects who develop vague cerebral and respiratory symptoms on reaching high altitudes. Early recognition and treatment are necessary to avoid rapid deterioration or cardiac failure. Malingering has to be differentiated from this condition.

Treatment Immediate treatment under field conditions is rest and administration of 100% oxygen at a rate of 4-6L/min for 15-30 min. Recompression using a portable hyperbaric bag will reduce symptoms if immediate descent



Fig. 15.1: X-ray chest: High altitude pulmonary edema
Note the bat-wing like opacities arising from the hilum

Important points

1. High altitude pulmonary edema is a serious complication occurring at heights of > 3000 m
2. Pulmonary hypertension and elevated capillary pressure secondary to hypoxia form the basic pathology
3. Radiographic abnormalities vary from patchy opacities in one lung to bilateral nodular opacities
4. Immediate descent and hospitalization are required in severe cases
5. Education of prospective mountaineers helps in prevention

High Altitude Cerebral Edema

This disorder is less common than pulmonary edema. Cerebral edema may follow acute mountain sickness several hours after reaching the high altitude. Vaso-dilatation, impaired cerebral autoregulation and elevated capillary pressure are the pathogenic mechanisms. Cerebral edema occurs due to cell swelling caused by increase in intracellular osmolality. Alteration of blood brain barrier secondary to hypoxia also contributes to the symptoms. The mediators are endothelium derived vasodilator growth factor, bradykinin and nitric oxide. Early clinical features consist of lethargy, insomnia, dreamy state, and irritability. Cheyne-Stokes respiration may develop. Severe cases develop intense headache, confusion and coma before ending fatally.

Treatment The patient should be administered pure oxygen (2-4L/min) and evacuated to a lower camp. Dexamethasone given intravenously or intramuscularly in a dose of 4-8 mg every 6 hours gives relief.

Chronic Mountain Sickness

Syn: Monge's disease, Chronic soroche, high altitude disease

Some persons living at high altitudes lose their acclimatization and develop symptoms. Most of such reports have come from South America. Males are affected more than females. The mechanism is not fully understood. Features include somnolence, hypoxemia, cyanosis, clubbing of fingers, polycythemia, mental depression and evidence of right ventricular failure. ACE inhibitors such as enalapril in doses of 5 mg daily have been shown to reduce polycythemia. Palliative measures are only of temporary benefit. Therefore it is advisable to remove affected individuals to low altitudes. The whole picture reverts to normal on reaching low altitudes.

is not possible. If oxygen is not available the patient should be evacuated to a lower camp, hospitalized and administered oxygen. Frusemide 40 mg should be given intravenously. Persistence of pulmonary edema is an indication for repeating frusemide. Nifedipine 10 mg initially followed by 20 mg repeated every 12 hours gives symptomatic relief. Physiological venesection by applying tourniquets proximally to the limbs helps to reduce pulmonary edema. Precipitating factors such as respiratory infection have to be looked for and treated appropriately.

Cases, which do not respond to the resuscitatory measures, should be evacuated to lower altitude urgently to prevent death.

Prevention Proper training and conditioning for 1-2 weeks should be undertaken before reaching high altitudes. Ascent should be gradual to permit acclimatization. On reaching high altitudes all unacclimatized persons should avoid physical exertion for 48-72 hours. Salmeterol inhalation 125 mg every 12 hours beginning 24 hours before the ascent is recommended to reduce incidence of high altitude pulmonary edema. Nifedipine 20 mg administered as a slow release preparation 8 h is also effective in preventing high altitude pulmonary edema.

Those planning to ascent 3000 m should carry supply of oxygen and equipment sufficient for several days.

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Drowning

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T.K. Suma, K.V. Krishna Das

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GENERAL CONSIDERATIONS

Definition: Drowning is the pathological state leading to death resulting from the aspiration of water into the respiratory tract or due to asphyxia immersion. More than 2 lakh persons die annually of drowning, 25% in sea and 75% in inland waters. Two types of drowning have been recognized - *dry drowning* and *wet drowning*. In dry drowning death is due to laryngeal spasm, which proves fatal in 20% of the subjects. This also prevents the entry of water into the lungs.

In wet drowning water enters the lungs. The consequences differ between fresh water and sea water drowning. In fresh water drowning, water is quickly absorbed from the lungs, leading to hemodilution and hemolysis with release of potassium from the red blood cells. In addition to hypoxia and ventilatory failure, hyperkalemia precipitates ventricular arrhythmias, which may prove fatal.

In salt water drowning the fluid in the lung is hyperosmotic. It absorbs more fluid into the alveoli causing pulmonary edema and respiratory failure. Hypernatremia follows later when the salt is absorbed into the circulation. In addition to the metabolic and local effects, impurities and contaminants give rise to local infection.

Secondary Drowning or *near-drowning* occurs a few hours or few days after the initial resuscitation due to the secondary changes in the lungs such as pulmonary edema, pneumonia, pneumothorax, electrolyte disturbances and metabolic or respiratory acidosis. This accounts for 25% of deaths.

Immersion syndrome. In this, sudden death occurs due to cardiac arrest caused by vagal stimulation brought about by sudden immersion into cold water.

PATHOLOGY AND CLINICAL FEATURES

Lungs: Pulmonary edema develops. Fresh water interferes with surfactant leading to formation of hyaline membrane, atelectasis and hypoxemia. Aspiration of foreign particles worsens the atelectasis. Bacterial infection leads to pneumonia or lung abscess.

Heart: Arrhythmias such as ventricular fibrillation and cardiac arrest may occur. Electrocardiogram may show nonspecific changes due to asphyxia.

Kidneys: Acute tubular necrosis may develop in near-drowning in fresh water due to hemolysis and prolonged hypotension.

Central nervous system: Asphyxia leads to loss of consciousness, cerebral edema and convulsions. Sequelae of anoxic encephalopathy such as transient hemiparesis, quadriparesis, choreoathetosis, aphasia and faciobrachial weakness may develop.

MANAGEMENT

First aid: (1) clear the airway of water and foreign bodies by putting the patient head low and by suction, (2) institute mouth-to-mouth breathing as early as possible, (3) closed chest cardiac massage should be instituted if heart sounds are absent, and (4) all cases must be hospitalized to prevent death from secondary drowning.

Hospital treatment: This aims at (1) maintenance of adequate oxygenation, (2) correction of metabolic and electrolyte imbalance and (3) prevention of secondary effects. Adequate oxygenation is achieved by the use of controlled ventilation with 100% oxygen, later to be reduced to 40%. If these measures fail to respond intubation and application of positive and expiratory pressure (PEEP) respiration should be resorted to. The PEEP increases the functional residual capacity, thereby minimizing intrapulmonary shunts and ventilation perfusion abnormalities, and promotes better oxygenation. If bronchospasm is present, an aerosol of salbutamol 200 mcg should be administered. Acidosis is to be corrected

with sodium bicarbonate given intravenously in a dose of 0.7 to 1 mmol/kg bw. Proper correction of electrolyte imbalance and acidosis should be monitored with laboratory estimations.

Constant observation and appropriate management of pulmonary edema, pneumonia and pneumothorax serves to prevent secondary drowning. Prophylactic antibiotics have to be used to prevent respiratory infections. Skiagram of the chest is necessary in all cases to detect complications. Atelectasis has to be managed with bronchoscopic aspiration. In severe cases of pulmonary edema, dexamethasone given in a dose of 0.5-1 mg/kg bw in 24 hours IM or IV has been successful. If signs of intracranial hypertension develop, it is treated with hyperventilation and IV infusion of 200 mL of 20% mannitol.

Prognosis

This depends on the extent and duration of hypoxia and the first aid. Patients presenting with coma and cardiac irregularities have higher mortality and morbidity.

Immersion in cold water causes death earlier due to rapid cooling, but survivors show less tendency to develop neurological sequelae. Residual complications of near drowning include convulsive disorders, intellectual impairment, cardiac neurosis and pulmonary atelectasis leading to bronchiectasis.

Prevention: Education of the public on the hazards in water and first aid measures to save drowning victims should be available in places of water sports, holiday resorts and beaches. Trained lifeguards should be available at public swimming places.

Important points

- 1. In dry drowning laryngeal spasm is the cause of death
- 2. In fresh water wet drowning hemodilution, hemolysis, ventilatory failure and ventricular arrhythmia may occur
- 3. Pulmonary edema and respiratory failure are the features in salt water drowning
- 4. Maintenance of adequate oxygenation, correction of metabolic and electrolyte imbalances and prevention of secondary effects are the mainstay of management

17

Injuries due to Ionizing Radiations

T.K. Suma, K.V. Krishna Das

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- Damage to Embryo by Irradiation in Fetal Life 101
- Local Radiation Injury 101

General Considerations

Ionizing radiations are either electromagnetic or particulate in nature. They are derived from natural or artificial radioactive isotopes, nuclear reactors, diagnostic and therapeutic equipment (e.g. X-rays, CT scan) and the complex shower of particles from the outer space known as cosmic rays. The radiations include alpha, beta, and gamma particles and electromagnetic waves.

Radiation injury is seen in survivors of nuclear war, after radiotherapy, persons engaged in industries involving radioactive materials, radiologists and radiotherapists. In some parts of the world radioactive sand accounts for low dose continuous radiation, e.g., the mineral beaches of Kerala. Radiation is harmful at all doses, the danger increasing with the rate and dose of exposure (Table 17.1). The age group 10-19 years is most susceptible. The maximal permissible radiation exposure for occupationally exposed workers is 0.1 rem per week for the whole body. Critical targets are the cellular nuclei.

The damage caused to the biological systems is of two types:

- 1. Direct absorption of radiation energy results in the formation of H⁺ ion, OH⁻ ion and hydrogen peroxide which all interfere with enzyme systems.

TABLE 17.1

The clinical response to different doses of whole body irradiation

Dose Centigray (cGy)	Clinical effects	Mortality
0-100	Men may develop temporary azoospermia	Nil
100-200	Nausea and vomiting starts in 3-6 hours and may persists for a whole day or so. In some cases, this starts after a latent period of even two weeks	Nil
200-600	Nausea and vomiting lasts for 1-2 days, there may be a latent period of 1-4 weeks, symptoms may recur for up to 8 weeks, and severe leukopenia, purpura, hemorrhage, infections and loss of hair may develop	Up to 90% in 2-12 weeks from hemorrhage or infection
600-1000	Nausea and vomiting start within 30 minutes and last for 2 days. There is a latent phase of 5-10 days followed by severe leukopenia, purpura, hemorrhage, infections and death	90-100% in 6 weeks from hemorrhage or infection
1000-3000	Nausea and vomiting start within 30 minutes and last for 1 day. The latent phase is for 7 days or less. This is followed by gastro-intestinal syndrome with diarrhea, fever and disturbed electrolyte balance. These last for 2-14 days	100% within 14 days from toxemia and circulatory collapse
More than 3000 respiratory	Nausea and vomiting start almost immediately followed by convulsions, tremor, ataxia and lethargy	100% in 48 hours from failure or brain edema

Note: X-ray and gamma rays used to be measured in rads. Exposure to 1 roentgen results in an absorption of about 1 rad equivalent to 100 ergs/g. At present the unit of measurement used is the Gray. 1 rad = 1 Centigray (cGy)

2. Direct injury to chromosomes lead to chromosomal breaks and abnormal cross links in the DNA or between the DNA and cellular proteins.

Dividing cells are more susceptible to radiation injury. The effects may be: (1) delay in mitosis, (2) reduction in the number of dividing cells, and (3) chromosomal changes.

The effects of radiation vary according to the degree and nature of exposure. Massive radiation exposure causes immediate effects, while small repeated exposures induce response that may not be perceived even for years. When the dose is large and exposure is extensive over the body, the acute radiation syndrome results. Excessive dosage delivered locally gives rise to localized damage, e.g., radiation dermatitis, radiation nephritis etc.

Pathological changes Radiation leads to arrest of mitotic activity, which progresses to cell damage and death. Tissues, which have a high rate of cell division such as bone marrow, intestinal epithelium and germinal cells of gonads, suffer most. Secondary complications include infection, hemorrhage and fibrosis. Loss of epithelium, neutropenia and depression of immune response favor bacterial invasion and septicemia. Infective lesions are most evident in the oropharynx and intestines. The brain and spinal cord are more sensitive to radiation than peripheral nerves.

ACUTE RADIATION SYNDROME

Acute exposure of the whole body to 300 cGy is fatal. Lethal doses produce maximal effects on the bone marrow and the intestinal epithelium. With high doses, intestinal

lesions predominate over marrow toxicity. With still higher doses neurological features such as disorientation, convulsions and shock predominate. Except in the fulminant neurological type of injury, the classical form occurs in four phases:

Phase 1 This phase occurs within minutes of exposure and is characterized by nausea, vomiting and diarrhea. Reduction in lymphocytes may occur in 24-30 hours due to direct destruction of these cells.

Phase 2 There is a latent period of about a week after which the third stage develops.

Phase 3 During this critical phase there is marrow failure leading to neutropenia and thrombocytopenia, which result in secondary infection and hemorrhage. Fever, vomiting, diarrhea, oropharyngeal ulceration, and purpura may be seen.

Phase 4 The survivors enter the fourth (recovery) phase in which the symptoms subside.

Temporary sterility may develop and persist for up to one year. Risk of developing malignancies such as chronic myeloid leukemia, cancers of the breast, thyroid, lungs and digestive organs is considerably increased in such persons.

Treatment It is supportive and aims at:

1. Correcting toxemia and infections,
2. Correcting fluid and electrolyte imbalances and
3. Treating hemorrhagic manifestations, profound anemia and neutropenia.

These patients are preferably managed in an aseptic environment. Adequate antibiotic therapy and transfusion

of neutrophils and platelets are life saving. Hemopoietic factors such as *filgrastim* and *sargamostim* help in the recovery of blood cells. Blood stem cell transplantation and bone marrow transplantation may be may be needed later.

Important points

1. The extent of damage due to radiation depends on the dose, rate and type of radiation and organ exposed
2. Tissues with high rate of cell division such as the bone marrow, gastrointestinal epithelium and gonads are affected mostly
3. Acute exposure of >300cGy may be fatal

DAMAGE TO EMBRYO BY IRRADIATION IN FETAL LIFE

Irradiation during stage of implantation results in fetal death. During the stage of organogenesis, fetal

malformation or abortion may result. After three months, by which time, the main organs would have formed, gross deformities are not produced, but stunting of growth, reduction of life span, sterility and tendency to develop leukemias and cancers have been noted. Radiation dose as low as 5 cGY can injure the growing fetus. The irradiation given out by modern X-ray machines for skiagram of the chest is only 1/100 cGY.

LOCAL RADIATION INJURY

Erythema develops over the area of exposure within days or weeks after acute exposure and this may progress to epidermolysis. Late complications are atrophy of the skin, subcutaneous fibrosis, telangiectasia, and later hyperkeratosis. These hyperkeratotic lesions may develop malignancy later.

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Electrical Injuries and Lightning

T.K. Suma, K.V. Krishna Das

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ELECTRICAL INJURIES

The risk of electrical injuries is often overlooked due to over familiarity. In most cases accidents occur from faulty domestic electrical apparatus, rarely it may be from high tension lines or other installations. Electrical characteristics of the exposed part, conductivity of tissues, extent of grounding and the duration of the contact determine the amount and the path taken by the current, which is important in relation to the severity of the injury. Electrical accidents are common where electrical installations are more such as surgical theaters, intensive care rooms and others.

The type and severity of injury depends upon the strength of the current, its type, duration of exposure and

the path taken by the current. Individuals vary in susceptibility to the effects of electricity. Injuries associated with electricity may be due to either direct electrical shock, or burns resulting from electrothermal effects and flames. Alternating current (AC) is more damaging than direct current (DC). A current of 100 mA flowing from hand to feet can induce ventricular fibrillation. Following the passage of the current, the myocardium is vulnerable and highly excitable. Fatal ventricular arrhythmias may occur.

Clinical features: Burns develop at the sites of entry and exit of the current. When the current is high, instantaneous ignition of clothing or nearby objects add to the injury. Electrical current may produce three distinct types of burns. Flash (arcing) burns, flame (clothing) burns and the direct effect of the current (Joule burn). Burns get secondarily infected in 2-3 days.

The nervous system is highly sensitive to electrical injury. Spinal cord may develop lesions leading to paraplegia and urinary retention. Convulsions, cerebral

edema, and cerebral thrombosis may develop. Current passing through the skeletal muscle can cause muscle necrosis and contractions severe enough to result in bone fracture. Peripheral nerve involvement can cause acute or delayed peripheral neuropathy. Cardiac symptoms include tachycardia, which may be persistent, shock, cardiac arrhythmias including ventricular fibrillation and cardiac failure. Pneumonia, pleural effusion and disorders of ventilation, and hypoxia are the common respiratory findings. Secondary hemorrhage from blood vessels and acute upper gastrointestinal bleeding may develop in a few days. Acute renal failure is a common sequel. Current passing through the abdomen may be complicated by damage to the viscera. Cataracts may form as late sequelae. If current passes through the heart or brainstem death is immediate.

Treatment: First aid includes immediate disconnection of the live contact and cardiorespiratory resuscitation. Due to muscle spasm, the limb holds on to the live wire. This prolongs the injury and this is the main cause of death. Urinalysis, Serum Creatine Kinase (CK) and CK-MB and an electrocardiogram should be done immediately. Administration of intravenous saline or Ringer lactate solution helps to combat shock. Dexamethasone 8 mg and 20% mannitol 250 mL given IV help to reduce cerebral edema. Furosemide 40-80 mg IV is given to overcome pulmonary edema and prevent renal shutdown. Sodium bicarbonate is given to prevent acidosis as an early measure. The prognosis is monitored by estimating the hematocrit, urine volume and arterial pH serially. Suspicion of visceral damage calls for imaging studies and surgical management.

Prevention Proper insulation is necessary while handling electrical equipment. Low plug sockets should be protected from the reach of children. While rescuing an electrocuted person the rescuer should take enough care in first insulating himself properly. Many deaths have occurred among rescuers who have failed to observe proper precautions.

LIGHTNING

Injuries due to lightning are encountered occasionally in the tropics. Lightning induces a high electrostatic charge on the victim. Identically charged particles repel each other, giving rise to disruptive forces, which lead to damage of organs. Organ damage may occur even without external injury. The high current produces violent muscular contractions and severe burns, and ignites inflammable objects on the body.

Clinical features The patient is usually restless, disoriented and may be comatose. Retrograde amnesia is common. Later on he may show psychiatric and hysterical manifestations. Severe vasoconstriction produces manifestations like cold limbs and transient ischemic palsies. Arterial spasm may result in loss of pulse in the affected limb. Increased vascular permeability results in massive edema of the affected part.

Cardiovascular manifestations include tachycardia, extrasystoles and electrocardiographic abnormalities such as elevation of ST segment and inversion of T waves. Sudden death may occur on account of respiratory center paralysis or cardiac arrest (asystole). Intracranial hemorrhage may develop.

Treatment If the vital signs are absent, immediate resuscitatory measures should be started. Even in apparently hopeless cases, gratifying results are not uncommon. Management of survivors consists mainly of supportive measures and treatment of the complications. Vasodilators and low molecular weight dextran help to prevent gangrene. Tetanus prophylaxis must be given if tissue injury has occurred.

Important points

1. Lightning usually involves high voltage
2. Organ damage occurs even without external injury
3. Multisystem involvement is common
4. Death is usually due to cardiac asystole rather than ventricular fibrillation

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Dangers of Nuclear Explosion

3

T.K. Suma, K.V. Krishna Das

The present day warfare makes use of nuclear explosion to increase destructive power. Many nations on the globe are having sophisticated nuclear weapons, the explosive powers of which exceed the power of several thousand tons of trinitrotoluene (TNT). Nuclear explosions may result from deliberate actions of warring nations or accidents in high power nuclear reactors. It is estimated that among the nuclear powers like the United States of America and Russia, the destructive power that can be generated by nuclear armament may be far in excess of that required to annihilate life totally from the surface of the globe. Many physicians all over the world consider a nuclear war as the worst and the last disaster that can happen to mankind and all other living organisms.

A nuclear explosion results when the fission of Uranium or plutonium proceeds in a rapid and relatively uncontrolled manner. The tremendous release of energy can produce severe explosive shock and temperatures exceeding one million degrees Celsius. The explosion is associated with several destructive phenomena.

The blast wave (also Known as shock wave or pressure wave) is transmitted to the surrounding medium with a highly destructive force. The blast arising from an ordinary nuclear bomb will destroy most of the commercial buildings, apartments and houses, within a radius of 1 km.

Thermal injury The high temperature produced by the explosion converts the materials of the explosive into a ball of very hot gases. This ball expands rapidly engulfing and incorporating the air it meets, becoming larger in the process and this progresses centrifugally. This causes severe burns, maximal at the centre and reducing towards the periphery. At Hiroshima, during the explosion of the atom bomb in the Second World War almost all persons within a radius of 1.6 km were burnt to varying degrees. Another consequence of thermal injury is flash blindness, which is transient blindness (which may become permanent) that results from too powerful a flash.

Ionizing radiation Nuclear explosion emits large amounts of ionizing radiations which themselves are highly injurious to life and health. In addition, they can make other objects also radioactive, so that these objects act as

sources of long-term radioactivity in that area, with consequent health hazards. Large areas may be made unfit for human existence for several decades. Long-term ill effects include higher incidence of several cancers, genetic mutations and congenital malformations. Since the radioactive fall out spills over a much wider area from the target of attack, these phenomena also involve neighboring countries. Radioactive materials may go up into the atmosphere to form radioactive clouds, move to other regions and cause '**radioactive rain**'. The radioactive particles may remain in the troposphere (layer of atmosphere extending up to 11 km from the earth) and stratosphere (layer above troposphere) for up to thirty days or more.

The very high temperatures produced by the explosion will ignite all inflammable materials and lead to large urban fires and forest fires. Liberation of soot and smoke into the atmosphere block the sunlight reaching the earth's surface and lead to a precipitous fall in temperature to well below minus 20 °C which may persist for several months. This phenomenon is referred to as "**nuclear winter**".

Other consequences of a nuclear explosion are common to all mass scale accidents, but on a much higher scale. These include total disruption of communication, breakdown of all rescue and medical facilities, disruption of essential services such as protected water and electricity, and occurrence of severe environmental pollution. These, in their turn start off problems such as starvation, widespread epidemic and famine.

Medical men from several countries have joined to form an international organization - **The International physician for the prevention of nuclear war (IPPNW)**- with a view to educate governments and the public on the possible ill effects of a nuclear war and to use the moral and social position of the doctors on the public and government to adopt nuclear disarmament.

India is a participant in this movement. It is the duty of every doctor to uphold and promote these aims. The National Association of Indian Doctors for the Prevention of Nuclear War (NAIDPNW) which was later changed to

Indian Doctors For Peace and Development (IDPD), has its office at 139-E, Kitchlu Nagar, Ludhiana- 141001 (Punjab)India

Important points

1. Release of energy during nuclear explosion produces severe shock and high temperature

2. Thermal injury causes severe burns and flash blindness
3. Ionizing radiation from nuclear explosion results in long-term effects like development of cancers, genetic and congenital abnormalities
4. Nuclear winter is a complication of nuclear explosion
5. It is the duty of all doctors to prevent nuclear warfare at all costs

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20

Adverse Effects due to Noise and Vibrations

T.K. Suma, K.V. Krishna Das

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Noise

Noise is unwanted sound and it produces adverse effects on man. With the progress in industry and transport, noise pollution is increasing in all countries. Continuous loud noises lead to impairment of hearing, irritability and accelerate fatigue. Noise disturbs sleep.

Noises occur in various forms. They may be pure tones (siren), narrow bands of frequencies (hiss of escaping stream), broad bands of frequencies (radio), impulses (explosive release of gas in gun fire) or impacts (hammer striking a steel plate). The stimulus may be continuous or intermittent and the intensity also varies. The unit of sound is the decibel. Decibel is 1/10 of a bel. Bel is the unit of sound pressure intensity and is measured as the logarithmic ratio of the particular sound to that of a reference sound, which has an intensity of 0.002 dynes/sq.cm at 1000 cycles per second.

Exposure to noise levels greater than 85 and 95 decibels for months to years can lead to cochlear damage. In the early stages, there is loss of hearing at or near frequencies of 3000 to 4000 cycles per second. Later the damage extends to both higher and lower frequencies. Higher tones are affected early, later extending to lower tones as well. The subject may not be aware of the hearing

loss until it is severe. Speech reception is not altered seriously until the loss of hearing is greater than 30 decibels in the speech frequencies (500,1000, 2000 cycles per second). Children are more susceptible for noise-induced hearing impairment than adults.

Noise induced loss of hearing has two phases. In the initial phase there is a rise in threshold of sound, which is temporary and in the latter phase this defect becomes permanent. Further a temporary threshold shift can be superimposed on permanent defect of hearing.

Persons vary in their sensitivity to the effects of noise. The factors, which influence the final outcome are:

1. Overall sound pressure levels of the noise,
2. Frequency bands of which the noise is composed,
3. Daily distribution and total duration of noise exposure, and
4. Susceptibility of the ear exposed to the noise.

The most striking finding in noise-induced loss of hearing is injury of degeneration of the sensory cells, mainly the outer hair cells of the organ of Corti. After exposure to noise the cilia in the inner and outer hair cells of the cochlea become fused and bent. After more prolonged exposure, there is degeneration of the outer and inner hair cells related to transmission of high-frequency sounds.

In old age there is a general tendency to develop hearing loss, (*presbycusis*) = due to degeneration of the striae vascularis of the cochlea. Presbycusis starts with loss of high frequency sound. Exposure to heavy background noise, smoking and high lipid diet accelerates this hearing loss.

EFFECTS OF IMPULSE NOISE ON MIDDLE EAR AND EAR-DRUM

Impulse noise can be defined as an acoustic event associated with sudden changes in pressure. The pressure wave initially travels faster than the speed of sound. Very high intensity impulse noises from explosions are known to damage the eardrum, middle ear and inner ear structures. The body reacts to impulse noise by increasing blood pressure, heart rate and respiration. Muscles become tense and there will be increased secretion of catecholamines. These changes can occur even during sleep and continuous exposures during the night may affect person's general health producing irritability and fatigue. Studies have shown that children studying in schools near airport subjected to chronic aircraft noise exposure have impaired reading comprehension, intellectual performance and long-term memory.

Mortality in relation to noise pollution Probably death due to cerebrovascular accidents, cardiovascular disease and cirrhosis of liver increases with increasing noise pollution. There is also increasing incidence of stroke, hypertension and peptic ulcer. It may affect fetal development.

Prevention of noise-induced loss of hearing involves regular audiometric screening of workers exposed to industrial noise and reducing the noise levels to the minimum and protection of exposed personnel. The recommended noise level at night is a maximum of 35 dB. For hospital wards an ambient level of 40 dB has been recommended.

Important points

1. Exposure to noise levels more than 85 to 90 dB can lead to cochlear damage
2. Children are more susceptible for noise-induced hearing impairment than adults
3. Noise induced hearing impairment may be permanent
4. Impulse noise damages the eardrum, middle ear and inner ear structures

VIBRATION

Vibratory tools and machines of various types including pneumatic hammer and drills are in common use at present. Frequencies of 250 Hz with an amplitude of 1 mm are most likely to cause damage. The group of symptoms and signs produced by exposure to vibration is known as **Hand-Arm Vibration Syndrome** or HAVS. This depends on a) the amount of vibration the tool produces, b) the length of time the tool is used each day, c) the total number of hours or days or month the tool has been used, d) the way in which tool has been held. HAVS results in vascular damage, neurological and musculoskeletal dysfunctions. Due to vascular damage episodic blanching of one or more fingers occurs, which will be well demarcated and is known as the *white finger*. This is usually triggered by cold. The latency period for development of *white finger* may vary from 6 months to 20 years. Neurological symptoms are tingling and numbness, reduced strength of grip and impaired dexterity.

Musculoskeletal damage caused by vibration includes:

1. Decalcification or cyst formation of carpal bones,
2. Injuries to the soft tissues of hand,
3. Arthritis of wrist, elbow and shoulder, and
4. Spasm of the arteries and *Raynaud's phenomenon* - "The White hand" or "dead hand"

Bone cysts rarely produce pathological fractures. Injuries to the soft tissues often involve the palmar aponeurosis and may produce adventitious bursae, which fill the palm. Arthritic symptoms are attributable to active damage of joint surfaces, caused by the large pneumatic tools. Once established, the damage persists. Very recently, Hand-Arm Vibration Syndrome has been reported following prolonged use of vibrating computer games especially in children.

21

Motion Sickness, Problems due to Air Travel and Road Accidents

T.K. Suma, K.V. Krishna Das

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MOTION SICKNESS

The term motion sickness refers to the clinical picture resulting from movement of an individual on land, sea or air when journeys are undertaken. Repetitive irregular movement as in a swing, a lift or even dancing, may bring on such symptoms.

It is mainly a disorder of gastric and intestinal functions brought on in susceptible subjects while traveling. Irregular and unaccustomed stimulation of the labyrinth causes nausea and vomiting and also disorders of function in the viscera innervated by the vagus or parasympathetic system. During sea voyage the roll and pitch of the ship causes excessive stimulation of the labyrinth. In the case of car and aeroplane travel, labyrinth is subjected not only to the effects of rotation of the body through planes to which it is not accustomed, but also to rapid acceleration, deceleration and altitude changes. Angular acceleration of train and the linear-angular acceleration of turbulent flights are important causes of motion sickness. Visual stimuli from moving objects and proprioceptive stimuli from muscles and joints contribute to the final outcome. Fear and anxiety make the condition worse. Early infancy is immune from this affection, since the orienting mechanism has not attained full physiological activity and old age is relatively immune, probably because of the lessened sensitivity of the nervous system. The signs and symptoms of motion sickness occur when sensory information about the body's position in or movement through space is contradictory to prior experience. Susceptibility and tolerance to motion sickness vary widely among individuals. Motion sickness is more common in women, especially during pregnancy or menstruation, in children aged 2-12 years, and in persons who have migraine headaches.

Clinical features The initial symptoms include loss of usual sense of well being, abdominal and visceral discomfort, salivation, nausea and yawning. The patient becomes pale and respiration becomes irregular. These symptoms are followed by retching, vomiting and desire to defecate. The vomiting may be mild and transient in some, while in others this may be violent, distressing and recurrent. Headache, giddiness, continued pallor, apathy, lassitude, weakness, dehydration and prostration follow. The skin may become cold and clammy, tongue coated, both breath and urine may contain acetone bodies, pulse and respiration become rapid and the blood pressure drops.

Diagnosis is easy when the symptoms are related to travel, but other causes of abdominal disorders must not be overlooked.

Course and prognosis The symptoms usually subside when the travel or the movement causing the condition comes to an end, but in some cases dizziness, headache and gastric symptoms persist for a long time. In cases of long voyages by seas, the symptoms may subside in a few days but may sometimes persist.

Prophylaxis and treatment Reclining posture, avoidance of visual stimuli and reduction in head movements to the minimum help to minimize the condition. Mental distraction may help to allay the symptoms.

Antihistamines given in small doses 30–60 minutes before starting the travel prevent motion sickness, e.g., diphenhydramine 25-50 mg oral. phenothiazines such as trifluoperazine 10 mg or hyoscine (0.3 mg) are good alternatives. To treat motion sickness higher doses of the same drugs have to be given. The choice of drug should be based on the underlying conditions if any.

MEDICAL PROBLEMS OF AIR TRAVEL

The long hauls and undue delay *en route* are matters of great concern to the severely ill patients. Psychological stress caused by frequent dislocation of connecting flights and fear of skyjacking adds to the problem. Travel by

modern aircrafts is safe and comfortable on account of the appropriate adjustment of cabin pressure, cabin atmosphere, air conditioning and oxygen supply. Many modern aircrafts fly at altitudes of 7,000-13,000 meters.

Problems due to reduction in barometric pressure and partial pressure of oxygen The commercial transport aircrafts are pressurized, but cabin pressure is subject to fluctuations. At 2,600 meters the ambient pressure is about 560 mm Hg, the partial pressure of inspired oxygen is 118 mm Hg, and that of alveolar oxygen 65 mm Hg. In patients with ischemic and hypertensive heart diseases this degree of hypoxia can cause angina or cardiac failure. Cerebral ischemia may manifest in atherosclerotic individuals. Sick cell crises may be precipitated in susceptible patients. There are many airports situated at altitudes more than 1800 meters above sea level and relative hypoxia at these levels can cause problems of high altitude in such individuals. Decreased barometric pressure results in expansion of gas trapped in body cavities. Blocking of sinuses and Eustachian tubes lead to severe facial or middle ear pain. Dental pain may develop due to expansion of air trapped in badly filled cavities. In pneumothorax and pneumoperitoneum the entrapped air expands and can cause rise in tension. The gas in the stomach and intestines (about 1 to 1.5 liters) can expand as much as 25%. This may cause a feeling of fullness and discomfort, acute abdominal colic, lower central chest pain and collapse resembling myocardial infarction. The risk of gastrointestinal hemorrhage is increased. Unsupported hernias strangulate more readily.

Problems in apparently healthy travelers Long flights result in rapid changes in climate and time zones. Rapid geographical transitions around the world disturb the natural biological rhythms of the individual. Motion sickness, sleeplessness, tension, headache, pain in the neck, shoulders and back, nausea, dyspepsia, urinary frequency and constipation are not unusual accompaniments of the flying stress. More serious symptoms such as cardiac arrhythmias, manic excitement, hallucination and paranoid delusions may develop in a few. As a result of long flying sessions and rapid changes of climate and time zones, symptoms like physical exhaustion, spurious sensation of mental alertness and mild euphoria may persist for one or two days after reaching the destination. Some passengers find it difficult to adapt quickly to the new climatic environment and they may develop sleep disturbance, intellectual under-functioning and psychosomatic symptoms. Reduction in fatty food and alcohol intake during flights help to reduce the symptoms to a great extent. Immobility during long flights may predispose to deep vein thrombosis.

Problems in chronically ill patients Facilities in commercial aircraft make it possible to airlift even acutely

ill and seriously injured persons, although isolation facilities may not always be available. Oxygen delivered by nasal masks is available in all modern aircraft for emergency use.

Cardiovascular diseases In view of the lower partial pressure of oxygen, it is advisable to avoid flying for six weeks following acute myocardial infarction.

Treated cardiac failure, occasional angina, old infarction, hypertension and chronic valvular diseases do not carry any added risk. During "check-in", patients with implanted pacemakers should avoid electronic and magnetic devices used for screening the passengers. Many major airports are equipped with emergency resuscitation equipment and trained volunteers who can attend to sudden cardiac events.

Cerebrovascular accidents and epilepsy Flying is contraindicated for six weeks following strokes. Flying at more than 3000 meters altitude may precipitate epileptic attacks if proper medication is not given.

Pulmonary diseases Persons with pulmonary decompensation at rest or on mild exertion should undertake air travel only when there are facilities for therapeutic oxygen. Patients with acute asthmatic episodes not relieved by self-medication, and status asthmaticus should avoid air travel till such attacks are well controlled. Rupture of emphysematous bullae producing tension pneumothorax is a possible risk on board of the aircraft.

Hematological diseases It would seem wise to restrict air travel if the hemoglobin level is less than 9 g/dL. Patients with sickle cell disease should undertake air travel only if the ambient oxygen tension can be maintained at 150 mm Hg. Splenic infarction and serious sickle cell crises can be precipitated if the oxygen tension is low.

Pregnancy Pregnancy beyond the 35th week may pose the risk of labour during flight.

Deep Vein Thrombosis

Many long distance travellers who sit crammed up in aircraft for flights exceeding eight hours may develop deep vein thrombosis (DVT) in the lower limbs particularly so in obese and elderly persons. Presence of thrombophilia adds to the risk. In addition to the mechanical obstruction to venous drainage and inactivity during the flight, there is evidence that continuous flights exceeding 8 hours may activate the coagulation cascade in predisposed individuals.

Fighter aircrafts Modern fighter aircrafts exceed human physiological limits to withstand head to foot acceleration forces (positive G2 forces). This may lead to sudden syncope with prolonged periods of incapacitation, especially in vagotonic individuals. Psychomotor

Disorder due to Physical Agents

performance may be impaired. All these adverse effects can be avoided by proper conditioning of the individuals during training.

All commercial airlines provide information on the facilities available with them for transportation of invalid passengers. All airports have facilities for attending to emergencies that may develop during air travel.

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Important points

1. Hypoxia may aggravate angina or cardiac failure in a hypertensive or patients with coronary artery disease
2. Atherosclerotic individuals may develop cerebral ischemia
3. Expansion of gases in body cavities produces various symptoms
4. Healthy individuals may be prone to motion sickness, cardiac arrhythmias and manic excitement
5. Chronically ill patients should take sufficient precautions before undertaking air travel
6. Deep venous thrombosis may occur in susceptible individuals during long flights

ROAD ACCIDENTS

General Considerations

In modern times mortality and morbidity caused by road accidents is on the rise. This is common in all countries of the world where fast traffic on the road is increasing.

In India 30 persons out of 100000 die annually due to road traffic accidents. The accidents may involve the vehicles or the pedestrians using the road. The major types of accidents are collision between vehicles, loss of control of the vehicle and collision with hard objects or overturning. The other type of accidents involves knocking down pedestrians or occupants of lighter vehicles such as two wheelers and light motor vehicles. In general the major damage and passenger injury occurs to the lighter vehicle.

The major factors contributing to road accidents can be classified as given below:

A. Causes attributable to the vehicles

1. *Speed of the vehicle*- The rate and severity of the accident increases with increasing speed of either vehicle. With the introduction of modern highways speed-related injuries have become much more common
2. *Mechanical defects in the vehicle*, which lead to failure of the controls.
3. *Exceeding the safety limits* prescribed for the vehicle in terms of speed, loading and maintenance.

B. Causes attributable to the driver

1. *Fatigue and sleep*- long driving exceeding 6 hours of continuous driving leads to driver fatigue, delay in the reflexes and tendency to sleep.

2. *Drunkenness*: Consumption of alcohol and less commonly other narcotic drugs impairs the efficiency of the driver
3. *Inattention, non-compliance with signals and rash driving*
4. *Inexperience of the driver*

Most of the major collision accidents occur on highways, especially in the early hours of the morning when driver fatigue and somnolence are maximal. Rarely accidents may occur due to organic disease in the driver such as epilepsy, cardiovascular disease, strokes and others.

Injuries to Pedestrians

Walking on highways and fast traffic roads is associated with injury to the pedestrians.

Elderly people, obese individuals, persons with movement disorders, alcoholics and children are involved more.

INJURIES CAUSED BY ROAD ACCIDENTS

Vehicular Accidents

Trauma to the driver and passengers due to the impact and damage and deformation to the vehicle are usually serious. This leads to injuries which may be instantaneously fatal. In motor car accidents, the luggage kept unsecured in the passenger compartment fly out and cause further missile- like injuries to the passengers. Trauma to vital parts such as head, chest cage, spine, bones, abdomen and major blood vessels, intracranial injuries, intracranial bleeding, tension pneumothorax, rupture of major blood vessels like aorta, injuries to the heart, rupture of solid organs and hollow viscera in the abdomen and pelvis and exsanguinating bleeding (both external and internal) are the causes of death at the site of accident or within a few hours. Pedestrian injuries cause death due to damage to vital structures, especially intracranial bleeding, chest injuries, intra abdominal injuries and exsanguination.

MANAGEMENT AT THE SITE OF ACCIDENT

Effective first aid helps to save life and reduce morbidity and delayed mortality. Mainly this consists of maintenance of the airway and attention to ventilation, tourniquets to arrest external hemorrhage, immobilization of parts of the body such as the neck and spine to avoid further damage to the vital neural structures, covering open chest injuries which interfere with ventilation and rapid transport to the nearest hospital with adequate facilities. *It is the duty of all medical men to give first aid in such a situation.* It is to be remembered that an obvious injury may distract the attention of the doctor from other invisible injuries such

as internal bleeding or rupture of viscera which can cause death.

When major accidents involving buses occur, a large number of persons will be simultaneously affected and this may cause a heavy strain on the medical facilities. In this situation, a senior medical officer has to inspect the victims and using the principles of 'triage', arrange for appropriate management. In such an emergency all medical personnel have to participate in the emergency management.

All road traffic accidents invite legal procedures which have to be complied with.

General guidelines to reduce road traffic accidents and their consequences

1. Education of the public on the safe use of roads and motor vehicles
2. Strict compliance with road traffic rules
3. Avoidance of alcohol and drugs before driving
4. Avoid driver fatigue and somnolence

5. Avoid the presence of unsecured luggage in the passenger compartment
6. Use the seat belts as prescribed.
7. Enforcement of traffic regulations by the appropriate authorities.

Note: In all developed countries, well coordinated emergency management teams attached to major hospitals are available, ready to render assistance at the site of accident, during transport to hospital, and later. This team consists of trained ambulance personnel, anesthetists, trauma care surgeons, other physicians and specialists, trained nursing team and paramedics.

Points to remember

1. Road accidents are increasing to reach epidemic proportions
2. Main causes are over speed and driver fatigue
3. Proper first and specialized care help to save life and reduce morbidity
4. Road accidents are preventable to a great extent

4

Toxicology

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Acute Poisoning: General Considerations

T.K. Suma, K.V. Krishna Das

4

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GENERAL CONSIDERATIONS

Acute poisoning accounts for 2-3% of admissions into major general hospitals in India. Poisoning may be suicidal, accidental or homicidal. The high incidence of poisoning is attributed to the widespread use and free availability of insecticides, pesticides and other harmful chemicals for use in agriculture and industry. Depending upon the cost and local availability, varied substances are used. In the order of frequency, the toxic agents include organophosphorus compounds, barbiturates, benzodiazepines, vegetable poisons, phenothiazines, corrosive acids, and several others. The precipitating factors, which drive persons to commit suicide, are depressive illness, financial problems, domestic conflicts, and frustration in studies and jobs or incurable illness. Among epileptics and alcoholics the incidence of suicidal poisoning is high. Accidental poisoning is common in children. Persons engaged in the use of toxic chemicals in agriculture and in industry are liable to suffer if proper safety precautions are not adhered to.

CLINICAL PRESENTATION

Though poisoning by many chemicals lead to characteristic clinical features, in the majority of cases symptoms are non-specific and may be mistaken for other acute illnesses. The common presentations are coma, acute psychosis, convulsions, gastroenteritis, circulatory collapse, or pulmonary edema.

112 Corrosive poisons produce noticeable lesions at the points of maximum contact such as the mouth, esophagus

and stomach. Other poisons affect specific organs maximally, e.g. liver damage in paracetamol poisoning, renal damage in copper sulphate poisoning, and cardiac dysfunction in *Cerebera odollam* poisoning. Poisons consumed on an empty stomach are absorbed more rapidly than if taken on full stomach. Also, if taken along with alcohol, many poisons are quickly absorbed and their damaging effects are cumulative.

Diagnosis Diagnosis is rendered easy if proper history or evidence of the material is obtained, but in many cases such help is not available. A high index of suspicion on the part of the physician is absolutely necessary for arriving at an early diagnosis in such cases.

Abrupt occurrence of acute illness in a person who is in good health should suggest acute poisoning as a possibility. Smell of alcohol or kerosene, severe respiratory depression, circulatory collapse, convulsions, constricted pupils, cardiac arrhythmias, dystonic postures, and muscle fasciculations add support to this diagnosis.

The outcome depends upon factors like:

1. The amount of poison and its mode of administration,
2. Presence of food in the stomach at the time of ingestion,
3. Delay in starting treatment,
4. Age,
5. General health and concurrent illness, and
6. Availability of specific antidotes.

Patients who are comatose due to acute poisoning face the twin dangers of the toxic-effects of the chemical and the grave consequences of an obstructed airway.

GENERAL MANAGEMENT

Acute poisoning is a medical emergency and is best treated in a well-equipped hospital with teams specially trained to handle such cases. Since in many cases the nature of the poison will not be evident at first, the aim of treatment is to keep the patient alive with support of vital functions, eliminate as much of the poison as possible from the body and prevent further absorption of poison. Specific antidotes are given as soon as the nature of the poison is

known. Selective antidotes are available only for 2% of such poisons.

Emergency Management Most important is to clear the airway and ensure adequate ventilation by positioning, suction, or by insertion of nasal or oropharyngeal airway. The respiration should be clinically assessed and if there is ventilatory impairment necessary support with supplemental oxygenation and mechanical ventilation should be instituted. Intermittent positive pressure respiration has to be started with endotracheal intubation, if conservative measures fail. The patient should be turned from side to side at four-hourly intervals to prevent aspiration and hypostatic pneumonia. Frequent bronchial suction helps to prevent atelectasis and aspiration pneumonia.

Shock is managed on the usual lines. Maintenance of fluid and electrolyte balance is of utmost importance in all cases.

Decontamination of skin Pesticides and other chemicals which are present on the cloths and skin get absorbed through the skin and worsen the condition. Similarly corrosive agents rapidly injure the skin and eyes. In these situations washing the affected area with large quantities of water and soap prevents further systemic absorption of the toxin. Normal saline is preferred for irrigation of the eyes.

General Measures

An intake output chart should be maintained and a urine output of at least 1500 mL should be ensured. Replacement of electrolytes and correction of acidosis should be done with proper laboratory monitoring. Maintenance of nutrition is equally important. Diet containing 2000 calories should be given orally if the patient is conscious. In unconscious patients food has to be given through a nasogastric tube. Parenteral nutrition has to be started in severely affected patients.

Repeated examination of blood and urine for the level of the toxic agent helps to monitor the progress with treatment.

Specific Measures

a. **Ingested poisons** In many cases of ingested poisons, considerable amounts remain in the gastrointestinal tract up to four hours; hence it is absolutely necessary to take appropriate measures for their removal. Induction of vomiting is safe in conscious patients. Vomiting is induced by tickling the pharynx or administration of gastric irritants such as concentrated common salt solution 200-400 mL. In the case of corrosive poisons and highly irritant substances like kerosene, emesis and gastric intubation are

contraindicated. Gastric lavage by using a stomach tube is an effective method to empty gastric contents rapidly and this can be done even in unwilling patients. This is the method of choice in all conscious patients who have consumed noncorrosive poisons. However, it is risky in comatose patients due to the danger of aspiration into the respiratory tract and in such cases aspiration through Ryle's tube is preferable. Gastric contents should be preserved in a sealed bottle for chemical examination and further medicolegal procedures. Use of activated charcoal, which adsorbs many toxins reduces gastric and intestinal absorption further. Dose is 50-200 g in 200 mL water initially and 50 g 6 hourly till recovery. The surface area of activated charcoal is increased several folds, compared to the parent substance and this large surface area adsorbs several substances non-specifically.

Purgatives such as magsulph. 15-30 g or sorbitol 1 g/kg bw (maximum of 150 g) orally followed by bowel wash 2 hours later help to eliminate the poison from the intestine.

b. **Removal of absorbed poisons** Forced diuresis enhances the renal excretion of many poisons. Hemodialysis helps to eliminate many water soluble substances.

Forced Diuresis

The kidneys can be made to eliminate poisonous drugs at a rate consistent with the urine output. Contraindications include congestive cardiac failure, renal failure, rhabdomyolysis and cerebral edema.

In an unconscious patient a Foley's catheter should be introduced to facilitate uninterrupted flow of urine and for proper monitoring of output.

Dialysis and Hemoperfusion

Dialysis Since most of the cases recover with forced diuresis, hemodialysis is indicated only in a few. Indications for hemodialysis are: (a) high blood levels of the drug, (b) renal failure, and (c) non-responsiveness to forced diuresis and (d) poisoning associated with deep coma, hypotension and fluid and electrolyte disturbances. In the absence of facilities for hemodialysis, peritoneal dialysis should be undertaken. Hemodialysis is 6-10 times more efficient than peritoneal dialysis.

Hemoperfusion is the process of passing the patient's blood through cartridges packed with activated charcoal, which adsorbs drugs and toxins such as barbiturates, carbamazepine, glutethimide, meprobamate, methaqualone and several others. Cartridges ready for use are available commercially at around Rs. 4000 per piece.

Multiple dose activated charcoal Doses of activated charcoal 1-2g/kg bw repeated every 2-4 hours hasten

TABLE 22.1

Specific antidotes to poisons commonly consumed

Organophosphates	Atropine	Loading dose 2 mg IV every 2–5 minutes until pupils dilate and salivation is reduced. Maintenance based on pupil size for hours to days.
	Pralidoxime	Loading dose 1-2 g IV repeat after 3 hrs.
Opiates (Opium, morphine, meperidine, propoxyphene, pentazocine, diphenoxylate)	Naloxone (Nalorphine hydrochloride)	Loading dose 0.4-2 mg IV repeat in 2-5 min, as is required
Methanol, ethylene glycol	Ethanol	Loading dose 0.6-0.7 g/kg. Maintenance: sufficient ethanol to keep serum alcohol level at 100 mg/dL (approx. 125 mg/kg/hr) and methanol concentration falls below 10 mg/dL
Cyanide	Amyl nitrate, sodium nitrite, sodium thiosulphate to be given sequentially	1. Start with amyl nitrate inhalation 1 amp. every 2-3 min 2. then give sodium nitrite 10 ml of 3% solution IV over 5 mts. 3. then give 50 ml of 25% sodium thiosulphate over 10 mts.
Acetaminophen	N. acetylcysteine	140 mg/kg oral, thereafter 70 mg/kg oral every 4 h for 17 doses (72 hours)
Iron salts	Desferrioxamine	If the patient is hypotensive 10 mg/kg/hr IV for 4 hours, then 5 mg/kg/hr IV until serum iron level is less than 100 mcg/dL. If patient is normotensive, 40 mg/kg IV every 4-12 hrs. Total daily dose should not exceed 6 g.

elimination of drugs by adsorption of drugs excreted into the gut lumen (gut dialysis).

Antidotes Antidotes are available for 2% of the poisonous substances. These may be chemical antidotes, which neutralize the action of the poison, or biological antidotes, which prevent their pharmacological response. They should be employed only after ascertaining the nature of the poison. In most cases, the antidote is indicated by the manufacturers on the packing of the toxic chemical (Table 22.1).

Many of the patients with suicidal poisoning attempt to repeat these episodes because of their psychiatric problems. Hence, it is necessary to instruct their relatives and also arrange for proper psychiatric treatment after the initial episode is treated.

Important points

1. Poisoning accounts for 2-3% of admissions into major general hospitals in India
2. Selective antidotes are available only for 2% of the poisons
3. Management goals include support of vital signs, enhancement of elimination of the poison, prevention of further absorption of the poison and administration of specific antidote
4. Forced diuresis, hemodialysis, hemoperfusion and peritoneal dialysis are methods by which absorbed poisons could be removed

APPENDIX

Methods to Eliminate Poisons

- Forced diuresis
- Peritoneal dialysis
- Hemodialysis
- Hemoperfusion

FORCED DIURESIS

This is employed when the toxin is removable by the kidney and the metabolites are toxic to the system. A substantial proportion of the poison is excreted in the urine unchanged. The poison should be distributed mainly in the extracellular fluid and only minimally bound or not bound at all to proteins.

Rationale Elimination of the toxic substance is enhanced by manipulation of the urine pH so as to render the toxin in the ionized form. Forced diuresis should be considered, and may be indicated, in poisoning due to the following substances.

Alkaline diuresis

- Phenobarbitone or barbitone
- Salicylates
- Phenoxyacetate herbicides

Acid diuresis

- Phencyclidine
- Amphetamine
- Fenfluramine

Potential complications

- 1. Fluid overload
 - 2. Pulmonary edema
 - 3. Cerebral edema
 - 4. Electrolyte and acid-base disturbances.
- Diuresis is induced by giving 5% glucose continuously IV as drip and frusemide IV in dose of 20 mg 6th hourly depending on the response.

Proper estimation of electrolytes and acid-base states should be undertaken during and after the procedure.

Forced acid diuresis The urine pH is adjusted to 5.5-6.5 by giving: 10 g arginine or lysine hydrochloride intravenously over 30 minutes followed by ammonium chloride 4 g 2 hourly, by mouth.

Forced alkaline diuresis The urine pH is adjusted to 7.5-8.5 by giving boluses of 50 mmol (approx 50 mL) of 7.5% sodium bicarbonate solution. Often 200-300 mmol is required in the first 1-2 hours. Since a large sodium load is being given with the bicarbonate cardiac failure may be precipitated in susceptible individuals.

DIALYSIS AND HEMOPERFUSION

In hemodialysis, materials, which are dialyzable including toxic materials, are dialyzed across a semipermeable membrane, using appropriate solutions, which will permit the removal of the toxic substance. Dialysis machines are available in several hospitals offering secondary care. Hemoperfusion is the removal of the toxic material by perfusion of blood through a cartridge containing material, which will adsorb the particular substance.

Requisites for Instituting Dialysis Procedures

- 1. The drug or toxic substance should diffuse easily through the peritoneum or dialysis membrane or be readily adsorbed to activated charcoal or uncharged resin.
- 2. A significant proportion of the poison should be present in plasma water or be capable of rapid equilibration with it.
- 3. The pharmacological effect of the substance should be directly related to the blood concentration.
- 4. Antidote is not easily available.

Depending on the situation any one of the procedures can be adopted. Compared to peritoneal dialysis, the other procedures are thrice more efficient.

Indications for Dialysis and Hemoperfusion

- 1. Severe clinical intoxication as shown by grade IV coma, hypotension, hypothermia and hypoventilation caused by hypnotic drugs.

Types of elimination procedure ideal for specific toxic agents	
Salicylates	1,2,3
Phenobarbitone	1,2-3
Barbitone	1-2-3
Methanol/ethanol	1-2-3
Lithium	1-2
Isopropanol	1-2
Short and Medium acting barbiturates	3-
Glutethimide	3-
Meprobamate	3-
Methaqualone	3-
Disopyramide	3-
Theophylline	3-
Key:	
1. Peritoneal dialysis 2. Hemodialysis 3. Hemoperfusion	

- 2. Progressive clinical deterioration, despite adequate supportive management.
- 3. High plasma concentration of the toxic agents.

Drugs that can be effectively dialysed includes barbiturates, phenytoin, primidone, paraldehyde, chloral hydrate, amphetamine, alcohols, methanol, ethylene glycol, salicylates, paracetamol, several antibiotics, isoniazid, quinine, quinidine, metallic salts including lithium, bromide, iodide and potassium, ergotamine, carbon tetrachloride toxic principles of mushrooms and others.

Contraindications

- 1. The toxic substance is a rapid acting metabolic poison.
- 2. The effect of the substance is irreversible, e.g. organophosphorus compounds.
- 3. The drug is relatively non-toxic, e.g. benzodiazepines.
- 4. The drug has a very large volume of distribution.
- 5. Cardiogenic shock.
- 6. Coagulopathy.

Potential Complications

- 1. Thrombocytopenia (about 30% reduction)
- 2. Leucopenia (about 10% reduction)
- 3. Loss of clotting factors.
- 4. Lowering of calcium, glucose
- 5. Bleeding tendency due to heparinization
- 6. Patient may disconnect shunt lines
- 7. Air embolism
- 8. Infection

The choice of elimination technique should depend upon the plasma level of the substance.

Elimination Procedures to be Adopted if the Plasma Level of the Toxic Substance is High

Salicylates			
500 mg/L + metabolic acidosis, or 750 mg/L	Alkaline diuresis	Methanol, ethylene or glycol 0.5g/dL	Peritoneal dialysis hemodialysis.
750 mg/L + renal failure, or 900 mg/L	*Hemodialysis or	Dialysis	is indicated if more than 30 g has been ingested or
All barbiturates except Phenobarbitone and Barbitone 50 mg/L	*Hemoperfusion Hemoperfusion		there is metabolic acidosis, mental, visual or fundusco-pic abnormalities. Many antifreeze solutions now contain methanol as well as ethylene glycol.
Ethchlorvynol 150 mg/L	-do-		Hemodialysis, significant hypotension is an important clinical indication for hemodialysis.
Glutethemide 50 mg/L	-do-		Peritoneal dialysis or hemodialysis. Forced diuresis is ineffective and an infusion of sodium chloride is dangerous as well
Meprobamate 100 mg/L	-do-	Isopropanol 0.4 g/dL	
Methaqualone 40 mg/L	-do-		
Trichloroethanol derivatives 50 mg/L	-do-		
Phenobarbitone and barbitone 75-100 mg/L	Alkaline diuresis Hemodialysis, hemoperfusion	Lithium 5 mmol/L (3470 g/L)	
150 mg/L	Hemoperfusion. Correction of hypokalemia is most important and this may obviate the need for hemoperfusion		
Theophylline 60 mg/L			

NB *Hemodialysis and hemoperfusion are two to three times more efficient than forced diuresis.

23

Common Poisons

T.K. Suma, K.V. Krishna Das

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Organophosphorus Compounds

These are the most widely used toxic agents for suicidal poisoning. Accidental poisoning occurs in workmen engaged in spraying operations. Contamination of food materials during storage or transportation has led to dramatic outbreaks of food poisoning in Kerala and many other parts of India. A dose of 40-100 mg proves fatal.

The commonly available products are methyl parathion (Folidol, Paramar, Metacid, Paramet), malathion (Malathion, Cythion) and phalone (Zolone, Sumithion, Faithion, Timidan, Ektakin).

Organophosphorus compounds irreversibly phosphorylate acetyl cholinesterase (AChE) leading to the accumulation of acetyl choline at the cholinergic nerve endings such as autonomic ganglia, parasympathetic nerve endings and motor end plates.

CLINICAL FEATURES

Symptoms start within 15-30 minutes after ingestion of the toxin. Consumption on an empty stomach and along with alcohol favours rapid absorption.

Gastrointestinal or neurological symptoms may predominate. Nausea, vomiting, diarrhea, involuntary defecation, blurring of vision, miosis, excessive sweating, lacrimation, salivation, and pulmonary edema constitute the muscarinic effects. Effects on central nervous system include drowsiness, coma, convulsions, and respiratory depression. Stimulation of pre-ganglionic fibres leads to sympathetic overaction and later paralysis, muscle twitching, fasciculation, weakness, and flaccid paralysis (nicotinic effects) (Table 23.1).

Diagnosis

In almost all cases, history, circumstances and the smell of the poison help to confirm the diagnosis. The chemical

compound can be identified by examination of gastric contents and blood.

Diagnosis is clinical, supported by evidence of consumption of the poison. Estimation of serum levels of pseudocholinesterase is helpful. Normal level of pseudocholine esterase in serum is 1750-3500 μ U/mL. Serum levels of the enzyme correlate inversely with the severity.

Reduction of serum pseudocholinesterase values below 50% of base line suggests poisoning.
Levels of 20-50% = mild poisoning.
10-20% — moderate severity
<10% — severe
Levels <200 IU are associated with ventilatory failure.

TREATMENT

The general measures for oral poisons should be instituted without delay.

Atropine

Atropine is the pharmacological antidote, and it is the sheet anchor of treatment since it antagonizes the peripheral effects of acetylcholine. It is freely available in all hospitals and cheap. This drug prevents pulmonary edema and excessive secretions. The dose requirement varies widely. In general, large doses have to be used. The ideal way to administer the drug is through an intravenous 5% glucose drip. A dose of 2 mg is given initially and 1 mg or more is repeated every 10 minutes (or even at shorter intervals) till the pupils are dilated to normal size and pulmonary edema and bronchorrhea is cleared. In many cases heroic doses, often several hundred ampoules of atropine may be required within a few hours to tide over the crises. The patient has to be observed very closely to prevent deterioration and death.

Maintenance dose is continued to keep the pupils in mid-dilation. It is usually possible to withdraw atropine after 24-48 hours but in some cases it may have to be continued for up to 5 days. Release of the toxin from lipid tissues after an interval of 2-3 days may result in return of symptoms and death after a period of apparent recovery. Hence, all patients have to be closely watched for at least 7 days after onset of the symptoms. In such cases, repetition of massive doses of atropine and supportive measures are to be undertaken.

Pralidoxime Hydrochloride

Pralidoxime hydrochloride is the specific antidote. It is given IV in a dose of 1-2 g initially and repeated 2-3 hrs later. It is available as 500 mg in 20 mL vials. Pralidoxime hydrochloride reactivates cholinesterase enzyme at the neuromuscular junctions by removing the phosphate group bound to the cholinesterase. It also binds to free

TABLE 23.1 Effects of AChE inhibition on cholinergic nervous system functions		
Muscarinic effects	Nicotinic effects	CNS effects
Excessive salivation	Muscle cramping	Restlessness
Lacrimation	Weakness	Headache
Urination	Respiratory failure	Emotional lability
Diarrhea		Drowsiness
G I distress		Tremor
Emesis		Slurred speech
Miosis		Confusion
Bronchitis		Delirium
Bronchospasm		General weakness
Bradycardia		Ataxia
Sweating		Seizures

organophosphate. The toxic effects of pralidoxime include tachycardia, cardiac arrhythmias, tachypnea, hypertension and relaxation of sphincters. The commercial preparation is 2 pyridine aldoxime ("aldopam"). Pralidoxime methane sulphate (Unichem laboratories) is also available in India. In addition to pralidoxime, atropine has to be continued for symptomatic therapy in the required doses till the enzyme levels reach normal.

A high dose regimen of pralidoxime consisting of a continuous infusion of 1g/h for 48 hours after a 2 g loading dose reduces morbidity and mortality in moderately severe cases of acute organophosphorus pesticide toxicity. This reduces the need for atropine, as well as duration of ventilatory support. The cost is around Rs. 20000/ for the first 48 hours of management.

Ref: Kirti S Pawar et al. Continuous pralidoxime infusion versus repeated bolus injection to treat organophosphorus pesticide poisoning: randomized controlled trial. The Lancet 2006. 368; 2136-2141.

Complications

Fatal bronchopneumonia may develop during convalescence. The neurological complications may take the form of **intermediate syndrome** occurring within 1-4 days of poisoning, characterized by bulbar, nuchal and proximal muscle weakness including respiratory paralysis or a distal sensorimotor polyneuropathy occurring 2-3 weeks later. The onset of intermediate syndrome usually coincides with the time of atropine withdrawal. Therefore oximes and atropine should be withdrawn carefully and gradually.

Prevention and first aid Accidental poisoning can be prevented by taking adequate precautions detailed on the commercial packing. Persons spraying insecticides should wear protective clothing and masks, and wash their bodies with soap and water thoroughly after the work, and before taking food or drink. Immediate first aid after accidental poisoning includes induction of emesis and removal of contaminated clothing and washing the body thoroughly with soap and water. The subject should be transported to a hospital without delay.

Organocarbamates

Organocarbamates (OC) are structurally similar to organophosphorus compounds and they inhibit acetyl choline esterase. The commonly available preparations are adicarb (TERMIK), aprocarb, bendiocarbonate, carbofuran (FURADAN), carbosulphan (MARSHALL), N-methyl carbamate (Carbamyl), propoxur (BAYGON) and others.

Duration of action of OC is shorter than that of organophosphorus compounds and therefore, generally the duration of symptoms in mild cases is shorter. This may not be true in severe cases.

Treatment: Atropine is quite effective as in the case of organophosphorus poisoning.

Glycopyrrolate which is a quaternary ammonium compound is an effective antidote. It is available as 1 mL ampoules containing 2 mg of the drug. The dose is 0.05 mg/kg IV or IM, to be repeated to achieve symptom relief. It does not reach the CNS and therefore the CNS side effects of atropine such as delirium and involuntary movements are avoided.

Important points

1. Organophosphorus compounds irreversibly phosphorylate acetyl cholinesterase enzyme
2. The symptoms include muscarinic and nicotinic features
3. Atropine is the pharmacological antidote to be given till features of atropinisation appear
4. Pralidoxime hydrochloride reactivates cholinesterase enzyme by removing phosphate group
5. Intermediate syndrome is a complication occurring 1-4 days after poisoning

Methanol

Poisoning with methanol may occur sporadically when industrial (methylated) spirit is consumed in the place of ethanol or epidemically when the supply of liquor is adulterated with methyl alcohol. Several outbreaks have occurred in closed communities from time to time. Minimum lethal dose is 30 g. Methanol is metabolized in the system to formaldehyde and formic acid by alcohol dehydrogenase enzyme. In addition, derangement of hepatic metabolism results in the accumulation of lactate. Severe metabolic acidosis results after a latent period of 8-12 hours. Optic neuritis develops as a specific toxic reaction.

CLINICAL FEATURES

Within hours of consuming methylated alcohol, patients develop restlessness, irritability, confusion, epigastric pain, vomiting and rapid loss of vision followed by metabolic acidosis. Visual loss is concentric. Ophthalmoscopy shows pale edematous discs. Coma may develop, which may become deep. Mortality in a large series is about 20%.

Treatment Aims of treatment are (1) correction of acidosis, (2) inhibition of methanol oxidation, and (3) removal of circulating methanol and its toxic products.

Acidosis is corrected by sodium bicarbonate given intravenously in adequate amounts. Hemodialysis helps to remove circulating methanol. Hemodialysis should be started without delay if the blood level of methanol exceeds 0.5g/L or the total quantity ingested exceeds 30 mL. Peritoneal dialysis is only one-eighth as effective as hemodialysis in removing methanol and, therefore, this should not be relied upon.

Ethanol should be given if methanol level in blood exceeds 20mg/dL. Blood ethanol concentration above 100 mg/dL inhibits the metabolism of methanol to formaldehyde and formic acid by competing for the enzyme alcohol dehydrogenase.

It is worth trying in any instance if the patient arrives early. The equivalent of 30-50 mL of ethanol is given orally at 2-4 hours interval for a few days. Once the optic nerve is affected, ethanol does not reverse the damage.

Folic acid or folinic acid in amounts of 10-15 mg intramuscular repeatedly is effective in reducing methanol toxicity in experimental animals.

Important points

1. Lethal dose of methanol is 30 g
2. Severe metabolic acidosis occurs within 12 hours and optic neuritis is a specific toxic reaction
3. Treatment aims at correction of acidosis, inhibition of oxidation of methanol by giving ethanol, and removal of the toxic products
4. Hemodialysis should be started if blood level of methanol is more than 0.5 g/L.

Barbiturates

Till recently barbiturates were the most common drugs used for suicide. Accidental poisoning is seen in epileptics, psychiatric patients and children who get regular prescription for these drugs.

The most widely used barbiturate is phenobarbitone and it is used as an anticonvulsant. Absorption and metabolism of phenobarbitone are slow. About 10% of the drug is excreted in urine unchanged. The lethal dose for adult is about 5 gm. Simultaneous administration of alcohol aggravates its effects.

CLINICAL FEATURES

Central nervous, respiratory and cardiovascular systems are affected the most. Drowsiness, slowing of respiration, and hypotension follow. Pupils are small and react to light. In severe poisoning when medullary centers are depressed, the pupils are dilated and fixed, which indicates a poor prognosis. Tendon reflexes are sluggish or absent. Necrosis of sweat glands and bullous lesions over the skin develop in a few as a hypersensitive reaction. These lesions heal slowly.

Diagnosis can be confirmed by detection of barbiturates in the gastric contents and estimation of barbiturate in blood.

Treatment In addition to general measures, forced alkaline diuresis and dialysis are helpful. Bemegride (megimide) considered to be a specific antidote but subsequent research has disproved this assumption. Repeated doses of activated charcoal and hemoperfusion are the modalities described. Since pneumonia is a fatal

complication, these patients should be observed for a week till recovery is complete.

Important points

1. The lethal dose of phenobarbitone, the most commonly used barbiturate, is 5 g
2. Central nervous system and cardiovascular systems are most affected by overdosage
3. Respiratory depression indicates poor prognosis
4. Forced alkaline diuresis and hemodialysis are the treatment options

Alcohol Intoxication

Alcohol is available in several forms commercially. The common forms are toddy (5%), beer (5%), wine (10%), arrack (40-60%), and gin, whisky and brandy (45-60%). Illicitly distilled liquor may contain several chemical impurities. One standard drink contains 12 g alcohol. It is made up by 180 mL wine, 360 mL beer or 45 mL 90% proof spirit.

Absorption of alcohol from the stomach and small intestine is rapid and detectable blood levels occur within five minutes of ingestion, reaching the highest levels in 30-90 minutes. The peak level is maintained for two hours. Fat in the food impedes absorption. Alcohol is widely distributed in tissues. It appears in the CSF, urine, and alveolar air. Alcohol is metabolized primarily in the liver. It supplies energy like carbohydrates, though it has no nutritive value.

Consumption of alcohol is not a criminal offence till it leads to alcoholic intoxication and antisocial behavior. Both the physical and psychiatric disturbances caused by alcohol fall under the purview of the physician.

Alcohol produces acute and chronic gastritis, acute intoxication ranging from excitement to coma, various nutritional and nervous disorders, and hepatic damage. Long-term use of large amounts of alcohol results in parenchymal damage to several organ systems like the liver, heart and brain.

Acute gastritis This occurs in people who consume spirits in large amounts. It is characterized by severe vomiting, abdominal pain and headache. The vomiting responds to any phenothiazine such as triflupromazine HCl. 10 mg IM (Siquil, marketed by Sarabhi). Oral antacids and intravenous fluids are required in cases which show persistent vomiting.

The cerebral effects of alcohol start within minutes of ingestion. The amount of alcohol and the extent of habituation of the patient determine the clinical picture. Slurring of speech and loss of refined mental and physical capacities occur when the blood level is 0.5 g/liter. At 3 g/liter ataxia, double vision, tremor, incoherent speech and serious loss of mental capacity are evident. Blood levels above 5 g/liter are fatal. Death occurs in coma and is caused by respiratory failure.

Diagnosis Alcoholic intoxication should be suspected from the smell of alcohol, clinical picture and the circumstances. Estimation of the levels of alcohol in urine, blood, or expired air help in confirming the diagnosis. Samples of 10 mL of urine and 2 mL of blood should be collected and sent in sealed bottles for chemical examination.

All other organic causes of coma, hysterical conversion reaction, psychiatric disorders, and malingering should be excluded.

4

Treatment Supportive treatment as in the case of coma is instituted without delay. The diuretic effect of ethanol may lead to dehydration. Intravenous administration of dextrose solution (500 mL of 20% solution followed by 1 liter of 5% solution) along with massive doses of vitamin B complex factors and vitamin C are beneficial. Early treatment improves the prognosis. Common complications include aspiration pneumonia and lung abscess. Psychiatric assessment and counselling with rehabilitation are required to avoid recurrence.

Important points

1. Symptoms of acute intoxication range from excitement to coma
2. Lethal blood level of alcohol is 5 g/L
3. Diagnosis is by clinical picture and estimation of levels in blood or urine
4. Correction of dehydration, intravenous dextrose and B vitamins are the treatment modalities

ALCOHOL WITHDRAWAL SYNDROME

This occurs typically within 5-24 hours after withdrawal of alcohol, in alcohol dependent subjects. The signs and symptoms are largely due to autonomic overactivity. Three groups of symptoms may occur.

1. Signs of autonomic overactivity occurring within a few hours of the last drink, and becoming maximal in 24-48 hours. These consist of tremulousness, sweating, nausea, vomiting, anxiety and agitation.
2. Signs of neuronal excitation such as generalized seizures occurring within 12-48 hours of abstinence.
3. *Delirium tremens*, characterized by tremor, auditory and visual hallucinations, confusion, disorientation, clouding of consciousness, hypokalemia, hypomagnesemia and prolonged autonomic hyperactivity leading to tachycardia, hypertension and tachypnea. Death may occur at this stage due to cardiovascular and respiratory collapse in less than 5% of cases. In many cases the symptoms are self-limiting within one week.
4. **Management** consists of supervised detoxifying regimes, sedation on demand, counselling, reassurance, and social support. Large doses of diazepam, 10-20 mg given at 2-hour intervals or chlordia-

zepoxide 25 to 50mg every 4-6 hours may be needed to sedate the patient. Once sedated, the drug is stopped. Repeated dosage may be required in a few. Seizures are also controlled by diazepam given in doses of 5-10 mg oral or 2-5 mg IV slowly or as a slow IV infusion, the total dose not to exceed 1-2 mg/kg bw in 24 hours. In those with hepatic damage, sedatives such as oxazepam 30 mg or lorazepam 20 to 30 mcg/kg IV should be given. They do not cause further damage to the liver. More serious complications such as Wernicke's encephalopathy, dehydration and electrolyte imbalance may develop. Prophylactic thiamine is given in a dose of 20 mg IM or IV b.d.

Management of alcohol withdrawal syndrome and de-addiction are specialized procedures requiring the combined effects of the physicians, psychiatric and social workers.

Important points

1. Alcohol withdrawal symptoms develop typically within 5-24 hours after withdrawal
2. Predominant symptom is autonomic hyperactivity
3. Delirium tremens is a serious complication wherein cardiovascular and respiratory collapse may occur
4. Management includes benzodiazepines and other supportive measures

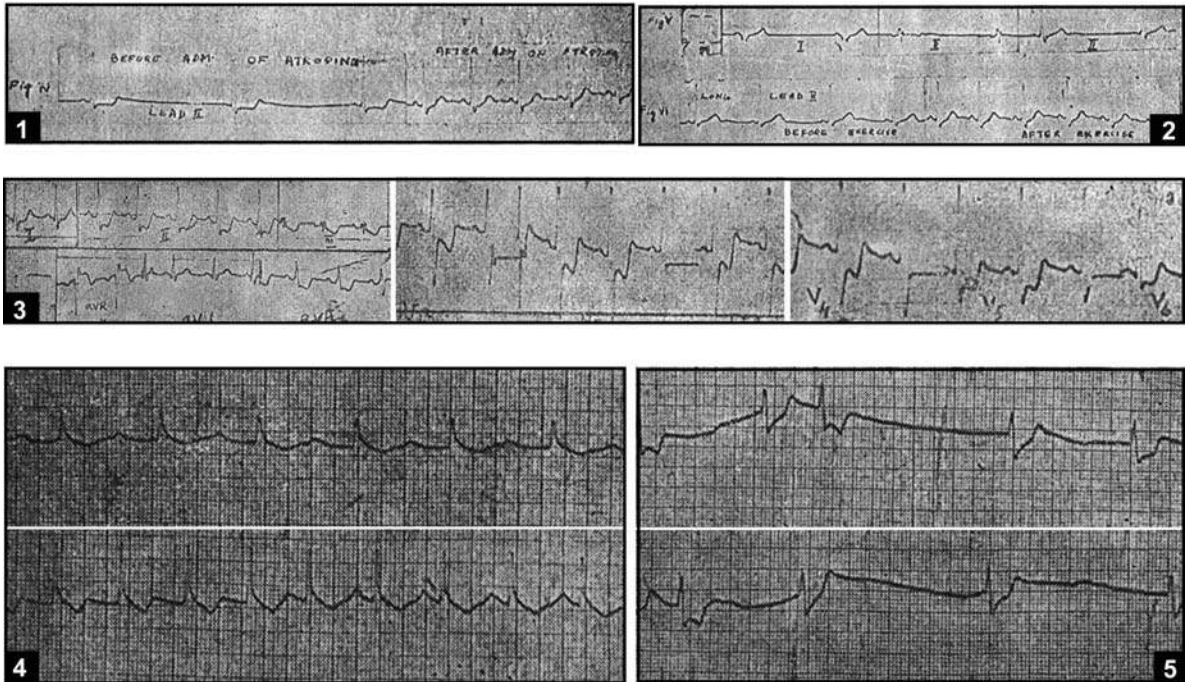
Cerebera Odollam

Cerebera odollam belonging to the family Apocynaceae is a small tree found all over India, is a frequent cause of poisoning especially in Kerala. Many cardiac glycosides have been isolated from the plants belonging to this family, e.g., stophanthin, ouabain, oleandrine, cereberin and thevetine. The active principles seen in *Cerebera odollam* are *cerberin*, *cerberoside* and *odollin*, which are seen in highest amounts in the kernels of the seeds. The seeds taste very bitter. The contents of a single fruit can be fatal if ingested.

Cerberin, like digitalis, reduces the heart rate by inhibiting sinoatrial and atrioventricular conduction, mainly by a vagotonic action, which can be partially reversed by atropine. In higher doses cerberin has a direct depressant action on the myocardium, which cannot be reversed by administering atropine. The majority of poisoning cases are suicidal.

Morbid anatomy Autopsy studies are not very rewarding. Except for subepicardial and subendocardial hemorrhages, the gross anatomy appears normal. The conducting tissue of the heart is histologically normal.

Clinical features Within an hour of taking the poison, retching, nausea, vomiting and abdominal pain occur. Later, the patient becomes weak and drowsy and may lapse into coma. Bradycardia, only partially responsive to atropine, is the most obvious finding.



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Fig. 23.1: ECG changes cerbera odollam poisoning

1. **Early stage:** Sinus bradycardia, responding to atropinisation
2. **Mild case:** Sinus bradycardia persisting for one week after recovery, Responding normally to exercise
3. **Moderately severe cases:** Note (a) tachycardia (b) ST depression in leads I, II, III aVF and V1-V6 (c) ST elevation in lead aVR (d) Biphasic T waves leads II, aVF and V1-V6
4. **First degree A-V block,** (top) responding to atropinisation (bottom)
5. **Severe toxicity:** Idioventricular rhythm. Often this is fatal

Ref: Kunhali et al Ind. Heart J. 1970;22.4:373-377.

Narendranathm et al. Ind. Heart J. 1975;27.4:283-286.

The ECG may show various types of bradyarrhythmias like sinus bradycardia, A-V dissociation, and junctional rhythms. Different grades of A-V block and S-A block have been described. Ventricular extrasystoles may occur rarely. The changes in the ST segment, the T wave and the QT interval are similar to those produced by digitalis. 60% of the patients show hyperkalemia

Treatment Management consists of the elimination of unabsorbed poison by stomach wash, purgatives, bowel wash and correction of bradyarrhythmias by intravenous atropine (0.5mg). In severe cases, the drug has to be repeated even at 15 minutes intervals, or it has to be administered as a continuous drip. Hyperkalemia should be treated by appropriate measures (Insulin glucose regimen). When bradycardia is not corrected by atropine, the patient may require cardiac pacing. The presence of hypotension, alteration of consciousness, bradyarrhythmias not responding to treatment, hyperkalemia, and significant electrocardiographic changes indicate severe poisoning and the outlook in such cases is poor with an overall mortality of 20-25%. Management in a cardiac intensive care facility is certainly likely to improve results,

although the experience is still limited. Once established, the cardiac phenomena persist for one to three weeks since the toxin is only very slowly eliminated. Hence prolonged observation is required.

Important points

1. Active principles of Cerebra odollam are cereberin, cereberoside and odollin
2. Cereberin has vagotonic action and direct depressant effect on the myocardium
3. Various types of bradyarrhythmias and hyperkalemia can occur
4. Treatment is with atropine, management of hyperkalemia and temporary cardiac pacing when required.

Cleisthanus Collinus Leaf

This is emerging as a common suicidal poison in Tamil Nadu. It is ingested in several forms. Main toxic effect is on the heart. Progressive bradycardia, sudden cardiac arrest and progressive respiratory failure follow. Hypokalemia occurs in over 70%. Prolongation of the corrected Q-T interval in the ECG above 0.45 second is associated with poor outcome. General measures, atropine

and temporary cardiac pacing have been employed in treatment.

Corrosive Acids

Acids like hydrochloric acid, sulphuric acid, and nitric acid are widely used in the laboratory. Cases of accidental and suicidal poisoning are not rare. Corrosive acids produce similar clinical picture, which is due to their direct chemical action on tissues.

4

Clinical features Sites of intimate contact like the lips, throat, palate, and posterior pharyngeal wall show scalding. They bleed easily and slough away leaving raw areas. Clinical features of acidosis occur if large amounts are ingested. Metabolic acidosis occurs as a result of cellular injury and from systemic absorption of acids. Complications like perforation of the esophagus and stomach, severe hematemesis, acute renal failure and severe shock are fatal. Esophageal stricture is a common sequel.

Treatment Emesis and gastric lavage are contraindicated. The acid in the stomach can be diluted by large volumes of water or milk. Pain is relieved by local anesthetics like xylocaine viscous and analgesics. Oral feeds should be avoided for a day or two after which swallowing of fluids like milk should be encouraged. Infection has to be prevented by the administration of ampicillin 1 g IV 6th hourly. If esophageal perforation is excluded, corticosteroids may be given parenterally in doses equivalent to hydrocortisone 25 mg 6 hourly for 3-5 days. This may prevent the formation of esophageal stricture.

Metabolic acidosis develops in most of the cases. This has to be corrected by the administration of IV normal saline and sodium bicarbonate, depending upon the requirement.

Treatment of shock, perforation, peritonitis and acute renal failure should be undertaken when they occur. Early institution of oral feeds helps to reduce the occurrence of esophageal stricture. If stricture occurs, the treatment is surgical.

ACETIC ACID

Acetic acid is used for coagulating rubber latex and, therefore, it is freely available to workers in rubber plantations. Poisoning is usually suicidal, rarely accidental. The fatal dose varies from 15-60 mL.

Clinical features Intense scalding and burning of the lips, mouth, pharynx, and throat occur over areas of direct contact. Dysphagia and burning pain along the esophagus and stomach follow. There is excessive salivation. The patient shows anxiety and is acidotic. Hemoglobinemia and hemoglobinuria develop within hours. Bronchitis,

bronchopneumonia, and aspiration pneumonia follow. Shock, severe acidosis, pneumonia, mediastinitis, perforation of the stomach or esophagus and renal failure result in death.

Treatment Diazepam in a dose of 5-10 mg is given intravenously to sedate the patient. Gastric intubation is contraindicated. Demulcents like egg albumin or milk may be given if the patient can swallow. Oral intake of fluids should be encouraged early, since this helps to prevent stricture. Glucose saline drip is started early to provide nutrition, fluids, and electrolytes. Acidosis is corrected by suitable doses of sodium bicarbonate. Frusemide 20 mg given intramuscularly may be beneficial to prevent the development of renal failure. Mortality ranges from 20 to 30%. Esophageal stricture may occur which will require surgical treatment.

FORMIC ACID

Formic acid and its salts are used in textile, leather and rubber industries. It is also a component in some descaling agents, disinfectants and preservatives. Suicidal attempts and accidental ingestion of formic acid are common in many rubber cultivating areas of Kerala and Tamil Nadu because of its free availability. Protoplasmic coagulation, precipitation or dissolution of proteins, and exudation of fluid occur at the sites of intimate contact.

Since in most cases of accidental ingestion, the person tries to spit out the acid, burns occur in and around the mouth. However, if acid is consumed with suicidal intent, the attempt to swallow evokes reflex cough because of its irritant vapors. Acid enters not only the esophagus but also the respiratory tract. This results in ulceration, bleeding, sloughing and perforation of the esophagus and stomach, tracheitis, bronchitis, pulmonary edema, and pneumonia. Systemic effects of the acids are acidosis, intravascular hemolysis, hemoglobinuria, and shock. Renal failure is common.

Hemoglobinuria and oliguria should portend the onset of renal failure, which demands early and repeated hemodialysis. Recent reports from Kozhikode medical college show that even superficial burns exceeding 20% of body surface caused by formic acid may lead to acute tubular necrosis and renal failure.

First aid treatment is to dilute the acid with water or neutralize with milk. Gastric intubation is contraindicated, antacids are given if the patient can swallow. Parenteral fluids are given to hydrate the patient and acidosis is combated by the intravenous administration of sodium bicarbonate. Frequent feeding with milk, egg albumin and other demulcents helps to reduce the incidence of stricture. Antibiotics, analgesics and respiratory physiotherapy are indicated in all cases. Late occurrence of esophageal stricture has to be treated surgically.

Important points

1. Corrosive acids produce burns or scalding in the lips, throat and posterior pharyngeal wall due to chemical reaction
2. Ulceration and perforation of esophagus and stomach, pulmonary edema and pneumonia are the usual manifestation of corrosive acids
3. Systemic effects include acidosis, intravascular hemolysis, hemoglobinuria and renal failure
4. Esophageal stricture is a common sequel

Alkalies

Strong alkalies are used in industry. Household cleaning materials contain alkaline substances. Ammonium hydroxide, potassium hydroxide, sodium hydroxide, potassium carbonate, sodium carbonate, and sodium and potassium phosphates account for the vast majority of alkali poisoning. Strong alkalies lead to scalding and ulceration of tissue. On ingestion, patients experience severe pain in the mouth, throat, chest and abdomen. Tongue, oral mucosa and pharynx show areas of erythema and necrosis. Metabolic alkalosis develops as a systemic effect. Sodium and potassium phosphates may cause severe reduction in serum calcium leading to tetany.

Treatment This consists of diluting the alkali by the administration of water or milk and maintenance of fluid and electrolyte balance. Local pain can be allayed partly by the use of xylocaine viscous. Tetany is managed by the administration of calcium gluconate intravenously. Prevention of secondary infection by the use of antibiotics and corticosteroids to prevent stricture of the esophagus have to be considered in selected cases. Endoscopy done within 24 hrs of admission helps to assess the severity of lesions in the esophagus and stomach and institute surgical treatment when appropriate.

Narcotics-Morphine and Opioids

Poisoning by Morphine and its allied narcotic analgesics leads to initial excitement followed by a depression of the nervous system. The patient is stuporose or comatose with pin-point pupils, slow and shallow respiration, cyanosis and hypotension.

Treatment In addition to supportive measures and gastric aspiration, ventilatory assistance is required in comatose patients. Specific antidote is nalorphine hydrobromide (Lethidrone) given intravenously 0.4-2 mg every 2-5 minutes till the respiration and blood pressure become normal. In general, the total dose is limited to 40 mg in any case.

Toxic effects of nalorphine include respiratory depression, hypotension, drowsiness and hypothermia.

Paracetamol**Syn:Acetaminophen**

Paracetamol is the most widely used analgesic at present. Due to its free availability, paracetamol poisoning is becoming more frequent. Doses exceeding 8 g can produce toxicity. Acute hepatocellular and less frequently renal tubular necrosis may follow ingestion of a single dose exceeding 10 g. A highly reactive metabolite of paracetamol N acetyl benzoquinonimine (NAPQI), which is normally inactivated by hepatic glutathione is responsible for the hepatic failure. With overdosage of acetaminophen, hepatic glutathione is rapidly depleted and NAPQI binds to cellular proteins causing necrosis of cells. Hepatic levels of glutathione are increased by N Acetylcysteine and methionine thereby protecting the liver from injury. Alcoholism, malnutrition and concurrent use of drugs which induce microsomal oxidase enzyme (P450) like anticonvulsants predispose to hepatic damage.

Clinical features Early symptoms are nausea, vomiting and sweating. The most dangerous complication is hepatic damage.

This becomes manifest 1-2 days after onset with jaundice, bleeding tendency, and hepatomegaly. A few cases progress to fulminant hepatic necrosis resulting in hepatic coma and this is associated with high mortality. Other serious but rare complications are acute tubular necrosis, pancreatitis, carditis, hypoglycemia, metabolic acidosis and hypersensitivity reactions.

Liver function tests become abnormal and the maximum damage is reached within 72-96 hours. SGPT levels go very high (even up to 10000 iu/L). Prothrombin time is prolonged. INR above 6.5 portend the possibility of fatal liver failure. Blood lactate levels are raised due to over production and diminished excretion. Values above 3.5 mmol/L in arterial blood persisting after fluid replacement should alert the physician about the risk of hepatic failure and the need for hepatic replacement.

(Note: Normal lactic acid level in plasma is 5-20 mg/dL—i.e. 0.5-2.0 MEq/L)

Treatment Correction of fluid and electrolyte imbalance should be started immediately. Gastric lavage should be performed to remove unabsorbed drug. Activated charcoal may help to adsorb the residual drug. In severe cases where the blood level of paracetamol is above 300 mg/liter at 4 hours, hemoperfusion is the best method for rapid elimination of the drug. Forced alkaline diuresis is ineffective.

Specific management is to give the antidote N-acetyl cysteine (NAC). In patients who have reached the hospital within four hours of ingestion, gastric lavage and activated charcoal may help to prevent systemic effects. Serum levels of paracetamol should be estimated after 4 hours

in order to assess the risk. Paracetamol levels above 100 mg/dL indicate high mortality and therefore demand the administration of NAC. It is given as IV infusion as follows:

Dose	NAC mg/kg	Volume of 5% glucose	Duration of drip
1.	150	200	15 minutes
2.	50	500	4 hours
3.	50	500	8 hours
4.	50	500	8 hours

An oral preparation of N-acetyl cysteine is also available. The dose is 140 mg/kg orally initially followed by 70 mg/kg 4 hourly for 72 hours. This should not be relied upon in an emergency.

Liver failure should be treated on the lines of fulminant hepatic failure. Paracetamol poisoning is one of the frequent causes of fulminant hepatic failure in western countries.

Important points

1. The toxic dose of acetaminophen is 8g
2. The highly toxic intermediate metabolite N acetyl benzoquinonimine produces hepatic cell injury
3. Fulminant hepatic necrosis is the cause of mortality
4. Specific treatment is N- acetylcystiene 150 mg/kg body weight

PETROLEUM PRODUCTS - KEROSENE

Accidental poisoning with kerosene is common in India because of its free availability in the household. Children suffer more. Cases of poisoning with other petroleum products like petrol, diesel oil, and paint thinners are encountered less commonly. Petroleum products are used as solvents in the manufacture and application of polishes, paints, and pesticides. Some persons develop the habit of sniffing paints and polish for the nervous effects produced by the solvents. They contain various amounts of aliphatic and aromatic hydrocarbons, which are mainly depressants of the central nervous systems. They cause damage to the cells on direct contact on account of their ability to dissolve cellular lipids. The low surface tension facilitates their spread along mucosal surfaces and the lungs even when only small amounts are ingested or inhaled.

Poisoning usually results from ingestion but can also result from inhalation. The clinical features depend on the quantity and route of poisoning.

Clinical Features

Symptoms pertaining to the central nervous system include headache, nausea, tinnitus, drowsiness, convulsions, and coma. Severe vomiting occurs when the

oral route is adopted. Kerosene reaching the trachea spreads widely throughout the respiratory tract resulting in the most common and potentially dangerous complications of pneumonia and pulmonary edema. Death may result due to respiratory embarrassment, ventricular fibrillation, or severe pneumonia.

Treatment All suspected cases of kerosene poisoning should be hospitalized for 24 hours to watch for aspiration pneumonia. Simple gastric lavage is better avoided. If it is deemed essential, a cuffed endotracheal tube should be introduced prior to gastric lavage to protect the respiratory tract.

Chemical pneumonia is treated with oxygen inhalation, corticosteroids and ventilatory assistance when indicated. Antibiotics should be employed to prevent secondary infection.

ORGANOCHLORINE INSECTICIDES

These common chemicals, which are used as insecticides in houses, gardens and in agriculture, have different chemical structures.

1. Chlorinated diphenyls, e.g., DDT, TDE, DFDT, and DMC
2. Chlorinated polycyclic compounds, e.g., Chlordane, Aldrin and Endrin.
3. Hexachlorobenzene compounds, e.g., Lindane.

These are insoluble in water, but freely soluble in organic solvents and lipids. Their solutions in petroleum, kerosene, or other organic solvents are used for spraying. Poisoning may be accidental or suicidal. Acute toxicity results from ingestion or inhalation of these substances. Variable amounts of these chemicals may be absorbed through the skin and can result in toxicity. They stimulate the central nervous system. When used in the form of solutions, the action of the solvent modifies the total effect. The fatal doses of these compounds are:

DDT	20 g
Lindane	3 g
Chlordane	1 g
Aldrin and Endrin	Less than 1g

Clinical features Early manifestations are nausea, vomiting, irritant cough, headache, and bodyaches. These are followed by nervous irritability, mental sluggishness, muscle twitching, tremors, incoordination, convulsions, paralysis and coma. Acute pulmonary edema and shock may occur if the exposure is heavy. Liver dysfunction is a prominent feature in Endrin poisoning.

Treatment The general measures are instituted without delay. Administration of activated charcoal and saline purgatives help to reduce absorption of the chemical. Convulsions have to be controlled with injection of

10 mg of diazepam. Calcium gluconate 1 g given intravenously has been found to reduce the convulsive tendency. Ventilatory assistance is required if respiratory failure sets in.

Widespread use of organochlorine compounds in agriculture has led to their slow absorption through food, milk and water and these chemicals accumulate in human and animal tissues. Chronic toxicity is a potential hazard.

Ethylene Dibromide Poisoning (EDB)

EDB is used as an insecticide against soil nematodes, insects and termites and also as a fumigant to protect stored products. It is a colourless volatile liquid with an ethereal odour, available as liquid, capsules or granules. Suicidal poisoning has been reported from Madhya Pradesh. Symptoms include vomiting, circulatory failure, pulmonary congestion, liver damage leading to hepatic

encephalopathy, and renal failure. Mortality may go up to 50%. Treatment is symptomatic.

Phosphide Poisoning

Both zinc phosphide and aluminium phosphide are freely available rodenticides. When ingested, they liberate phosphine gas on coming into contact with moisture. This toxic phosphine is lethal to cells by reacting with the enzyme cytochrome oxidase. Zinc phosphide produces early vomiting and diarrhea within 20 minutes when ingested and severe cough, breathlessness and pulmonary edema when inhaled. Metabolic acidosis, hypocalcemic tetany and hypokalemia follow. Organs affected include the heart (toxic myocarditis), pleura (effusion) and lung (RDS). Fatal shock may ensue. Magnesium sulphate infused IV at a rate of 3 g in the first 3 hours and then 6 g in the next 24 hours is being evaluated in treatment. The results are equivocal.

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Food Poisoning

T.K. Suma, K.V. Krishna Das

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General Considerations

Sometimes, articles of food cause toxic reactions. This toxicity, in general, is caused by the following factors:

1. The food may be naturally toxic, e.g., poisonous mushrooms, toxic fish, etc.
2. Toxicity may be imposed upon the food material by the polluted environment, e.g., contamination of fish by mercury from industrial effluents, infection of oysters by Salmonella due to fecal contamination.
3. Contamination of food during collection, transportation, storage, cooking, or serving by:
 - a. Chemicals (accidental or by addition of adulterants),
 - b. Microbial agents - bacteria, viruses, protozoa, and
 - c. Preformed toxins contaminating the food articles.
4. Allergy to the food materials.

Episodes of food poisoning are characterized by several distinctive features, which help to diagnose them and study their epidemiology.

1. They occur in small outbreaks in several persons who have shared a common item of food.
2. The symptomatology is similar in all cases, but severity varies depending on the quantity of the food ingested, age of the individual and weight. Children suffer more than the adults.
3. The incriminated food material may show abnormalities such as putrefaction, distaste and altered consistency. Tinned food packed in vacuum shows bloating of the tins.

For preventing spread of the outbreak and to help in investigating the cause, the primary physician has to follow a set procedure. At the first suspicion of food poisoning, the incriminated food should be isolated and even small quantities should not be consumed further. Those who are apparently well and who would have consumed the food should be advised to induce vomiting by tickling the throat after drinking a glass of water and as much of the food as is possible should be removed, by repeated vomiting. This single measure reduces the risk considerably.

1. The appropriate health authorities should be notified.
2. Proper clinical records should be maintained.
3. Remnants of food should be preserved for chemical and microbiological tests.
4. Vomitus, urine and feces should be collected sealed, and sent for chemical analysis.
5. If death occurs, medicolegal autopsy is indicated and the stomach, intestines, liver and other organs have to be sent for chemical examination.

The general principles of treatment are similar to those for chemical poisoning.

Toxin Type of Food Poisoning

Preformed toxins present in food are responsible for this condition e.g., organisms like *Staphylococcus aureus*, *Bacillus cereus*, *Clostridium botulinum*, *Cl. perfringens*, and *Salmonellae* are the common agents responsible for such outbreaks. The most dangerous among them are the soil *Clostridium species* which are gram + *Cl. perfringens* causes food poisoning and necrotizing hemorrhagic enteritis. *Cl. Botulinum* is capable of producing toxin mediated food poisoning termed botulism, wound infection and intestinal infection. In all cases the absorption of toxin is the crucial pathogenic event. Staphylococcal contamination usually results from pustules in the udder of the cow or from the skin or nose of food handlers. *Bacillus cereus* is usually seen in contaminated fried rice.

STAPHYLOCOCCAL FOOD POISONING

It is caused by the enterotoxin of *Staph. aureus*. The common articles of food include stored cooked meat, milk and cheese. The onset is acute with vomiting, diarrhea and crampy abdominal pain developing 1-6 hours after ingestion of the food. Shock may supervene, but recovery in 24-48 hours is the rule. Treatment is symptomatic.

BOTULISM

This results from the ingestion of the toxin of *Cl. Botulinum*. The organism grows under anaerobic conditions in contaminated meat foods like sausages, fish, etc. The organism is present in the soil and it spreads through the spores, which can resist boiling for considerable periods. The toxin, which can be separated into fractions A, B and E acts on the nervous system and it inhibits release of acetylcholine at the neuromuscular junction and blocks neuromuscular transmission in cholinergic nerve fibers. The toxin rapidly fixes to the nerves and once endocytosis occurs, its effects cannot be reversed. The toxin consists of seven serologically distinct, but structurally similar components A, B, C, D, E, F and G of which only types A, B, E and F cause illness in humans. The paralysis persists for 2-3 months or even more. Botulism may occur in one of three forms, food borne botulism, infant botulism and wound botulism. In addition to its role as a cause of food poisoning, *Cl. botulinum* can contaminate wounds and also grow in the intestinal tract and elaborate toxins.

Symptoms start in 12-36 hours after ingestion with diplopia, blurring of vision and paralysis of cranial nerves. Other features are dry mouth, dysphagia and dysphonia. Progressive muscular involvement results in respiratory paralysis. Death is caused by respiratory failure or pneumonia (10-20%). Neurological sequelae in the form of motor paralysis may persist for several months in a few.

Diagnosis Other conditions leading to neuromuscular paralysis such as Guillain-Barré syndrome, myasthenic crises, cobra or krait bites, and vascular accidents of the brainstem have to be differentiated. Myasthenic crises responds to Tensilon whereas in botulism this is not so.

Treatment Adequate ventilatory support and general supportive measures should be instituted. Guanidine hydrochloride in a dose of 15-50 mg/kg/day has been used but without proven effect. A trivalent preparation containing anti-toxin is available it is given I V in doses of 50000 units stat and repeated after 2 hours. This vaccine is not freely available in India.

Infant Botulism

This is caused by *Clostridium botulinum* colonizing in the colon of infants. They produce the toxin which is absorbed and leads to systemic effects. Infant botulism is defined as an illness consistent with paralysis typical of botulism

toxin. The typical organisms are cultured from feces or enema material. Treatment consists of giving botulinum immune globulin containing neutralizing antibodies.

Anaerobic Food Poisoning

C. perfringens food poisoning: The usual source of contamination is meat. Heat resistant spores survive improper cooking. They germinate when the food is cooled. On reaching the intestine they sporulate and produce exotoxin which causes abdominal cramps and diarrhea.

INFECTION TYPE OF FOOD POISONING

In this group, organisms enter along with contaminated food and multiply in the gut to produce the lesions after an incubation period ranging from 24-72 hours. The organism may be noninvasive or invasive depending on their action on the intestinal mucosa. The organism may be noninvasive such as *enterotoxigenic E. coli* or *Klebsiella*. They produce diarrhea by locally acting enterotoxins, which stimulate adenyl cyclase and cyclic AMP mechanisms.

The intestinal mucosa is not destroyed. Stools are watery and generally devoid of inflammatory cells. Clinical features of severe dehydration predominate with relatively mild constitutional symptoms.

Invasive group includes organisms like *Shigella*, *Salmonella typhimurium*, *Salmonella enteritidis*, *Yersinia enterocolitica*, invasive strains of *E.coli* and *Vibrio parahemolyticus*. They produce inflammatory lesions. They destroy the intestinal mucosa and the feces contain abundant inflammatory cells and erythrocytes. Constitutional symptoms of varying severity accompany this syndrome.

In the infection type of food poisoning antimicrobial therapy is indicated to arrest the multiplication of the organism in the gut. Systemic antibiotics are indicated in the invasive type. General measures of treatment of gastroenteritis are indicated.

Chronic Food Poisoning

Some cases of chronic food poisoning, caused by repeated exposures to fish contaminated by industrial effluents, have been reported.

1. **Haff disease** is produced by eating fish poisoned by toxic resinous acids from cellulose. This condition produces myoglobinuria in the affected persons.
2. **Minimata disease** is caused by consumption of fish, which has ingested methyl mercury compounds. Out-breaks of mercury poisoning occurred in cats and people living in fishing villages in Japan.

Due to the rapid growth of industry and the present day tendency to interfere with natural ecosystems, such examples are likely to be on the increase, unless sufficient care is taken to prevent them.

MUSHROOM POISONING

Mushrooms are delicacies on the table. In India, they are grown commercially in Himachal Pradesh and many other parts including the southern states. Many people eat wild mushrooms collected seasonally and some of them cause accidental poisoning. The common toxic mushrooms include - *Amanita phalloides*, *Amanita verna*, *Amanita virosa*, *Helvella esculenta* and *Galerina species*. All these species contain amatoxin, which is a potent cytotoxin. Deaths have resulted from the ingestion of even 50 g of mushrooms. The toxic principles vary in different species.

Amanita muscaria contains three toxic principles. (1) A parasympathomimetic alkaloid- muscarine, (2) a neurotoxic substance, and (3) an alkaloid with atropine like action. The toxins of *Amanita phalloides* and related species are cytotoxic alpha amanitin and phalloidine. These toxins inhibit protein synthesis. The toxic principles are thermostable and, therefore, resist cooking.

Pathogenesis The toxin leads to severe cholinergic overactivity similar to organophosphorus poisoning. Autopsy shows extensive cellular degeneration, necrosis, edema and hemorrhage in the liver, kidney, gastrointestinal tract and brain.

Amanita muscaria Signs of toxicity develop sometime after the consumption of contaminated food. Symptoms may be atropine like including, excitement, delirium, flushed skin, dilated pupils and muscular twitchings. Other features include hypotension, convulsion, delirium and coma.

Early recognition and treatment give good results with complete recovery within 24 hours. In addition to general measures, specific treatment is with physostigmine 0.5-1 mg IV which corrects the anticholinergic effects of the poisoning.

Amanita phalloides The clinical picture develops in two phases. The first phase starts after a latent period of 8-12 hours and essentially resembles acute gastroenteritis ("belated mycetismus cholericiformis") with muscle cramps, vomiting, profuse diarrhea, dehydration and circulatory collapse. The second phase sets in 2-3 days later even after apparent initial recovery. The features resemble acute yellow atrophy of the liver, progressing to hepatic and renal failure. The prognosis is poor. Mortality may exceed 50%. In those who survive recovery is slow.

Sometimes mushrooms belonging to *Coprinus* species produce an antabuse-like reaction if consumed with alcohol. *Panaeolus* produces atropine toxicity like picture and *Helvella* produces hemolytic reaction.

General Management

Stomach wash should be given early. Oral administration of 25-50 g of activated charcoal helps to bind amatoxin

for which it has high affinity. This simple procedure is very helpful if instituted within 36 hours of poisoning.

Several drugs have been employed as possible antidotes, some of them are still experimental. These include massive doses of penicillin, vitamin C, silymarin and thioctic acid.

Thioctic acid (alpha lipoic acid) is given intravenously in doses of 200-300 mg twice daily. The results are encouraging. Hemoperfusion over charcoal has been found to be beneficial in severe cases. All patients with suspected mushroom poisoning should be observed for at least 24 hours since in a few cases the onset of symptoms could be delayed.

Important points

1. There are different species of Mushrooms with varied toxic principles
2. Most of the very toxic species contain amatoxin, which is a potent cytotoxin and deaths have been reported within minutes of intake.
3. Symptoms vary from gastrointestinal irritation, anticholinergic effects, muscarinic or hallucinogenic effects depending on the species
4. Haemoperfusion using charcoal is beneficial in severe cases and several antidotes have been tried

FISH POISONING

In many parts of India toxicity to fish is encountered seasonally from time to time. This may occur as small outbreaks confined to families or may be widespread. The term 'ichthyotoxism' refers to poisoning by intrinsic toxins in fish. The toxic principles may be sarcotoxic (flesh and viscera are toxic), ootoxic (only the reproductive organs are toxic) or hemotoxic (where the toxicity is predominantly in the blood). Some varieties of fish become toxic to man only in particular seasons.

Several factors such as glandular activity during spawning season, consumption of toxic dinoflagellates or toxic plants in the sea, and contamination by industrial effluents can make the fish toxic. Toxic principles may be confined to the liver in many fishes. During certain seasons, the livers of some fishes may contain very high levels of vitamin A (600,000 units/100g). Ingestion of such livers leads to acute vitamin A toxicity characterized by headache, nausea, vomiting, prolonged sleep or drowsiness followed later by extensive exfoliative dermatitis. Another type of toxicity is related to the very high histidine content of scombroid fish. On storage, due to the action of marine bacterial flora, histamine and saurine are produced. These reach high levels causing an acute histamine intoxication syndrome with headache, flushing, urticaria, vomiting and circulatory failure (scombrototoxicity).

Dinoflagellate-induced toxins lead to neuroparalytic syndromes.

Acute renal failure following consumption of gallbladder of raw carp-*Ctenopharyngodon idellus* has been described from Manipur, India. This presented with vomiting and rapid onset of oliguric renal failure. The pathology is likely to be tubular necrosis due to direct nephrotoxicity. These cases responded well to conservative treatment including peritoneal dialysis.

Singh N.S et al. Acute renal failure following consumption of raw fish gallbladder –*Jl Ass Phys Ind* 2004,52,743-745).

Diagnosis of ichthyotoxism can be made from epidemiological and clinical considerations. Bacterial food poisoning has to be excluded. Treatment is only symptomatic and in majority of cases, complete recovery is the rule.

ACUTE CASSAVA TOXICITY

Cassava or tapioca (manioc) is a staple diet among the poor people in many parts of the world, especially in Africa and Southern States of India. Certain bitter varieties (*Manioc utilis*) are toxic during particular seasons due to *linamarin*, which contains cyanogenic glycosides and a glucosidase enzyme. The toxins are maximum in the outer coat, which can be removed by peeling. Bruising, soaking in water, cooking in insufficient quantity of water or prolonged storage serves to bring together the glycoside and the enzyme and liberate hydrocyanic acid. A lethal dose of hydrocyanic acid (60 mg) may be acquired from 300 G of partly damaged cassava.

Symptoms of acute poisoning include giddiness, headache, mental confusion, coma and collapse. Death occurs because of asphyxia. Convulsions and incontinence of sphincters may precede death, which usually occurs within 2 hours of the meal.

Treatment Early gastric lavage with 1% sodium bicarbonate should be given. Specific measures are those for cyanide poisoning. These are :

1. Oxygen inhalation
2. Specific antidote is amyl-nitrate, which is given by inhalation every 2 minutes. This is followed by intravenous administration of 10 mL of 3% sodium nitrite, taking 5 minutes for the injection and later 50 ml of 25% sodium thiosulphate over a period of 10 minutes.
3. This course should be repeated if required. Blood level of methemoglobin should be estimated and this should be kept below 40%.
4. Dicobalt-acetate in a dose of 300-600 mg given intravenously in one minute is a chelating agent used for removing cyanide.

Cassava toxicity should be prevented by avoiding bruised tubers and taking care in storage and cooking. Boiling the tuber in a large quantity of water and

discarding the supernatant removes the toxic content. The increased content in cassava has been implicated in the causation of several conditions such as calcific pancreatitis, Konzo- which is a form of tropical myelopathy first detected in Africa, and possibly other conditions as well.

In India the Tuber Crops Research Stations have helped to develop newer less toxic varieties of cassava, which have become very popular. The occurrence of cassava toxicity has come down in recent times. Far from its original position as poor man's staple, at present cassava has gained the position of being a delicacy on the table.

Important points

1. The toxicity of cassava is due to linimarin which contains cyanogenic glycosides and a glucosidase enzyme
2. Acute poisoning may produce giddiness, headache, mental confusion, coma and collapse.
3. Treatment is as for cyanide poisoning
4. Cassava toxicity has been implicated in calcific pancreatitis, tropical myelopathy etc

Onyala

This is an acute purpuric disease, characterized by hemorrhagic bullae inside the mouth, seen in Africa. It is attributed to the mycotoxin of *Bhoma sorghina* isolated from the cereals, millet and sorghum, though its etiology is not fully known.

Hepatic Veno-occlusive Disease

Syn: Veno-occlusive disease of Jamaica

Though originally described from Jamaica, cases have subsequently been reported from all over the world. The toxic principles of *senecio* and *crotonaria* are responsible for this syndrome. These plants are taken as bush teas. Malnourished children in the age group 2-5 years are particularly vulnerable. The toxin causes proliferation of intimal cells and swelling of subintimal tissues. This leads to occlusion of centrilobular veins of the liver. Liver cells atrophy and are replaced by centrilobular fibrosis. Outbreaks have been reported from Central and North India.

Clinical features varies in severity. In the acute form hepatomegaly, ascites, and rapidly progressive hepatic failure develop. Many cases recover completely. Rare sequelae include asymptomatic hepatomegaly or gradual progression to cirrhosis liver and portal hypertension.

Treatment consists of prompt withdrawal of the offending materials and dietary supplementation with high quality protein. No specific antidote is available (see also section 9, chapter 87).

Aflatoxicosis

Aflatoxins are products of fungi particularly those of *Aspergillus flavus*. These are widespread in several articles of human and cattle food and, therefore, aflatoxicosis involves wide population groups. Groundnuts, cereals or pulses are invaded by the fungus, especially when stored in damp environment. The damaged grains show obvious abnormalities. The toxin contains several components (B_1 which is most toxic, B_2 and G_2). Acute toxicity occurs when mouldy cereals, pulses or nuts are consumed. Aflatoxin is hepatotoxic to many animals and birds. Fungus affected grains are likely to be consumed during periods of drought, famine and non-seasonal rains. Generally, the poor socioeconomic sections of the communities are affected. The clinical picture may be that of acute hepatitis, cirrhosis of the liver or hepatoma depending on the dose and duration of exposure. The outbreaks reported from western India and Rajasthan resembled viral hepatitis and mortality ranged from 10-25%.

Diagnosis In all outbreaks of acute hepatitis, aflatoxicosis should be considered. Diagnosis is based on the clinical picture, exclusion of other conditions, and the epidemiological evidence. Treatment is supportive with rest in bed, adequate supply of glucose and B complex factors and maintenance of fluid and electrolyte balance. Complications have to be treated symptomatically as they occur. Chronic aflatoxin exposure is an important etiological factor in the production of hepatocellular carcinoma in India.

Important points

1. Aflatoxin is a product of fungus *Aspergillus fumigatus*
2. Aflatoxin is hepatotoxic and may produce hepatitis, cirrhosis liver or hepatoma
3. Chronic exposure is an etiological factor for hepatocellular carcinoma
4. Treatment is with symptomatic measures

Epidemic Dropsy

Syn: Toxicity due to *Argemone mexicana*- Yellow Mexican Poppy

Argemone mexicana grows wild in the cold season all over India and is known by different names as *Bharamdandi* or *Pildhatura* (Maharashtra), *Sialkanta* (Bengali), and *Satyanashi* (Gujarati). The seeds resemble mustard seeds. Argemone oil is used as an adulterant of mustard oil, more during times of famine and drought. The toxic principles are sanguinarine and dihydrosanguinarine, the former being more toxic. Poisoning occurs due to consumption of adulterated mustard oil used as cooking medium. Several outbreaks have occurred and are still being reported in Bengal, Bihar, Orissa, Madhya Pradesh, Uttar Pradesh, Gujarat and Maharashtra.

A outbreak which occurred in Delhi in August-September 1998 in which 212 adults were studied is reported in the Journal of Association of Physicians of India (JAPI- 2000-48, 877-880). It also followed the classic description.

Clinical features The onset is insidious with loss of appetite, diarrhea and pitting edema over the legs. Sometimes the edema may be massive and effusion into pleura and pericardium may occur. Cardiac enlargement and failure develop. The extremities are warm due to vasodilatation. Subcutaneous telangiectasia or even hemangiomas develop. These are seen on the mucus membrane of the cheek, gums, tongue, and nose as fleshy dark red or warty growths (sarcomas). Tingling and numbness of the extremities and calf tenderness are present. About 10% cases develop glaucoma. Electrocardiogram reveals nonspecific changes resembling myocarditis. Serum albumin is lowered and alpha-2-globulin is raised. Death is caused by cardiac failure. Withdrawal of the toxic oil leads to recovery in most cases.

Treatment The treatment is supportive with nutritional supplements. Cardiac failure should be treated symptomatically. A simple method to detect the presence of argemone oil is to mix the suspected sample with an equal volume of nitric acid, when a crimson colour develops in case of contamination.

Lathyrism

Syn: Epidemic spastic paraplegia

Chronic ingestion of the toxic principles of *Lathyrus sativus* leads to spastic paralysis of the lower limbs. This pulse is known in various parts of India as *Kesari dal*, *Teora*, *Matra*, *Batura*, *Gharas*, *Lang*, *Lakh* and *Latri dal*. Lathyrism is more prevalent in Madhya Pradesh, Bihar and Uttar Pradesh in India. It has also been reported from Greece, Iran, Russia, Italy, Spain and parts of Africa. Men are more affected than women. The toxic principles are probably *B-n-oxalyl aminoalanine* or *alkaloids like B-amino propionitrile*. The latter is present in the weed *akta*, which contaminates lathyrus peas. Pathological lesion is demyelination of the pyramidal tracts in the lumbar region and some degeneration of the anterior horn cells.

Clinical features The onset is acute or subacute in 90% of cases with muscular pain in the back followed by paraplegia or paraparesis within days to weeks or even after several months. In those with acute onset cramping pain in the calf muscles and muscles of the thigh may occur. This may be followed by rapid onset of paralysis of varying degrees. In those with subacute onset stiffness and heaviness of the lower limbs start after about a month and paralysis sets in and proceeds to varying severity. In the typical case, paralysis and spasticity progress to cripple

the patient. Sensations and autonomic functions are normal. The paralysis tends to be permanent.

Treatment It is symptomatic. There is no specific antidote.

Prevention The toxin can be removed by steeping the cereal in four times its volume of hot water for one hour before cooking. Education of the public on the methods to identify *Lathyrus sativus* will help in wiping out this disease.

Important points

1. Chronic ingestion of toxic principles of *Lathyrus sativus* leads to lathyrism
2. Pathology is demyelination of pyramidal tract and degeneration of anterior horn cells at the lumbar level
3. In a typical case paralysis and spasticity progress to crippling
4. No specific antidote is available

Ergotism

This is caused by the toxin of the fungus *Claviceps purpurea*, which infects rye and other cereal grains. Ergot alkaloids are highly variable mixtures of toxins, the most important one being ergotamine. When ingested, the toxin produces either cardiovascular or neurological manifestations. The former includes vasoconstriction, mental confusion and convulsions. Ergot alkaloids and their derivatives are widely used in therapeutics for their various actions. One of the alkaloids lysergic acid diethylamide (LSD) is a hallucinogen.

LEAD POISONING

Lead poisoning may occur in households among children and in industrial workers. Lead is widely used in paints, storage batteries, petrol and several industries. Ingestion, inhalation or absorption from the skin may lead to acute poisoning. Workers engaged in printing, lead smelting, ship building, tank cleaning are at risk of developing chronic toxicity. Children may eat flaked paint as a form of pica. Lead accumulates in the body and it is deposited in bone and other tissues.

Acute lead poisoning Initial symptoms are metallic taste, irritation of throat, salivation and intense thirst. These are soon followed by colicky abdominal pain, painful spasm of abdominal muscles, hematemesis and constipation. The stools are black due to the formation of lead sulphide. More serious cases develop drowsiness, headache, muscular cramps, convulsions, paralysis of lower limbs, hemolysis and renal failure.

Treatment Calcium disodium versenate (EDTA) in a dose of 1 g in 250 to 500 mL of 5% dextrose intravenously twice daily (50 mg/kg/d) for 8-10 days or longer helps to eliminate the lead. Symptomatic treatment is indicated as the condition warrants.

Chronic lead poisoning (Plumbism) The main symptoms are abdominal colic, constipation, hemolytic anemia, paralysis and cerebral, cardiac and renal damage. It manifests initially as tubular damage going on to chronic renal failure. There is no threshold level for lead to initiate toxicity. Severe intestinal colic and constipation may be mistaken for other alimentary disorders.

Most of the lead in blood is present in erythrocytes. In chronic lead poisoning the lead is deposited in cortical bone. Lead impairs the enzyme delta-aminolevulinic acid dehydrogenase which is needed for haem synthesis. Moderate to severe hemolytic anemia occurs. The peripheral blood shows punctate basophilia and reticulocytosis. In long term lead poisoning the lead is deposited in cortical bone. Motor neuropathies manifest as wrist drop and foot drop. Shoulder girdle muscles may be affected rarely. Sensory symptoms are usually absent. Lead encephalopathy manifests as headache, loss of memory, epileptiform convulsions and coma. Optic neuritis may occur. Urine may show protein, delta amino levulinic acid, and coproporphyrin III. Blood pressure is elevated. Deposition of lead in the gingival margins results in the formation of a black line in people with poor oral hygiene. In edentulous subjects this lead line (*Burtonian line*) does not form. Chronic renal failure may develop. It manifests initially as tubular damage, later, tubular atrophy and interstitial nephritis. Exposure to lead during intrauterine life leads to erosion of cognitive skills with subclinical but permanent reduction in IQ. This may result in permanent impairment in performance standards in adult life.

Ref: Grandjean P, Landrigan PJ: Developmental neurotoxicity of industrial chemicals. The Lancet 2006; 368 2167-78.

Diagnosis The clinical diagnosis is confirmed by the elevated levels of lead in blood. Levels above 80 mcg/dL are diagnostic. A test for chronic lead accumulation is EDTA mobilization test. Urinary loss of >600 mcg of lead in 72 hours indicates lead poisoning.

Treatment In severe toxicity EDTA is administered as described earlier. In less severe cases, other than EDTA an oral chelator, Succimer (dimercaptosuccinic acid) has been used in a dose of 10mg/kg orally every 8 hours for 5 days.

Prevention Proper washing of the hands before eating and provision of protective clothing and masks reduce absorption of lead. Provision of 300 mL of milk to such workers may be helpful in reducing toxicity. Persons working in risky occupations should be periodically monitored. Pollution of the environment by lead salt is a major concern in recent years. The use of lead in automobile fuels has resulted in the discharge of appreciable amounts of lead into the atmosphere. In many states of India the use of leaded petrol is restricted.

Important points

1. Acute lead poisoning presents with predominantly GI symptoms and in serious cases drowsiness-convulsions, hemolysis and renal failure may occur
2. Chronic lead poisoning is characterized by abdominal colic, constipation and basophilic stippling of RBCs
3. Motor neuropathies, optic neuritis and lead encephalopathy can also occur in chronic lead poisoning
4. EDTA is the mainstay of treatment

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Endemic Fluorosis

T.K. Suma, K.V. Krishna Das

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Endemic fluorosis is caused by chronic fluoride intoxication acquired by ingestion of water containing high concentration of fluorides. It is characterized by dental and skeletal changes.

EPIDEMIOLOGY

The disease is present in many states in India where fluoride content of drinking water exceeds 2 ppm. Andhra Pradesh, Punjab and North Karnataka show high prevalence. Endemic areas have also been found in Tamil Nadu, Haryana, Rajasthan, Uttar Pradesh and Delhi and its surrounding areas. In Kerala three districts are affected. The disease is present in certain parts of China, Japan, South Africa, Saudi Arabia and USA.

The disease is more prevalent in males who are engaged in hard manual work because of their higher consumption of water. Total hardness of drinking water (calcium and magnesium hardness) has a protective role.

Presence of fluoride up to 0.5 to 0.8 ppm in drinking water is considered safe in India. With higher levels, fluoride accumulates in the skeletal system and teeth.

Pathophysiology Ingestion of fluoride causes reduction of ionized calcium. This hypocalcemia leads on to secondary hyperparathyroidism and increased osteoclastic activity. Increased levels of lactic acid and citric acid are produced from the osteoclasts thereby increasing the hydrogen ion concentration and lysis of lysosomes. Lysosomal enzymes like protease, collagenase and hyaluronic acid produce disintegration of hydroxyproline and other ground substances of bone and other calcified tissues like teeth. This is responsible for the signs and symptoms of fluorosis like dental hypoplasia with areas of hypocalcification, hypomineralization and softening. The bones are heavier and irregular. There is excessive subperiosteal bone formation at the sites of muscular, fascial and tendinous attachments. Ligaments show various grades of calcification. The most advanced changes are seen in the spine. There is narrowing of the vertebral canal, which leads to compression of the spinal cord. Marked changes are seen in the ribs, pelvis, sternum, mandible, and skull. Over a period of 10-20 years, the subject develops crippling deformities.

CLINICAL FEATURES

Dental fluorosis Enamel and dentin of teeth have strong affinity for fluoride during the formation of teeth. Mottled enamel is an early, sensitive and easily distinguishable manifestation in children. This has been taken as an index of endemicity in epidemiological surveys. Dental fluorosis develops only if the child has lived in the endemic area during dentition. It can be graded depending on the severity.

- Grade-I: White chalky opacities or patches on enamel without faint yellow lines.
- Grade-II: Distinct brownish discoloration.
- Grade-III: Besides pigmentation there is pitting of enamel surface, sometimes with chipping of edges (Figs 25.1 and 25.2).



Fig. 25.1: White chalky opacities in mild dental fluorosis



Fig. 25.2: Severe dental fluorosis

Premature loss of teeth is not rare. Both permanent and deciduous teeth may be affected.

Skeletal fluorosis Skeletal fluorosis is not easily recognizable in the early stages. The initial symptoms are nonspecific such as pain in the neck and back associated with rigidity, joint pains, and paresthesia of the limbs. These cases may be mistaken for rheumatoid arthritis, ankylosing spondylitis or osteoarthritis.

The physical findings include kyphosis, limitation of movements of the spine and exostoses. Exostoses can easily be palpated along the anterior border of the tibia, over the olecranon, and along the medial border of the scapula. These are diagnostic. In advanced fluorosis, kyphosis, fixed flexion deformities of hips and knees and paraplegia, may develop (Fig. 25.3).

Non-skeletal manifestations: These include neurological manifestations like tingling sensation in fingers and toes, weakness and stiffness of skeletal muscles, nervousness and depression, gastrointestinal manifestations like non ulcer dyspepsia, abdominal pain, diarrhea and/or constipation. The red blood cell membrane becomes more pliable due to decreased calcium and forms into echinocytes. Early destruction of echinocytes results in anemia. Fluoride has inhibitory effect on iodine uptake and so may cause enlargement of thyroid.



Fig. 25.3: Fluorosis advanced skeletal changes

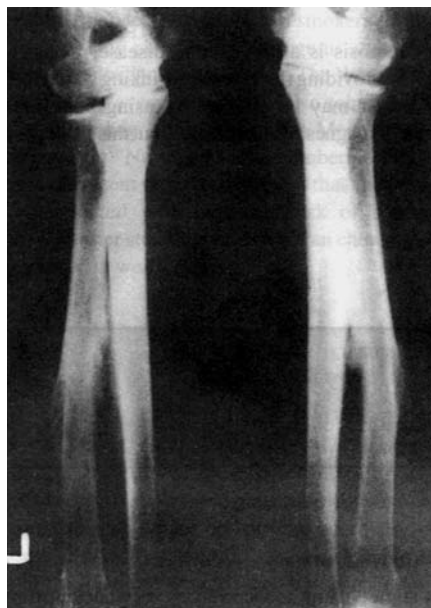


Fig. 25.4: Skiagram forearm showing calcification of interosseous membrane

Complications About 8-10% of cases show compression of spinal cord and the roots by protruding osteophytes. The vertebral arteries may also be occluded. The clinical picture may resemble cervical myeloradiculopathy, cervical myelopathy or radiculopathy, dorsal myelopathy and peripheral neuropathy. Bladder involvement manifests as precipitancy of micturition or retention of urine.

Occasionally, peripheral neuropathy manifests as acroparesthesia, but with only minimal sensory or motor defects. Cranial nerve involvement is rare.

Investigations Radiologic and biochemical investigations should be carried out.

Radiology The classic features are osteosclerosis, irregular osteophyte formation, and calcification of ligaments, especially in the vertebral column. In advanced cases, the bones look chalky white. Irregular subperiosteal new bone formation may be observed along the muscular, fascial, and tendinous attachments. Interosseous membrane of the forearm shows calcification and this has been taken as a definite radiological index of skeletal fluorosis (Fig. 25.4). Skull shows thickening and sclerosis of the vault.

CT and MRI CT of the bones may show prominent cortical thickening and increased density with irregular contours. Bony excrescences are detected in both the pelvic bones and the lower extremities. The sacroiliac joints may be narrowed. MRI may show reduction in the intervertebral disc spaces and multiple disc prolapse. The medullary canal may be narrowed by bony excrescences and by the ossified posterior longitudinal ligament.

Biochemistry Fluoride content is increased in the blood, urine, and bone ash. Serum fluoride level varies from 0.05

to 0.8 mg/dL. Serum alkaline phosphatase is moderately raised (15-30 KA units). Serum calcium, phosphorus and magnesium are normal.

Treatment

Endemic fluorosis is a preventable disease, which can be eradicated by providing fluoride-free drinking water. Defluoridation of water may be affected by using bone meal and metasilicate of magnesium (serpentine) but this is not yet widely used. Vitamins and antioxidants have been tried in many cases. Changing the dietary habits by restricting use of fluoride rich food is also important.

There is no effective treatment for the established case. Patients with skeletal fluorosis, when fed with fluoride-free drinking water, seem to improve over the years. Improvement in the dental changes is reported within weeks. Cases of spinal compression require laminectomy.

Prevention of Endemic Fluorosis

In endemic areas fluorosis can be prevented by reducing the fluoride content of water to less than 1 ppm. Two methods are available for defluoridation of water, the Nalgonda technology and the activated alumina technology. In Nalgonda technique alum and lime are used in various proportions depending on fluoride content of water. In activated alumina technology activated alumina is used in domestic filters. Encouraging the use of calcium, vitamin C and vitamin E may help to reduce the skeletal changes.

Important points

1. Ingestion of water having high fluoride content over several years results in fluorosis
2. Fluorosis leads to reduction in the level of ionized calcium. Osteoclastic activity increases

3. Dental fluorosis, skeletal fluorosis and non skeletal manifestations occur.
4. Established skeletal lesions tend to be permanent.
5. Fluorosis can be prevented by defluoridation of drinking water

Tobacco and Health

T.K. Suma, K.V. Krishna Das

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GENERAL CONSIDERATIONS

Man has started using tobacco from very ancient times. At present tobacco is consumed for smoking (beedi, cigarette, pipe, cigar, hookah, etc.) or for chewing with or without other constituents such as betel, arecanut, and lime or as snuff applied to the nasal or oral mucosa. All these habits are very much prevalent in all societies in India.

The Indian Council of Medical Research (ICMR) estimates that about 8,00,000 death are due to tobacco related diseases in India annually. In India among smokers men predominate. In all countries, the prevalence of smoking in women is increasing. About a third of the world population use tobacco in one form or other. World Health Organization (WHO) estimates that there are 3.5 million deaths occurring annually all over the world from tobacco related diseases. This figure is likely to go up to 10 million by 2030 AD if the present situation is not rectified and tobacco related morbidity will top the list of global disease burden.

In India about 4,20,000 hectares are under tobacco cultivation, with an annual production of 6,00,000 tonnes of tobacco and contributing 7% to the total world production. More than 3.4 million persons are engaged in the tobacco cultivation and industry. Over 20 companies

manufacture more than 100 brands of cigarettes. In addition beedies are made in smaller establishments as cottage industry. Twenty percent of tobacco produced in India is used for cigarettes, 40% go into beedies and the rest used for chewing. Developed countries have been successful in reducing the prevalence of smoking while developing countries including India have not done so. Multinational tobacco manufactures are selectively targeting developing countries for sales promotion.

Tobacco smoke contains several constituents, which irritate the respiratory tract and inhibit ciliary action. The tar that is produced is carcinogenic to the respiratory tract. Depending upon the brand of cigarette and the manner of smoking the level of carbon monoxide in the smoke may vary from 1-5%. Nicotine present in tobacco is responsible for the addiction. Sympathomimetic effects of nicotine give rise to higher heart rate, elevation of systolic and diastolic blood pressure, increase in cardiac output and peripheral vasoconstriction. The threshold for ventricular tachycardia and ventricular fibrillation is lowered. By increasing platelet aggregation, platelet adhesion, plasma fibrinogen and viscosity of blood, nicotine favors intravascular thrombosis. There is reduction in platelet survival and clotting time. Atherogenesis is favored by the rise in total cholesterol, low density lipoproteins and free fatty acids, and also fall in high density lipoproteins (HDL) brought about by nicotine. Blood levels of carboxyhemoglobin are elevated. Oxygen carrying capacity of blood is reduced. Rise in blood carbon monoxide leads to intimal hypoxia, increase in the permeability of arterial intima and lipid deposition.

Cigarette smoking is associated with mild airway obstruction and impairment of lung function in

adolescents. Females are affected more. Heavy smokers suffer from tachycardia, palpitation, cardiac arrhythmias, hypertension, tremors, anorexia, agitation and insomnia.

In those who practice the chewing habit, in addition to absorption of nicotine from the buccal mucosa the local irritation caused by the cud leads to precancerous and cancerous changes.

SMOKING

Tobacco is a highly habit forming agent. Several studies have been shown that the first cigarette exposes the individual and the addiction will occur even with the second or third 'smoke'. Children of smoking parents acquire this habit more freely.

The harmful ingredients taken up by the smoker and exhaled by him depend upon several factors such as the number of cigarettes smoked and their frequency, depth of inhalation, smoking the cigarette only partially or fully and the environment in which the smoker smokes - whether open or confined space. Inhalation of the exhaled smoke by others nearby is termed passive smoking, which is also associated with adverse effects in various degrees.

There is irrefutable evidence that smoking is a major risk factor for chronic bronchitis, emphysema and cancers of lung, larynx, esophagus, bladder, kidney, pancreas and cervix uteri. Coronary heart disease, hypertension, strokes, peripheral vascular occlusions, thromboangitis obliterans, peptic ulcers and several other conditions are directly or indirectly attributable to tobacco. Tobacco is the most important cause of cancer and cancer death, affecting several organ systems. Both main stream and second hand smoke are group-1 carcinogens, i.e. included among the highest cancer causing agents in humans. Lung cancer is several times more common in smokers compared to nonsmokers. 90% of bronchogenic carcinoma is related to smoking, either direct or passive. Smoking contributes to 50% of the death of cigarette smokers, with half of these deaths occurring in middle life. Smokers lose 10 years of their life expectancy, compared to non-smokers.

In India oral cancer, which is the most common cancer, shows a strong association with tobacco chewing or smoking habit. One-third of the cancers reported from western countries are probably tobacco related.

Smoking by parents has an adverse effect on their children. Smoking mothers have an increased risk of spontaneous abortion and their children have lower birth weights, higher perinatal mortality and a greater risk of sudden infant death syndrome. Medical associations of several countries have urged their governments to undertake measures to restrict the spread of tobacco habit. These include restriction of sales of tobacco to those below the age of 18 years, ban on advertisement, education in schools and through public media, prohibition of smoking in public places and public transport, heavy

taxation on cigarettes and withdrawal of aids to tobacco industry.

The role of the physician is paramount in controlling the smoking habit. He should set the example by giving up the habit of using tobacco. Smokers should be motivated to give up smoking by counselling and providing information on the ill effects. Governmental measures to restrict sales by imposing penal taxes and statutory directions to exhibit the dangers caused by smoking on the cigarette packs have made only minimal impacts. Many governments in Indian states have prohibited smoking in public places. Assistance to smokers to give up the habit, by replacing nicotine chewing gums and nicotine skin patches have helped to a small extent. *The WHO has declared the 31st of May every year as the "No tobacco day". During 2005 WHO had developed a "code of practice" on tobacco control for health professional organizations (Ref: <http://www.who.int/tobacco>).* Despite all the vigorous efforts, reduction in smoking habit is coming down only slowly. More of youth and females are probably taking to the habit.

Nicotine replacement products like nicotine gum, nicotine patch, nicotine nasal spray, nicotine inhaler, nicotine lozenges, and the antidepressant drug bupropion have been approved to help people to quit smoking.

Tobacco Chewing

There are recent reports from India that chewing tobacco is also associated with increased risk of cardiovascular morbidity. Further studies are needed. Betel chewing as a cause of oral cancer is well known. Several brands of such proprietary preparations (Pan Masalas) are available in the Indian market. These are being used by a large number of persons, especially the youth. Their role in the genesis of oral cancer and other systemic diseases is not yet fully assessed.

Occupational Health Problems among Tobacco Workers

In India tobacco is cultivated mainly in Gujarat and Andhra Pradesh. The varieties of tobacco include Virginia tobacco (cigarette tobacco) and non-virginia tobacco. Persons may be exposed to tobacco during agricultural operations or curing processes. Ill effects of tobacco are considered to be due to absorption of nicotine through the skin or respiratory tract. The levels of nicotine and its metabolic product cotinine are increased in urine.

The symptom complex occurring in the exposed workers is collectively known as *green symptoms*. These consist of neurological symptoms like headache, giddiness, nausea, vomiting, prostration and respiratory symptoms such as cough and dyspnea. Usually, these symptoms are transient. The occurrence of *green*

symptoms is associated with raised urinary levels of nicotine and cotinine. Virginia tobacco is less toxic than the non-virginia variety. The respiratory symptoms may be aggravated by aero-allergens such as pollen and fungi belonging to the species *Gladosporium* and *Altemaria*.

The nature of contact with tobacco also partly determines the clinical manifestations. Persons who pluck the leaves generally get headache and giddiness, while those carrying the leaves for curing get nausea and vomiting. In agricultural workers engaged in curing, entry of tobacco is through the respiratory tract.

Treatment Since the symptoms are usually mild, and last only for a few hours, removal from the surroundings is

itself curative. The local practice among the workers is to take tea and jaggery followed by rest.

Important points

1. It is estimated that 3.5 million deaths occur annually all over the world from tobacco related diseases
2. Nicotine present in tobacco increases sympathetic activity, favors vascular thrombosis and atherogenesis
3. Smoking is a major risk factor for acute bronchitis, emphysema, carcinoma of lungs, larynx, urinary bladder, coronary artery disease, stroke and peripheral vascular disease
4. Nicotine replacement products and bupropion are being given as treatment for cessation of smoking.

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Nutrition

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Nutrition:
General Considerations

K.V. Krishna Das

5

Chapter Summary

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The term Nutrition came from the Latin Word 'nutrire' meaning-to suckle, nurse or nourish. In the English language it meant supplying or receiving nourishment. Hippocrates advised "let your food be medicine and your only medicine be your food." The close relationship between food, life and health has been amply stressed in the Indian Vedic texts. Ayurveda discusses the role of food and specifies elaborate dietary management of several diseases.

Modern Concepts in Nutritional Science

Nutritional science has been defined as the science of foods, and other substances, their use, actions, interactions and balance in relation to health and disease: the process by which the organism ingests, digests, absorbs, transports and utilizes nutrients and disposes their end products. A simpler definition will be "the area of knowledge regarding the role of food (dietary inputs) in the maintenance of health.

The essential requisites (dimensions) of health should include the following:

1. Achieving optimal growth and development reflecting full expression of the genetic potential.
2. Maintenance of the structural integrity and functional efficiency of body tissues necessary for an active and productive life.
3. Mental well-being.
4. Ability to withstand the inevitable process of aging with minimal disability and functional impairment, and

5. Ability to combat diseases such as:

- a. Resisting infections,
- b. Retarding the progress of degenerative diseases and cancer, and
- c. Resisting the effects of environmental toxins and cancers.

This newer concepts of nutritional science has come out as a result of the progress made in the studies of immunology, molecular biology, oncology, geriatrics, phytochemistry and similar others.

Assessment of Nutritional Status

Nutrition of communities can be assessed by large surveys. These surveys are of epidemiological importance. The methods employed to assess the nutritional status in communities are listed below:

- i. Studies on food production or total food availability in relation to total food needs.
- ii. Measurement of food and nutrition intake.
- iii. Studies on dietary habits and practices.
- iv. Special studies on foods to assess biological value and prevalence of interfering substances like toxins and goitrogens.
- v. Studies based on sociocultural parameters.
- vi. Vital statistics like morbidity and mortality rates.
- vii. Studies on health conditions indirectly related to the nutritional status of the population such as infections and parasitic diseases.

Nutrition in individuals can be assessed by clinical examination, anthropometric measurements and biochemical and other laboratory tests.

Clinical assessment This forms an important part of all nutrition surveys (Table 27.1).

Anthropometry: Anthropometry, which involves measurement of growth and physical development, is particularly useful in children. The most commonly employed measurements are: (i) height (Ht-linear growth), (ii) weight (Wt-body mass), (iii) head circumference (HC-possible relationship to mental development), (iv) mid-

TABLE 27.1

Prominent clinical features in undernutrition

General signs	Apathy, loss of weight and recent emaciation, dependent edema, delayed puberty
Hair	Lack of lustre, sparseness or thinness, straightness, dyspigmentation, easy pluckability
Face	Diffuse pigmentation, nasolabial dyssebacia, moon face
Eyes	Pale conjunctiva, Bitot's spots, conjunctival xerosis, corneal xerosis, keratomalacia, angular palpebritis
Lips	Angular stomatitis, cheilosis
Teeth	Mottled enamel
Gums	Spongy and bleeding gums
Skin	Xerosis, follicular hyperkeratosis, pellagrous dermatitis, flaky paint dermatosis, scrotal and vulval dermatosis
Nails	Koilonychia
Muscular and skeletal	Muscle wasting, craniotabes, frontal and parietal-bossing, epiphyseal enlargement, systems beading of ribs, persistently open anterior fontanelle, knock-knees, bow-legs
Systemic signs	Hepatomegaly, alteration in mental functions, peripheral neuropathymyelopathy, cardiac changes

arm circumference (MA-variations being mainly due to changes in muscle mass and fat calories), (v) chest circumference, and (vi) skin fold thickness (fat calories). The measurements are related to expected standards for age. When the exact age of the child is not known, age-independent indices are made use of. These are wt/ht, wt/ht², wt/hC, MA/HC, etc. The Indian Council of Medical Research (ICMR) has laid down norms for the Indian subjects.

The traditional gold standard to estimate the fat content in the body has been hydrodensitometry under-water weighing—which is not practicable universally. Fat is less dense than muscle and bone. Dual energy X-ray absorptiometry (DEXA) is now replacing densitometry on account of its precision and availability. Other methods used to assess body fatness are the circumference of the waist and the hip and their ratio, the body mass index (BMI), also known as quetelet index which is the weight in kilograms divided by the square of the height in meters. The BMI has gained popularity on account of its reliability, relationship with morbidity and mortality and ease of performance. BMI above 25 suggests fatness, values below 20 should suggest under-weight.

Laboratory examination At present sensitive methods are available for the accurate determination of vitamins and trace elements in body fluids and tissues, but these are expensive and cannot be employed universally. Moreover, the values of nutrients in blood and tissues show a wide range of levels in normal individuals. No test is specific for a particular kind of malnutrition. Conditions of collection, storage, and technique of estimation can all introduce variations. Table 27.2 lists the main tests employed.

Malnutrition

Malnutrition results from deviations from normal nutrition. Frank clinical signs and definite biochemical abnormalities occur in gross malnutrition, but only borderline changes occur in the majority of cases.

Malnutrition may be primary when it is caused by defective intake, or secondary when it results from other disease processes. In clinical practice one seldom comes across isolated deficiencies. More often the malnutrition is generalized, but one or other nutrient deficiency predominates.

Malnutrition results basically from inadequate or improper food consumption. The abnormality may be quantitative, qualitative, or both. In addition to poverty which is the main cause, social, cultural, agricultural and educational factors modify the form and extent of malnutrition. Diarrhea, helminthic infestations, and other infections aggravate malnutrition resulting in high mortality and morbidity.

Social aspects of nutrition In addition to the nutritive values of diet, food is a part of security, social behaviour and civilization. Occurrence of malnutrition in an individual is only an index of the same disorder in the household and the community as well. So identification of an index patient should be the starting point for further case detection and the treatment should cover the entire community.

Etiological Factors

1. Inadequate supply of food due to poverty
2. Ignorance of dietary principles
3. Wrong practices of cooking and storage of food
4. Malabsorption of nutrients

TABLE 27.2

Biochemical investigations in malnutrition

Nutrient deficiency	Tests
Proteins	Serum protein fractions, especially albumin, amino acid imbalance, hydroxyproline excretion. urinary urea, urinary creatinine excretion/unit time
Vitamin A	Serum vitamin A, serum carotene
Vitamin D	Serum alkaline phosphatase (in young children), calcium, phosphorus, serum vitamin D metabolites
Ascorbic acid	Serum ascorbic acid, leukocyte ascorbic acid, urinary ascorbic acid-load test
Thiamine	Urinary thiamine, blood pyruvate-lactate, RBC transketolase load test
Riboflavin	Urinary riboflavin, erythrocyte riboflavin loading test
Niacin	Urinary NI-methyl nicotinamide load test
Folic acid	Hemoglobin, serum folate, RBC folate—'Figlu' test
Vitamin B ₁₂	Hemoglobin, serum B ₁₂ , Schilling's test
Iodine	Urinary iodine tests for thyroid function
Minerals	Calcium: serum calcium, bone calcium, calcium turnover studies, serum alkaline phosphatase Iron: serum iron, iron binding capacity, tissue iron, serum ferritin
Trace elements	Analysis of hair

* Note: Recently the importance of chemical analysis of the hair in determining levels of trace elements has been recognized. The advantages are: (1) It reflects the variation in the level of trace element over a long period, (2) hair is easy to be preserved and transported. Trace elements are concentrated in the hair.

5. Parasitism
6. Loss of nutrients through urine, stools, bleeding, etc.
7. Increased demands due to pregnancy, intercurrent illness, or repeated deliveries
8. Interference with metabolism
9. Other environmental factors like general insanitation, intercurrent illness, overcrowding; rapid population growth, and political instability

Nutritional disorders often present as multiple deficiencies and only rarely as isolated entities. The most pronounced deficiency manifests clinically, the others remain subclinical. In such cases supplementation of the missing nutrient without overall dietary correction leads to temporary improvement, but sooner or later another malnutrition becomes evident. Irrespective of the type of nutritional disorder, overall dietary correction is mandatory. The presenting symptoms should be treated with additional supplementation of the deficient factor.

Care should be taken to prescribe a proper diet suitable to the patient's cultural and economic state, and made up of articles cheaply and freely available in the locality. Prescription of a diet unsuitable to the socio-cultural background of the patient is the most common cause for non-compliance.

In health, many nutrients are stored in the body and therefore, dietary deprivation initially leads to depletion of the stores. This period is totally asymptomatic. Symptoms occur only when the deficiency is far advanced. Hence, it is essential to continue nutrient therapy for at least 4-6 months after full correction of the clinical condition to replenish the stores. Natural foods are more palatable, but they are slow in action and several factors

influence their absorption and utilization. Therefore, therapeutic preparations are employed for immediate correction and thereafter dietary measures are continued. It is absolutely essential to detect the primary cause in each case otherwise many underlying serious diseases like cirrhosis of liver or malignancy may be missed, till the condition becomes advanced beyond treatment. All cases of secondary malnutrition should be fully investigated to detect the primary cause.

Functions of Food

Living organisms cannot create energy but can only transform energy. The food provides calories for energy needs, proteins to build and maintain the body tissues, and vitamins and minerals to regulate the biochemical processes essential to maintain health and offer resistance against disease.

Carbohydrates, fats and proteins together are called the proximate principles. These substances share the common property of chemical degradation with the release of utilizable energy. Under normal dietary conditions, however, the contribution of proteins to energy supply is minor. The unit of energy used at present in nutrition is the joule, though till recently the unit was kilocalorie (Kcal).

1 kcal = 4.184 kJ.

Energy value of the proximate principles The value of energy yielded by carbohydrates, proteins, and fats are 4.0, 4.0, and 9.0 kcals respectively.

Carbohydrates Carbohydrates are the main sources of energy. They are not indispensable if other sources of energy are available, but in most parts of the globe carbohydrates are the most easily available and cheapest food sources.

Carbohydrates account for 45% of total energy in the western diets and over 80% in the diets of many communities in India. In India most of the carbohydrates are in the form of unprocessed starches, along with dietary fiber, whereas in the West the starches have been progressively replaced by sugars.

Glycemic index of a carbohydrate relates to its rate of absorption and elevation of post-prandial blood glucose levels. High-glycemic-index foods are characterized by rapid absorption, attainment of high postprandial blood-glucose level and insulin response. They are particularly harmful if given to diabetic patients.

Fats Dietary fats are composed of triglycerides, phospholipids and sterols. Triglycerides which supply energy are made up of fatty acids and glycerol. Most of the fatty acids occurring in nature are even carbon atom fatty acids.

Functions of Fats

1. Source of energy
2. Body building
3. Vehicles for fat soluble vitamins A,D,E and K
4. Source of antioxidants, e.g. carotene, tocopherols
5. Addition to taste and acceptability of food.

Fatty acids are classified as saturated and unsaturated according to the presence and number of double bonds. Saturated fatty acids have no double bonds, e.g. myristic acid (14C), palmitic acid (16C), and stearic acid (18C). Unsaturated fatty acids may contain one or more double bonds. Oleic acid contains one double bond. Poly-unsaturated fatty acids contain two or more double bonds. They can be further divided into Omega 6 and Omega 3 families according to the position of the omega terminal double bond. Of these, linoleic acid (18C-2), linolenic acid (18C-3), and arachidonic acid (20C-4) are named essential fatty acids, since they have to be supplied at least in small quantities in the diet. The essential fatty acids are the precursors of the prostaglandins and they are required for formation of cell membranes and phospholipids. Vanaspathies and margarines are prepared by hydrogenating oils with high content of poly-unsaturated fatty acids. In this process they are converted into saturated fatty acids.

In India the poor sections of the population derive only 10% of their energy needs from fats whereas up to 35% of the energy requirement may be provided by fats in the diets of the affluent groups. Visible fat comprises the oils and fats used for cooking and on the table whereas invisible fat consists of lipids incorporated in articles of

food such as cereals, spices, nuts, oil-seeds, coconut, vegetables and others. The invisible fat accounts for up to 10% of the total energy needs in all groups. ICMR has recommended the addition of visible fat at 5% of energy needs for adults and children, 12.5% for pregnant women, and 17.5% for lactating women.

Consumption of fats has increased in affluent countries, since fats increase the taste and acceptability of food.

Vegetable oils with the exception of coconut oil and palm oil provide adequate amounts of poly-unsaturated fatty acids. Animal fats except fish liver oil are generally saturated, with very little of poly-unsaturated fatty acids. Fish liver oils contain good amounts of poly-unsaturated fatty acids, eicosapentaenoic acid and docosahexaenoic acid which lower VLDL in plasma.

Functions Attributed to Essential Fatty Acids

1. For cell membrane mechanisms and messenger actions.
2. Immune response: PUFAs have antibacterial, antiviral and antifungal properties. They indirectly modulate T-cell response.
3. Possibly anticancer activity.
4. Inhibits the development of atherosclerosis.
5. For normal brain development and neurological functions in the fetus and newborn.

Several beneficial effects of EFAs are being recognized and they have attained a place in modern therapeutics.

Increase in the total quantity of saturated fats in the diet above 25% of energy needs elevate serum cholesterol levels and also adversely affect the HDL/LDL ratio. Ideally at least 3% of the dietary fat should be poly-unsaturated. Apart from the total quantity, the quality of the fat also plays a role. Hydrogenation of vegetable oils convert the unsaturated fatty acids into saturated trans fatty acids. Trans fatty acids elevate LDL and reduce HDL thereby promoting atherogenesis in arteries and increasing the risk of coronary and cerebral vascular occlusions.

By a regular process of dietary education in the community and the provision of health foods, most of the developed nations have brought down their per-capita consumption of dietary fat. The population has been rendered diet conscious. Even items of confectionary such as chocolates and ice creams are made to contain less fat. Such measures have served to bring down the incidence of coronary artery disease and myocardial infarction. Attempts in this direction are only in the initial stages in India at present.

Proteins Proteins, together with water, form the basic building units of tissues. In addition, they function as enzymes and hormones and also take part in transport mechanisms. Of the twenty amino acids present in

BV, NPU and chemical score of proteins			
Food	BV	NPU	Chemical score
Whole egg	96	91	100
Cow's milk	84	75	66
Liver	77	65	66
Meat	80	76	70
Fish	85	72	60
Rice	64	57	60
Wheat	58	47	42
Bengal gram	56	45	42
Groundnut	54	45	44
Coconut	67	56	52

proteins, eight have to be supplied to man through dietary sources almost continually. For adults the essential amino acids are lysine, methionine, valine, leucine, isoleucine, tryptophan, phenylalanine, and threonine. For infants histidine is also essential. Animal proteins are rich in essential amino acids, whereas vegetable proteins are deficient in one or more of them.

An ideal protein is one which contains all essential amino acids in optimal amounts and is completely digestible and utilizable. For the human infant, mother's milk fulfills these requirements. Whole egg proteins are considered the next best and this is given a rating of 100 arbitrarily. Other proteins are compared with whole egg protein. Biological value (BV) and net protein utilization (NPU) are most popular indices used for comparison. In addition, chemical method, i.e., chemical score (CS), is also widely employed to assess dietary protein quality.

Vegetable proteins have lower quality ratings than animal proteins. In the ordinary Indian diet, cereals, pulses and other vegetable sources also contribute proteins. The biological efficiency of such a mixed protein source is far higher than the average to be expected. The enhancement in protein quality resulting from a mixture of vegetable sources is known as the supplementary value of proteins.

Protein deficiency in the later part of fetal life and early childhood will lead to structural and functional derangements in the development of neural structures in the brain. This may lead to permanent impairment of cognitive and other higher functions. The importance of the adequacy of protein supply in pregnant and lactating women cannot be overemphasized.

Protein deficiency leads to T-cell dysfunction and immunological deficiency. Malnutrition related diabetes mellitus (MRDM) has been attributed mainly to protein malnutrition. Normocytic anemia may occur rarely as a result of protein deficiency.

Well-balanced traditional Indian diets are quite adequate to supply the protein requirements. An important reason for protein deficiency in India is the availability of foods in amounts far too short to supply energy needs.

Standard Nutrition Tables

The Indian Council of Medical Research (ICMR) has prescribed standard dietary allowances for the Indian people at different stages of life (Tables 27.3 to 27.7).

Table 27.8 gives the standard height and weight for Indian subjects.

Bioactive Phytochemicals in Food

In addition to the proximate principles, several articles of food contains substances which alter cellular metabolism and thereby promote or impair health and well being, e.g. beta carotene, ascorbic acid, tocopherols and selenium. In addition to their primary nutritional roles, they help to promote health, and prevent disease process. Nearly twenty such substances have been identified. These belong to the classes.

- 1. Phenolic compounds—indoles
- 2. Flavonoids—anthocyanine
- 3. Isoflavonoids—isothiocyanates
- 4. Coumarins—diterpenes
- 5. Lignans

TABLE 27.3 Balanced diet for pre-school children (2-6 years)				
Food item (g/day)	2-3 years		4-6 years	
	Vegetarian	Non-vegetarian	Vegetarian	Non-vegetarian
Cereals	150	150	200	200
Pulses	50	40	60	50
Green leafy vegetables	50	50	75	75
Other vegetables including roots and tubers	30	30	50	50
Fruits	50	50	50	50
Milk	300	200	250	200
Fats and oils	20	20	25	25
Meat, fish, eggs	—	30	—	30
Sugar or jaggery	30	30	40	40

TABLE 27.4

Balanced diet for school children (7-12 years)				
Food item (g/day)	7-9 years		10-12 years	
	Vegetarian	Non-vegetarian	Vegetarian	Non-vegetarian
Cereals	250	250	320	320
Pulses	70	60	70	60
Green leafy vegetables	75	75	100	100
Other vegetables including roots and tubers	50	50	75	75
Fruits	50	50	50	50
Milk	250	200	250	200
Fats and oils	30	30	35	35
Meat, fish, eggs	—	30	—	30
Sugar or jaggery	50	50	50	50

TABLE 27.5

Balanced diets for adolescent boys and girls						
Food item (g/day)	Boys 13-15 years		Boys 16-18 years		Girls 13-18 years	
	Vegetarian	Non-vegetarian	Vegetarian	Non-vegetarian	Vegetarian	Non-vegetarian
Cereals	430	430	450	450	350	350
Pulses	70	50	70	50	70	50
Green leafy vegetables	100	100	100	100	150	150
Other vegetables	75	75	75	75	75	75
Roots and tubers	75	75	100	100	75	75
Fruits	30	30	30	30	30	30
Milk	250	150	250	150	250	150
Fats and oils	30	40	45	50	35	40
Meat and fish	—	30	—	30	—	30
Eggs	—	30	—	30	—	30
Sugar and jaggery	30	30	40	40	30	30
Groundnuts	—	—	50*	50*	—	—

* An additional 30 g fats and oils can be added in place of groundnuts

Food items such as cabbage, cauliflower, carrots, tomatoes, chillies, onions, garlic, citrus fruits, amla, guava, green leafy vegetables, ginger, cloves, sesame, tea, sunflower oil and palm oil contain them. Bioactive phytochemicals acts as antioxidants, detoxifying agents and anticancer agents.

Substances such as carotinoids, ascorbic acid and tocopherols present in green leafy vegetables, fruits, palm oil and others act as antioxidants.

Normal cellular metabolic processes involve reactions requiring pre-oxidants and antioxidants. The former promote the release of O₂ for energy and cellular metabolism. The latter neutralize deleterious oxidants and free radicals generated during normal metabolism and environmental stresses such as smoke, carcinogenic-chemicals, industrial effluents, food additives and the like. Free radicals promote peroxidation of membrane lipids. They impair cellular function and damage cellular proteins and DNA. Peroxidation of circulating lipoproteins convert

them into more harmful substances. Cumulative tissue injury caused by free radicals lead to aging, atherosclerosis, cancer and so on.

Toxic molecules are detoxified and converted into excretable forms by microsomal oxidase and conjugase enzymes. Indole derivatives present in various foods such as cabbage, tomatoes, strawberries, pineapple, green peppers and tea are mainly involved. Garlic can inactivate carcinogens present in food. The various dimensions played by food in addition to the nutritive value has led to the concept of “total health value of food”. The present day recommendation is to consume 800-1150 g of fresh vegetables and fruits daily. This helps to reduce the incidence of ischemic heart disease, strokes and cancers.

The term “functional foods” is coined by food processors, in order to promote their sales. Functional foods are those which exert beneficial effects beyond their nutritional effects on specific body functions which promote health and well being and prevent disease. Some

TABLE 27.6

Balanced diets for adult men and women
(Figures in brackets give the requirement for women)

Food item (g/day)	Sedentary work		Moderate work		Heavy work	
	Vegetarian	Non-vegetarian	Vegetarian	Non-vegetarian	Vegetarian	Non-vegetarian
Cereals	400 (300)	400 (300)	475 (350)	475 (350)	650 (475)	650 (475)
Pulses	70 (60)	55 (45)	80 (70)	65 (55)	80 (70)	65 (55)
Green leafy vegetables	100 (125)	100 (125)	125 (125)	125 (125)	125 (125)	125 (125)
Other vegetables	75 (75)	75 (75)	75 (75)	75 (75)	100 (100)	100 (100)
Roots and tubers	75 (50)	75 (50)	100 (75)	100 (75)	100 (100)	100 (100)
Fruits	30 (30)	30 (30)	30 (30)	30 (30)	30 (30)	30 (30)
Milk	200 (200)	100 (100)	200 (200)	200 (100)	200 (200)	100 (100)
Fats and oils	35 (35)	40 (35)	40 (35)	40 (40)	50 (40)	50 (45)
Meat and fish	—	30 (30)	—	30 (30)	—	30 (30)
Eggs	—	30	—	30	—	30
Sugar or Jaggery	30 (30)	30 (30)	40 (30)	40 (30)	55 (40)	55 (40)
Groundnut	—	— (40)	—	—	50* (40)	50*

* An additional 30 g of fats and oils can be added in place of groundnut.
Note: During pregnancy and lactation an all allowance of 50-100 g cereals, 10 g pulses, 25 g leafy vegetables, 125 mL milk, 15 g fats, and 10-20 g sugar is to be added.

TABLE 27.7

Daily allowance of nutrients for Indians (Nutrition Expert Group of ICMR, 1968)

Group particulars	Energy	Protein	Calcium	Iron	Retinol	Thia- mine	Ribo- flavin	Nico- tinic acid	Ascorbic acid	Folic acid	Vitamin B ₁₂	Vitamin D
	Cal	g	mg	mg	µg	mg	mg	mg	mg	µg	µg	i.u.
Man Sedentary work	2400	55	400-500@	20	750	1.2	1.3	16	50	100	1	200
Woman Sedentary work	1900	45	400-500@	30	750	1.0	1.0	13	50	100	1	200
Children												
1 year	1200	17	400-500*	15-20	250	0.6	0.7	8	30-50	55-100	0.5-1.0	-do-
2 years	1200	18	400-500*	15-20	250	0.6	0.7	8	30-50	55-100	0.5-1.0	-do-
3 years	1200	20	400-500*	15-20	250	0.6	0.7	8	30-50	55-100	0.5-1.0	-do-
4-6 years	1500	22	400-500*	15-20	300	0.8	0.8	10	30-50	55-100	0.5-1.0	-do-
7-9 years	1800	33	400-500*	15-20	400	0.9	1.0	10	30-50	55-100	0.5-1.0	-do-
10-12 years	2100	41	400-500*	15-20	600	1.0	1.2	14	30-50	55-100	0.5-1.0	-do-
Adolescent boys												
13-15 yrs	2500	55	600-700+	25	750	1.3	1.4	17	30-50	55-100	0.5-1.0	-do-
Adolescent girls												
13-15 yrs	2200	50	600-700+	35	750	1.1	1.2	14	30-50	55-100	0.5-1.0	-do-
Note: for all age groups vit D should be supplied at 200-400 i.u./day.												
Note: *				New US recommendation								
+				-Do-								
@				-Do-								
				1200 mg								
				1200 mg								
				800 mg								

TABLE 27.8							
Weight and height chart for males and females							
Height (cm)		Normal weight (kg)		Overweight limit (+ 20%)		Underweight limit (– 20%)	
Males	Females	Males	Females	Males	Females	Males	Females
148	148	47.5	46.5	57.0	56.0	38.0	37.0
152	152	49.5	48.5	59.0	58.0	39.0	39.0
156	156	51.5	50.5	62.0	60.5	41.0	40.5
160	160	53.5	52.5	64.0	63.0	43.0	42.0
164	164	56.0	55.0	67.0	66.0	45.0	44.0
168	168	59.0	58.0	71.0	69.6	47.0	46.5
172	172	62.0	60.5	74.5	72.5	49.5	48.5
176	176	65.5	64.0	78.5	77.0	52.4	51.0
180	180	68.5	67.0	82.0	80.5	55.0	53.5
184	184	72.0	70.5	86.5	84.5	57.5	56.5
188	188	75.5	74.0	90.5	89.0	60.5	59.0
190		77.5		93.0		62.0	

of the common examples include bran which relieves constipation and low sodium high potassium foods which lower blood pressure.

Immunological competence and nutritional status are two of the most important determinants of morbidity and mortality. Malnutrition, immunodeficiency and infection create a vicious cycle in which each factor contributes to the adverse outcome. Primary immunodeficiency may also lead to secondary nutritional disorders.

Prescription of a Balanced Diet

Energy Energy requirements are determined by: (1) physical activity, (2) body size and composition, (3) age and sex, (4) physiological state, and (5) climate and

environment. Generally, the energy requirement of people living in tropical countries is lower than those in the colder climates.

Pregnancy, lactation and repeated infections and infestations widely prevalent in India increase the need for protein. Since the nutritive value for proteins varies widely, it is convenient to express the requirements of protein in terms of a reference protein with an assumed NPU of 100, which is fully digested and utilized. The reference protein can be converted into proteins of customary diets using the formula:

$$\frac{\text{Ref. protein requirement}}{\text{NPU of dietary protein}} \times 100$$

The NPU of Indian diets is approximately 65.

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Starvation

K.V. Krishna Das

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GENERAL CONSIDERATIONS

Severe starvation on a mass scale occurs during special situations like prolonged war, drought, and other natural or political calamities. Chronic starvation of different grades affects large number of people in the developing countries, even during normal times. Several famines have occurred during the 19th and early part of the 20th centuries. Famines were a regular occurrence in Bengal during the colonial rule. Though acute and chronic food shortage occur from time to time in various parts of India as a result of floods, drought or earthquakes, widespread famine has not occurred in the latter part of this century. In addition to food shortage, inability to ingest or digest and absorb food also results in starvation. Individuals may resort to starvation voluntarily or this may result from psychiatric abnormalities.

Loss of weight amounting even up to 50% of body weight is the most prominent feature. The weight loss is initially caused by the loss of fluid. Later on it is owing to catabolism of tissues to meet energy needs. The body stores of carbohydrate (liver and muscle glycogen) are depleted within two to three days and fat is mobilized in the form of free fatty acids which is used as fuel by the muscles. Glucose is spared for the brain. Tissue proteins are also broken down in order to meet the energy needs.

Protein synthesis is diminished and alanine is released by the muscles to the liver for conversion to glucose, which is made available to the brain. During prolonged starvation, brain metabolism can adapt to use beta-hydroxybutyrate and acetoacetate also as fuel. Generalized emaciation results. Liver and intestines are the first to lose tissue, and this is followed by muscles and skin. The brain is preserved right till the end.

CLINICAL FEATURES

The patient is apathetic and irritable. The loss of fat around the buttocks, thighs, back, and buccal region gives the characteristic appearance with prominence of bones and dry, thin, inelastic, loose skin. A brownish, patchy pigmentation is generally encountered. The hair becomes characteristically dry and easily pluckable. During cold weather cyanosis of extremities may develop.

Systemic disturbances Cardiovascular changes include bradycardia, lowered systolic and diastolic pressure, and reduction in venous pressure and cardiac output. The heart size is also reduced. Respiratory rate is lowered, so also the vital capacity. Growth hormone level is decreased. Basal metabolism is lowered. Corticosteroid is normal. In both sexes sexual function is diminished leading to loss of libido in males and amenorrhea in females. Hypothermia may develop on exposure to cold. Though personality changes may be manifest, the intellect usually remains clear till the end. Capacity for work is reduced due to loss of muscle mass. Mild normocytic normochromic anemia is not uncommon.

In some individuals dependent edema appears even without lowering of plasma albumin. Nocturnal polyuria is common though the renal function is not grossly affected.

TREATMENT

The course of treatment should depend upon the severity of the disorder. Mild cases of starvation require only oral feeds. Overzealous dietary supplementation may lead to diarrhea and death. In the early stages, gradual introduction of easily absorbable and predigested food may be necessary till the alimentary functions return to normal. Fats and fatty foods have to be avoided to prevent diarrhea. Skimmed milk is superior to whole milk. Skimmed milk powder reconstituted to give 10-15% strength is well tolerated if given as small feeds (up to 100 mL) frequently. A daily intake of about 3,000 kcal

and 100 g proteins should be aimed at. Severely debilitated patients should be fed using an intragastric tube in order to ensure adequate intake. After the initial rapid gain in weight due to correction of dehydration, a steady increase of 1-1.5 kg/week can be considered as adequate response.

In all cases of severe starvation especially if complicated by intercurrent illnesses and diarrhea,

parenteral nutrition should be resorted to without delay. If starvation occurs on a wide scale, relief camps have to be organized to provide shelter, food, potable water and general sanitation.

Community kitchens may have to be set up to provide food. In these endeavours, the medical personnel have to work in close liaison with social service organizations and governmental agencies.

29

Protein-Energy Malnutrition

K.V. Krishna Das

5

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GENERAL CONSIDERATIONS

Protein-energy malnutrition (PEM) has been defined by WHO and FAO (1973) as “a range of pathological conditions arising from coincident lack of protein and calories in varying proportions occurring most frequently in infants and young children and commonly associated with infections”.

The clinical spectrum includes a variety of clinical syndromes, with ‘marasmus’ and ‘kwashiorkor’ at the two extremes and the intermediate forms (marasmic kwashiorkor) and nutritional dwarfism in between. Mild cases may present only with apathy and retardation of growth. Childhood malnutrition has been graded taking the weight for age as the criteria (Table 29.1).

Etiology and pathogenesis: Protein-energy malnutrition is an environmental disease, caused by deficient intake of protein and calories. It results from the combined influences of low food availability, poverty, ignorance, illiteracy and cultural taboos, frequent infections and poor environmental sanitation.

TABLE 29.1

Grades of PEM	
Grade	Percentage weight to the reference standard (Harvard)
I	71-80%
II	61-70%
III	51-60%
IV	50% and below

Note: ‘K’ in front of a grade denotes kwashiorkor. (Recommendation of the nutrition subcommittee of the Indian Academy of Pediatrics).

CLINICAL FEATURES

Marasmus (Fig. 29.1 (2))

Severe restriction of food in an infant, as in cases of gross inadequacy of breast milk, leads to arrest of growth. Due to starvation the subcutaneous fat and muscles are used up as energy sources. The baby becomes emaciated. Unlike as in kwashiorkor, there is no edema. Loss of the buccal pads of fat give the infant a withered and ‘old man’s’ look. The weight is below the sixtieth percentile. The height depends upon the onset and duration of undernutrition. In the early stages the infant eats well but appetite is lost as the condition progresses. Initially, inadequacy of food leads to constipation, but later on diarrhea sets in with green stools containing mucus. In the well-established form the baby is apathetic.



Fig. 29.1: (1) Kwashiorkor, and (2) Marasmus

Moderate anemia may develop. The skin and hair are usually normal.

KWASHIORKOR (FIG. 29.1 (1))

This name was coined by Dr Cicely Williams in 1933, to denote 'disease of the child deposed from the breast by the conception of a new fetus'. Children between the ages of 1 and 3 years are affected more. The disease starts when the baby is weaned from the breast.

Pathology Main changes are seen in the small intestines, liver, pancreas and thymus. Small intestinal mucosa shows blunting of villi and atrophy of brush border, so that the columnar epithelium appears to become cuboidal. The total absorbing surface is reduced. Lactose intolerance is common because of disaccharidase deficiency. Liver shows fatty infiltration of the parenchymal cells. The pancreatic acini are atrophic and enzyme activity is reduced. Thymus is markedly atrophied and this may contribute to deficiency of cell mediated immunity.

Clinical features This child is stunted and skeletal muscles are wasted. The presence of fairly normal amounts of subcutaneous fat and edema give a deceptively plump appearance. Pitting edema is a prominent feature. The child is apathetic, irritable and drowsy. Characteristic skin changes occur in many and when present; these are diagnostic. These include flaky paint dermatosis seen over areas of pressure and trauma, fissuring and ulceration at the flexures and a mosaic like appearance (crazy pavement appearance). The hair becomes thin, sparse, brownish and lusterless. They may fall off. Regrowth of normal pigmented hair heralds nutritional recovery. Since periods of nutritional deprivation and partial correction of nutrition alternate in many cases, the hair shows alternate bands of pigmentation and depigmentation (flag sign). The appetite is poor. Diarrhea is a frequent feature. There may be concomitant deficiencies of iron, folate, fat soluble vitamins and B complex factors. Hepatomegaly occurs in

a third of the cases. This is due to fatty infiltration. With recovery the liver reverts to normal without sequelae.

MARASMIC KWASHIORKOR

In this condition, features of marasmus and kwashiorkor are present simultaneously. The body weight is less than 60% of the normal. Dependent edema is present. Mental changes, skin and hair changes and hepatomegaly are evident.

Secondary infection is very common in protein energy malnutrition. This is due to the fact that both humoral and cellular immunity are defective. The intestinal flora is altered and this may account for the diarrhea. Episodes of infection further jeopardize the nutritional status.

Laboratory investigations The total protein content of the body is reduced, and this is reflected most prominently as hypoalbuminemia. The plasma levels of essential amino acids are low, but the non-essential amino acids remain normal or even elevated. Basal metabolic rate is reduced. Hypoglycemia occurs commonly.

Total body water is increased and all the compartments show increase of fluid. The plasma osmolality is reduced. Renal plasma flow is diminished and this results in impairment of renal function. Plasma sodium is increased with reduction in potassium and magnesium. Gross reduction of serum sodium is associated with a poor prognosis.

Prognosis depends on the severity of the disease at diagnosis and promptness of treatment. Marked weight loss, severe infections, fluid and electrolyte imbalance, hypoglycemia, hypothermia, cardiac failure, elevation of serum bilirubin and liver enzymes, drowsiness and xerophthalmia indicate poor prognosis. In severe cases mortality goes up to 20%. The disease is entirely preventable by ensuring adequate caloric and protein intake to the growing child in the first three years of life. Proper management in the established case gives rise to full recovery, catch up growth and restoration of normal parameters. Recurrence is likely if the adverse environment is not corrected.

Treatment

Treatment is aimed to supply a diet rich in calories, proteins and other essential nutrients. For success of treatment supplementation should be with natural foods available locally. 150 Kcal/kg of energy and 3.3 g/kg of proteins are optimally required for catch-up growth. Fats are administered to supply adequate calories without increasing the bulk. Children with lactose intolerance do not tolerate carbohydrates, but they tolerate fats. As the child gains appetite the frequency of feeding is increased. If there is severe anorexia, forced feeding has to be resorted to. Salt should be restricted to avoid congestive cardiac failure. The National Institute of Nutrition,

Hyderabad has formulated an energy-protein rich mixture to treat PEM at home. It consists of whole wheat 40 g, Bengal gram 16 g, groundnut 10 g, Jaggery 20 g (total 86 g). This supplies 330 calories and 11.3 g proteins. Skimmed milk, eggs and cereals are added as the condition improves. In addition to nutritional correction, intercurrent infections have to be controlled simultaneously.

Initial recovery is heralded by the disappearance of edema. The major biochemical abnormalities are corrected within 2-3 weeks. Complete correction of all reversible changes, referred to as 'clinical recovery' occurs only in 2-3 months.

Prevention and Rehabilitation

PEM is a preventable disease. Three levels of prevention have been formulated. Primary prevention is achieved by

nutrition education to prevent occurrence of PEM. Secondary prevention is aimed at early detection and proper treatment. Tertiary prevention consists of nutritional rehabilitation of an established case.

The importance of breast feeding as a prophylactic against protein calorie malnutrition cannot be overemphasized. Correct feeding practices, both during health and disease, proper sanitation, deworming and family planning methods have to be employed simultaneously to achieve lasting benefit.

Nutrition rehabilitation is employed to prevent residual nutritional handicap and prevent recurrence of protein energy malnutrition. Even at the initial stages of treatment the mother should be made to participate in the selection, preparation and administration of food. This measure helps to impart nutritional education to her, prevent recurrence and detect relapse early.

30

Fat Soluble Vitamins

K.V. Krishna Das

Chapter Summary

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Vitamins are organic substances which have to be supplied in food in minute quantities to maintain the biochemical and structural integrity of many cells and tissues. The human body cannot synthesize them. Most of them are integral parts of certain coenzymes required for biochemical reactions at tissue levels.

The vitamins have been classified into fat-soluble and water-soluble groups based on their presence in natural foods. By synthetic processes water soluble, preparations of some of the fat soluble vitamins have been produced,

e.g. vitamin K. The fat-soluble vitamins are A, D, E and K. The water-soluble vitamins are C and B complex group consisting of thiamine, niacin, riboflavin, pyridoxine, biotin, cyanocobalamin, folic acid and pantothenic acid.

Vitamin A

Syn: Retinol

Vitamin A has a crucial role in normal visual processes and the maintenance of health of epithelial cells. Deficiency of vitamin A is one of the major causes of preventable blindness occurring in many developing countries. This deficiency is widely prevalent in India and about 10% of school children are affected. Its prevalence is higher in the southern states.

Source of intake Vitamin A is found exclusively in animal foods. Rich sources of animal origin are liver, especially fish, liver, butter, ghee, cheese, egg yolk, and milk. Vegetable sources contain the precursor for vitamin A, i.e. carotene especially beta carotene. Rich sources of

carotene include dark green leafy vegetables such as spinach and amaranth, yellow vegetables like carrot and pumpkin, and fruits like mangoes and papaya. Red palm oil is a very rich source of carotene. In the body carotene is converted into vitamin A. Six parts of carotene are equivalent to one part of vitamin A. Vitamin A is stable at temperatures below 100°C. Vitamin A is stored in the liver as retinyl esters and these stores can last for 6-9 months.

Mechanism of action Vitamin A aldehyde is present as rhodopsin in the retina. The changes undergone by rhodopsin form the molecular basis of visual excitation. Vitamin A is required for growth, reproduction and maintenance of life. Synthesis of glycoprotein, essential for proper epithelial function also may be a major function of vitamin A. Vitamin A is essential for proper metabolism and integrity of epithelial cells in many sites. In the absence of vitamin A the epithelium undergoes squamous metaplasia and the flattened epithelial cells are heaped upon one another. Dryness of the eyes leads to xerophthalmia. Bitot's spots develop as whitish scaly plaques on the sclera and they consist of heaped up metaplastic epithelium. The cornea softens, opacifies, ulcerates and necroses and this condition is called keratomalacia. This leads to blindness.

Even in subclinical vitamin A deficiency the conjunctival epithelium shows changes in 90-95% of cases. The conjunctiva is made up of epithelial and goblet cells. Conjunctival impression cytology using a multipore filter (pore size 0.45/μm) applied to the conjunctiva for 2-3 minutes is diagnostic. On staining this with PAS, the epithelial abnormality can be made out.

Daily requirements	
Man	750 μg
Woman	750 μg
Infants	300-400 μg
Children	400-600 μg
Adolescents	750 μg

A dose of 1 μg of retinol is equivalent to 3 international units of vitamin A and 6 μg of carotenoids. An additional 400 μg should be provided during lactation.

Primary vitamin A deficiency generally results from inadequate intake of the vitamin or the carotenoids in the diet. Deficiency of other nutrients usually coexists.

Secondary vitamin A deficiency occurs due to intestinal malabsorption, liver diseases like cirrhosis and enhanced renal excretion.

Clinical features Earliest symptom is night blindness, followed by degenerative changes in the retina. The bulbar conjunctiva becomes dry, and rough greyish triangular foamy raised patches appear (Bitot's spots). A solution of 1% Rose Bengal instilled into the eye stains Bitot's

spots dark pink and makes them stand out prominently. Both night blindness and xerosis of the conjunctiva readily disappear on administering vitamin A. When the cornea also becomes dry and lusterless it is called xerophthalmia. More serious complications are keratomalacia involving the cornea with ulceration and necrosis. These changes follow if xerophthalmia is left untreated. Keratomalacia is more common in children aged 1-5 years. It leads to perforation, prolapse of the iris, and endophthalmitis leading to blindness. Skin changes include dryness and hyperkeratosis. A variety of infantile hydrocephalus has been attributed to vitamin A deficiency.

Vitamin A deficiency should be suspected in all malnourished children. Normal serum level of vitamin A is 20 μg/dL. Serum levels less than 10 μg/dL are indicative of deficiency.

Several secondary benefits are attributable to proper Vitamin A nutritional status. Epidemiological studies report increased mortality due to diarrhea and measles in children who are deficient in Vitamin A.

Treatment A mixed diet with adequate amount of protein is recommended. Vitamin A may be administered orally as retinol, 30 mg (9,000-10,000 IU) for 3 days. In more advanced cases retinol acetate or palmitate may be intramuscularly in a dose of 5000-10,000 units. The corneal lesions clear up within 48-72 hours. The vitamin preparation in a dose of 8-10 mg/day should be given for a month and thereafter maintenance dose of 1.5 mg/day should be continued regularly. Patients with ocular complications should be referred to the ophthalmologist.

Prevention The diet should contain at least 100 g of green vegetables and adequate amounts of animal products. Occurrence of vitamin A deficiency in 5% or more of the population calls for mass treatment. In poor communities 60 mg retinol palmitate or acetate administered orally once in 6 months or 300,000 IU once a year under supervision has been found to be extremely useful. Vitamin A deficiency occurring during pregnancy and lactation leads to poor vitamin A stores in the fetus and low vitamin A content of breast milk. These can be prevented by adequate supplementation during pregnancy.

Treatment schedule for xerophthalmia for all age-group-children.

Time schedule	Vitamin A dosage
Immediately on diagnosis	
6 months of age	50,000 IU
6-12 months	1,00,000 IU
12 months	2,00,000 IU
Next day and two weeks later	Same doses to be repeated

High dose universal distribution schedule for prevention of vitamin A deficiency.

Age	Vitamin A dosage
Infants < 6 months	50,000 IU/orally
Infants 6-12 months	100,000 IU/oral once in 4-6 months
Children >12 months	200,000 IU/orally once in 4-6/months
Mothers	200,000 IU orally within 8 weeks of delivery

Overdosage of carotene Excessive intake of carotene containing foods, principally carrots, leads to hypercarotenemia. It is a cosmetic problem due to yellowish pigmentation of skin. The serum is yellow but sclera is white. The pigmentation disappears with the elimination of excessive carotene from the diet. Hypothyroid patients are very susceptible to hypercarotenemia. Hypercarotenemia does not lead on to hypervitaminosis A.

Vitamin A toxicity This may be due to self-medication or large scale ingestion of livers of fish or polar bear having enormous quantities of vitamin A.

Acute toxicity Symptoms include abdominal pain, nausea, vomiting, headache, and desquamation of the skin. Recovery occurs spontaneously on removing the source of the vitamin from the diet.

Chronic toxicity This is seen in people who take 40,000 units or more of vitamin A daily for a prolonged period. It is characterized by bodyaches, arthralgia, hair loss, anorexia, benign intracranial hypertension, weight loss and hepatomegaly. Chronic overdose of Vitamin A may be associated with osteoporosis and increased incidence of hip fractures, have been reported in Scandinavian countries.

Clinical diagnosis can be confirmed by demonstrating raised vitamin A concentration in the serum and normal retinol binding protein. Withdrawal of the vitamin from the diet brings about prompt relief.

Vitamin D

Syn. Calciferol

Vitamin D is required for normal metabolism of calcium and phosphorus and for bone formation. It enhances the absorption of these minerals from the gut, their mobilization from bone and the reabsorption of phosphorus by the kidney. Vitamin D₁ is the essential precursor for 1-25 alpha dihydroxy vitamin D₁ which is the steroid hormone required for the development of bone, growth in children, maintenance of bone mass in adults and also for the retardation of osteoporosis and prevention of fractures in the elderly.

The two different forms of vitamin D active in man are vitamin D (calciferol) obtained by ultraviolet irradiation of ergosterol (also called ergocalciferol or

provitamin D₂) which is of plant origin, and vitamin D₃ (cholecalciferol) which is formed by activation of 7-dehydrocholesterol present in the epidermal cells of human skin as a provitamin D₂. This activation is effected by the ultraviolet rays ranging in wavelength from 296 to 310 Å obtained from sunlight naturally. Exposure to sunlight for 20-30 minutes daily ensures adequate supply of Vitamin D. Excessive exposure does not lead to overdose of the vitamin. Skin damaged by burns will not be capable of producing Vitamin D on exposure to sunlight.

Vitamin D₂ is obtained from the diet and vitamin D₃ is formed endogenously. On an average the endogenous source supplies about 80% and diet about 20% of the total requirement. Vitamin D₂ and D₃ which are identical in potency, differ only in the configuration of the side chain. Vitamin D₃, though formed in the skin is also absorbed through the small intestine. Further metabolism of vitamin D₂ and D₃ is identical and these together are referred to as vitamin D.

In the liver vitamin D undergoes its first metabolic change, being hydroxylated to 25-hydroxy vitamin D (25-OH D) which is the major component in circulation. In the plasma the vitamin remains bound to a protein called vitamin D-binding protein. In the proximal convoluted tubule of the kidney several metabolic changes occur, and the most active end product 1,25-dihydroxy vitamin D₂ (1,25-(OH)₂D) is formed, which is about 1000 times more active than the parent substance. The enzyme 25 hydroxyvitamin D₃ 1-alpha hydroxylase present in the kidney is the key enzyme regulating the formation of the active product.

Vitamin D supply depends on the amount of exposure to sunlight and the dietary intake. Conversion of vitamin D to 25-hydroxy vitamin D is not rate controlled and therefore the circulating level of 25-OH D indicates the amount of vitamin available to the body. On the other hand conversion of 25-OHD to 1,25-(OH)₂D is rate-controlled by several factors such as serum phosphate levels, concentration of parathormone and levels of other hormones such as prolactin and sex hormones. Fall in the serum phosphate levels and rise in parathormone stimulate the formation of 1,25-(OH)₂D. Vitamin D and its metabolites are all conjugated to form glucuronides and sulphates in the liver during enterohepatic circulation. Since vitamin D is itself biologically inactive and have to be converted into active metabolites in the system, it is often referred to as a pro-hormone.

Biological actions of vitamin D metabolites:

1. Increase the absorption of calcium and phosphate from the small intestine by promoting active transport.
2. Increase mobilization of calcium from bone by promoting osteoclastic activity.
3. Stimulation of reabsorption of calcium and phosphate at the renal tubules.

The overall result of all these processes is to increase serum calcium and phosphate. Deficiency of vitamin D results in impairment of mineralization of bone leading to nutritional rickets in children and osteomalacia in adults.

Dietary sources of vitamin D are milk, butter, cheese, egg yolk and fish liver oils. This vitamin is heat stable. One international unit (IU) is equivalent to 0.025 µg. The daily requirement varies depending on the age.

Daily requirement	
Infants and children	400 IU
Age 19-50 years	200 IU
51-70 years	400 IU
71 and above years	600 IU

RICKETS

Prevalence Rickets is prevalent in India, more so in the north than in the south. Premature babies are more vulnerable. The disease is more florid during winter months when exposure to sunlight is minimal. Prevalence is more among the poor and illiterate classes. Indians who have emigrated to affluent countries still show a higher prevalence of rickets. Osteomalacia is more common in multiparous women who have nursed their babies repeatedly. Rickets has been ranked among the most frequent childhood diseases affecting children in the developing world. There is evidence that dietary deficiency of calcium may also lead to rickets.

In rickets, the arrangement and normal regenerative processes of cartilage are abnormal. Subsequent calcification of the cartilaginous matrix and osteoid do not proceed normally. The osteoid and cartilage which remain uncalcified are deposited irregularly. These give rise to a wide irregular frayed zone of non-calcified cartilage and osteoid termed rachitic metaphysis. These in turn account for many of the skeletal deformities. In the subperiosteal region also, while resorption of cortical bone continues normally, new bone is not laid down, resulting in softening and rarefaction of the bone shaft.

In vitamin D deficiency, since absorption of calcium and, phosphorus from the gut is defective, serum calcium and phosphorus levels fall. Lowered level of serum calcium stimulates the secretion of parathyroid hormone which in turn, leads to mobilization of calcium from the bone. Thus, the serum calcium is usually maintained normal for considerable periods, tetany developing only rarely. Since parathyroid hormone (PTH) decreases reabsorption of phosphorus by the renal tubule, the serum phosphorus falls. The serum alkaline-phosphatase is elevated due to increased osteoblastic activity.

CLINICAL FEATURES

Early manifestations These include irritability, flabbiness of muscles, prominence of abdomen and delay in the appearance of milestones, except speech.

Skeletal manifestations These are the most characteristic features. They develop several months after the deficiency is established. The bones which have the maximum rate of growth at the time of onset of the deficiency show gross abnormalities.

In children below the age of 1 year the lesion is cranio-tabes, characterized by abnormal softening of the skull in the occipital region. In children aged 2 years or more epiphyses of the wrists and ankles are widened and costochondral junctions are enlarged and beaded.

In advanced rickets, deformities of bones are aggravated because of muscular action, gravity and weight bearing.

Head Craniotabes disappears by 1 year of age, but the excess of osteoid and non-calcified cartilage gives rise to frontal and parietal bossing giving the skull a ‘hot cross bun’ appearance. Due to softening of the skull bones the calvarium is asymmetric. The head may be larger in size and closure of the anterior fontanelle may be delayed. The teeth erupt late; show defective enamel, and are more susceptible to develop caries. Permanent teeth also show grooving, pitting and hypoplastic enamel.

Rib-cage Costochondral junctions are thickened (rachitic rosary) and the sternum projects forwards (pigeon chest deformity). A horizontal groove (Harrison’s sulcus) develops along the diaphragmatic attachment due to muscular pull of the diaphragm on the softened bone.

Spine This shows kyphosis and scoliosis when the baby starts sitting and later lordosis in the erect posture.

Pelvis In lordotic subjects the pelvis shows a corresponding deformity. The pelvis is small and deformed (triradiate pelvis), and in female subjects the obstruction caused to the pelvic outlet gives rise to dystocia during parturition.

Extremities The femur, tibia and fibula bend producing deformities like knock knees, coxa vara, etc. The thickened epiphyseal ends may be more prominent. Deformities of upper limbs develop if rickets sets in when the infant is crawling. Long bones may develop green stick fractures and pseudofractures. The sum total of bony deformities of the spine, pelvis, and legs leads to rachitic dwarfism.

Other general manifestations include hepatosplenomegaly, tetany, laryngismus stridulus, convulsions and frequent respiratory infections.

Diagnosis Rickets should be suspected in any child showing deformities of skull, long bones and ribs and in those with apathy, flabbiness, delayed milestones of development, laryngismus stridulus or convulsions.

The clinical diagnosis is supported by the history of inadequate vitamin D in the diet or chronic diarrhea interfering with absorption of vitamin D, and it is confirmed by radiological investigations and biochemical tests.

X-ray findings in active rickets Routine skiagrams of the wrists give clues in diagnosis and are helpful for following the progress. The distal ends of radius and ulna appear concave (cupping), widened (flaring) and irregular (fraying). The distance between the distal ends of the ulna and the radius and the metacarpal bones is apparently increased since the uncalcified rachitic metaphyses is translucent to X-ray. Shafts of long bones show decreased density and prominent trabeculations. Subperiosteal osteoid may give a double contour to the shaft.

With treatment, the lesions tend to heal. A line of preparatory calcification (LPC) appears. This is separated from the distal end of the shaft by a zone of translucency caused by the uncalcified osteoid. As healing progresses, the osteoid becomes calcified and shaft apparently grows towards the LPC and unites with it.

Measurement of serum 25 hydroxy vitamin D gives a reliable indication of the adequacy of the nutritional status. Normal values are above 15 ng/mL. Values below 8 mg/mL indicate severe deficiency.

Biochemical changes In florid cases the serum phosphorus is low (1.5-3.5 mg/dL) Serum calcium may usually be normal, but in advanced cases it is reduced especially in cases with tetany. Serum alkaline phosphatase is raised to 20-60 KA units/dL (Normal 5-15). With correction of the lesion alkaline phosphatase level falls and serum phosphorus level goes up.

Normal serum vitamin D levels range from 35 ± 3.5 ng/mL (80 nmol/L) and $1,25(\text{OH})_2\text{D}$ is 35 ± 3 pg/mL. In active rickets these levels are lowered.

Prognosis for growth and cosmetic recovery is excellent if the condition is recognized early and treated before deformities develop. Intercurrent infections make the prognosis worse. If treatment is started after the bony deformities are established and the epiphyses are ossified, the deformities tend to persist.

Treatment Oral administration of vitamin D in doses of 1500-5000 IU daily brings about rapid improvement in the vast majority of cases. Radiological improvement will be demonstrable in 2-4 weeks. A single dose of 600,000 units is preferable for advanced cases. The dose may be given orally or as in intramuscular injection. An oily preparation is available for intramuscular injection which is effective for 3 months. Three to four injections are given at intervals of two weeks. Parenteral administration is mandatory in cases showing malabsorption. If there is no improvement even after two parenteral doses of vitamin D, the case is considered to be resistant to vitamin D.

After complete healing of the lesion vitamin D should be given in doses of 400 units daily for preventing recurrence. **Children should be encouraged to get exposure to sun for 20-30 minutes daily.** Early bone lesions will be corrected with simple medical treatment. If treatment is started late and deformities are permanent, orthopedic correction is indicated.

Vitamin D-resistant rickets This may be acquired, as in chronic renal failure or inherited as in congenital enzyme defects.

In chronic renal failure conversion of 25-OH D_3 into the active metabolite $1,25(\text{OH})_2\text{D}_3$ becomes defective due to the progressive deficiency of the enzyme in the renal tubules. Such patients develop features of rickets (renal rickets) forming part of renal bone diseases.

Inherited forms of rickets Pseudo-vitamin D deficiency: Two types are known. Rickets develop early in life. Hypotonia, weakness, seizures and growth failure develop.

Vitamin D dependent rickets type I This is an autosomal recessive trait in which the gene for expressing the renal enzyme 25 hydroxy vit D_3 1-alpha hydroxylase is defective, and so this enzyme level is low or absent. Plasma levels of $25(\text{OH})\text{D}_3$ are normal, but $1,25(\text{OH})_2\text{D}_3$ are low. The gene is located on chromosomes X 12 q 13.3.

Vitamin D dependent rickets type II Two forms exist. In one form, the gene for vitamin D receptor is mutated. Hypocalcemic rickets develops. In the second form, also known as X-linked hypophosphatemic vitamin D resistant rickets the phosphate regulating gene (PEX gene) with homology to endopeptidases on the X chromosome is defective. All these forms respond to $1,25(\text{OH})_2$ vitamin D.

OSTEOMALACIA

Definition Osteomalacia denotes those disorders where mineralization of newly formed bone matrix (osteoid) is defective.

Etiology Osteomalacia may be of two different types:

1. Nutritional inadequacy of vitamin D, calcium or both.
2. Vitamin D-resistant osteomalacia. The latter occurs in the following conditions.
 - a. In renal tubular defects which produce hypophosphatemia and chronic metabolic acidosis.
 - b. Chronic administration of diphenylhydantoin which leads to excessive metabolism of vitamin D.
 - c. Osteoporosis.
 - d. After parathyroidectomy for osteitis fibrosa or hyperthyroidism in which rapid formation of new bone outstrips bone resorption.

Clinical features Osteomalacia presents with vague pain which starts as aches and pains insidiously, in the lumbar

spine and thighs and spreading later to the arms and ribs. The pain is frequently felt over the bones themselves, and not at the joints. The pain is usually symmetrical and non-radiating and is accompanied by tenderness of involved bones. Proximal muscles are weak and there is difficulty in climbing up stairs and getting up from squatting position. Occasionally, localized acute bone pain develops rapidly. These sites correspond to the development of pseudofractures. Classical radicular pain may develop due to compression fracture of the vertebra.

Physical signs include deformities, which may be missed if not specifically looked for. The usual deformities are triradiate pelvis and spinal kyphosis (due to action of gravity). Pathologic fractures due to weight bearing and avulsion of tendinous attachments may develop. Biochemical features resemble those of rickets.

Characteristic radiological features are the appearance of “pseudofractures” (Milkman’s lines and Loser’s zones). These are linear zones of decalcification which tend to be symmetrical and extend perpendicular to the cortex. The common sites are the pubic rami, ischium, the neck of the femur, the outer edge of the scapula, ribs and vertebrae. Occasionally, Loser’s zones may extend right across a long bone simulating complete fractures. They are called pseudofractures because the gap is bridged by uncalcified osteoid tissue. They do not reveal any discontinuity of bone clinically. The pseudofractures are caused by the decalcification along the course of the major arteries entering the bones especially in areas of muscular attachment, namely the adductor insertion in the pubic ramus and attachment of gluteal muscles to the trochanters of the femur.

Vertebral bodies show compression and widening of intervertebral spaces to produce biconcave or “cod-fish” vertebrae.

However, in patients who develop osteomalacia secondary to renal tubular disorders or chronic renal failure, there is marked cortical thickening and increased density of trabeculae in spongy bone. The reason for this hyperostosis is not clear. Despite the radiological appearances the bone is abnormally brittle and prone to develop fractures.

Treatment Nutritional osteomalacia responds well to daily administration of 2000-4000 IU of vitamin D (0.05-0.1 mg) for 6-12 weeks followed by maintenance doses of 400-600 IU daily.

Dietary supplementation of calcium in the form of milk 500 mL per day hastens recovery. Medicinal calcium in the form of calcium gluconate, lactate or carbonate can be given as tablets or suspensions orally in doses of 250 to 500 mg daily. Supplementation has to be continued as long as the diet is deficient in calcium.

Adequate supplements of calcium are provided in the form of milk 500-750 mL per day or calcium lactate tablets 1 g along with food.

HYPERVITAMINOSIS D

Prolonged administration of massive doses of vitamin D results in vitamin D intoxication. This causes hypercalcemia. Symptoms include nausea, vomiting, constipation, drowsiness, and signs of renal impairment. Metastatic calcification occurs in several tissues including the kidneys, lungs, gastric mucosa and blood vessels. Renal function may deteriorate before other signs of toxicity are manifest. Subjects receiving high doses of vitamin D should have regular monitoring of serum calcium and if it is above 2.6 mmol/liter (10.5 mg/dL), the intake of the vitamin should be stopped.

Vitamin E

Syn: Anti-sterility Vitamin

Vitamin E is a tocopherol. Among the tocopherols alpha tocopherol is the most easily absorbed and biologically most active compound. All vegetable oils, wheat-germ, cotton seeds, egg yolk, butter and peas contain this vitamin and the average Indian diet contains the daily requirement which is 15 IU or 5 mg. Vitamin E which is a strong antioxidant prevents the peroxidation of cellular and subcellular membrane phospholipids. It is probably involved in preserving the integrity of cell membranes. In cattle and poultry, vitamin E deficiency may lead to infertility. Nutritional deficiency of vitamin E is rare. Excess of free fatty acids in the diet increases the requirement for vitamin E. In premature infants fed on artificial diets containing iron and high concentrations of fatty acids, conditioned deficiency may develop, leading to the production of hemolytic anemia.

In doses of 400-800 mg, vitamin E acts as an effective antioxidant, thereby retarding the development of atheromatous changes in arteries.

Vitamin K

Syn: Coagulation Vitamin

This vitamin which is chemically a substituted naphthoquinone is present in adequate amounts in vegetable oils and green leafy vegetables as vitamin K₁ (phytomenadione). Vitamin K comprises of several molecular forms that have a common 2-methyl-1, 4-naphthoquinone ring, but different side chains at the 3-position. In green leafy vegetables and legumes and vegetable oils such as rapeseed oil and soyabean oil vitamin K occurs as phyloquinone (old name K₁). Bacteria synthesize vitamin K which is named menaquinone (MK-n) which occurs in several molecular forms. Milk is a poor source. The colonic bacteria synthesize this vitamin (Vitamin K₂) and this supplements the dietary source. Naturally occurring vitamin K is fat soluble. The synthetic form of this vitamin is vitamin K₃.

which is water-soluble. This can be given intramuscularly or intravenously, unlike the oily preparations which can be given only intramuscularly. Daily requirement is not clearly known, but is probably 1 µg/kg body weight. Body sources are limited and, therefore, signs of deficiency develop within 3 to 4 weeks of dietary deprivation.

Oxidative phosphorylation processes which take place in cellular mitochondria require the presence of vitamin K. Vitamin K occurs in large amounts in liver and bone. In the liver it takes part in the synthesis of precursors for coagulation factors, protein C and protein S. Vitamin K-dependent coagulation factors (factors II, VII, IX and X) are produced in the inactive form by the liver, and vitamin K is required for their biological activation. The inhibitors of coagulation—Protein C and Protein S are also produced in the liver and these are also vitamin K dependent. Coumarins inhibit the enzyme vitamin K epoxide reductase and thereby inhibit further actions of Vitamin K.

Prothrombin (factor II) is synthesized in the liver as an inert precursor, termed *protein induced by vitamin K absence (PIVKA)*. This is carboxylated to form prothrombin by the vitamin K dependent enzyme—*gamma carboxylase*. In the absence of vitamin K or after administration of vitamin K antagonists such as coumarin PIVKA appears in the plasma.

Vitamin K is needed for the formation of several proteins concerned with calcium homeostasis. Vitamin K promotes the conversion of protein-bound glutamate residues to gamma-carboxy glutamate (Gla). Proteins containing Gla are present in several tissues such as bone, kidneys, placenta, pancreas, spleen and lungs.

Vitamin K also takes part in bone metabolism—both bone formation and resorption. *Two of the important Vitamin K dependent proteins are osteocalcin and matrix Gla protein.*

Vitamin K Deficiency

Vitamin K deficiency occurs in conditions associated with malabsorption of fat such as obstructive jaundice and mal-

absorption states. Prolonged treatment with broad spectrum antibiotics destroys the colonic bacteria which synthesize this vitamin. Deficiency manifests as mild or severe bleeding tendency occurring from injection sites, mucous membranes, and skin. Injections of vitamin K in doses of 5-10 mg corrects the defect, if hepatic parenchymal function is normal. In the presence of hepatic failure, vitamin K may not be effective.

HEMORRHAGIC DISEASE OF THE NEWBORN

Hemorrhage may develop in newborn infants occasionally. Prematurity predisposes to this condition. Vitamin K deficiency in the mother and anticoagulant medication aggravate this disorder. Hemorrhagic tendency develops on the second or third day of delivery. This is due to exaggeration of the physiological hypoprothrombinemia which develops before the colon is colonized by bacteria. A dose of 1 mg of vitamin K₁ given intramuscularly to the baby brings about relief. Synthetic vitamin K is also effective. Larger doses have to be avoided since these lead to hemolysis. Administration of 5-10 mg vitamin K to the mother in late pregnancy abolishes this risk in the newborn.

Anticoagulant therapy Use of coumarin drugs or warfarin leads to alteration in the synthesis of coagulation factors. As a result proteins antigenically similar to factors II, VII, IX and X are produced but they lack the procoagulant properties. Excess of anticoagulants leads to hemorrhagic tendency.

Bleeding occurs from injection sites, urinary tract, gastrointestinal tract and uterus. Intramuscular injection of 10 mg vitamin K is usually effective. When the bleeding tendency is severe, large intravenous doses (50-75 mg) may be required. For severe cases transfusion of fresh blood or vitamin K-dependent coagulation factors may also be necessary. See also Chapter 165.

31

Water Soluble Vitamins

K.V. Krishna Das

5

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Thiamine**Syn: Vitamin B₁—Aneurine**

Thiamine plays an essential part in the metabolism of carbohydrates by acting as a coenzyme required for the decarboxylation of pyruvate to acetyl coenzyme A. It also takes part in other steps of the Krebs's tricarboxylic acid cycle. Cereals contain the vitamin, which is maximal subjacent to the bran. Thiamine content of rice is lost during milling and polishing. Parboiling allows the vitamin to penetrate the grain and conserves it to some extent. Other good sources of the vitamin are sprouting pulses, green leafy vegetables, liver, pork, and legumes. Part of the vitamin is lost by washing or discarding the water used for cooking. The daily requirement is 0.4 mg/1000 kcal, i.e. 1.2 mg/day. Requirement is partially influenced by the intake of carbohydrates.

Deficiency States

Pathology of deficiency In thiamine deficiency the cells cannot utilize glucose aerobically. Nervous system is affected first. Pyruvic and lactic acids accumulate and this leads to vasodilation. The myocardium shows loss of striation, vacuolation of fibers, fragmentation and edema. Cardiomyopathy, encephalopathy and peripheral neuropathy may develop. Sensory, motor and autonomic nerves show demyelination and degeneration.

Clinical features Cardiovascular involvement results in 'wet beriberi' and nervous system involvement results in 'dry beriberi' (see also Chapter 187).

Cardiovascular system Peripheral vasodilation leads to high output circulatory state, myocardial failure and retention of sodium and water leading to edema. The pulse is of high volume. The extremities are warm owing to vasodilation and tender owing to neuropathy. Acute fulminant cardiac failure may be rapidly fatal. *Wet beriberi* may occur in breastfed infants aged 2-8 months. The child presents with edema, oliguria and an aphonic cry. If not clinically suspected, this condition may be missed. Sudden death may occur.

Neurological involvement This manifests as symmetrical sensori-motor polyneuropathy with muscle wasting. Foot-drop and wrist-drop are common. Deep hyperaesthesia occurs and it manifests as calf tenderness.

Wernicke's encephalopathy This is an acute neurological manifestation which is more common in alcoholics. Pathological changes occur in the upper part of the mid-brain, hypothalamus and the walls of the third ventricle which show congestion and petechial hemorrhages, most marked in the mammillary bodies. The onset is sudden with vomiting, confusion, bilateral ophthalmoplegia, loss of consciousness, nystagmus, ataxia and psychological disturbances. Confusion proceeds to coma and death. Korsakoff's syndrome is characterized by retrograde amnesia, impaired ability to learn and confabulation. Wernicke's encephalopathy is associated with high mortality. Prompt administration of thiamine rapidly restores normalcy (see also Chapter 187).

Diagnosis of thiamine deficiency The condition has to be suspected clinically. It can be confirmed by demonstrating raised levels of blood pyruvate. Normal blood pyruvate is 62.5 to 125 mmol/liter and it may rise to 375 mmol/liter (3.3 mg/L). Measurement of erythrocyte transketolase activity, before and after the addition of thiamine pyrophosphate gives the most reliable diagnostic test.

Treatment: When beriberi is suspected or diagnosed, 50 mg thiamine should be given intramuscularly daily for several days. After controlling the acute symptoms 2.5-5 mg should be given orally as maintenance. Wet beriberi and Wernicke's encephalopathy have to be treated as medical emergencies. A dose of 25-100 mg of thiamine should be given intravenously to save life. Dramatic recovery with diuresis occurring within hours of injection confirms the diagnosis.

Infants with beriberi should be given 10 mg thiamine intramuscularly followed by oral doses. The mother also should be treated with oral doses of 10 mg twice daily for several days. Since polyneuropathy and Korsakoff's psychosis are more resistant to treatment, the vitamin has to be given for prolonged periods. Once neuropathy is established, residual paralysis persists even after therapy. Adverse side effects to thiamine include sensitization and anaphylactic shock.

Riboflavin

Syn: Vitamin B₂

Riboflavin is essentially required in all oxidation reduction reactions involving the coenzymes flavin mononucleotide and flavin adenine dinucleotide which take part in tissue oxidation and respiration. It is moderately heat resistant, but boiling in alkaline media or exposure to sunlight destroys this vitamin.

Good dietary sources include liver, meat, eggs, kidney, milk, other dairy products, green leafy vegetables, and sprouted cereals and pulses. Daily requirement is 0.60 mg/1000 kcal, i.e. a total of 1.5-2 mg.

1. **Signs of deficiency** Angulostomatitis, cheilosis, nasolabial seborrhea, and possibly vascularization of the cornea are the characteristic features. Angulostomatitis may also occur in deficiencies of niacin and folic acid. Mucosa of the lips appears red and denuded in cheilosis. On taking hot and spicy food there may be soreness. Vascularization of the cornea has been described in some surveys. In glossitis the mucosa over the tongue is red, swollen and painful (Fig. 31.1). This responds to riboflavin therapy. Some cases show lesions in the oral mucosa, eyes, and genitals (oculo-oro-genital syndrome) (Fig. 31.2). *The oculo-oro-genital syndrome* presents as blepharo-conjunctivitis, angular stomatitis, bright red atrophic tongue and dermatitis of the pubic region. This syndrome may occur in pyridoxine deficiency as well.
2. **Treatment** Riboflavin in a dose of 2-5 mg thrice a day cures the condition in a few days. The drug can be given orally as tablets or syrup or by injections. Treatment of oculo-oro-genital syndrome is to give riboflavin up to 100 mg/day and pyridoxine 150 mg/day. The lesions clear within 7-10 days.



Fig. 31.1: Glossitis and angulo stomatitis



Fig. 31.2: Angulo stomatitis

Niacin

Syn: Nicotinic Acid, Nicotinamide, Antipellagra Vitamin, Vitamin B₃

Nicotinic acid forms an integral part of nicotinamide adenine dinucleotide (NAD) and its phosphate (NADP) which act as coenzymes in the metabolic pathways of glucose and proteins. Nicotinic acid and nicotinamide have equal biological potency and are together referred to as niacin. Tryptophan is converted into niacin in the body, 60 mg of tryptophan giving rise to 1 mg niacin. Dietary sources include liver, pulses, whole cereals, fish, meat, groundnuts, milk, eggs, and to a smaller extent, vegetables. Coffee contains appreciable amounts of this vitamin. Rice and other cereals contain this vitamin, major portion of which is lost by milling. In maize niacin is present in an unabsorbable form 'niacytin'. Moreover, maize is poor in its content of tryptophan. One-fourth of

the vitamin may be lost in washing and cooking, though cooking alone does not destroy it. Daily requirement is 6 mg/1000 kcals (15-18 mg/day). Deficiency of niacin causes pellagra.

PELLAGRA

This disease was widely prevalent in India among the maize eating communities in all states, especially Andhra Pradesh, Tamil Nadu and Rajasthan. Consumption of sorghum or jowar also predisposes to this tendency. Newer varieties of maize and sorghum with better nutritive value have helped to reduce the incidence of pellagra. Alcoholism and malabsorption states precipitate pellagra. Inborn disorders of metabolism such as Hartnup disease in which the absorption of tryptophan is impaired lead to pellagra in rare cases.

Pathology Dermatitis, changes in the oral and intestinal mucosa and degenerative changes in the central nervous system are seen. Ulcers may develop in the intestines. Chromatolysis of ganglion cells occur in the central nervous system. Patchy demyelination occurs in the spinal cord.

Clinical features Generalized malnutrition is evident in most cases. The most well-known features are the three Ds—dermatitis, diarrhea and dementia, but these characterize the very advanced stage of the disease. Pellagra should be diagnosed much before this classical picture develops, since the advanced stage is associated with high mortality.

Skin changes These are seen over areas exposed to sunlight. These start with erythema which may resemble sunburn. This progresses to vesiculation, ulceration, secondary infection, and crusting. In chronic pellagra the skin becomes rough, thickened, scaly and pigmented. In home-bound patients not exposed to the sun, pellagra may develop without the skin changes—“*Pellagra sine pellagra*”.

Mucous membrane changes are evident in the mouth and vulva. Skin of the perianal region shows degenerative and inflammatory lesions. The tongue is raw and beefy in appearance. Angulostomatitis may be present.

Alimentary symptoms Vague alimentary symptoms like anorexia, nausea, vomiting, and dyspepsia are invariably seen. Diarrhea is common but not always present. The stools may be watery or rarely dysenteric.

Neurological features Anxiety, depression, irritability and failure to concentrate are early symptoms. Advanced cases show delirium, dementia and psychiatric manifestation. Mental symptoms may be mistaken for primary psychiatric disorders.

Course and prognosis Advanced cases are fatal due to diarrhea, secondary infections, or other associated

nutritional disorders. Early treatment reverses the symptoms completely.

Treatment Well-balanced diet containing adequate supply of proteins should be instituted. Nicotinamide is well absorbed if given orally. It is given in a dose of 100 mg every 6 h for 2-3 weeks. In the advanced cases 50-100 mg may be given intramuscularly or intravenously. Supplements such as the other B complex vitamins and iron should be concurrently administered. Local application of antihistamine creams and protective clothing gives relief to the skin lesions.

Prevention In maize eating communities other sources of niacin should be provided along with. In non-endemic areas pellagra may develop in the elderly, inmates of mental homes, etc. Such groups require vitamin supplementation.

Pyridoxine

The active form of this vitamin is pyridoxal. Pyridoxal phosphate acts as a coenzyme in several reactions, especially in the metabolism of amino acids and biological amines such as catecholamines and 5-hydroxytryptamine. It takes part in the biosynthesis of gamma-amino-butyric acid in the brain. Yeast, liver, meat, whole grain cereals, peanuts, bananas and legumes are good dietary sources. Normal daily requirement is 1.25 mg and it is present in the ordinary Indian diets and hence nutritional deficiency is rare. Drugs like INH, oral contraceptives and hydralazine may interfere with the metabolism of this vitamin and produce conditioned deficiencies.

Clinical features include dermatitis, cheilosis, angulostomatitis, glossitis, dizziness, vomiting and peripheral neuropathy. Infantile convulsions have been attributed to nutritional pyridoxine deficiency. Pyridoxine deficiency is known to produce one form of sideroblastic anemia which responds to high doses of this vitamin. Concurrent administration of 6 mg of pyridoxine prevents the development of neuritis in subjects treated with INH (see also Chapter 187).

Pantothenic Acid

Pantothenic acid is converted to coenzyme A in the body. This vitamin is widely distributed in animal and vegetable foods and hence dietary deficiency is very rare. Though the exact requirement is not clearly known, 10 mg may represent an adequate daily intake. Deficiency in experimental animals leads to dermal and hair changes, neuromuscular degeneration and fatal adrenal hemorrhage.

Calcium pantothenate has been used for other conditions like paralytic ileus, and streptomycin toxicity based on empirical findings. There is no conclusive proof to support these claims.

Biotin

This is an organic acid functioning as a coenzyme in several carboxylation reactions. It is present in several articles of food and is also synthesized by intestinal bacteria. Daily requirement is about 100 mcg. Naturally occurring deficiency is rare, but conditioned deficiency may develop by overfeeding exclusively with white of egg. This is due to the presence of avidin which antagonizes biotin. Infants who are on parenteral feeding with biotin deficient diets may develop symptoms such as lassitude, irritability, paresthesiae, anorexia, rashes, and hair loss. All these improve with the administration of biotin.

Inherited disorders of biotin metabolism occur rarely. Two types are known. One type may present in the first few weeks of life with metabolic acidosis and a rash. The other presents in the first few months of life with rash, keratocconjunctivitis, alopecia, ataxia, hypotonia, and metabolic and lactic acidosis. Both groups respond dramatically to large doses of biotin.

Cyanocobalamin

Syn: Vitamin B₁₂

Deficiency of vitamin B₁₂ or folates leads to abnormality in DNA synthesis, characterized by megaloblastic erythropoiesis and similar changes in many tissues in the body. Due to its fatal outcome in pre-vitamin B₁₂ days, it was called pernicious anemia.

Absorption of B₁₂ The dietary vitamin B₁₂ which is bound to proteins has to be liberated from them to enable absorption. Cooking converts a part of these into dialysable form. Low pH achieved in the stomach helps further liberation of this vitamin. After liberation, cobalamin is bound to the intrinsic factor (IF) which is a glycoprotein with a molecular weight of 44,000 present in the gastric juice. Proteolytic enzymes of the pancreas play a part in this process.

The vitamin B₁₂-IF complex is taken up by receptor sites present in the microvilli of the ileum by passive absorption. In the plasma cyanocobalamin remains bound to a polypeptide of molecular weight 38,000 known as transcobalamin II (TC II). This complex passes into cells and its B₁₂ is liberated by lysosomal enzymes. Liver can store up to 2 mg of vitamin B₁₂ which is adequate for several years. The daily requirement of B₁₂ is 1-2 mcg. Meat, liver, eggs, dairy products, and yeast contain adequate amounts of this vitamin. Purely vegetable sources are deficient in vitamin B₁₂. Therefore, vegans (persons who do not take any form of animal foods or dairy products) suffer from nutritional deficiency. Normal levels of vitamin B₁₂ in serum ranges from 120-900 pg/mL in Indian subjects.

Vitamin B₁₂ deficiency is less common than folate deficiency.

Etiology of Vitamin B₁₂ Deficiency

1. Malabsorption states—diseases of the ileum.
2. Dietary inadequacy—vegans.
3. Intrinsic factor deficiency—pernicious anemia. This is usually acquired, rarely this may be congenital.
4. Chronic disorders destroying the gastric mucosa and partial or total gastrectomy.
5. Blind loop syndromes-with colonization of the small intestine by bacteria.
6. Pancreatic insufficiency.
7. Familial deficiency of transcobalamin II.
8. Inherited disorders of vitamin B₁₂ metabolism.
9. Interference with absorption of vitamin B₁₂ by drugs, e.g. PAS, colchicine, phenformin, neomycin.

Effects of B₁₂ Deficiency

Megaloblastic anemia develops owing to diminished red cell production and dyserythropoiesis. In addition, cells from other organs with rapid cell turnover such as the gastrointestinal tract and cervicovaginal mucosa also show similar abnormalities. The central nervous system and peripheral nerves are also affected. The neurological lesions include subacute combined degeneration of the spinal cord, optic neuritis, and demyelination of the cerebral white matter and peripheral nerves.

Neurological damage occurs due to impaired DNA synthesis and myelin formation (See also Chapter 187). The occurrence of neuropathy does not bear any direct relationship to the severity of anemia.

Treatment Dietary deficiency can be corrected by giving 1-2 µg of vitamin B₁₂ orally. If megaloblastic anemia has developed, larger doses are required (100 µg/day) oral, if absorption is reliable. Otherwise 1000 µg of hydroxocobalamin is given intramuscularly once a week for 3-4 weeks, and thereafter the daily dietary supplementation of 1-2 µg is continued.

There is evidence that vitamin B₁₂ can be absorbed from the buccal mucosa when applied sublingually. This route can be made use of for therapy in mild deficiency states.

Folic Acid

Syn: Pteroylglutamic Acid

Folic acid molecule consists of a pteridine ring, para-amino benzoic acid and l-glutamic acid. The free form does not occur commonly in nature. Foods and tissues contain several folate compounds (pteroylpolyglutamates). The main form present in human plasma and CSF is 5-methyltetrahydropteroyl monoglutamate. Rich dietary

sources are yeast, liver, nuts, green vegetables, and chocolate. Folic acid is lost by boiling the articles of food in a large volume of water. Average requirement is 200-300 µg/day. The vitamin is absorbed in the proximal small intestine after hydrolysis of polyglutamates. Human body can store about 6-10 mg, especially in the liver. Megaloblastic anemia has developed in volunteers after 10-20 weeks of dietary deprivation. Dietary deficiency is widely prevalent in India. It is seen most in pregnant women and children. A study conducted in Balrampur dist in UP, India by Anil Cheriyan et al 2002-2003 revealed neural tube defects in 6.57-8.2 children out of 1000 live birth. This figure is one of the highest in the world. The main reason was deficiency of folates, vit B₁₂ and other deficiencies such as Vit B₆ together or singly (The Lancet 2005. 366- 930-931).

Causes of Folate Deficiency

1. Dietary inadequacy of animal foods and green vegetables.
2. Malabsorption states.
3. Increased demands due to pregnancy, lactation, growth and intercurrent illnesses in children.
4. Alcohol intake increases folate requirements.
5. Accelerated erythropoiesis as in hemolytic anemia.
6. Other disorders like tuberculosis, rheumatoid disease, and malignancy increase folate requirements.
7. Several drugs interfere with the metabolism of folates, e.g., amethopterin, pyrimethamine, trimethoprim, hydantoins, oral contraceptives.
8. Folate losses may occur in several disorders of skin and the intestinal tract.
9. Inborn errors of metabolism may interfere with the utilization of folate.

Folate deficiency leads to megaloblastic anemia and similar changes in several rapidly proliferating tissues. In the body the metabolic pathways of folates and vitamin B₁₂ are closely interrelated. In many cases of nutritional anemias, combined deficiencies of iron, folate and to a smaller extent B₁₂ operate.

Normal serum folate levels are 4-10 ng/mL and red cell folate is above 100 ng/mL.

Folic acid deficiency occurring in the early period of gestation when the neural tube of the embryo develops, may result in the higher incidence of neural tube defects such as spina bifida and anencephaly. Supplementation of 400 mcg of folate starting from 28 days before and continuing for 28 days after conception reduce the risks of neural tube defects substantially.

Treatment: Dietary deficiency can be corrected by giving 5-10 mg of folic acid orally, in addition to the dietary improvement. Pregnant and lactating women, children and alcoholics require prophylactic supplementation. In poor communities routine folic acid supplementation in

pregnancy (1 mg/day) reduces the incidence of premature births. Premature infants should be given folate supplementation.

Folate and vitamin B₁₂ deficiencies are known to elevate serum homocysteine levels and this may lead to abnormal thrombotic tendency.

Ascorbic Acid and Scurvy

Syn: Antiscorbutic Vitamin—Vitamin C

James Lind, a Scottish naval physician, recognized the antiscorbutic properties of citrus fruits in 1753 and this was considered an important discovery with far-reaching effects.

Dietary sources Ascorbic acid is present in a wide variety of foods. In the process of cooking about 50% of vitamin C passes into water and 20% gets destroyed. Fresh fruits, green leafy vegetables and germinating pulses are rich in ascorbic acid. The Indian gooseberry and guavas are particularly rich sources. Animal food like milk and meat contain only small amounts of this vitamin. The vitamin is present in potato in the layer just below the skin. If the potatoes are boiled whole with the skin, the vitamin diffuses into the deeper layers.

The minimum daily requirement for an adult is 30-40 mg and for infants 5 mg per kg body weight. Normal plasma levels vary between 0.7 and 1.5 mg per dL. Leukocytes, platelets, and adrenal glands contain large amounts of vitamin C. Deficiency of vitamin C causes scurvy.

Physiological actions Vitamin C is a strong reducing agent. It takes part in biological oxidation-reduction reactions. Vitamin C is required for the formation of collagen by the hydroxylation of proline. It takes part in the formation of hemoglobin, erythrocyte maturation and the conversion of folic acid to tetrahydrofolate. Ascorbic acid reduces ferric iron to ferrous iron which is more easily absorbed. Body stores of ascorbic acid are small and, therefore, dietary deficiency leads to the development of scurvy.

SCURVY

Deficiency of vitamin C in the diet over a few weeks or months will lead to scurvy.

Clinical features of scurvy Classic scurvy is seen only infrequently in India since small amounts of vitamin C are obtained in vegetables and pickled berries which form essential items of the Indian diet. Cases do occur among inmates of mental homes, elderly persons and among the very poor.

Manifestations of scurvy vary in children and adults. Early symptoms include weakness, lassitude, and normocytic normochromic anemia. In infancy and

childhood subperiosteal hemorrhages occur, which lead to painful swellings over long bones. Scurvy in infancy produces pseudoparalysis owing to pain. This condition may mimic arthritis, osteomyelitis, or poliomyelitis. X-ray abnormalities may develop over the sternal ends of ribs and ends of long bones. Bleeding from the gums occurs commonly at the sites of erupted teeth. Retrobulbar, subarachnoid, and cerebral bleeding may develop in a few cases.

In adults early manifestation is follicular hyperkeratosis over the skin of the lower limbs. The lesions are papular with perifollicular hemorrhages which appear as purpura. Hemorrhage into the deep tissues of the thighs and legs cause tense induration ("woody leg"). Other sites of hemorrhage include joints, nail beds and viscera. The gums are hypertrophied and the interdental papillae are red and prominent (scurvy-buds). They bleed easily. Edentulous subjects do not get gingival abnormalities. The gum changes are aggravated by infection. The teeth become loose and may fall off. The hair assumes cork-screw shape since the follicles are obstructed by keratin

plugs. Wound healing is delayed and resistance to infection is reduced. The condition is fatal if untreated.

Treatment Scurvy is a potentially fatal disease and sudden death may occur unexpectedly. Treatment should be started without delay. In infants and children 25-50 mg of ascorbic acid given daily three times a day is sufficient to replete the body stores. In adults 500 mg is given daily in divided doses up to a total of 4 g. A diet rich in vitamin C should be given to prevent relapse.

Prevention Infant foods should contain fruit juices or vitamin C supplements. Children, convalescent subjects and elderly people who are liable to be neglected, should receive 25 mg of vitamin C daily. As an alternative, 500 mg may be given once a month.

Adverse effects of vitamin C Side effects like digestive upsets and hypoglycemia occur if the drug is given in doses exceeding 3 g/day. Oxaluria and oxalate stone formation in the urinary tract may result from prolonged overdosage.

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Minerals

K.V. Krishna Das

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Fourteen elements are absolutely essential for normal body metabolism. These minerals are sodium, potassium, calcium, magnesium, iron, iodine, copper, zinc, cobalt, phosphorus, sulphur, chromium, selenium and fluorine.

Though several other elements are detectable in tissues, their role in nutrition is not clearly understood the term trace elements denote these elements whose concentration in biological fluids does not exceed 1 mcg/mL.

Calcium

(See also Chapter 72)

The total body content of calcium is 1200 g in an adult. This is present in the skeleton, teeth, plasma, and in all tissues. Of the total body calcium, 98% is present in the bones as calcium phosphate (hydroxyapatite) held in a protein matrix (osteoid). Calcium gives the strength and rigidity to the skeleton. In the plasma calcium is present as the free ions, albumin-bound form and as complexes which are diffusible. In health, serum calcium level ranges from 9-10.5 mg % (2.2-3.6 mmol/L). Calcium and phosphorus levels vary inversely with each other and the

product $\text{Ca} \times \text{P}$ is almost constant around 40. The normal function of cell membranes and the electrical activity of excitable tissues like the muscles, nerves, and heart depend upon ionized calcium. Calcium ions facilitate the release of acetylcholine from the vesicles in the motor end plates. Coagulation processes require small amounts of calcium.

The main sources of calcium is the diet. Milk, cheese, eggs, meat, peas, beans, certain leafy vegetables, dried fruits and nuts contain good amounts of calcium. Milk protein (casein) is the richest and most reliable source. One liter of milk contains about 1.2 g calcium. An egg contains about 30 mg of calcium. Drinking water may also contain a variable, but significant, amounts of calcium in many areas. Calcium from vegetable foods is not well absorbed since it is present as oxalate. In cereals calcium is found in the form of phytates which are not absorbed and hence excepting millets the cereals are poor sources.

Calcium is absorbed actively from jejunum and passively from the ileum. Intake of vitamin D, acidic pH and presence of proteins in the food favour absorption. In growing children, and pregnant and lactating women absorption is increased. In older age groups absorption falls. High fat diet, phytates, oxalates and alkaline pH impair calcium absorption. Normally 70-80% of ingested calcium is lost in feces unabsorbed. In steatorrhea calcium soaps are formed and excess calcium is lost in stool. Calcium is also lost in the urine.

Urinary calcium level depends on the blood levels. Normal adults excrete 300-400 mg calcium in 24 hours. Lowering of dietary calcium does not lower urinary calcium correspondingly. As a result, very low calcium intake results in negative balance. Lowering of serum calcium stimulates the secretion of parathyroid hormone which mobilizes calcium from bones. The metabolism of calcium is intimately related to those of vitamin D, parathyroid hormone and calcitonin (See also Chapter 99).

Recommended daily intake is 500 mg for adults, 1200 mg for pregnant and lactating women and 700 mg for adolescents. Postmenopausal women should have 500 mg of elemental calcium (available form 1250 mg of calcium carbonate or other calcium salts in suitable doses) as supplement to diet. Daily administration of 1000 mg of calcium carbonate with 400 units vitamin D_3 has shown to reduce hip fracture in post menopausal women. There was a slight increase in the incidence of urinary calculi.

Hypercalcemia leads to anorexia, nausea, vomiting, constipation, hypotonia, mental depression, lethargy, and coma. Persistent hypercalcemia leads to calcification around joints, ligaments, gastric mucosa, cornea, and kidneys. Hypercalcemia further depresses the renal function. Hypocalcemia leads to tetany.

Phosphorus

(See also Chapters 72 and 99)

Most of the phosphorus (85%) in the body is present in bones and teeth. In all tissues this element is present intracellularly as phosphates. The total body content of phosphorus is 800-900 g. In the plasma it occurs as inorganic orthophosphate at a concentration of 2.8-4.5 mg/dL (0.8-1.5 mmol/L). Around 88% of phosphorus is in ionic form and the rest is present in the protein-bound form. Phosphorus is widely distributed in dietary articles and hence dietary deficiency is rare. Though the exact requirement of phosphorus has not been determined, probably it is the same as calcium. Dairy products, eggs, cereals, and meat are rich sources.

About 80-90% of ingested phosphorus is absorbed. The serum level is controlled mainly by the renal excretory mechanism. Around 85% of filtered phosphate is absorbed at the proximal tubule and only 10-15% is lost in urine. Negative phosphate balance is usually caused by the abnormalities of renal clearance. In renal failure, serum phosphate goes up and in renal tubular dysfunctions it may fall. Aluminium hydroxide binds phosphates and makes it unabsorbable so that in prolonged antacid therapy, phosphorus absorption may suffer.

Facts about Phosphorus

85% in skeleton
15% in extracellular fluid and soft tissues
Normal diet supplies 800-1400 mg/day
Absorption from gut is passive. 60-80% absorbed.
 $1\text{-}25(\text{OH})_2\text{D}_3$ promotes absorption
Normal plasma levels 2.8-4.5 mg/dL or 0.89-1.44 mmol/L
Plasma levels are higher in children and they fall with age.

Hypophosphatemia

The serum level is below 2.5 mg/dL (u) 0.8 mmol/L.

Causes

- Redistribution between internal compartments*
e.g.: respiratory alkalosis, recovery from starvation, recovery stage of diabetic ketoacidosis, endocrinopathies, avid uptake of phosphorus by bone (hungry bone syndrome)
- Increased urinary losses*
e.g.: hyperparathyroidism, vitamin D deficiency, renal tubular defects, alcoholism, metabolic and respiratory acidosis. (See also Chapter 99).
- Diminished absorption*
e.g.: malabsorption states, fall in dietary phosphorus, vitamin D deficiency, antacid over use.

Manifestations include proximal myopathy, dysphagia, intestinal ileus, rhabdomyolysis, thrombocytopenia, respiratory muscle weakness and encephalopathy.

Management: If the serum phosphorus level is near about 0.32 mmol/L, oral supplementation with sodium or potassium phosphate in a dose of 2-3 g/day is sufficient. Cow's milk contains 1 mg phosphorus per mL. In an emergency sodium phosphate can be given I.V. as infusion in a dose of 2.5 mg/kg body weight over a period of 6 hours. Infusion of phosphate leads to fall in plasma calcium level.

Hyperphosphatemia

Plasma level of phosphorus exceeds 1.5 mmol/L.

Causes

- Increased exogenous load**
I.V. infusion, heavy oral intake, feeding cow's milk to premature babies, vitamin D overdose, abuse of phosphate-containing enemas, acute phosphorus poisoning.
- Increased endogenous production**
Tumor lysis syndrome, rhabdomyolysis, bowel infarction, hemolysis, malignant hyperthermia, lactic acidosis, diabetic ketoacidosis, respiratory acidosis.
- Reduction in urinary elimination**
Renal failure, hypoparathyroidism, acromegaly, vit. D intoxication, phosphonate therapy, magnesium deficiency.

Pseudo-hyperphosphatemia

This is the condition in which spuriously high blood levels are seen if colorimetry is adopted for estimation. This occurs in multiple myeloma, hypertriglyceridemia and if haemolysis occurs in the blood sample after collection.

Clinical features Acute hyperphosphatemia depresses plasma calcium levels and precipitates tetany. Chronic elevation of the $\text{Ca} \times \text{P}$ level above 70 leads to metastatic calcification.

Treatment Induce intestinal malabsorption of phosphate by administering phosphate binding salts of aluminium, magnesium or calcium. In the presence of renal failure, aluminium salts should be used with caution.

Iron

The total content of iron in healthy adults is 4.2 g. Of this, 58-66% is present in hemoglobin. Part of the iron is present in myoglobin which is present widely in cardiomyocytes and skeletal myofibrils. It is a small monomeric cytoplasmic tissue hemoglobin which facilitates the transport of oxygen from erythrocytes to the mitochondria to maintain oxidative phosphorylation for myocardial contractility. Neuroglobin is a tissue hemoglobin discovered in vertebrate brains. It is likely that it may function during hypoxemic episodes and protect against damage.

Iron also exists in combination with the iron storage proteins such as ferritin and hemosiderin, in the macrophages seen in the muscles, liver, and bone marrow. Stored iron is demonstrable by Prussian blue reaction histochemically. Stored iron available for erythropoiesis is about 1.2-2 g. Tissue iron is mainly present in enzymes. This amounts to 300 mg and is not available for erythropoiesis. Total plasma iron is 3-4 mg and the levels range from 80-120 µg/dL. Animal foods like meat, liver, kidney, fish, and egg yolk are rich in iron. Vegetable sources are green vegetables and fruits, onions, cereals, pulses, oil seeds, jaggery, raisins, grapes, apricots, and dates. The daily average intake of iron is 10-20 mg, out of which 1-2 mg is absorbed. Significant amounts of iron may be obtained from water sources and from iron cooking vessels (See also Chapters 148 and 149).

Absorption and further metabolism of dietary Iron

Iron is one of the most highly conserved elements in the body. Dietary iron occurs in two forms

- Heme iron found in hemoglobin and myoglobin, obtained from animal foods and
- Non-heme iron present in green vegetables, fruits and cereals. They are absorbed by different mechanisms. All forms of dietary iron are absorbed in the duodenum and upper jejunum where the contents are acidic.

Heme iron bound to proteins is released by acid and proteases in the stomach. Ferrous iron in the heme is oxidised to ferric iron and heme is converted to hemin which is absorbed as such without interaction with other dietary factors and without any regulatory mechanisms. The enterocytes – (lining cells of the small intestine) play a crucial role in iron absorption. Heme enters the enterocytes with the aid of heme receptors. It is degraded into free iron, bilirubin and carbon monoxide by the action of heme oxygenase.

Non-heme iron is present as green vegetables, fruits and cereals. Non-heme iron is released from food by the action of acid either in the ferrous or ferric state. Iron is absorbed only in the ionic state. In the alkaline pH of the duodenum ferric iron salts are insoluble whereas ferrous iron is soluble. Therefore most of the absorbed iron is in the ferrous form. Absorption of iron is influenced and moderated to a great extent by the availability of iron stores and the needs of the body.

Passage into the gut-epithelium and circulation

The enterocytes which line the epithelium of duodenum and upper jejunum play a major role.

Absorption occurs in 3 stages

- Entry of iron into the apical cell membrane

- Intracellular processing of the iron and transfer to the baso-lateral membrane
- Transfer of the requisite amount of iron through the basolateral membrane into the portal circulation

The enterocyte regulates the entry of iron into it and transport across it to the portal circulation. When enterocytes are shed after their life span of 2-3 days the iron contained within them are lost in feces.

Iron entering the enterocyte is either temporarily stored in the cell or transported across the basolateral membrane to the capillary network. The fate of the iron entering the enterocyte depends on the availability of body stores and the body's need for iron.

5

Factors participating in iron metabolism

Hemoglobin: Each molecule of hemoglobin has a central ferrous iron to which oxygen is loosely attached. Each molecule of hemoglobin contains 0.34% iron by weight (i.e.) 1 mL of packed erythrocytes contain 1 mg of iron. Major portion of the absorbed iron is used for the formation of hemoglobin.

Hemosiderin is the storage form of iron seen mainly in the monocyte-macrophage system. It is composed mainly of ferric hydroxide crystals which are deprived of their apoferritin coat. It contains 25-30% of iron by weight. It is demonstrable by Pearl's staining.

Ferritin

It is an alpha 2 globin which binds iron. It is a compound formed from apo ferritin and ferric hydroxide (FeOOH). It is a very efficient storage form of iron- Ferritin contain two types of monomers- the light (L-monomer) and the heavy (H-monomer). The L-monomer which is basic, binds very readily and tightly to iron. This property makes it suitable for storing iron. L-monomer-rich ferritin is seen mainly in the liver, spleen and serum. L-monomer is in excess of H-monomer.

H-monomer which is acidic takes up and releases iron readily. It is found in the heart, kidney, placenta, monocytes lymphocytes and erythrocytes. There are 20 isoforms of ferritin. Apart from its storage function, ferritin has a role in metal detoxification and diversion of excess iron. Unbound iron is toxic to tissues since it causes free-radical injury. The level of apoferritin in blood regulates the absorption of dietary iron.

Transferrin

Transferrin is the most dynamic part of the iron-metabolic chain. It is a glycoprotein which binds to ferric iron and can exist in monoferric or diferric forms. It is synthesized in the liver as apotransferrin. By combining with iron it becomes transferrin. Its rate of synthesis is inversely proportional to the iron stores.

Transferrin Receptor (TfR)

These are transmembrane glycoproteins which exist in two forms TfR1 and TfR2. They both bind to transferrin. TfR1 has high affinity, TfR 2 has only low affinity. TfR1 binds to plasma transferrin and delivers it to the erythroblasts. The TfR1- transferrin complex is internalized into the erythroblast via an endocytic vesicle. In the cell, the iron dissociates from the complex- the iron is delivered to the cytoplasm and the TfR1 goes back to the cell surface. All cells in the body have TfRs on their surface, but maximum number (80%) is on erythroblasts.

TfR2 which has low affinity to transferrin is seen mostly in hepatocytes and erythroid cells. It has also a role in regulating iron metabolism. Most tissues regulate their iron content by modulating TfR expression Truncated portions of TfR are shed into the circulation. These can be estimated using laboratory kits as serum transferrin receptor (sTfR). Concentration of sTfR is directly proportional to the rate of erythropoiesis. In iron deficiency anemia, sTfR levels are high, whereas they are low in anemia of chronic disease.

Mobiliferrin

This is a cytosolic protein that transports iron across the enterocytes and other cells in the body. It is also responsible for receiving iron from transferrin which transports iron in the plasma.

Ferroportin-1 and hephaestin

These are also transport proteins subserving iron transport across cells. Their functions are being studied further.

Hereditary Hemochromatosis Gene Product (HFE)

HFE binds transferrin receptor with an affinity equalling that of transferrin and competes with transferrin binding. HFE might facilitate the sensing of the need for iron absorption across the enterocyte. In hereditary hemochromatosis there is decrease in the amount of functional HFE protein.

Hepcidin

This is a newly identified iron regulator that appears to communicate the status of the body's iron stores and the demand for erythropoiesis to the enterocytes and thereby regulate iron absorption. Hepcidin levels are low in iron overload and high in iron deficiency.

The absorption and utilization of iron which are complex processes can be summarized as given below

- Absorption of ferrous iron through the apical membrane of the enterocyte; The rate of absorption

depends directly on the level of apoferritin in blood.

2. Transport across the enterocyte; The iron that is absorbed is either stored in the enterocyte or transported across the basolateral membrane to the circulation as an active process. The cells lining the intestinal crypts (base of the villi) act as sensors of the iron status of the body.
3. Transferrin transports the iron in ferric form in the circulation and delivers it to cells, with the aid of TfR
4. Most of the iron is utilized for heme synthesis in erythroblasts. Iron is also taken up by macrophages by the process of erythrophagocytosis. This iron in the macrophages does not re-enter the circulation.

Excretion of iron occurs through shedding of enterocytes, exfoliation of skin, sweat and urine. Loss of blood from the body contributes to the major source of blood loss.

Development of Iron Deficiency

The bioavailability of iron in the average Indian diet is low. Milk is a poor source of iron and hence babies fed solely on unfortified milk develop iron deficiency within 6 to 12 months. Iron from animal foods is absorbed better (11-22%) than that from vegetable sources (1-7%). Animal proteins and vitamin C enhance iron absorption, while phytates and phosphates retard it. Iron is absorbed from the duodenum and upper jejunum. Iron is lost in desquamated epithelial cells of the gastrointestinal tract, urinary tract and skin, and through the loss of nails and hair. Menstruation, pregnancy, parturition and lactation account for further losses in women who suffer from iron deficiency more than men. Dietary requirement is higher for women. Daily requirement is 10-20 mg for men and 30-40 mg for women. Infants require 1 mg/kg body weight.

Considerable periods elapse between the onset of iron deficiency and the clinical manifestations. Since large stores are present normally, clinical symptoms do not occur till the stores have been depleted. Pure nutritional deficiency manifests clinically only a few years after institution of a diet poor in iron. In actual practice, anemia manifests much sooner since in the vast majority of cases there is also concomitant blood loss.

In India about 20-40% of pregnant women show iron deficiency. Depletion of iron in the mother during pregnancy results in diminution of iron stores in the fetus. Premature infants have lower iron stores and are vulnerable to develop iron deficiency states.

Effects of iron deficiency Iron deficiency state manifests in different stages. The earliest stage is depletion of iron stores, during which time the condition is asymptomatic. The second stage is one of tissue iron deficiency. This

manifests as subtle disturbances of function of many organ systems.

At this stage, general symptoms such as fatigability, disinclination for work, poor mentation in children and diminished performance at school are common. Often these are overlooked and therefore many cases go on to more severe forms of iron deficiency. The third stage is one of iron deficiency anemia.

Microcytic hypochromic anemia occurs on account of diminished hemoglobin synthesis. Non-hematological manifestations include koilonychia, dysphagia, glossitis and rarely raised intracranial tension.

Iron deficiency is one of the most widespread nutritional disorders present all over the world.

Prevention of iron deficiency Vulnerable groups of persons require prophylactic iron supplementation. These include premature infants, persons after upper gastrointestinal tract surgery, pregnant and lactating women, and those with chronic blood loss.

At the community level, iron deficiency can be prevented by fortifying food with iron. Several articles like bread and infant foods have been fortified in many countries. The Indian Council of Medical Research has suggested fortification of cooking salt with iron. Initial field trials are encouraging.

Siderosis

Siderosis denotes excessive accumulation of iron which is seen in persons who have excessive inputs of iron over prolonged periods. The iron is deposited in the liver, which may undergo fibrosis. Excessive dietary intake occurs in South African Bantus who ingest about 100 mg of iron derived from iron cooking and brewing pots. Iron overload can occur in persons having thalassemia, sickle cell disease or aplastic anemia, who are repeatedly transfused with blood (usually more than 100 transfusions). Iron absorption is very high in hemochromatosis and thalassemia. Elimination of iron can be enhanced by chelating agents such as desferrioxamine.

Note: Refer to the topics Nutritional anemias (ch. 150), hemochromatosis (ch. 93) and thalassemias (ch. 151).

Iodine

Iodine is widespread in nature and it is obtained especially from sea water, salt, sea fish, vegetables, drinking water, and milk. The daily requirement is about 150-250 µg. Adolescents and adults require about 150 mcg iodine daily. For pregnant and lactating women the requirement goes up to 200 mcg/day. Calcium retards absorption of iodine.

Iodine is concentrated by the thyroid gland for the formation of thyroid hormones. Though the diets of the majority of Indians supply adequate amounts of iodine, the iodine content of diet and water is low over vast areas on the globe and iodine deficiency goiters are widespread. More than 400 million people are affected in Asia alone. In India such goiter belts occur in the foothills of the Himalayas, several parts of north India and midlands and highlands of Kerala. In man and animals chronic iodine deficiency produces characteristic responses. A wide spectrum of iodine deficiency disorders are seen.

The importance of widespread iodine deficiency has been brought out by recent work. Several developmental disorders are prevalent among goitrous communities. Iodine deficiency is the single most important and prevalent cause of preventable brain damage. During pregnancy the fetus does not produce thyroxine during the first trimester and it is entirely dependent on maternal thyroxine. During the subsequent two trimesters it derives thyroxine from its own thyroid, and it is supplemented by maternal thyroxine. In endemic iodine-deficient areas the maternal and fetal thyroid function is subnormal. In mild cases it leads to mental retardation in the child. In severe cases neurological consequences such as spasticity, ataxia and deaf-mutism also develop. Provision of iodine supplements to the mother even in the latter half of pregnancy allays the ill effects in fetus. There is increased total mortality, abortion rates and congenital malformations in the endemic regions—all of which clear up with supplemental iodine.

Goitrous Cretinism

Goitrous cretinism is common in iodine deficiency areas. The thyroid gland hypertrophies under the influence of increased levels TSH, and tries to trap more iodine. Iodine turnover is faster. The urinary loss of iodide is reduced. The cretinism take two forms (1) neurological and (2) myxedematous. Prevention of iodine deficiency disorders has been achieved to some extent in India and other countries by fortification of common salt with potassium iodide at the rate of 60 p pm. It is estimated that with the introduction of this program the global population at risk of iodine deficiency has come down from 28.9 to 13.7% during the years from 1994 to 1997. The aim is to give 150 mcg iodine daily.

Another intervention is to give an annual injection of iodized oil intramuscularly to susceptible population at risk. Poppy seed oil and rapeseed oil have been used as vehicles. **Brassidol** which is derived from rapeseed oil contains 376 mg/mL of iodine. Early goiters will also recede with iodine supplementations.

Iodine induced hyperthyroidism (IIH) syn: Jod Basedow phenomenon. This is caused by the increased proliferation of thyrocytes, and increase in the mutation rates of the cells. This leads to hyperthyroidism.

Other adverse effects include the development autonomous thyroid nodules and possibly autoimmune thyroiditis.

Despite minor adverse effects, iodine supplementation has served to reduce iodine-deficiency disorders, especially brain dysfunction in the young. Strong political lobbies working against the 'universal iodisation of salt' programme have resulted in slowing the progress in this direction (See also Chapter 98).

Fluorine

Fluorine is present in small amounts in human bones and teeth. Fluoride is obtained from drinking water, tea and sea fish. Water sources are more important. Daily requirement is 1 to 2 mg. Fluoride is deposited in the enamel of developing teeth. Once the teeth are fully developed, fluoride is not further incorporated. Low levels of fluoride in drinking water are associated with higher prevalence of dental caries. In many countries addition of 1 ppm fluoride to drinking water has served to reduce the incidence of dental caries. Such a legislation does not exist in India. On the other hand in many parts of India, drinking water contains higher amounts of fluoride and this leads to fluorosis. Increase in the content of fluoride in drinking water above 100-150 mg/L gives rise to acute toxic symptoms consisting of nausea, vomiting, diarrhea, abdominal pain and paresthesia. Death may occur at times.

Note: Refer Section—Fluorosis.

Copper

Copper is widespread in all foods and hence dietary deficiency of copper is very rare. Copper is necessary for the proper formation of hemoglobin and several enzymes. Young children fed solely on milk formulas may develop copper deficiency. The main features include anemia, neutropenia, retardation of growth and rarefaction of bones.

Daily requirement is 2-3 mg. Meat, liver, shellfish, nuts seeds, legumes and whole grains contain copper. Copper takes part in the synthesis of hemoglobin in association with iron. It is an integral part of several oxidative enzymes.

Absorption and Metabolism

Copper is absorbed in the upper part of the small intestine and is transported into the epithelial cells through the medium of a copper transporting protein. The copper is incorporated into the intracellular enzymes such as superoxide dismutase, cytochrome oxidase and others.

Excess copper is fixed to the Golgi apparatus and eliminated when the epithelial cell is shed.

Copper reaches the hepatocytes, bound to albumin. In the hepatocytes copper is bound to ceruloplasmin and in this bound form copper circulates in blood. Excess copper, unbound to ceruloplasmin is excreted by the hepatocytes into bile. Both these processes are facilitated by the copper transporting protein.

Normal ceruloplasmin level in blood is 20-40 mg/dL. It is low in Wilson's disease in which the production is normal, but its degradation is accelerated. In Wilson's disease the levels of plasma ceruloplasmin are below 20 mg/dL. Normal level of hepatic copper is below 55 µg/g of dry weight. In Wilson's disease the hepatic copper level may exceed 250 µg/g. Other conditions in which ceruloplasmin levels are low include nutritional hypoproteinemia, nephrotic syndrome, hepatic diseases and congenital ceruloplasmin deficiency. The major regulating mechanism in copper homeostasis is the excretion of excess into bile, which is 1-2 mg/day.

Nutritional deficiency of copper may occur in premature infants, generalized malnutrition, malabsorption states, and prolonged parenteral nutrition. Nutritional supplementation is by giving copper sulphate 2-3 mg tds orally.

Reduction or absence of ceruloplasmin is a genetic abnormality which leads to Wilson's disease. Wilson's disease is an autosomal recessive disorder.

Menkes' disease is an X-linked disease affecting the copper metabolism. It is characterized by features resembling Ehlers-Danlos syndrome. Serum ceruloplasmin is low. Clinical features include mental retardation, abnormalities in bone formation, lability of temperature regulation, susceptibility to develop infections, cutis laxa and tendency to develop vascular rupture. Death occurs in early life.

Note: Refer to Wilsons' diseases. Chapters 93, 191.

Magnesium

(See also Chapter 72)

This is the fourth most abundant cation in the body, next only to sodium, potassium and calcium. It is the second most prevalent intracellular cation. The importance of magnesium in health and disease has been brought out by recent studies.

- Total body content
1000 mmol (22.6 g)
- Distribution
50-60% in bone
The rest is intracellular in all tissues
- Extracellular part 1%
- Serum levels 0.75-0.95 mmol/L
(i.e.) 1.7-2.2. mg/dL
- Dietary intake 300-350 mg/day

Absorption from gut is by passive diffusion.

The total body content is determined by the balance between intestinal absorption and urinary loss. It is absorbed by a process of passive diffusion, which is a self limiting process. The rate of absorption is inversely proportional to the intake.

Dietary sources include a wide range of foods, especially cereals, animal foods and water.

Functions of Magnesium

1. Integral part of several enzymes participating in ATP and DNA metabolism
2. Stabilization of cell membranes
3. Neural transmission
4. Stabilizing calcium channel activity

Both hypo- and hypermagnesemia cause adverse effects. The former is more common. These are described in Section 7.

Zinc

Zinc is present in many enzymes. Highest concentration occurs in the liver, voluntary muscle, bone, prostate, and ocular structures. Foods such as meat, fish, peas and cereals contain zinc. Daily requirement is not clearly known, but is around 15 mg. Dietary deficiency is very rare. Zinc deficiency leads to impairment of maturation and immunodeficiency. In malnourished subjects zinc deficiency may result in thymic atrophy. A syndrome of dwarfism and hypogonadism seen in Egypt and Iran has been attributed to zinc deficiency. Oral zinc sulphate corrected this clinical picture. Acrodermatitis enteropathica is an inherited disorder resulting from the malabsorption of zinc, probably due to an enzymic defect. Administration of zinc sulphate 30-150 mg/day results in complete remission. Oral zinc sulphate 100 mg/day has been found to stimulate the growth of granulation tissue in chronic ulcers. Oral supplementation of zinc 10 mg (5 mg) in children less than 1 year of age for 16 months reduced overall all-cause mortality by 7%. This study is being pursued.

Ref: Sazawal S, et al. The Lancet 2007;369:927-34.

Selenium

Selenium is a constituent of selenoproteins. It has structural and enzyme roles and it acts as an important antioxidant. It is a catalyst for the production of thyroid hormone. Other functions include: (1) proper functioning of the immune system, (2) sperm motility, (3) maintenance of proper mood and mental state, (4) resistance against cancer. Selenium retards the progress of AIDS. Daily

requirement is 400-450 µg/day. Dietary sources includes Brazil nuts, kidney, crab, liver, shellfish, fish, meat, poultry, wheat and some vegetables. In animal foods selenium is present as selenocystine. In vegetable sources it occurs as selenomethionine.

Probiotics and Prebiotics

Micro-organisms especially bacteria can be used to improve health. A bacterium which confers specific health benefits in addition to nutritional improvement is known as probiotic. Yoghurt and butter milk are examples. They contain lactobacilli such as *L. rhamnosus*, *L. reuteri*, *L. casei* and others which help to stop diarrhea, especially after rotavirus infection. Prebiotics are non-digestible food ingredients which selectively affect the gut flora and

Chapter Summary

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General Considerations

Increase in body weight of 10-20% above the normal, caused by excess accumulation of fat is termed obesity. Healthy young men and women have a total body fat content below 20 and 25% respectively. When excess calories are supplied in any form, they are stored as fat. In addition to general appearance and weight, measurement of skin fold thickness over the biceps, triceps, subscapular and suprailiac regions is helpful in the assessment of obesity. The skin fold thickness over the triceps for normal Indian subjects is below 20 mm. The proportion of body fat can be assessed from the skin fold thickness using nomograms. Obesity has become the sixth common cause for disease burden world wide. Adipose tissue in the body, in addition to its role as a source of stored energy, is emerging as an endocrine organ producing hormone and cytokines. In general the ideal weight of an individual should be (height in cm minus 100) kg .For example an adult male 175 cm tall should have a weight of 75 kg ± 5%.

Body Mass Index (BMI)

Body weight is only a crude indicator of obesity. A more reliable parameter is the BMI.

TABLE 33.1

Shows the recommended values		
Weight class	global	Asians
Normal	18.5-24.5	18.5-22.9
Over weight	25-29.9	23 – 24.9
Obese	> 30	>25
Severely obese	> 40	

$$BMI = \frac{\text{(Weight in Kg)}}{\text{(height in m}^2\text{)}}$$
 For Asians separate norms have been proposed (Table 33.1)

About 10% of the population in India is obese. Small community-based surveys done in several parts of the country give figures ranging from 17-38% BMI above 28 is associated with higher incidence of strokes, ischemic heart disease and diabetes mellitus. The distribution of fat deposition in the body is also important. For this purpose the circumference at the waist and the hip are taken as reference measurements. Waist is measured after an overnight fast at the mid point between the lower costal margin and iliac crest. Hip is the widest part over the gluteal region. Waist hip ratio above 1.0 in men and above 0.9 in women is an independent risk factor for higher incidence of insulin resistance, hypertension, rise in LDL, lower levels of HDL, hyperuricemia, cardiovascular disease, type 2 diabetes and stroke. Ideal waist to hip ratio is below 0.85 in men and 0.75 in women. The waist circumference above 102 cm (40³) is an independent risk factor. Abdominal obesity with accumulation of fat in the abdominal viscera is more associated with metabolic complications. The waist/hip ratio shows a graded and

highly significant direct relationship with the risk for myocardial infarction.

Etiology

1. *Excessive consumption of food* accounts for the vast majority. Training in early childhood and social factors influence eating habits. Both in anxiety and depression, excessive eating may be resorted to. It is not uncommon to develop obesity after recent bereavement or change of job. An increase of 0.5% in food consumption above the optimal caloric intake can lead to an annual rise in weight of 1 kg. Pregnancy and contraceptive pills tend to predispose to obesity. Persons show strong genetic predisposition to obesity and the amount of food leading to obesity varies widely between subjects. Therefore prescription of dietary management has also to be individualized.
2. *Hormonal and other factors* Obesity may be part of the clinical pictures of well-known endocrine disorders such as type 2 diabetes, hypothyroidism, Cushing's syndrome, gigantism, acromegaly, insulinomas and others. In addition several hormones regulate appetite and modulate intake of food and fat accumulation. Insulin and cholecystokinin acting on the central nervous system retard the appetite regulating mechanism.
3. *Genetic factors* do play a role. Metabolically, some individuals are more efficient in conserving energy and thus they put on fat, while others require more energy for the same amount of work performed. Moreover, obesity may run in families.

The role of leptins There is strong evidence that body fat is biologically regulated. Most cases of obesity probably reflect a multigenetic predisposition for excess intake of food, low level of physical activity and accumulation of excess amounts of fat. Leptin encoded by the *Lcp* gene is a cytokine-like molecule synthesized and secreted by adipose tissue in proportion to adipose tissue mass. It has several biological effects, an important one being reduction of food intake. Leptin deficiency leads to hyperphagia, obesity, and several endocrine abnormalities such as infertility, diabetes, reduction in metabolism, impairment of somatic growth and elevated levels of glucocorticoids. Leptin deficiency and resistance to leptin may be genetically determined.

Several other hormones also influence food intake and body weight. A gut hormone fragment *peptide-Y3-36* (*pYY*) reduces appetite by acting on the appetite centers in the hypothalamus.

Ghrelin is a hormone primarily secreted by the stomach and duodenum. Plasma ghrelin levels are higher before meals and their levels fall after meals. Ghrelin has been implicated in causing hunger at meal

times and also the long-term maintenance of body weight.

Drugs

Several drugs lead to weight gain. Prominent among them are antipsychotics, anti depressants anticonvulsants, oral contraceptives, progestogens, oral hypoglycemic agents, insulin, corticosteroids, beta adrenergic blockers, antihistamines and others.

Childhood obesity occurring below 3 years of age without parental obesity is not a risk factor for obesity in adulthood. On the other hand obesity which persists beyond 6 years of age it is a predictor of adult obesity irrespective of the parental status. Presence of obesity in the parents doubles the risk.

4. *Physical activity* which causes loss of calories is closely related to obesity. Modern amenities such as automobiles and lifts which tend to minimize day-to-day physical exertion favour the development of obesity. Obesity is more evident when there is a sudden cessation of physical activity. Eating habits are also influenced by physical work. Moderate work is associated with optimal food intake whereas both physical inactivity and overexertion lead to overeating.
5. *Alcohol* being a good source of non-diet calories tends to aggravate obesity in the mild and moderate alcoholics. Cessation of smoking leads to recovery of appetite and gain in weight.

Pathology Obese subjects have increase of both fat and non-fat mass. In obesity developing from childhood, there is probably increase in the number of fat cells and a generalized increase in adipose tissue.

In others there is hypertrophy of the fat cells. Distribution of obesity may be android (abdomen and shoulder predominantly) or gynoid (buttocks, thighs, breasts, arm and face predominantly). Obesity leads to impairment of carbohydrate tolerance, elevation of cholesterol level in blood, and mild elevation of blood pressure.

It predisposes to premature atherosclerosis. Obesity is associated with an absolute increase in energy expenditure, lower respiratory quotient and insulin-resistance. Though obese subjects have to spend more energy for the same amount of work done by their normal counterparts, they tend to restrict their physical activity further and accumulate more fat.

CLINICAL FEATURES

Middle-aged persons are more affected though no age is immune. Women outnumber men and the male to female ratio is 1:5. Multiparity is associated with increasing grades of obesity. The patient may not complain of her obesity on account of its gradual development and, therefore, it has to be identified

during general examination. Common symptoms include exertional dyspnea, sluggishness, angina, arthralgias of knees and hips, or any of the complications.

Complications These develop invariably in all cases depending on the severity and duration of the disorder.

1. *Ill effects of increased weight:* Slowness of movement, proneness to falls and accidents, osteoarthritis of weight-bearing joints like knees, hips, and spine.
2. *Skin:* Abnormal skin folds develop and these give rise to fungal infection (moniliasis), recurrent bacterial infections, and chafing of the skin of the thighs and axillae. In extreme obesity, striae may develop.
3. *Cardiovascular system:* Atherosclerosis, hypercholesterolemia, angina, ischemic heart disease, hypertension, varicose veins, venous thrombosis, and recurrent embolism. Increase of 10% of weight above the ideal weight leads to 30% rise in the risk of heart disease.
4. *Respiratory system:* Exertional dyspnea, reduction in vital capacity due to restriction of diaphragmatic movements and the increased mechanical effort required to move the thoracic cage, recurrent bronchitis, and in extreme cases, respiratory failure. 'Pickwickian syndrome' is the condition where obesity is associated with central depression of respiration and somnolence. Sleep apnea and the related complications are more common in them (Figs 33.1 and 33.2).
5. *Abdomen:* The skin over the anterior abdominal wall hangs down as a fold ("abdominal apron"). Hernias develop owing to the increase in the intra-abdominal pressure. Gallbladder lesions are more common.



Fig. 33.1: Nutritional obesity boy 18



Fig. 33.2: Morbid obesity: Woman aged 50 years

6. *Metabolic complications:* Diabetes mellitus, hyperlipidemias, gout, and cholesterol gallstones are more common.
7. *Psychological abnormalities:* Obese persons may develop depression because of their unattractive physical appearance and mechanical disability. They tend to avoid company and become socially isolated.
8. There is evidence that cancer of the colon, breast, uterus, ovaries and prostate may be more common in the obese.

Course and prognosis The condition is gradual in its progress. Complications increase the mortality in them. Mortality rate is 30% higher in persons 25-30% overweight and 50% higher in persons 35-40% overweight. Death is caused by cardiovascular, metabolic or respiratory complications. Obesity is an independent risk factor for higher mortality.

DIAGNOSIS

Clinical diagnosis is based on weight, physical appearance and measurement of skin fold thickness. Sophisticated methods are available to establish the diagnosis in a borderline case. Dual energy X-ray absorptiometry (DEXA) imaging gives a reliable assessment of the adipose tissue mass.

Increase in weight occurring during pregnancy, fluid retention, hypothyroidism, hypothalamic lesions, and other endocrine disturbances should be differentiated from obesity due to nutritional causes. So also overweight may be caused by excessive muscular development in wrestlers, weight-lifters and boxers. Estimation of BMI, and the waist to hip ratio help to assess the risk of complications further. The aim of management is to reduce weight, achieve metabolic and physical fitness, reduce morbidity and achieve cosmetic results. A negative

TABLE 33.2

Subcaloric diet for obesity for adults with moderate activity. Total allowances for a day are given				
Article of food	Vegetarian	Cal.	Non-vegetarian	Cal.
Cereals	150 g	600	150 g	600
Dal or lentils	50 g	200	20 g	80
Fish or lean meat not cooked in oil or fats	—	—	100 g	250
Milk or curd in any form	300 mL	180	100 mL	60
Green vegetables	150 g	80	150 g	80
Fruits: very sweet fruits like grapes, and mangoes, are to be avoided. Papaya, melon, small bananas, guava, and apples, are preferable	150 g	80	150 g	80
Total Calories		1140		1150
Note: 1. Sugar, sweets, honey and similar high-caloric articles of food and alcohol are to be strictly avoided. 2. Timing of the diet and the menu should be adjusted to conform to the occupation and dietary habits of the individual. 3. When the optimum weight reduction has been achieved, graded increases in the diet can be made under supervision, taking care not to restore the original weight and to ensure balanced nutrition.				

balance of 8000-9000 calories has to be achieved to clear 1 kg of adipose tissue.

Treatment

Dietary Regulation

Strong motivation of the patient is absolutely essential for successful management. Dietary regulation is the basis of modern therapy. Calorie intake should be reduced below the basal requirements and the patient has to be kept on negative energy balance over prolonged periods of time. The excess fat is catabolized and weight is lost.

The therapeutic diet should contain 500-1000 Cals less than the energy expenditure of the individual. An ideal weight reducing diet should be:

1. Deficient in calories
2. Otherwise nutritionally adequate, and
3. Acceptable socio-culturally.
4. The diet should be suitably timed to avoid long intervals between eating (Table 33.2).

Since dietary fats account for the palatability of food and they provide the maximum amount of calories the first step should be to cut fat intake to the maximum. This is the most effective single step to bring down weight rapidly in the initial stages. Young and tall subjects lose weight more efficiently than older and shorter people. On an average, daily intake has to be limited to 800-1000 calories. More drastic cuts on foods are frequently resented and result in non-compliance. For optimal results the diet should be acceptable, sufficient in volume and conforming to the general eating habits of the individual.

Bulk is provided by adding moderate amounts of fresh vegetables (not curried) and low-calorie fruits. Vegetables when made into curries with coconut, oil, dhal and condiments become very rich in calories. Clear instructions on the exact quantity of food and its timing are very essential. Regular follow-up is necessary for proper motivation and assessment. Patients put on the sub-calorie diets lose weight steadily after an initial latent period ranging from days to weeks. It is ideal to reduce the weight by 1 kg a week. Vitamin and mineral supplementation is advisable, since the restricted diet may fail to meet these requirements.

Obese persons do not generally comply with diets. The low caloric diet should be maintained indefinitely since the tendency to regain weight persists. Strong motivation of the patient is needed to achieve good results. Initial motivation to reduce weight may be easy, but persistent efforts to maintain the ideal weight are generally slackened and so a major proportion of patients regain their weight and may even overshoot the original levels. Even moderate reduction in weight such as 6-10% of the body weight is accompanied by reduction in metabolic risks and blood pressure.

Exercise Moderate exercise augments the beneficial effect of dieting. Walking slowly up to 4-5 km, day, swimming, or games are ideal, depending upon individual preferences. Prescription of the exercise regime should take into account the cardiovascular status and exercise tolerance of the patient. Preferably it should be supervised by trained staff.

Drugs Several drugs are available which reduce appetite. These anorectic drugs have been employed on short-term basis when the patient is not able to resist the desire to eat. Drugs may be needed when the BMI exceeds 30. Sympathomimetic drugs with amphetamine-like action reduce appetite and increase energy expenditure. These are contraindicated in persons with cardiovascular disease. Serotonin reuptake inhibitors are good appetite suppressants. Fenfluramine and fenoxetone can be given on a short-term basis over weeks to a few months. When given over prolonged periods they may lead to the development of primary pulmonary hypertension. Acquired defects of the mitral and aortic valves may also develop. Dose Fenfluramine 20-120 mg twice a day given orally one hour before meals. Since these drugs cause dependence, they should preferably be withdrawn after 3 months of administration. Side effects include dryness of the mouth, abdominal pain, drowsiness, alopecia, mental depression, confusion and impotence. These drugs are contraindicated in patients with psychiatric illness.

Sibutramine is an appetite suppressant which can be given in doses of 5-15 mg once a day. It produces loss of weight by reducing appetite and increasing energy expenditure. Side effects include dryness of mouth insomnia and constipation. Sibutramine should not be given to patients with ischemic heart disease heart failure, arrhythmia and stroke. Sibutramine leads to a mean weight loss of 4-5 kg.

Orlistat: It is a lipase inhibitor which prevents absorption of dietary fat. The dose is 120 mg t.i.d.

Side effects include flatulence, fecal urgency, and malabsorption of fat soluble vitamins. Orlistat leads to a mean weight loss of 3 kg.

Rimonabant is an endocannabinoid receptor antagonist. The dose is 20 mg given orally daily. It reduces body weight on an average of 4-5 kg. It improves the metabolic syndrome as well. Adverse effects include nausea dizziness, diarrhea and depression. When obesity is extreme and rapid weight reduction is desired, more

drastic measures are employed. These include total starvation programmes and surgical procedures.

Total starvation This can be undertaken under strict medical supervision for 2-3 weeks. Only water, salts and vitamins are allowed during this period. Complications include starvation ketosis, ventricular arrhythmias and sudden death. Due to these risks, total starvation should be undertaken only under exceptional circumstances. Wiring of the jaw to prevent ingestion of solid foods has been practised on persons unable to undertake starvation. Rapid weight loss is achieved by total starvation. Follow-up treatment consists of sub-caloric feeding.

Surgical measures Surgical measures done to produce short-circuiting of digestive and absorptive portions of the intestines may be required for severe cases. The procedures include jejuno-ileal bypass and gastric bypass. Gastric plication may be done with a view to reduce the capacity of the stomach. Extirpation of excessive fat and plastic surgical procedures to remove redundant skin folds remaining after achieving weight loss help to correct cosmetic disability and also to augment the effects of dietary treatment. Liposuction is a surgical technique which removes large amounts of fat from localized areas such as the abdomen, gluteal regions, breasts, arms and face. This procedure is gaining popularity, being safe and cosmetically rewarding. The surgical management of obesity, as a part of cosmetic surgery is known as *bariatric surgery*.

In general, loss of weight up to 5-10 kg is easy but further reduction and maintenance of the optimal weight demand great motivation on the part of the patient and skill on the part of the physician. Once the optimum weight is reached, the patient should slowly increase the diet to prevent further weight loss, and try to adhere to the optimum weight. Even an occasional dietary excess results in rapid weight gain. All the complications of obesity can be arrested and may even regress if normal weight is maintained for long periods. Secondary obesity should be treated by adopting dietary measures and giving due attention to the primary cause.

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34

Infections:
General Considerations

S. Bhasi

6

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INTRODUCTION

Microbes are abundant in nature, the vast majority of them harmless to man and many of them essential to life. They are mostly commensals and a few are pathogens. The organisms capable of establishing themselves and multiplying in hosts are called parasites, which may be commensals or pathogens. All our body surfaces have an indigenous bacterial flora. This normal flora protects us from infection by multiple mechanisms 1, compete with pathogens in utilizing nutrients. 2, producing antibacterial substances inhibiting growth of pathogens. 3, inducing host immunity that is cross reactive and effective against pathogens (Table 34.1).

Pathogens lead to adverse effects on hosts while commensals cause no harm to their hosts and exist in harmony. Commensals may cause disease when host resistance is lost or when transferred to an inappropriate site, e.g. oropharyngeal commensals aspirated into lung.

TABLE 34.1

Gives the approximate bacterial count in the human body

Skin general	10 ³ /g
Skin groin/axilla	10 ⁶ /g
Bile, liver	nil
Stomach	10 ³ /mL
Small intestine	10 ⁴ /mL
Large intestine	10 ¹⁰ /mL
Lungs	nil
Nasal secretions	10 ⁵ /mL
Saliva	10 ⁸ /mL
Urine	10 ³ /mL

Infection: Infection is defined as multiplication of microbes in the tissues of the host with or without producing disease. Infections without disease manifestations are called subclinical infections.

Infections remain one of the main causes of morbidity and mortality in man worldwide. Poverty and overcrowding in the underdeveloped countries increase this burden.

Infectious agents include bacteria, viruses, fungi, protozoa, helminths and prions.

Types of Infections

1. *Exogenous infections:* Infection from external source.
2. *Endogenous infection:* Infection by organisms harbored by the individual.
3. *Primary infection:* Initial infection of a host by an organism.
4. *Secondary infection:* Host suffering from an infectious disease invaded by another organism.
5. *Re-infection:* Subsequent infection by same organism.
6. *Focal infection:* Infections confined to one area/organ e.g. Tonsillitis.
7. *Nosocomial infection:* Infection acquired after admission to hospital.
8. *Super infection:* Patient receiving broad spectrum antibiotics get colonized by resistant pathogens and infection produced by them.
9. *Opportunistic infection:* Organisms that ordinarily do not cause infection in healthy individuals but do so in individuals with markedly reduced resistance (Immunocompromised hosts).
10. *Latent infection:* Pathogen remains in the tissue without producing disease but may lead to disease when host resistance is lowered.

Source of infection: Infection may be obtained from human, animal or other sources. When the source of infection is man, the infectious agent may originate from patients or carriers.

A carrier who harbours the pathogenic organism without developing any disease due to it, is called *healthy carrier*.

A **convalescent carrier** is one who harbours the organism for some period after recovering from the disease.

Zoonoses are infections transmitted from wild or domestic animals to man e.g. plague, rabies.

Some infections are transmitted by insect vectors e.g. Anopheles mosquito transmits malaria.

Direct contact is necessary for transmission of organism like *Staphylococci*. Respiratory diseases such as influenza, tuberculosis, pneumonia and others spread by air-borne droplets. Food or Water borne transmission occurs in typhoid, hepatitis A and E, cholera and others. Sexual transmission is the main route for syphilis, gonorrhea and HIV. *Vertical transmission* i.e. from mother to fetus occurs in diseases like rubella and syphilis.

PATHOGENESIS

The pathological lesions, symptoms and signs may be produced by several mechanisms:

1. Caused by the organism directly e.g. Boils, abscesses, pneumonia, dysentery, tuberculosis.
2. Organisms like *C. diphtheriae* and *Cl. tetani* multiply locally without entering the system and elaborate toxins (exotoxins) which are absorbed into the system producing the manifestations.
3. *Vibrio cholerae* elaborates an exotoxin having local effect on the intestinal mucosa producing secretory diarrhea.
4. Many gram negative bacteria produce endotoxins by disintegration in the tissues producing direct effect on tissues and liberation of chemical mediators of inflammation like cytokines which are mainly responsible for the manifestations.
5. Activation of immunological mechanism is one of the most important pathogenic mechanisms of tissue damage in several infections.
6. Infections like HIV and syphilis suppress the immune mechanism of the host by acting upon the lymphocytes.
7. Some infectious agents are oncogenic i.e. giving rise to tumours- e.g. HIV, EB virus, hepatitis B and others. Medical care itself increases the patient's risk of acquiring infection in several ways:
 1. Contact with pathogens in the hospital.
 2. Breach of skin (e.g. incisions, IV devices) or mucous membranes (e.g. endotracheal tube, indwelling catheter).
 3. Alteration of normal flora by antibiotics.
 4. Reduction of immunity by immunosuppressive drugs.

The body's mechanisms to prevent and overcome the infections are local defenses, phagocytic cells, antibodies (immunoglobulins), immunocytes and nonspecific defense aids such as lysozymes, complement and properdin.

Changing scenario of infection worldwide: The pattern of infectious agents and pathogenesis are changing due to several factors such as changes in environment, influence of polymicrobial therapy and alterations in host defences.

Newly recognized infections are AIDS, severe acute respiratory distress syndrome (SARS), avian influenza and others.

Rebound of diseases like, malaria, tuberculosis, rheumatic fever and others thought to have been eradicated from developed countries.

Recognition of role of infectious agents in the causation of diseases previously thought to be non-infectious e.g. *Helicobacter pylori* in the causation of peptic ulcer, *Human papilloma virus* in carcinoma cervix.

Human Polymicrobial Infections

In the immunocompetent state, colonization by one organism inhibits colonization by another. This is known as microbial interference e.g. *S. pneumonia* and *S. aureus*.

At present, due to the prevalence of different kinds of immunosuppressed states, polymicrobial disease caused by combination of viruses, bacteria, fungi and parasites are being recognized. In this situation, presence of one micro-organism causes a niche for the other pathogen to colonize and thrive e.g. measles, tuberculosis and *S. aureus*; EB virus and retrovirus; HBV and HIV; HIV and tuberculosis.

Immunodeficiency states may be congenital or acquired. The latter include malnutrition, extremes of age, loss of surface epithelium, diabetes mellitus, cancer, cancer chemotherapy, chronic renal failure, chronic hepatic failure, immunosuppressant drugs, HIV infection and others. The resultant degree of immune suppression is the total effect of all the contributory factors.

Immunodeficiency may be general or specific towards specific pathogens. Neutropenia and reduction of other phagocyte cells predispose to infection by extra cellular bacterial pathogens, both endogenous and exogenous. Suppression of T-cell mediated immunity predisposes to viral infections. Multiple intubations, hospitalization and management in intensive care facilities predispose to infections.

Clinical features of infection in the immunocompromised host differ from those in immunocompetent hosts. Signs of infection in the immunocompromised hosts include:

1. confusion
2. faint erythematous rashes
3. lymphangiectatic streaks on the skin
4. pleurisy dyspnoea or cough with clear chest X-ray
5. minimal erythema with serosanguineous discharge at sites of insertion of catheters, surgical sites, abscess or drains

Diseases Caused by Infections

- 6. minimally elevated values of liver function tests, and serum levels of LDH (lactic dehydrogenase) and C K (Creatine kinase) and
- 7. unexplained rise or fall of leukocytes and platelet counts.

Antimicrobial resistance: As we developed newer antimicrobial drugs, microbes developed the ability to elude our best weapon. Antibiotic resistance is developing at an alarming rate. Multidrug resistant pathogens such as *E. coli*, *Klebsiella*, *Pseudomonas*, *Staph. aureus*, *M. tuberculosis*, HIV, and others are extremely common. Especially in the ICUs these get disseminated.

Biotorrism: Use of biological infectious agents such as anthrax spores, plague, small pox and others may be resorted to as potential weapons for stealthy warfare.

Eradication of infectious diseases like smallpox totally from the world and polio from most countries has been achieved.

General Symptomatology

Fever

Fever is perhaps the most common manifestation of ill health due to infection. It is an early and non-specific body response to many infectious and non-infectious causes. In humans, metabolic processes are critically temperature dependent. In a healthy individual, body temperature is kept constant around 37°C within a very small range despite larger difference in surrounding temperature.

Normal Temperature

In healthy individuals, normal body temperature varies from 36.6 to 37.2°C, usually 98.4°F (36.9°C). The normal diurnal variation is approximately 1°F with maximum between 4. 00 pm and 8.00 pm and minimum between 2.00 am and 6.00 am. In fever this variation is exaggerated. In old age, body temperature may be lower due to low metabolic rate. Women in the reproductive period show elevation of body temperature 24 to 48 hours after ovulation due to increased progesterone level. Temperature may also increase after exercise if normal heat loss is prevented.

Recording of Temperature

In all conscious, co-operative adults and older children oral temperature is ideal for clinical use. Equilibrium time with mercury- in -glass thermometer is a minimum of 90 seconds. Axillary temperatures are less reliable since they are considerably altered by environmental factors. On an average axillary temperature is 0.3 to 0.6°C (0. 5 to 1°F) less than oral temperature. Temperature of the inner tissues and viscera (core temperature) is about 0.6°C (1°F) higher

than oral temperature. Rectal temperature represents the core temperature. Rectal temperature has to be used in unconscious patients, undergoing intensive care and during major surgery.

Definitions

Normal temperature	37°C (98.4°F)
Fever	>37.2°C
Hyperpyrexia	>41.5°C
Subnormal temperature	< 36.6°C
Hypothermia	< 34.4°C
Note: 1°C = 1.8°F	0°C corresponds to 32°F
C-centigrade	F- Fahrenheit
also called Celsius	

Regulation of Body Temperature

Temperature is regulated by thermoregulatory center in the hypothalamus, which receives information from cold and warm receptors of peripheral nerves and temperature of blood perfusing the area. Heat is produced by metabolic process and muscular activity. Normal heat production by metabolic processes is in excess than is necessary to maintain body temperature and the same is dissipated by heat loss through lungs and skin. Rapid rise in temperature is effected by increasing metabolism, rapid muscle contractions (rigor) and conserving heat by peripheral vasoconstriction. Heat loss by radiation convection and conduction from the surface is slow. Rapid loss of heat is achieved by evaporation of sweat. Presence of cold extremities and rigor preced rapid rise of temperature. Diaphoresis (excessive sweating) accompanies rapid fall of temperature.

Fever is defined as the elevation of body temperature above normal (37°C). This occurs as a result of increase in hypothalamic “set point” for temperature. Once hypothalamic set point is raised neurones in the vasomotor center are stimulated leading to peripheral vasoconstriction especially in the limbs, leading to decrease in heat loss from the skin. The person feels cold. Metabolic processes being slow, they elevate body temperature only gradually, but steadily. If there is need for rapid increase in temperature, shivering occurs. Due to vigorous muscle contraction with rapid heat production temperature rises sharply. When hypothalamic set point is re-set downwards (either by reduction in pyrogen concentration or by antipyretics) heat loss occurs by vasodilatation and sweating. Exposure of the body to the environment, leads to dissipation of heat.

In the vast majority of febrile states, temperature does not exceed 104 to 105°F (40°C).

Hyperpyrexia

This denotes temperatures above 41.5°C (107°F). This may complicate conditions such as malaria, septicemia

heat stroke, pontine hemorrhage and others. The term hyperthermia is at times used synonymously with hyperpyrexia but in general the former denotes elevation of body temperature caused by endogenous heat production combined with exposure to high environmental temperature: e.g. work or exercise in a hot environment, over insulating clothing, thyrotoxic crisis, heat stroke and neuroleptic malignant syndrome produced by drugs like phenothiazines. Uncontrolled increase in heat production far in excess of the body's ability to dissipate heat leads to hyperpyrexia.

Once the body temperature rises above 41°C, the thermoregulatory mechanism fails and the body behaves like poikilothermic organism. Unless managed as an emergency to lower the temperature, hyperpyrexia is fatal due to damage to vital cells.

Pathogenesis of Fever

Pyrogens are substances causing fever. These may be exogenous or endogenous. Exogenous pyrogens are molecules which interact with host cells to induce secretion of pyrogenic cytokines. Most of these are microbial products, microbial toxins or whole micro-organisms. The best example is the lipopolysaccharide endotoxin found in the cell wall of gram-negative bacteria. Enterotoxin of *S. aureus* and Group A and B streptococci are other examples. Endogenous pyrogens are cytokines which are small molecular weight proteins most important being interleukin.1 (IL-1), IL-2 and tumour necrosis factor alpha (TNF α). The synthesis and release of pyrogenic cytokines are induced by a wide spectrum of exogenous pyrogens most of which are of bacterial, fungal or viral origin. In addition, inflammation, trauma, tissue necrosis and antigen-antibody complexes induce production of pyrogenic cytokines. Main source of pyrogenic cytokines are monocytes and macrophages, and to a lesser extent neutrophils and lymphocytes.

Pyrogenic cytokines stimulate production of the prostaglandin – PGE₂ from arachidonic acid near the hypothalamic thermoregulatory centre. Arachidonic acid is released from cell membrane by the enzyme – Phospholipase A2. PGE₂ raises the set point in the thermoregulatory center. Pyrogenic cytokines also induce production of PGE₂ in the periphery which is responsible for myalgia, arthralgia and malaise that accompany fever.

Fever as a Defense Adaptation

There is suggestive evidence that, for some microorganisms at least, a febrile host response may assist in curtailing infection and speedy recovery. Experimental data support the notion that raised body temperature interferes with growth and / or virulence factors of some bacterial and viral pathogens. Fever, slightly increases

immune reaction and increases chemotactic, phagocytic and bactericidal activity of polymorphonuclear leukocytes. In immunocompromised individuals and those at the extremes of age, a prompt febrile response may not develop even in the presence of severe infection. Such persons are at greater risk of succumbing to the infection.

Systemic Responses in Fever

- **Increase in metabolic rate** - Oxygen consumption increases by 13% for each 1°C rise of temperature. Hence fever may aggravate or precipitate pre-existing cardiac, cerebrovascular or pulmonary insufficiency.
- **Increase in heart rate.** For every 1°C rise of temperature above normal, the heart rate increases by 18/minute. In some fevers like pneumonia and rheumatic fever, heart rate may be disproportionately high (*rapid pulse fever*). In typhoid, some viral infections, meningitis, brucellosis, drug induced fever and many cases of leptospirosis; pulse rate may be disproportionately slow (*slow pulse fever*).
- **Blood pressure** may increase during the period of rise of temperature because of vasoconstriction and decrease during the period of defervescence because of vasodilation.
- **Fluid loss increases** due to evaporation and sweating—average of 360 mL excess fluid is required for 24 hours for 1°C rise in temperature.
- **Increase in respiratory rate** occurs with fever. The usual ratio of 1:4 with heart rate is maintained except in the case of primary respiratory diseases such as pneumonia and pleural effusion.
- **Chills occur** in the initial phase because of peripheral vasoconstriction.
- **Rigors** accompany rapid increase in temperature. They are due to vigorous muscle contractions. Repeated occurrence of rigor is most typically seen in malaria, filariasis, urinary tract infections, and abscess formation anywhere in the body. Rigor may occur in many types of continuous fever treated intermittently with antipyretics. When the effect of the drug wanes off rigor occurs in an attempt on the part of the body to resume the high temperature.
- When the high temperature falls to normal or subnormal within a few hours, it is called **Fall by Crisis**, and when the temperature reaches normal slowly over several days, it is called **Fall by Lysis**.
- **Headache** may accompany any type of fever but severe headache and photophobia are characteristic prominent features of intracranial infections and sinusitis.
- **Delirium** – This is toxic confusional state. It is more common in the very young and very old. Fever may induce mental changes in those with organic brain syndrome. The cytokines TNF α and IL-1 cause release

of endorphins in the brain and may precipitate delirium.

- **Excessive sweating** is the regular accompaniment of defervescence. Particular patterns of sweating like “night sweats” are characteristic of tuberculosis and lymphoma. In almost all fevers fall of temperature is accompanied by sweating.
- **Muscle pain** – (*myalgia*) is characteristic of infections such as influenza, enterovirus, dengue fever, leptospirosis and others.
- **Herpes labialis** - Fever may activate the latent viral infection *Herpes simplex* which causes vesicles at muco-cutaneous junctions of the nose and lips. Pneumonia and meningitis are common to produce Herpes labialis whereas typhoid is very rare to do so.
- **Feverishness**: This is a subjective feeling of fever which may be experienced even without rise in temperature. Feverishness has not got the same pathological importance of fever. Therefore it is essential to record the temperature to distinguish between the two conditions.

Approach to a Patient with Fever

In the diagnosis of the cause of fever, science and art of Medicine come together. History is most important. History of travel to a malaria - endemic area may give a clue. Presence of nasal symptoms and sore throat suggest viral etiology. Severe myalgia may suggest Influenza, Dengue fever or Leptospirosis. Eye congestion, sub-conjunctival hemorrhage and muscle tenderness may suggest leptospirosis. Skin rashes and mucous membrane lesions give diagnostic clue. Erythematous blanching rash indicates viral exanthematous fever as the most likely cause. Palatal petechiae along with posterior cervical lymphadenopathy and grey white tonsillar exudate suggests infectious mononucleosis. Enlarged tender tonsillar lymph nodes with tonsillar exudate and neutrophilic leukocytosis suggest streptococcal tonsillitis. *Koplik's spots* in the buccal mucosa indicate measles. Dysuria and loin pain with tenderness suggests pyelonephritis.

Duration of Fever: This is an important point which helps in clinical diagnosis. Regular recording of temperature, pulse rate and respiration rate are routinely done in all hospitals. Fever of more than 5 to 7 days with gastro intestinal symptoms with or without malena and just palpable soft spleen may suggest typhoid fever. Onset may be abrupt in infections like pneumonia or may show a step-ladder type of rise in typhoid. Fever with clubbing of fingers and splinter hemorrhages in the nail bed in a patient with congenital or rheumatic valvular heart disease should suggest infective endocarditis.

Patterns of Fever: Recording the pattern of temperature is an important clinical clue to diagnosis. In the ordinary febrile patient, temperature is recorded thrice daily, but in special cases where large fluctuations occur and in acute care settings temperature has to be recorded more frequently.

Continuous Fever (Fig. 34.1) Temperature is persistently elevated with diurnal variation of less than 1°C e.g. Typhoid in the 2nd week, typhus, viral infections and others.

Remittent Fever – Temperature is persistently elevated with diurnal variation more than 1°C – typhoid in 1st week, brucellosis, leptospirosis and others.

Intermittent Fever – Temperature is discontinuous, touching normal at least once in 24 hours. This may be seen in pyogenic infections, lymphomas, tuberculosis, bacteremias, malaria and others.

Periodic Fever: These show a regular periodicity in their occurrence. Fever occurring on alternate days with one day interval in between is called *tertian periodicity* e.g. vivax malaria (benign tertian). Fever occurring every 4th day with 2 days' afebrile period in between is known as *quartan periodicity* e.g. quartan malaria. Continuous and remittent fevers may be converted to intermittent fever by repeated doses of antipyretics.

Drug Induced Fever Several drugs can produce fever by various mechanisms. These includes allergy, systemic metabolic effects and agranulocytosis. Drug induced fever becomes a diagnostic problem in patients receiving multiple drugs for long periods, especially in hospitals.

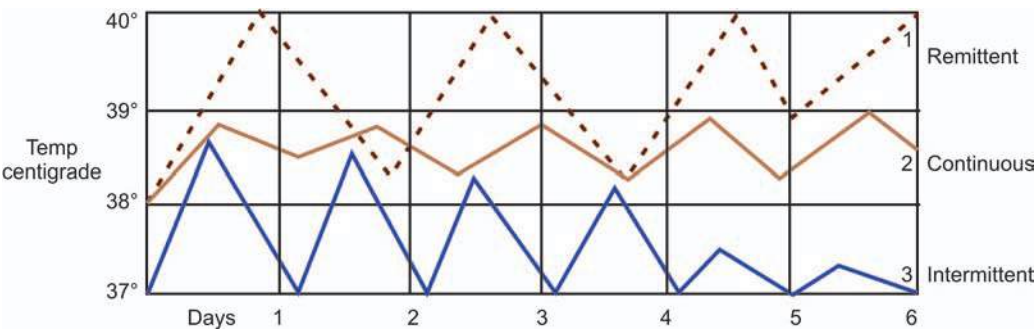


Fig. 34.1: Patterns of fever

Of the medications that cause fever, antibiotics are the most frequent—especially penicillins and cephalosporins, sulfonamides, nitrofurantoin, antituberculosis agents and others. Antiepileptic drugs especially phenytoin are also known to cause fever. Drug induced fever does not have specific characteristic features. Most often, it occurs 5 to 10 days after starting the drug, but can occur even after the first dose itself.

Laboratory Investigations

Leukocyte Patterns

Neutrophil Leukocytosis and presence of juvenile or band forms of neutrophils and toxic granulations in neutrophils usually suggest bacterial infections. The severity of leukocytosis may also indicate the severity of sepsis. Total leukocyte counts above 10,000/cmm with more than 70% as neutrophils are very suggestive of pyogenic infection. Leukemoid reaction may accompany severe leukocytosis.

Neutropenia, mild to moderate, is usually seen in many viral infections, about 25%, of typhoid, brucellosis, leishmaniasis, tuberculosis, histoplasmosis and others.

Leukopenia with relative or absolute *lymphocytosis* occurs in several viral infections. Many viral infections show moderate or even severe thrombocytopenia with or without bleeding manifestations.

Atypical lymphocytes – are seen in some viral infections especially Epstein–Barr virus, cytomegalo virus, HIV, dengue, rubella, viral hepatitis, varicella and others.

Monocytosis is commonly seen in typhoid and tuberculosis.

Eosinophilia: Occurs in parasitic infections, filariasis, tropical pulmonary eosinophilia and hypersensitivity to drugs.

1. *Isolation or identification of the infective agent* in blood/urine/body fluids/pus and tissues specimens
 - a. *Culture*: Proper collection of sample without contamination and transport to the lab is important e.g. blood culture in sepsis, urine culture in UTI, CSF in meningitis, sputum in pneumonia, pus in abscess.
 - b. *Gram stain* of specimen may help e.g. sputum, CSF, pus, urethral discharge and others. The findings on gram stain should correspond to the results of culture, to be diagnostic.
 - c. *Demonstration of parasites* like malaria and microfilaria in blood, leishmania in bone marrow and liver biopsy specimens, vegetative amoeba in stool or scrapings from abscess wall.
2. *Demonstration of antibodies to specific pathogen* e.g. Widal in typhoid, IgM antibodies against many viruses like hepatitis A, E and dengue virus.
3. *Detection of bacterial/fungal/viral antigens* in blood/body fluids even when cultures are negative or practically difficult e.g. HBsAg in virus B hepatitis.
4. *Detection of very minute quantities of foreign nucleic acid* by techniques such as PCR (polymerase chain reaction) that allow amplification of specific DNA/RNA sequences.
5. *Histopathology*: e.g. tuberculosis, histoplasmosis, sarcoidosis and others can be diagnosed by biopsy of lymph node, liver and other organs.

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Fever of Unknown Origin (FUO)

S. Bhasi

Chapter Summary

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Syn: Pyrexia of Unknown Origin (PUO)

FUO is the term used to denote fever that does not resolve spontaneously in the period expected for self limited infections and whose cause could not be ascertained even after reasonable investigations.

Diseases Caused by Infections

This presents one of the most difficult diagnostic problems in Medicine. Atypical presentations of common illnesses are responsible for majority of such cases.

Definition

FUO was defined by Petersdorf and Beeson in 1961 as temperature $> 38.3^{\circ}\text{C}$ (101°F), lasting for more than 3 weeks and failure to reach a diagnosis, even after 1 week of inpatient investigations. A subsequent definition in 2003 stated that failure to get a diagnosis after 3 days of inpatient investigations or three outpatient visits should qualify for the term FUO.

Etiology

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A. Infections: 30–50% are caused by infections. These include the following:

1. **Occult tuberculosis:** Extrapulmonary tuberculosis affecting the lymph nodes, intestines, mesentery, vertebrae, joints, liver, pleura, pericardium, and genital organs may remain latent without any local symptoms; but causing fever. The local lesion may become evident only after several weeks or months.
2. **Intra-abdominal infections:** Renal, retroperitoneal paraspinal, subdiaphragmatic, and pelvic abscesses may remain silent and cause diagnostic problems. Complicated urinary tract infection and infections of the biliary tree may also present as FUO.
3. **Other infections:** Infective endocarditis, brucellosis osteomyelitis, dental and sinus infections, enteric fever with atypical presentation, malaria, amebiasis, syphilis, leprosy, leishmaniasis and prostatitis may present as FUO.
4. **Viral infections:** Infectious mononucleosis and cytomegalovirus infection may present as FUO.
5. **Fungal infections:** Examples are histoplasmosis and cryptococcosis.

B. Malignancy: These form about 20% Leading malignancies presenting as FUO are:

1. Leukemias, lymphomas and multiple myeloma
2. Solid tumours like renal cell carcinoma, liver, colon stomach and pancreatic cancers.

C. Connective Tissue Diseases (About 15%): SLE, rheumatoid arthritis, rheumatic fever, polyarteritis nodosa, temporal arteritis, polymyalgia rheumatica, Wegener's granulomatosis, adult Still's disease and others.

D. Miscellaneous (About 20%): Inflammatory bowel disease, cirrhosis of the liver, granulomatous hepatitis, sarcoidosis, atrial myxoma, thyroiditis, thyrotoxicosis, drug reactions, hemolytic anemias, hematomas, deep vein thrombosis (DVT) and pulmonary embolism.

Undiagnosed: About 15 % may remain undiagnosed.

Factitious fever: This is elevation of temperature, self induced by patients with psychological problems – mostly young women working in health profession. They may induce disease or may devise methods to make the thermometer record higher temperature even when they are normal.

Nosocomial FUO: This term denotes fever above 38.3°C , (101°F) lasting for more than 72 hours, developing in a patient who is afebrile on admission to hospital. Most common causes are pneumonia, urinary tract infection, catheter related infections, *Clostridium difficile* colitis, *Cytomegalovirus* infection, sinusitis, septic thrombophlebitis and pulmonary embolism.

Neutropenic FUO: This is fever more than 38.3°C (101°F) lasting for more than 72 hours in a patient with absolute neutrophil count less than 500/cmm or expected to reach that level in 1-2 days. Most commonly this is produced by bacterial infections – bacteremias, pneumonia and soft tissue infections. Infection of the perianal area is also common. If neutropenia is prolonged, fungal and viral infections also supervene.

Human immunodeficiency virus (HIV) associated FUO: Fever is a common accompaniment of HIV infection when it leads to immunodeficiency. The most common infective agents are *Mycobacterium tuberculosis*, *Mycobacterium avium* complex, *Pneumocystis carinii*, disseminated cryptococcosis, toxoplasmosis and nocardiosis. Uncomplicated HIV infection itself can be the cause of prolonged fever.

DIAGNOSTIC APPROACH TO FUOS

Careful attention to history and a complete physical examination, repeated when necessary may reveal the etiology in many. Enquire about possible recent exposure to sexually transmitted disease, injected illicit drug use, which may predispose to hepatitis B and C, HIV, and infective endocarditis. Travel history may give a clue Occupational history may be significant and give evidence of exposure to birds (psittacosis) or animals (toxoplasmosis, brucellosis). Examination ocular fundi may reveal etiological clues – Roth spots in infective endocarditis, choroid tubercles in miliary tuberculosis and CMV retinitis. It is important to reassess the patient clinically at regular intervals. Look carefully for skin rash, skin nodules, conjunctival petechiae, clubbing and splinter hemorrhage. Digital rectal examination may suggest the cause occasionally – perianal disease suggest inflammatory bowel disease, local sepsis and abscess, rectal carcinoma, prostatitis, prostatic malignancy.

Even though the first clinical examination may be negative, repetition at weekly intervals or (shorter) will

bring out diagnostic clues and therefore this is an important diagnostic procedure.

Investigations: Investigations must be individualised based on the most probable suspected diagnosis. Differential diagnosis will depend upon the geographical area, age of the patient and co-morbid conditions. In general non invasive investigations should be done first before resorting to invasive investigations such as biopsy endoscopy and others.

A complete blood count and erythrocyte sedimentation rate (ESR) is to be done in all cases. ESR above 80 mm/hr is seen in tuberculosis, malignancy, connective tissue diseases and temporal arteritis. A peripheral smear is to be examined for abnormal cells, malarial parasite and atypical lymphocytes.

Mid stream urine is to be collected for microscopy and culture. Bacterial counts above 10^5 organisms/mL indicate urinary tract infection.

Isolation of Infective Agent

Blood culture should be done routinely in all fevers persisting more than a week. Many a times repeated blood cultures may have to be done to isolate the organism e.g. infective endocarditis.

Polymerase chain reaction (PCR) is very valuable in detecting the nuclear or cytoplasmic components of infecting organisms early in the disease. It is specific and reliable, but false positive results may occur.

Rise in serum uric acid level may suggest rapid cell turnover occurring in malignancies like lymphomas. Rise in alkaline phosphatase, especially the hepatic isoenzymes should indicate liver cell involvement.

Mantoux test: This is a commonly done test to detect allergy to tuberculo-protein. Positive Mantoux test indicates the possibility of tuberculous infection – past or active. In active tuberculosis the Mantoux test is generally hyperactive, but it may be misleadingly negative in miliary tuberculosis and immunocompromised persons. The specificity of this test is only moderate.

Imaging Studies

X-ray imaging: This is the most time honoured, almost universally available, relatively cheap and non-invasive imaging modality which is very helpful in the diagnosis of lesions in the chest e.g. pneumonia and tuberculosis, paranasal sinuses, bones and joints and others. Plain skiagrams and specialized procedures are available to delineate almost all organ system.

Ultrasound imaging: The morphology of several organ systems in the body can be imaged by ultra sound using appropriate probes and computer techniques. Abdominal

organs, genitourinary tract, uterus and any other part can be studied in detail. This modality has become a very useful and commonly used investigation to detect organomegaly in the abdomen, detection of fluid in the abdomen and the plural cavities, pericardium, cardiac structures and almost all other organs in some form or other. Examination of the abdomen may detect abnormalities in the liver (tumour, abscess), biliary system, kidneys, retroperitoneal nodes, pus and fluid collations, ascites and organomegaly.

Echocardiography is useful in detecting cardiac vegetations, atrial myxoma, and other cardiac abnormalities. Therefore this is a very valuable investigation to rule out or confirm a diagnosis of infective endocarditis. In infective endocarditis trans-esophageal probes have to be used if the conventional transthoracic probes are not fully informative.

Limited skeletal survey is useful in suspected multiple myeloma.

Other imaging modalities: These include CT scanning, MRI scanning, PET scanning and their further modifications appropriate to the organ and the disease to be studied.

Isotope bone scan is useful in detecting malignancy, osteomyelitis and septic arthritis.

Selected Serological Tests

A. **Infections:** Example typhoid, leptospirosis, brucellosis, dengue fever, Epstein Barr virus, cytomegalovirus, chlamydiae, mycoplasma, Q fever, amebiasis, leishmaniasis, toxoplasmosis and others.

Detection of specific antibodies against infecting organisms or their products, e.g. Widal reaction detects antibodies against Salmonella. Antistreptolysin-O (ASO) titre estimates the antibody to the toxin of streptococcus. Specific serological tests are available for diagnosis of connective tissue diseases, e.g. rheumatoid factor, in rheumatoid disease, antinuclear antibodies (ANA) in systemic lupus erythematosus which all can mimic infective fevers. Nonspecific tests such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) indicate the presence of an inflammatory process, non specifically. Once the infection is identified, serial determination of ESR or CRP helps to assess progress.

B. **Diseases of connective tissue and vasculitis:** Antinuclear antibody (ANA), anti ds DNA, anti neutrophil cytoplasmic antibody (ANCA).

Selection of further investigations needs careful consideration of the likely benefit and the cost involved. Gastrointestinal endoscopy with biopsy is indicated if symptoms or findings on imaging studies suggest diseases

Diseases Caused by Infections

of the abdominal hollow viscera such as inflammatory bowel disease, intestinal tuberculosis or cancer.

Bronchoscopy and bronchoalveolar lavage for culture of organisms and cytology for malignant and other pathognomonic abnormalities may be considered in selected cases.

Role of biopsy in the diagnosis of FUO: All biopsy procedures are invasive and associated with at least moderate or serious risks to life and health, even though, small. Therefore biopsy procedure should be reserved for cases where diagnosis is not arrived at by simpler procedures. Biopsy specimen can be obtained either by open biopsy or fine needle aspiration cytology (FNAC). Biopsy specimen should also be sent for culture of the organisms and sensitivity studies as well.

6 Liver biopsy: This procedure may help to diagnose miliary tuberculosis, sarcoidosis, lymphoma, and histoplasmosis if the lesions are generalized and tumours or localized inflammation such as granulomas if they are large enough. Guidance with ultrasound helps to reach the target precisely. Yield is generally low if liver function test and liver imaging are normal.

Bone marrow aspiration and biopsy: This is most useful in diagnosing hematological disorders such as leukemias, myeloma and anemias. Among infections visceral leishmaniasis is diagnosed by bone marrow examination. Typhoid, brucellosis, tuberculosis and other infections can be diagnosed by bone marrow culture and this is done when blood culture is negative.

Lymph node biopsy – This is useful when nodes are enlarged, as in lymphomas, tuberculosis, secondary malignant deposits, and others. In generalized lymphadenopathy it is better to take a node which is moderately enlarged. Since the inguinal nodes are likely to show non-specific changes, they are preferably avoided.

Management

Symptomatic Treatment for Fever

Fever demands treatment on its own right when it becomes uncomfortable or positively harmful as in hyperpyrexia.

Physical methods such as sponging with lukewarm or room temperature water and exposure to breeze, help to dissipate heat and lower the temperature rapidly, but the effect is transient. Ice caps applied to the forehead help to remove heat and provide comfort. Water-cooled beds and cooled baths are available for lowering body temperature in specialized patient care settings. Physical methods assume importance especially so when drugs are ineffective or are contraindicated.

Antipyretics

These are drugs which reduce the body temperature and help to maintain it so.

Paracetamol is a commonly used, safe, and freely available antipyretic and analgesic drug, often obtainable even as a non-prescription drug.

When given in doses of 500-750 mg tds oral, the temperature starts falling within 10-15 minutes with sweating and it remains normal or elevated to a lower level for 3-4 hours after which the temperature shoots up again when the effect of the drug wanes. Adverse effects include allergy, gastrointestinal upsets and in very large doses (exceeding 6g/day), hepatic dysfunction.

Aspirin, in doses of 300-400 mg qid or any non-steroidal anti-inflammatory drug (NSAID) such as diclofenac sodium 50-75 mg given orally are also commonly used analgesic antipyretics. Aspirin and NSAIDs show potent antipyretic effect, but they are not recommended for routine use because of their common side effects like acute gastritis, hemorrhagic gastritis and renal damage in some individuals. Many short viral fevers, especially dengue fever, leptospirosis, malaria and sepsis may be associated with thrombocytopenia. NSAIDs and aspirin may aggravate bleeding in them. Since renal involvement is common in dengue fever, leptospirosis, falciparum malaria and sepsis, NSAIDs which are nephrotoxic should be used with caution. There is no indication to give antipyretics if the fever is tolerated by patient comfortably and the fever itself does not rise to hyperthermic levels. Indiscriminate use of antipyretics lead to the following disadvantages:

- Diagnostic clues from the pattern of fever are lost.
- Beneficial effect of fever in infections is lost.
- Response to specific treatment cannot be assessed.
- The drug may induce rigors with return of fever – once antipyretic effect is over.
- Excess sweating with fluid loss and occasionally hypotension may develop.

Definite Indications for Antipyretics

Hyperpyrexia is the most urgent indication to bring down the temperature.

- Significant somatic symptoms like headache, bodyache.
- Coexisting symptomatic coronary artery disease and cardiac Failure.
- Cerebrovascular disease, nervous system dysfunction and head injury.
- Epileptic patients
- Children with history of febrile convulsions.

Pregnancy and psychiatric illness are relative indications to lower the temperature since complications are more likely in them.

Diet in Fever

Since fever increases metabolism, high calorie diet is recommended. Adequate fluid and electrolyte are also

important to avoid dehydration. Observe oral hygiene. Diet containing at least 1500 Calories and 3.5 -4 L of fluids in various forms should be administered. It is preferable to avoid foods which produce a sense of bloating and discomfort.

Antibiotics

Fever is to be treated with antipyretics and not with antibiotics. It is a common practice to give a trial of empirical antibiotics in short febrile illness. Favourable response is not a proof of bacterial infection. Most of the short febrile illnesses are due to viral infections, which are self-limiting. In immunocompetent subjects antibacterial antibiotics should not be used empirically. They are indicated only if there is clinical or investigation evidence of bacterial infection. There is no need for general use of prophylactic antibiotics except in special situations (Refer Chapter 5). Glucocorticoids should not be used as general antipyretics since they may lead to several adverse effects (Refer Chapter 6). "Shotgun mixtures of antibiotics and steroids are to be condemned, because they usually solve nothing, confuse the clinical picture and are not without hazards."

1. **Treatment of Classic FUO** - If the condition is stable and no etiological diagnosis is arrived – avoid empirical therapy. However, if an undiagnosed patient is too ill to permit prolonged observation, empirical treatment may be considered based on the best clinical judgement. It is also to be emphasized that "Initiation of empirical therapy does not make the end of diagnostic workup; rather, it commits the physician to continue thoughtful re-examination and evaluation" so that the empirical therapy does not cause further harm.
2. **Treatment of Neutropenic FUO** – After sending specimens for culture of organisms, empirical broad spectrum antibiotic coverage for pseudomonas such as ticarcillin/piperacillin with gentamicin/ amikacin is to be initiated. If clinical features point to fungal

infection antifungal drugs such as amphotericin in the usual dose has to be given.

3. **Treatment of HIV Associated FUO** – Acute onset fever with hypoxia in an HIV infected patient is often treated for Pneumocystis carinii infection after sending specimens to confirm the diagnosis. In undiagnosed prolonged fever, empirical antituberculosis therapy is usually given because of the high prevalence of tuberculosis in these patients. Specific treatment for HIV should also be started simultaneously.
4. **Treatment of Nosocomial FUO** – Many patients may be critically ill. IV lines may have to be changed and cultured. Empirical antibiotics may have to be given depending on the microbial prevalence in the environment.

Prognosis: This depends on the success of the investigation to arrive at the specific etiological diagnosis and prompt therapy. The overall mortality in FUO is 20 to 30%. It is higher as age advances. If FUO persists undiagnosed for more than 6 to 12 months, the likelihood of a specific diagnosis diminishes.

Conclusion

Fever of unknown origin is a common challenge to the practicing physician. *Many patients are placed in FUO category, because the attending physician overlooks, disregards or rejects an obvious clue. Physicians who care for febrile patients need to talk to them, observe them, and think about them. There are no substitutes for these simple clinical principles.*

Points to remember

1. FUO is a not- uncommon problem in the medical wards. Invariably, these are due to atypical and unsuspected presentations of common infections.
2. Less commonly rare infections may cause PUO.
3. Dyscollagenoses, malignancy, drug fever and factitious fever may cause problem in diagnosis. Proper clinical examinations, repetition of investigations and clinical follow up will reveal the diagnosis in the majority.

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Sepsis and Septic Shock

S. Bhasi

6

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- Pathogenesis 185
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Introduction

The clinical syndrome of sepsis is defined as *infection with evidence of systemic inflammatory response*.

In 1992, the American College of Chest Physicians and the Society of Critical Care Medicine (ACCP/SCCM) developed a consensus statement on the definition of sepsis and its sequelae.

Systemic inflammatory response syndrome (SIRS) may have an infective or non - infective etiology. When sepsis is associated with dysfunction of organs distant from the site of infection, it is termed *severe sepsis*. When severe sepsis is accompanied by hypotension which is not

correctable by appropriate intravenous fluid infusions, the condition is termed *septic shock*. Sepsis, severe sepsis and septic shock can be considered as points on a continuous process, depending on increasing severity of the condition.

Epidemiology

The yearly incidence of sepsis is 50-90 cases/100000 persons and it is on the increase. About 10% of sepsis progresses to severe sepsis and 3% of severe sepsis develops septic shock. Advancing age, diabetes mellitus, malignancy, immunodeficiency and chronic organ failure predispose to the development of shock. Males are more prone than females to develop septic shock.

Etiology

In the past, majority of cases were due to gram negative bacterial infection. At present approximately 50% are due to gram positive organisms as well. Common gram negative organisms causing sepsis are *E.coli*, *Klebsiella*, *Pseudomonas*, *Enterobacter* and *proteus*. Common gram positive organisms include *Staphylococcus aureus*,

ACCP/SCCM Definitions

Term	Definition
Bacteremia	Presence of viable bacteria in the blood
Systemic inflammatory Response syndrome (SIRS)	Severe inflammatory response characterized by 2 or more of the following : Temp > 38°C or < 36°C Heart rate > 90 beats/min Respiratory rate > 20/minute White blood Cell count >12000 cells/mm ³ or < 4000/mm ³ or > 10 % band forms
Sepsis	Presence of systemic inflammatory response syndrome with definitive evidence of infection
Severe sepsis	Sepsis associated with organ dysfunction, hypoperfusion or hypotension (systolic blood pressure < 90 mm Hg) or a decrease of 40 mm Hg from baseline systolic blood pressure
Septic shock	Sepsis with hypotension (systolic blood BP <90 mm Hg) persisting despite adequate fluid resuscitation and the development of abnormalities such as oliguria, altered mental status or lactic acidosis
Multi-organ dysfunction syndrome(MODS)	Presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention

enterococcus, coagulase negative *staphylococcus*, *Streptococcus pneumoniae* and *Streptococcus pyogenes*. Less frequently bacterioides and clostridia may cause sepsis. Viruses, rickettsiae and fungi are responsible at times. Polymicrobial infection is not uncommon. 25% of the infections are multidrug resistant. Common sites of infection producing sepsis are lungs, intra-abdominal tissues, other soft tissues such as muscles, fascial planes and anatomical cavities such as paranasal sinuses and peritoneal recesses, traumatic tissue destruction, implanted foreign bodies, indwelling vascular appliances and indwelling urinary catheters.

Pathogenesis

Pathogenesis of sepsis is very complex. Activation of immune system during microbial infection is generally protective, properly regulated and contained, with a balance set between inflammatory and anti-inflammatory mediators.

Th₁ lymphocytes are pro-inflammatory. Tumour necrosis factor alpha (TNFα), interleukins 1 and 2 (IL 1 and 2) and interferon γ (IFN γ) are pro-inflammatory. Th₂ lymphocytes and IL 4 and 10 help to restrain the inflammatory process and reduce tissue damage. In severe sepsis this balance is upset and the inflammation is uncontrolled, poorly regulated, self sustaining, widespread and involving distant organs away from the site of infection as well.

The products of microorganisms include lipoteichoic acid, endotoxins which are lipopolysaccharides-(LPS), exotoxins and various microbial antigens. When liberated, these act directly on the host tissues. They stimulate the production of pro-inflammatory cytokines such as TNFα, IL-1, and IFN and enzymes such as proteases. TNFα and IL-1 produce fever, vasodilation, hypotension, gluconeogenesis, lypolysis, myocardial depression,

hypoxia and increased capillary permeability. This leads to extravasation of plasma and cells with resultant low intravascular volume, hypoperfusion and shock. Nitric oxide is also released producing excessive vasodilation. Endotoxins also activate the alternate complement cascade. This results in the release of anaphylotoxins such as C3a and C5a leading to vasodilation, increased vascular permeability, aggregation of platelets and neutrophils and disseminated intravascular coagulation (DIC). This is the result of activation of factor XII by LPS and decreased concentration and function of the inhibitors of coagulation such as anti-thrombin III, activated protein C and tissue factor pathway inhibitor. TNFα, IL-1 and reactive oxygen species might inhibit mitochondrial respiratory chain leading to tissue hypoxia and lactic acidosis.

Clinical Manifestations

These may be classified as 1. Features of the primary disease and 2. Features of the septic shock.

- 1. Findings at the primary site of disease: These include the organ system which is primarily affected e.g. pneumonia, cellulitis, pyelonephritis, or traumatic lesions.
- 2. General effects of sepsis and septic shock: Varying degrees of fever occur in the vast majority, but in 15% of patients temperature may be normal or even sub-normal. Hypothermia may be seen in 15%. Tachypnea, tachycardia with weak thready pulse, hypotension, cold clammy skin, cyanosis, oliguria and alteration of sensorium are common. Cyanosis may be peripheral in shock or central in ventilatory failure. In the early stages of sepsis the mental state may be normal, urine output normal and extremities are warm due to hyperdynamic circulation. Tachypnea may produce respiratory alkalosis. Metabolic acidosis occurs in later stages.

EFFECTS OF SEPSIS ON INDIVIDUAL ORGAN SYSTEMS	
System	Effects
Pulmonary	Increased microvascular permeability leads to deposition of protein rich edema within lungs and alveolar collapse due to surfactant deficiency. This causes ventilation- perfusion mismatch. Decrease in lung compliance leads to development of ARDS and hypoxia.
Cardiovascular	Sepsis leads to hyperdynamic circulation with increase in heart rate. Later fall in cardiac output and hypotension ensue. Hypodynamic circulatory state occurs with fall in cardiac output and rise in pulmonary vascular resistance. Myocardial oxygen demand increases. Loss of vasomotor regulation leads to inability to maintain adequate blood flow to vital organs. This results in hypo perfusion and hypoxia.
CNS	Inadequate oxygen delivery leads to agitation, delirium, mental confusion and coma. Depression of the cough reflex predisposes to accumulation of secretions in the air way and respiratory infection.
Bone marrow and blood	Hematopoiesis, particularly thrombopoiesis and myelopoiesis are depressed. DIC and alteration in RBC deformability lead to occlusion and thrombosis in the microcirculation.
Renal	Hypoperfusion and ischemic tubular necrosis lead to oliguria and acute renal failure. Use of IV contrast dyes and aminoglycoside antibiotics precipitate renal failure.

The condition deteriorates, shock worsens, multi-organ failure occurs and the condition becomes irreversible. At this stage mortality exceeds 80%. Death is often due to multi-organ failure and DIC.

Diagnosis

A careful history, physical examination and appropriate imaging and laboratory studies are to be conducted in all cases.

Leucocytosis with shift to left with toxic granules in the neutrophils, thrombocytopenia and hyperbilirubinemia are present early in the course. Leucopenia may develop later. The primary site of infection – respiratory, intra-abdominal, urinary tract, soft tissues or intravenous line-related, should be identified.

Investigations

These include all appropriate investigations detailed in Chapter 35.

The circulatory state, the hematological abnormalities, respiratory function, renal function and fluid –electrolyte status should be assessed from time to time in order to institute life saving measures.

Course and Prognosis

Unless recognized early and managed with intensive care or acute care facilities, septic shock is invariably fatal due to circulatory and multi-organ failure. The risk is evaluated from the onset and during the course by Acute Physiology and Chronic Health Evaluation (APACHE) protocols. Higher scores indicate higher risk. The main criteria of APACHE score are given at the end of this chapter.

Treatment

Antimicrobials: Early institution of specific antimicrobial therapy is life saving. Blood and other relevant specimens should be sent for culture before starting antimicrobials. The choice of the agent depends on knowledge of the likely pathogen, the specific site of infection, sensitivity pattern of organisms in the institution, immunocompetence of the patient and whether the infection is hospital acquired or community acquired. The empirical initial choice would be bactericidal broad spectrum antimicrobial drugs with activity against gram positive and gram negative organisms given intravenously in the maximum recommended dosage. Therapy may have to be modified after culture report. Consider coverage of anaerobic flora also when indicated.

Recommended antibiotics are:

- Inj. ceftriaxone– 1-2 g IV bd (ceftazidime / cefepime in neutropenic patients to cover pseudomonas)
- Ticarcillin clavulanate 3.1 g 4 to 6 times daily by IV infusion

- Piperacillin / Tazobactam 3.375 g 4-6 times daily IM, IV or infusion
- Imipenem cilastin 500 mg 4 times day IM or IV or meropenam 1 g by IM or IV injection 3 times a day.

An Aminoglycoside may be added to any of the above drugs in selected cases.

Patient allergic to β -lactum may be given ciprofloxacin or levofloxacin 400 mg IV BD with clindamycin 600 mg 3 or 4 times a day by IV infusion. Vancomycin 500 mg 6 h by slow IV infusion over 60 minutes may be added if MRSA is suspected. Antifungal therapy may be needed in immunocompromised neutropenic patients. The duration of therapy and periodic alteration in dosage have to be based on microbiological investigations.

1. **Attention to the focus of infection:** Drainage of abscesses, debridement of infected necrotic tissue and removal of potentially infected devices and foreign bodies are necessary early in the disease.
2. **Fluid therapy:** Hypovolemia is common in sepsis and early fluid and electrolyte replacement to maintain adequate intravascular volume and to keep central venous pressure (CVP) at 8-12 cm improves survival.
3. **Vasopressors and ionotropes:** These are to be used when hypotension persists despite fluid replacement. Aim is to maintain mean arterial pressure (MAP) > 65 and systolic blood pressure (SBP) > 90 mm of Hg. Noradrenaline is currently the recommended first choice. Low dose vasopressin (0/01 to 0/04 units/kg bw) is a useful add-on drug in selected patients if the hypotension does not improve.

Blood glucose control: Patients with septic shock tend to develop glucose intolerance. Tight blood glucose control around 110 to 120 mg/ dL is absolutely necessary to hasten recovery and reduce mortality. Blood sugar has to be controlled by insulin therapy as indicated.

DVT prophylaxis: Increased incidence of deep vein thrombosis (DVT) occurs in sepsis, requiring suitable preventive measures.

4. **Activated Protein C:** This may be used in severe sepsis with multi-organ dysfunction. It has anti-inflammatory, anti thrombotic, pro-fibrinolytic effects. It is available as Drotrecogin alfa manufactured by Eli Lilly using r DNA technology. In severe cases with APACHE score >25 the drug reduces mortality by 30%. The drug is very expensive and may produce bleeding complications, especially intracranial, in 3-4% of cases. The price for 1 year of life saved is around \$ 50000. In less severe forms of sepsis this drug is not indicated.
5. **Glucocorticoids:** High doses increase mortality. Many patients with severe sepsis have relative deficiency of adrenal cortical function. In such patients hydrocortisone 200 mg/ day in divided doses may be

Drugs commonly used for circulatory support			
Drug	Mechanism of action	Clinical effect	Dose
Epinephrine	Alpha and beta adrenergic agonist	chronotropism,ionotropism, vasoconstriction	5-20 µg/min
Nor epinephrine	Alpha and beta adrenergic agonist	chronotropism, ionotropism, vasoconstriction	5-20 µg/min
Dopamine	Beta adrenergic-agonist, Progressive alpha-adrenergic effect with increasing doses	chronotropism, ionotropism, vasoconstriction	2 to20 µg/kg/min
Isoproterenol	Non-selective beta adrenergic agonist	chronotropism, ionotropism	0.01 µg/kg/min
Dobutamine	Beta- adrenergic agonist	chronotropism, ionotropism,vasodilation	5 to 15 µg/kg/min

beneficial. Levels of serum corticosteroid in normal persons with acute illness range from 10-34µg/dL. Levels below 15µg/dL indicate adrenocortical deficiency.

6. **Ventilatory support:** This improves survival if there is hypoxemia and ARDS.
7. Blood and blood products are life saving if used appropriately with care. Whole blood, packed cells, platelets, plasma and coagulation factors have to be used when indicated.
8. **Renal replacement therapy:** This is needed in those who develop renal failure, best results are obtained with early dialysis.
9. **Nutrition:** Sepsis is a hypermetabolic state. High calorie high protein diet with supplementation of micronutrients and maintenance of electrolyte balance is important. Oral feeling is ideal. If this is not possible parenteral feeding has to be instituted.

Points to remember

Management of septic shock is a very delicate and complicated therapeutic exercise demanding full facilities for acute intensive care, laboratory tests, expensive drugs and coordinated skills of different specialists. It is therefore essential that patients who might develop septic shock or those who have already developed it are straight away transferred to intensive care facilities for prompt management from the beginning. Delay in treatment and inadequate procedures produce dismal results.

Appendix APACHE Score

The Acute Physiology and Chronic Health Evaluation (APACHE) is a system for classifying patients in the intensive care unit. Patients are evaluated by physiologic scores and evaluation of chronic health status. Physiologic scores correlate with severity of illness. Results of the evaluation can be used to estimate the mortality rate for patients in the ICU and during the hospitalization.

Physiologic classes of variables (total 8 classes with 34 variables):

Maximum score		
1. Cardiovascular	7 variables	27
2. Respiratory	3 variables	12
3. Renal	3 variables	12
4. Gastrointestinal	6 variables	18
5. Hematologic	4 variables	16
6. Septic	4 variables	16
7. Metabolic	6 variables	24
8. Neurologic	1 variable	4
Total	34	129

Scoring

- The physiologic data is evaluated during the first 32 hours after admission to the ICU. Each variable is assigned a value of 0 to 4, based on significance of deviation from normal, with more severe deviations given higher values.

APACHE score =The total score obtained by adding the scores for all the eight systems

Preadmission health status: is also taken into consideration and classified as A to D, A being prior good health with no functional limitations and D being severely disabled.

Interpretation

- Minimum score: 0
- Maximum score: 129

Probability of death in hospital based on APACHE score	
Score	Mortality rate
0-5	2.3%
6-10	4.3%
11-15	8.6%
16-20	16.4%
21-25	28.6%
26-30	56.4%
31+	70%

*Further details can be obtained from the Internet
Yahoo search-apache*

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Systemic Diseases
Caused by Cocci

K.V. Krishna Das

6

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Streptococcal Infections

GENERAL CONSIDERATIONS

Streptococci are among the most common pathogens of man. The lesions which are caused by direct streptococcal invasion include *pharyngitis* (sore throat), *tonsillitis*, *erysipelas*, *cellulitis*, *impetigo*, *scarlet fever*, *septicemia*, *necrotising fasciitis*, *toxic shock syndrome*, and *myositis*. Immunologically mediated postinfectious complications include acute rheumatic fever and acute glomerulonephritis.

Streptococci are gram-positive cocci 1 µm in diameter, non-motile and non-sporing. Many strains are capsulated. Majority are facultative anaerobes, but some are strictly anaerobic. Streptococci are classified on the basis of the type of hemolysis. Beta hemolytic strains possess *streptolysins O and S*. Majority of the pathogenic strains of streptococci are beta hemolytic. These have been further subdivided into broad groups A-H and K-V by Lancefield, based on the group specific polysaccharide antigen of the cell wall. *Str. pyogenes* belongs to group A. This strain is further subclassified by Griffith based on surface protein antigens—M, T and R. Of these M is the most important and it exists in approximately 60 different antigenic forms each of which is present in a different serotype 1, 2, etc. Determination of serotype is important to trace source of infections during epidemiological investigation. Over 80 different serotypes of group A streptococcus have been identified. Based on the serotype and the ability to produce the bacterial products pathogenicity varies.

Principal types of streptococci and enterococci pathogenic to man.

Species	Lancefield group	Type of hemolysis on blood agar
<i>Str. pyogenes</i>	A	beta
<i>Str. agalactiae</i>	B	beta
<i>Str. pneumoniae</i>	none	alpha
<i>Str. mutans</i>	none	none

Humans carry streptococci in the nose, throat, skin and mucous membranes. Common route of entry is the upper respiratory tract or direct inoculation into other sites. Nearly 5% of the population are carriers of pathogenic streptococci. Streptococci spread by inhalation of large droplets or intimate contact with contaminated secretions

Various products secreted by streptococci, which aid in their pathogenicity include *streptolysins O* and *S*, *deoxyribonucleases*, *hyaluronidase* and *erythrogenic toxins*.

Effects of streptococcal products on the host	
<i>Erythrogenic toxins</i> —	3 types: Pyrogenic, cytotoxic, suppression of reticuloendothelial activity, immunosuppression and inducing susceptibility to endotoxin
<i>Streptolysin O</i>	Lysis of erythrocytes, cytotoxic action on neutrophils, platelets and cardiac tissue
<i>Streptokinase</i>	Fibrinolysis
<i>Deoxyribonucleases</i>	Hydrolyse nucleic acids and nucleoproteins. These are antigenic
<i>Hyaluronidase</i>	Spreading factor, helps the organism to spread in tissues
<i>Nicotinamide adenine dinucleotidase (NADase)</i>	Antigenic

Streptococcal Pharyngitis

The incubation period is 2-4 days. This presents with abrupt onset of sore throat, dysphagia, headache, malaise, anorexia, and fever. The posterior pharyngeal wall is red and edematous. The tonsils are enlarged, red and covered with yellowish exudate, which can be easily removed with a swab. Anterior cervical lymph nodes are enlarged and tender. The disease runs a short course, lasting for about a week. Thirty to forty percent of tonsillitis and pharyngitis are streptococcal, the rest is viral or caused by mycoplasma.

Scarlet Fever

This is characterized by the occurrence of an erythematous rash on the second day of illness. The primary lesion is in the throat. Erythrogenic toxin of the streptococcus is responsible for the rash. The rash is seen over the neck

and trunk, the palms and soles are generally spared. The rash blanches on pressure. The rash subsides with extensive desquamation after 4-5 days.

Scarlet fever has to be differentiated from other exanthems, drug rashes, allergic dermatitis and infectious mononucleosis.

Diagnosis is established by isolating group A streptococci from the exudate obtained from the tonsillar crypts.

Treatment: Streptococcal lesions respond promptly to penicillin. A single intramuscular injection of benzathine penicillin G 600,000 units for children less than 25 kg and 1.2 million units for all others is enough to clear the infection. Phenoxymethyl penicillin (penicillin V) 250 mg orally four times daily for 7-10 days is also equally effective. Erythromycin 250 mg 6 hourly for 7-10 days is a suitable alternative for subjects allergic to penicillin. If suppuration develops, surgical drainage of the pus may be required.

Erysipelas

Erysipelas is an acute spreading infection of the skin and the subcutaneous tissue by streptococci. Face is commonly affected. The disease sets in abruptly with malaise, chills, headache and vomiting. The skin lesions are erythematous with clear advancing margins which may show vesicles. The part is tender and local lymph node enlargement may occur. If left untreated, the lesions rapidly spread. In immunocompromised individuals (e.g. diabetics) septicemia may develop.

Streptococcal Impetigo

This is inflammation of the skin characterized by isolated pustules which become crusted. Sites of predilection are around the mouth and nostrils – If left untreated they may ulcerate to produce shallow ulcers with crusts or scabs which may lead to pigmentation and scarring.

This stage is called ecthyma.

Cellulitis

This is spreading inflammation of the subcutaneous tissue due to entry of the organism through the abrasions of the skin. There is pain, tenderness, erythema, fever, and often regional lymphadenopathy.

Lymphangitis

Acute lymphangitis may follow local trauma. This condition presents in the form of linear red streaks radiating from the site of entry to the draining lymph nodes.

Streptococcal Bacteremia

Irrespective of the focus of entry and primary lesion, streptococcal bacteremia gives rise to metastatic foci of

Diseases Caused by Infections

infection such as suppurative arthritis, osteomyelitis, peritonitis, endocarditis, meningitis, or visceral abscesses.

The toxic shock syndrome may be produced by streptococci.

Necrotizing Fasciitis—

Syn: Streptococcal gangrene

This is a progressing destructive lesion of the subcutaneous tissue leading to necrosis of fascia and adipose tissue, but often sparing the skin. The organisms enter through trivial wounds, but within 24 hours the part is hot, swollen, tender and edematous. The edema and violaceous hue spread in all directions. Within 48 hours bullae develop, which go on to gangrene within 4-5 days. The gangrenous area gets demarcated. General symptoms include severe prostration, toxemia, mental clouding and delirium. If the diagnosis is missed, mortality is high.

Differential diagnosis includes infection by *Cl. septicum*, *Cl. perfringens*, and *Staph. aureus*. Treatment consists of the administration of benzyl penicillin and gentamicin in usual doses and aggressive fasciotomy and surgical debridement. In severe cases with toxemia and rapid progression clindamycin should be employed. This drug effectively arrests the growth and toxin-production of streptococci.

Streptococcal Myositis

This is an uncommon lesion. Infection reaches the muscles by the bloodstream. Onset is with severe pain and swelling of muscles. Muscle compartment syndromes may develop. If unrecognized, mortality is over 80%. Streptococcal myositis has to be differentiated from spontaneous gas gangrene. Presence of superficial crepitus favours the diagnosis of gas gangrene. Treatment includes the administration of broad spectrum antibiotics and early surgical debridement.

Pneumonia and Empyema

Streptococcal pneumonia usually follows a viral infection, and it manifests as bronchopneumonia. In many cases empyema develops as a complication.

Most of the strains of streptococci are sensitive to penicillin. Benzyl penicillin G (crystalline penicillin) given IM or IV in a dose of 600,000 units to 1 million units 6 h for 5-10 days generally clears the infection. Some strains have developed resistance to penicillin. Such infections have to be treated with broad spectrum bactericidal antibiotics.

Streptococcal Toxic Shock Syndrome

Infection by group A streptococcus may lead to vascular collapse and organ failure. M-protein which is a constituent of the cell wall is the virulence factor, which

plays the major role in the pathogenesis of toxic shock syndrome. It forms large aggregates with fibrinogen, in blood and tissues. These activate polymorphonuclear leucocytes intravascularly and this leads to the production of toxic shock syndrome.

OTHER PATHOGENIC STRAINS OF STREPTOCOCCI

Group B Streptococcus—*Syn: Str. agalactiae*

This is a major pathogen found in the female genital tract, rectum and also throat. Chorioamnionitis, septic abortion and puerperal sepsis may occur during pregnancy. Urinary tract infection may occur in both sexes. Hematogenous spread may result in endocarditis, pneumonia, empyema, meningitis and peritonitis. Immunocompromised hosts and elderly subjects are more susceptible.

Neonatal infections are caused by Group B streptococcus. The lesions include neonatal sepsis and meningitis. Early infection of the newborn leads to septicemia. Infection a few days after birth usually leads to purulent meningitis.

Streptococcus viridans

This is a heterogenous group consisting of *Str. mutans*, *Str. sanguis* and *Str. mitis*. They produce either alpha hemolysis or no hemolysis in culture. They are normal inhabitants of the oral cavity. Viridans streptococci account for more than 40% cases of infective endocarditis. *Str. mutans* which colonizes dental plaques is an important cause of dental caries.

Organisms closely related to streptococci are *Str. pneumoniae* and peptostreptococci.

Enterococci

These are gram positive cocci originally classified with streptococci. The name indicated its abundance in the gut. The most common species is *Streptococcus faecalis*, followed behind by *Streptococcus faecium*. In the mid 1980s, nucleic acid studies indicated that enterococci were not closely related to streptococci and therefore these are classified as a separate genus and the nomenclature of the species is *E. faecalis*, *E. faecium*, *E. durans* and others.

They colonize the intestines and vagina. They are pathogenic and the lesions include urinary tract infections, biliary tract infections, septicemia, peritonitis, infective endocarditis and abdominal suppuration. They are best known as antibiotic resistant opportunistic pathogens especially in patients who have been treated with several antibiotics with prolonged hospitalization.

Treatment: Enterococci are notorious for developing multidrug resistance. Many strains are resistant to vancomycin, aminoglycosides and beta-lactam antibiotics. Teicoplanin which is a glycopeptide is active against

vancomycin resistant strains. The fluoroquinolones, especially the newer preparations such as moxifloxacin, clinafloxacin, gatifloxacin and sitafloxacin offer the advantage of greater potency over ciprofloxacin. Chloramphenicol may be effective against some strains. The newer drug quinupristin/dalfopristin which is a streptogramin related drug is effective against vancomycin resistant strains. Linezolid which is a new oxazolidinone antibiotic is active against vancomycin resistant enterococci.

Acute Rheumatic Fever

Rheumatic fever is not an uncommon disorder seen in the pediatric age group in India. It is clinically characterized by fever, polyarthritis, carditis, chorea, skin manifestations and pleurisy. The underlying cause is hypersensitivity reaction to group A streptococci. Rheumatic fever follows 2-3 weeks after an attack of streptococcal pharyngitis. Rheumatic valvular disease accounts for a major proportion of cardiac morbidity occurring below 40 years of age in India.

Epidemiology

Though rheumatic fever is worldwide in distribution, it is more common in the developing countries. Group A hemolytic streptococci may occur as commensals in the throat in a small proportion of people. Sometimes, these streptococci become virulent and produce outbreaks of upper respiratory tract infections, especially in children living in closed communities like schools and dormitories. Rheumatic fever occurs only in humans. Repeated infection by streptococci increases the chance of developing rheumatic fever. Spread of group A streptococcus occurs rapidly from person to person by contact.

WHO estimates that 15.6 million people have rheumatic heart disease (RDH) globally. In India 0.5 million develop acute rheumatic fever annually, out of which 300,000 may develop heart disease. Annual incidence is 54/100,000 population (Padmavathy.S.Ind Heart J 2001 53: 35-37). RHD is the result of cumulative damage produced by repeated attacks of rheumatic fever. Prevalence of RHD increases with age, maximum is in the age group 25-34 years. In India both rheumatic fever and RHD are seen at much younger age groups compared to other countries.

Since overcrowding and poor living conditions predispose the spread of streptococcal infection, rheumatic fever is more common in the poorer socioeconomic groups. The risk of developing rheumatic fever after an attack of streptococcal tonsillitis is 0.3 to 3%. The most vulnerable age group is 5-15 years, though any age may be affected. In India the mean age of affection is 6 years. Both sexes

are affected and a familial predisposition is noticed in many cases. Rarely skin infection by streptococcus may lead to acute rheumatic fever, otherwise it may increase the susceptibility to it. After several decades of freedom from rheumatic fever, small outbreaks have been reported from many developed countries in the recent past.

Pathogenesis

In 80% of cases the disease follows streptococcal tonsillitis. In 20-30% cases the episode of tonsillitis may go unnoticed. Over 80% of subjects with rheumatic fever show rise in antistreptococcal antibodies within two months. Extrapharyngeal streptococcus infection does not generally lead to rheumatic fever. The M-protein of streptococci contain epitopes that cross-react with cardiac tissues and other tissues such as synovium and brain. The antigens contained in streptococcus show similarity to several tissue antigens in the human body, especially myocardial sarcolemma. Antibodies produced against streptococcal antigens cross-react with tissue antigens resulting in a type II antigen antibody reaction and consequent inflammation. Lesions are most evident in the connective tissue.

The M serotypes 3, 5, 6, 14, 18, 19 and 24 have strong association with cardiac disease. Throat infection is more commonly caused by serotypes 12, 1, 25, 4 and 3. ASO titre is more elevated in infections of the throat than in skin infections. Strains of streptococci leading to rheumatic fever increase more of streptolysin O than streptolysin S. Strains giving rise to skin infections give rise to greater elevation of ADNase B titres (Table 37.1). Rheumatic fever represents an autoimmune reaction triggered by pharyngeal infection by the appropriate strain of group A streptococcus and amplified by recurrent infection by the same or related group A streptococci.

Pathology

The pathological process consists of an exudative stage which is seen in the acute phase and a proliferative stage which is a more prolonged process. In the exudative stage, fibrinoid necrosis of the connective tissue is seen. There is edema of the collagen fibers which later undergo fragmentation. Immune response affects myosin in muscle

TABLE 37.1			
Comparison to the streptococcal lesion in acute rheumatic fever (ARF) and glomerulonephritis (GN)			
	ARF	GN	
1. Site of lesion	Mostly throat	Throat or skin	
2. Prior sensitization	Essential	Not necessary	
3. Serotypes of streptococci	3,5,6,14,18,19	12,44,2,52,55,57,4	
4. Immune response	Marked	Moderate	

leading to myocarditis - In the valves which lack myosin, the attack is against laminin which is present in the basement membrane and around the endothelium.

The hallmark of the proliferative phase is the formation of **Aschoff's bodies**. These are small granulomas consisting of a central zone of fibrinoid necrosis surrounded by round cells, epithelioid cells, *Aschoff's giant cells* and fibroblasts. This histological appearance is similar in all tissues showing rheumatic lesions.

Heart: All the layers are involved to produce endocarditis, myocarditis and pericarditis (pancarditis). Endocarditis affects the valvular or mural endocardium. When the valvular endocardium heals, it results in scarring and deformity of the valves. Scarring alter mural endocarditis may be seen as the **MacCallum's patch** in the posterior wall of the left atrium. Affection of the myocardium may be mild or severe. Lesion in the pericardium is a fibrinous inflammation. The pericardium shows a 'bread and butter' appearance microscopically. Pericardial effusion may develop. Adhesive pericarditis may follow rarely.

Joints: Rheumatic lesions involve large synovial joints producing acute synovitis. Effusions develop which clear up completely without any residual deformity.

Other organs: Rheumatic granulomas found in the subcutaneous tissues, are seen as subcutaneous nodules. Respiratory involvement manifests as a pneumonia with or without evidence of pleurisy. The basal ganglia of the brain are affected. The lesions take the form of aseptic focal encephalitis which clears completely. Autoantibodies to caudate and subthalamic nuclei are detectable in patients with rheumatic chorea. These antibodies can be absorbed by group A streptococcal membranes. These also cross-react with the sarcolemmal membranes of the heart. In India, the occurrence of cutaneous and neurological lesions is distinctly less when compared to the descriptions from the west.

CLINICAL FEATURES

In some cases prodromal symptoms include epistaxis (bleeding from the nose), *erythema nodosum*, and vague discomfort. Rheumatic fever starts abruptly as a remittent or intermittent pyrexia with characteristic sweating. In many cases other manifestations may not develop for considerable periods, so that the diagnosis may be unsuspected in them. In 20-25% of cases the fever is accompanied by polyarthritis and carditis. *Sometimes these are mild and go unrecognized, especially in children.*

Arthritis: Acute arthritis affecting the major joints is the characteristic involvement. The joints show signs of acute inflammation and exquisite pain which make the subject immobile. Knees and ankles are most often affected

followed by hips, elbows, wrists, and shoulders. Small joints of the hands and feet and axial joints are affected only rarely. The arthritis is migratory and fleeting and leaves behind no residual changes. Sometimes the manifestation may be subacute with arthralgia, pain and tenderness over the neighbouring tendons and muscles. This may be mistaken for growing pains in children.

Jaccoud's arthritis: Jaccoud's arthropathy may affect the hand in up to 50% of cases. It is characterized by reducible, non-erosive joint deformities with preservation of hand function. The pathogenesis of this condition is probably extra-articular secondary to inflammation and shortening of the tendons. The condition clears up with treatment.

Carditis: There may be clinical features of endocarditis, myocarditis, and pericarditis in varying combinations. Tachycardia out of proportion to fever, arrhythmias, gallop rhythm, and congestive cardiac failure should suggest the presence of myocarditis. Mild cardiomegaly may be evident in the skiagrams. Arrhythmias include frequent ectopics, paroxysmal tachycardias, atrial fibrillation, and heart blocks.

Presence of endocarditis is evidenced by the appearance of murmurs or change in the quality of the already existing murmurs. Mitral, aortic, tricuspid, and pulmonary valves are affected in the order of frequency. Acute valvulitis may lead to mitral and aortic regurgitation. Sometimes a low pitched mid-diastolic murmur may be heard in the mitral area due to acute mitral valvulitis (*Carey-Coombs murmur*). It is transient and disappears as the valvulitis subsides. As the valvulitis heals, fibrosis occurs and this distorts the valve apparatus resulting in stenotic and regurgitant lesions.

Pericarditis is clinically manifested as chest pain, presence of pericardial rub, or a small pericardial effusion.

A prospective study conducted at Kottayam Medical College revealed that echocardiographic studies including Doppler are of great value in detecting acute rheumatic valvulitis. Combination of arthritis and carditis occurred in 56.6% of cases of rheumatic fever. Carditis without arthritis occurred in 19.4%. Acute aortic regurgitation occurred in about 50% but most of them (43%) cleared-up on follow up. Sequelae included mitral regurgitation, mitral stenosis, a few cases of aortic regurgitation and occasionally tricuspid regurgitation. Pericardial involvement is also easily detected by echocardiography. (See also Section 13, Chapter 119).

Rheumatic chorea (*Syn: Sydenham's chorea, St. Vitus dance, minor chorea*)

Chorea generally occurs 1-6 months after the onset of rheumatic fever. Since chorea sets in much later than the other manifestations of rheumatic fever, in many cases it may be the only abnormality encountered. Chorea is more common in females and that too in children. It is

characterized by involuntary movements which are quasi-purposive non-repetitive, rapid and jerky and these involve mainly the distal joints. Upper limbs are mostly involved, but lower limbs, face and tongue may also be involved to a lesser extent. These movements may be mistaken for tantrums or fidgety behaviour. Emotional disturbances are frequent and these aggravate the chorea. The limbs are hypotonic and when the hands are held outstretched they assume characteristic postures (choreic hand). The movements disappear during sleep.

Diagnosis of chorea is clinical and there is no pathognomonic investigation. The cerebrospinal fluid is normal. Sydenham's chorea is almost always rheumatic in nature. For chorea and indolent carditis evidence of streptococcal infection need not be stressed upon for diagnosis (WHO Expert consultation-Geneva Oct-Nov 2001-WHO publication 2004).

Chorea is self-limiting and it completely disappears within weeks or months without leaving any neurological sequel. Subjects developing chorea have a higher incidence of cardiac involvement. Except during pregnancy, rheumatic chorea is rare in adults. Rarely chorea may be caused by systemic lupus erythematosus.

Treatment of chorea: Salicylates and steroids have no effect on chorea. The patient is put to bed in a quiet room. Involuntary movements can be controlled by diazepam, chlorpromazine, or phenobarbitone, given in the usual doses. Haloperidol is very effective in controlling the chorea if given in a dose of 0.25 mg 6 h. Rarely intravenous immunoglobulin (IV Ig) may be required in an intractable case (See also Section 19, Chapter 191).

Skin manifestations

Subcutaneous nodules: They are firm, nontender, pea-sized nodules seen over the extensor aspects of the forearm, elbows, ankles, scalp and scapulae. These last for 1-2 weeks and disappear. The risk of carditis is high in those who develop rheumatic nodules.

Erythema marginatum: These are erythematous non-pruritic annular lesions with serpiginous borders, usually seen over the anterior aspects of the chest and abdomen and over the thighs. They spread peripherally like ripples with central clearing. The lesions blanch with pressure. In coloured races this lesion is difficult to identify, unless carefully examined in good light. This rash falls in the category of toxic erythema.

Other rheumatic manifestations: Pleurisy and pneumonitis are not generally evident clinically, these are made out more often by investigations.

Course and progress: Rheumatic fever tends to subside spontaneously over a period of weeks or months. The arthritis subsides but the cardiac lesion progresses. Recurrence of streptococcal infection results in

exacerbation of the rheumatic process, and hence relapses invariably occur. The course of the disease extends over several months or even a few years with remission and relapses. The risk of developing fresh cardiac lesions and worsening of the existing lesions is increased with successive relapses. Mortality in the acute phase is due to sudden cardiac failure, fatal arrhythmias or heart block. In India the course of the disease is accelerated when compared to the west, so that established valvular disease is seen even as early as 6-7 years of age.

Diagnosis: Clinically rheumatic fever should be considered in all cases of prolonged fever in India. Rapid pulse, arthritis, skin manifestations, and carditis suggest the diagnosis.

Streptococcal infection may be demonstrable either by throat swab culture or by serological methods. Moderate neutrophil leukocytosis occurs in many cases.

Serodiagnosis: Several antibodies to streptococcal antigens have been identified.

1. Anti-streptolysin O titer (ASO)
2. Anti-streptokinase (ASK)
3. Anti-deoxyribonucleotidase B (AntiDNase B)
4. Anti-nicotinamide-adenine dinucleotidase (Anti-NADase)
5. Anti-hyaluronidase (AH)
6. Anti-streptozyme test (ASTZ)

Anti-streptolysin O titer has been widely accepted as one of the more easily available diagnostic tests and any value above 250 Todd units in adults and 333 Todd units in children is suggestive. However, the diagnostic levels vary in different places and it is related to the prevalence of antibody levels in the local population. Antistreptolysin O titer does not correlate with the clinical severity. Anti-streptozyme test is a highly sensitive hemagglutination test.

Acute phase reactants: These are laboratory tests which are helpful in the acute phase of the illness. Values of ESR and C reactive proteins are elevated.

The presence of carditis is suggested by the presence of electrocardiographic abnormalities which may show sinus tachycardia, ectopic beats, or first and second degree heart blocks. The voltage of QRS complexes is low; ST elevation and T inversion are seen in the presence of pericarditis. It should be remembered that in many cases with carditis, ECG may not show any abnormalities and hence a negative ECG does not rule out cardiac involvement.

The American Heart Association has accepted the **modified "Jones' criteria"** (1965) for diagnosis which are relevant in Indian conditions as well. The major criteria denote the more specific lesions whereas the minor criteria are nonspecific. For the diagnosis of rheumatic fever two major or one major and two minor criteria should be present. In any case there should be evidence of previous streptococcal infection. In Indian subjects polyarthralgia

TABLE 37.2

Jones' criteria (revised)*

Major manifestations	Minor manifestations
Carditis	Previous rheumatic fever or history of rheumatic heart disease
Polyarthrititis	Fever
Chorea	Acute phase reactants
Erythema marginatum	Prolongation of PR interval in the ECG
Subcutaneous nodules and evidence of preceding streptococcal infection, i.e., ASO titer	
*Duckett Jones	

is also taken as a major criterion if supported by the evidence of streptococcal infection (Table 37.2).

Differential Diagnosis

Infective endocarditis may present with fever and heart lesions. Presence of clubbing, hepatosplenomegaly, absence of arthritis, and development of embolic complications help to distinguish this condition. Henoch-Schönlein purpura may resemble rheumatic fever when purpura is insignificant. Acute leukemia may present with arthralgia and arthritis and produce difficulty in diagnosis before the blood picture becomes diagnostic. Presence of severe pallor, bleeding tendencies, non-migratory arthritis, hepatosplenomegaly, and fundal hemorrhages should alert the physician about the possibility of leukemia. Septic arthritis is usually monoarticular and the source of primary infection may be evident. Gonococcal arthritis, Reiter's syndrome, systemic lupus erythematosus, polyarteritis nodosa, allergic arthritis and serum sickness have to be excluded in atypical cases. Acute or subacute rheumatoid arthritis may cause genuine diagnostic difficulty especially in children.

Chronic rheumatic heart disease has to be differentiated from congenital heart diseases and other acquired heart diseases.

TREATMENT

Treatment may be divided into: (i) management of the acute stage, (ii) eradication of the streptococcal infection, and (iii) prevention of recurrences (secondary prevention).

Acute Phase

Strict bed rest should be instituted since it is absolutely essential to limit the carditis and reduce the incidence of chronic heart disease. It is to be continued till ESR comes down to normal.

Anti-inflammatory agents: The drug of choice is aspirin which has a dramatic effect. The antirheumatic dose of

aspirin is 90-100 mg/kg/day, given in four divided doses after food. Since in this high dose the drug may produce gastric irritation, antacids such as aluminium hydroxide or magnesium trisilicate may be given simultaneously. The dose of aspirin is reduced when fever subsides and it should be continued in a small dose for 10 days after disappearance of all the symptoms. Adverse side effects of aspirin include nausea, dizziness, tinnitus, deafness, vomiting, hyperventilation, hemorrhagic tendency, and psychosis. Idiosyncrasy to aspirin ingestion may lead on to asthma, and nasal polyposis. Aspirin sensitivity can be allayed by desensitization using incremental doses under supervision.

Alternatively corticosteroids may be given. Corticosteroids and salicylates are equally effective in the management of rheumatic fever. Corticosteroids are preferable in those with carditis, since it controls the cardiac lesion, whereas aspirin may not. The common preparation is prednisolone in a dose of 40-50 mg daily given orally. Withdrawal of steroids may result in exacerbation and hence it should be tapered off under the cover of aspirin.

Streptococcal infection is controlled by giving procaine penicillin intramuscularly in a dose of 500,000 units/day for 7-10 days. Erythromycin and cephelexin are suitable alternative drugs.

Secondary prophylaxis: Since rheumatic recurrence is invariably precipitated by streptococcal reinfection, benzathine penicillin 1.2 mega units is given once every three weeks to prevent streptococcal reinfection and rheumatic recurrence. As an alternative, oral penicillin 200,000 units twice daily may be given. Penicillin-sensitive individuals may be treated with erythromycin 250 mg/day. It is desirable to continue rheumatic prophylaxis life long but the chance of recurrence comes down with increasing age and the passage of time after the acute attack. It is mandatory to continue penicillin prophylaxis at least till the age of 25 years or for 5 years after the initial attack, whichever is later.

Primary prevention has been achieved very effectively in most of the developed countries by early diagnosis and prompt treatment of streptococcal infections. Sporadic cases occur when this policy is slackened.

Primary prevention by early prompt treatment of acute streptococcal pharyngitis and tonsillitis and secondary prophylaxis by prolonged antibiotic therapy have served to bring down the incidence of rheumatic fever and heart disease.

Attempts to produce anti-streptococcal vaccine are also going on.

Poststreptococcal Glomerulonephritis (GN)

This may follow either cutaneous or pharyngeal lesion by group A streptococcus. Ten to fifteen percent of children

getting recurrent skin infections may develop glomerulonephritis. Serotypes 12,44,2,52,55,57 and 4 are more often nephritogenic. Latent period for the development of acute GN is 10 days after pharyngitis and 3 weeks after pyoderma. Streptococcal infection supervening on scabies is a common cause for acute glomerulonephritis in India.

This described in section 16, ch. 170.

Staphylococcal Infections

General Considerations

Staphylococci are the most ubiquitous organisms affecting man. Staphylococci are gram-positive cocci 1 µm in diameter, capable of aerobic and anaerobic metabolism. They produce lesions by direct invasion. Many strains are toxigenic and several syndromes result from toxic effects. Incubation period for local lesions is 2-3 days.

Staph. aureus is coagulase positive. *Staph. epidermidis* and *Staph. saprophyticus* are coagulase negative. All are pathogenic, the most common type is *Staph. aureus*.

Epidemiology: Healthy people carry staphylococci in the nose and to a lesser extent in the perineum. The organism is spread by direct contact, through fomites, dust, or by airborne droplets. Large number of organisms are shed from superficial lesions and from the respiratory tract. Though, initially, staphylococci were sensitive to sulphonamides and penicillin, many strains have developed resistance to several antibiotics in common use. Penicillin is inactivated by penicillinase (betalactamase) and this is the basis of penicillin resistance. Resistance can be transferred from one strain to another by transduction through the mechanism of plasmids. At present most hospital strains of staphylococci are resistant to several antibacterial agents. Methicillin resistant staphylococci are resistant to several other beta lactam antibiotics. Therefore resistance to methicillin is tested to identify such strains.

Pathogenesis: Staphylococci invade hair follicles and sebaceous glands. Incidence of infection is higher in diabetics and obese subjects. Subjects recovering from influenza and measles are more susceptible to staphylococcal infection. The organism multiplies in the lesions and leads to suppurative inflammation.

Lesions produced by staphylococci

Staph. aureus: Pyogenic lesions such as boils, carbuncles, wound infection, abscesses, impetigo, mastitis, osteomyelitis, pneumonia, septicemia and pyemia.

Coagulase negative staphylococci: Infection of cardiac and vascular prostheses, endocarditis, ventriculitis (cerebral), peritonitis in continuous ambulatory peritoneal dialysis, septicemia, cystitis.

Toxin-mediated lesions: Food poisoning, toxic shock syndrome, scalded skin syndrome, pemphigus neonatorum.

Toxins of staphylococci: *Staphylococcus aureus* elaborates toxins like hemolysins, leucocidins, enterotoxin, hyaluronidase, fibrinolysin, nuclease, lipase and protease. In addition, nontoxic substances like coagulase, which facilitate invasion, are also produced.

Toxins produced by strains of *Staph. aureus* and the syndromes produced

Enterotoxin A-E	Gastroenteritis
Epidermolytic toxin A and B	Blisters of skin, pemphigus neonatorum, scalded-skin syndrome
Toxin-1	Toxic shock syndrome

Superficial Lesions

Furuncle: A furuncle is an acute necrotic infection of a hair follicle. It presents as a small follicular inflammatory nodule, soon becoming pustular and then necrotic. It heals after discharge of the necrotic core to leave a violaceous macule and ultimately a permanent scar.

Carbuncle: It is a large furuncle or an aggregate of interconnected furuncles accompanied by intense inflammatory changes in the surrounding and underlying connective tissue. Sites of predilection are the back of the neck, the hips and thighs. It starts as a hard red lump, at first smooth and acutely tender. It slowly increases in diameter to reach 3 to 10 cm. Suppuration begins after 5 to 7 days and pus is discharged from multiple follicular orifices. Constitutional symptoms are usually severe. Carbuncles are particularly common in diabetics and those with lowered general resistance.

Impetigo: Bullous impetigo is purely staphylococcal. It usually occurs in newborns and infants. Face is more often affected although lesions may occur in the palms and soles. The lesions consist of multiple pustules.

Ecthyma

Both staphylococci and streptococci can cause ecthyma. The lesion is characterized by small bullae or pustules on an erythematous base, soon developing into a hard crust. Irregular ulceration is evident when the crust is removed. The sites of predilection are the buttocks, thighs, and legs.

Sycosis Barbae

This is seen in males after puberty and the lesions are seen on the beard region. The lesion starts as an edematous, red, follicular papule or pustule, centered by a hair. The individual papules remain discrete.

Follicular Impetigo of Bockhart

This is staphylococcal infection of the hair follicle seen commonly in childhood. It occurs mainly in the scalp or scalp margins.

The Scalded Skin Syndrome

(Syn: pemphigus neonatorum, Ritter's disease, toxic epidermal necrolysis)

This is a generalized exfoliative dermatitis caused by *Staph. aureus*. It is characterized by generalized painful erythema and large bullae which can be easily disrupted by finger pressure. Newborns are commonly affected.

Staphylococcal Pneumonia

Staphylococcal pneumonia occurs as a complication of influenza, measles or other viral infections. It starts with high fever, chills, dyspnea, cyanosis, cough, and pleural pain, sputum may be bloody or purulent. Scattered fine to coarse rales and rhonchi may be heard over the involved areas. Typical consolidation is rare. Primary staphylococcal pneumonia may occur in infants and young children and this causes pneumothorax, pneumatoceles, or empyema. Hematogenous secondary staphylococcal pneumonia is frequent in drug addicts who also develop endocarditis. Staphylococcal pneumonia carries a higher mortality, especially in the old and debilitated patients.

Osteomyelitis

Majority of cases of primary osteomyelitis are due to staphylococcus.

Staphylococcal Bacteremia

The primary source consists of local staphylococcal infections, urinary catheters, foreign bodies, or infected intravenous shunts. The onset is marked by high fever, tachycardia, cyanosis and vascular collapse. Pyemic abscesses may form in the skin, bone, kidneys, brain, or lungs. Fulminant sepsis may lead to death within 24 hours.

Other staphylococcal lesions include endocarditis, pericarditis, arthritis, polymyositis, parotitis, and urinary tract infection.

Staphylococcal Food Poisoning

Staphylococcal food poisoning occurs as a result of ingestion of preformed enterotoxin in food contaminated by *Staph. aureus*. Canned food, processed meat, milk, cheese and others account for the majority of cases. Symptoms start within 6-8 hours and the patients present with varying grades of gastroenteritis or dysenteric symptoms. There is mild fever.

Staphylococcal enterocolitis is due to direct invasion of the bowel mucosa, sometimes seen in surgical patients. Gram staining of feces reveals the organisms.

Tropical Pyomyositis

This is more commonly described from Africa, but cases occur in India too. Large abscesses develop in the muscles of the limbs or trunk in apparently healthy adults. The spread of the organism is probably hematogenous. In

addition to systemic therapy surgical evacuation of pus is also necessary.

Diagnosis of Staphylococcal Infections

Clinical diagnosis should be confirmed by culturing the organism from the exudates. Phage typing is employed for identifying the strains in epidemics and tracing the carriers.

Treatment

Superficial skin infections respond to proper cleaning and application of topical ointments containing chlorhexidine or cetrimide. In systemic infections or when the lesions are deep, systemic antibiotics are required. Benzyl penicillin is the most effective antibiotic if the organisms are sensitive.

Infections acquired from the community may be sensitive to benzyl penicillin in usual dosage. Up to 90% of hospital acquired infections may be resistant to penicillin and other beta-lactam antibiotics due to the production of penicillinase. *Methicillin*, *cloxacillin*, *fluocloxacillin*, *cephalosporin*, *clavulanic acid* and *sulbactam* resist penicillinase and, therefore, these may be effective.

Hence it is ideal to get culture and sensitivity results where circumstances permit. Pending the result *cloxacillin* or *flucloxacillin* may be started in a dose of 250-500 mg orally six hourly. If the organism is penicillin sensitive, the most effective drug is benzyl penicillin. *Procaine penicillin* in a dose of 600,000 units IM daily for 6-10 days clears the infection. Resistant cases may require other antibiotics such as *gentamicin*, *clindamycin*, *fusidic acid* or *erythromycin*. *Vancomycin* is usually effective in multidrug resistant cases and it is the drug of choice. *Rifampicin* in dose of 400-600 mg daily orally acts synergistically with vancomycin.

Quinupristin/dalfopristin which is a streptogramin antimicrobial agent recently licenced in the UK and USA for the treatment of gram-positive organisms, especially methicillin resistant *Staphylococcus aureus*, coagulase negative *Staphylococcus aureus* with intermediate glycopeptide resistance (i.e. to teloplanin), vancomycin resistant *Enterococcus faecium* and penicillin resistant and macrolide resistant *pneumococci*. It is inactive against *enterococcus faecalis*. It can be given as IV infusion, preferably through central venous catheter over a period of 60 minutes. Adverse side effects include rashes, gastrointestinal upsets and irritation at the site of injection.

Staph. epidermidis cystitis responds to *cotrimoxazole* or *norfloxacin*.

PREVENTION

Patients with open staphylococcal lesions should be isolated. Surgeons and hospital staff should be periodically

checked for carrier state and positive cases are treated by local application of neomycin and chlorhexidine. Topical application of antiseptics such as hexachlorophene are found useful in preventing staphylococcal infection in selected cases. The importance of proper hand washing by the attending staff cannot be overemphasized.

Multidrug resistant *Staphylococcus aureus* (MRSA) is found to colonize the nose, wounds and other parts in 30-40% of patients undergoing prolonged hospitalization. During an outbreak of MRSA infection in hospitals, application of mupirocin ointment to the nose helps to eradicate the nasal carrier state. The whole genome sequence of methicillin resistant *Staph. aureus* has been unravelled by Japanese workers (Kuruda M *et al*, The Lancet 2001: 357, 1255-40). About 70 genes have been identified to contribute to drug resistance.

Toxic Shock Syndrome

This syndrome described first in 1978 consists of sudden development of shock associated with high fever, headache, sore throat, diarrhea, and erythroderma. It was noted in young girls using certain brands of vaginal tampons during menstruation. This syndrome is caused by a diffusible toxin produced by staphylococci (phage type 1) which grows in such tampons. Blood cultures are negative. Mortality is high in untreated cases. This syndrome can develop even when the source of infection is different.

Treatment: Emergency measures to combat septic shock should be instituted. Betalactamase-resistant antibiotics should be used in full dosage from the onset. Corticosteroids have helped to reduce toxemia in some cases. Further use of such tampons should be avoided. Strong clinical suspicion is absolutely necessary to save life in such situations.

Pneumococcal Infections

Syn: *Diplococcus pneumoniae*,
Streptococcus pneumoniae

General Considerations

Pneumococci are found in the upper respiratory tract of about half of the population. On the basis of capsular precipitation reactions using type specific antisera, about 84 serotypes have been identified. All are pathogenic to man but the most commonly encountered types are 1, 2, 3, 4, 7, 8 and 12. These are gram-positive nonmotile encapsulated ovoid or lanceolate organisms 1 µm in length occurring in pairs. Most strains are facultative anaerobes, some are strictly anaerobes.

Pneumococcal polysaccharide plays the major role in virulence and it protects the organism to some extent from phagocytosis. The capsule is the most important determinant of virulence. It is important for immunization.

Though capsular polysaccharides have similar physico-chemical properties, some strains are more pathogenic and only some strains are frequently associated with bacteremic illness. The capsule by itself is not toxic. Invasiveness is related to the size of the capsule and more importantly to its chemical composition. Route of entry in the respiratory tract by droplet infection. The normal respiratory tract offers adequate resistance to invasion by pneumococcus. Patients with underlying lung diseases such as bronchiectasis, carcinoma, or chronic obstructive airway disease are predisposed to develop pneumonia. Aspiration of infected material, respiratory irritants, pulmonary edema and trauma to the chest reduce the local resistance and favour the growth of pneumococci. Respiratory viral infections predispose to infection by *S. pneumoniae*. Large droplet size and close contact favour infection.

Alcohol intoxication and anesthesia impair leucocyte migration. The mucinous secretions of the respiratory tract protect the pneumococci and these multiply and lead to further outpouring of proteinaceous fluid.

The normal defence mechanisms consist of the migration of polymorphonuclear leucocytes and phagocytosis. These are enhanced by the presence of antibodies. Breakdown of these defence mechanisms result in bacteremia and the development of metastatic lesions in the meninges, joints, peritoneum, or the endocardium. Recovery from infection starts with the formation of type specific antibodies in the circulation and this is clinically marked by a fall in temperature by crisis. Treatment with antimicrobials reduces the bacterial population and enhances the host defence mechanism which is still important in the elimination of bacteria. Necrosis of lung parenchyma is uncommon.

Spread of pneumococci from the nasopharynx to the adjacent structures results in the development of otitis media, mastoiditis, paranasal sinusitis, or conjunctivitis.

Pneumococcal Pneumonia

Syn: *Lobar pneumonia*

Pneumonia is the most common pneumococcal lesion in adults. In adults commonly the pneumonia is segmental or lobar in distribution, but in children and the aged the lesion may be bronchopneumonic.

Pathology: Invasion of the lung by pneumococci leads to the formation of an inflammatory exudate in several alveoli and this depends upon the virulence of the organism. Segmental boundaries are not preserved and the bronchi which are relatively uninvolved, remain patent.

The inflammatory exudates contain a large number of neutrophils and red cells. In the initial stages the alveoli are filled with red blood cells and fibrin, and the pulmonary capillaries are widely dilated (*red hepatisation*). In the next stage neutrophil leucocytes predominate. They phagocytose the bacteria. The capillaries become less congested (*grey*)

hepatisation). It is uncommon for the inflammatory process to proceed to necrosis. As resolution starts, the inflammatory exudate liquefies and it is absorbed through lymphatics and removed by the alveolar macrophages. It takes considerable periods of time for complete recovery.

Clinical features: Pneumonia is often preceded by coryza or other upper respiratory tract infections. Incidence of pneumonia is higher in males. The onset is sudden with fever and chills in the majority of cases. There is marked tachycardia and tachypnea. The alae nasi are seen to move when the patient breathes. Severe pleuritic pain and cough with expectoration of pinkish or rusty mucoid sputum follows. The respiration becomes rapid and shallow and may be associated with grunting. Respiratory embarrassment results in cyanosis. The patient becomes very ill and toxic. In the untreated case fever persists continuously for 7-11 days after which it comes down by crisis. It is common to get a crop of labial herpes simplex during the fever.

Physical examination reveals rapid pulse fever and signs of consolidation over the affected lobe of the lung. As resolution starts, coarse creptitations develop. If pleurisy occurs, pleural friction rub may be elicitable. In uncomplicated cases, once the temperature comes down, the patient feels well and recovery starts. However, the pulmonary lesions resolve completely only after a few weeks.

Early institution of specific therapy can prevent the development of consolidation and the general symptoms, but if consolidation has been established, resolution takes time, depending on the body's natural defences. The response to penicillin therapy is dramatic. With the widespread use of antibiotics from the start of fever, the classic picture of lobar pneumonia is seldom seen at present.

Laboratory findings: Sputum is rusty in colour. Pneumococci can be demonstrated by gram staining. Blood culture is positive in 20-25% of cases in the early stage of the disease. There is marked leukocytosis ranging from 12,000 to 25,000 cells/cmm and neutrophils from 85 to 90% of the total. Absence of leukocytosis or even leukopenia may sometimes be observed in patients with overwhelming infection and bacteremia. The prognosis in such cases is very poor. Skiagram of the chest shows a homogeneous opacity corresponding to the lobe or segment involved (Fig. 37.1).

Bacterial organisms in respiratory infections			
	<i>S. pneumoniae</i>	<i>H. influenzae</i>	<i>M. catarrhalis</i>
Acute sinusitis	42	29	22
Acute otitis media	42	38	17
Acute exacerbation of chronic bronchitis	15	32	13
Community acquired Pneumonia	20-75	3-10	—

Complications: Local complications include atelectasis, lung abscess, and delayed resolution.

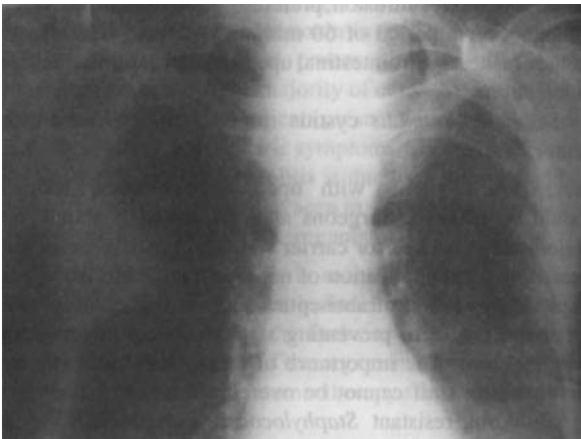


Fig. 37.1: Skiagram chest lobar pneumonia – right (pneumococcal) See well demarcated homogenous opacity right mid zone

Spread of inflammation to adjacent structures leads to pleural effusion, empyema, pericarditis, and peritonitis.

Hematogenous spread results in septicemia, meningitis and acute endocarditis. Gastrointestinal complications include paralytic ileus, gastric dilatation, impairment of liver function, and jaundice.

Prognosis: In the vast majority of cases the lesion subsides and recovery is complete. Adverse prognostic signs include leucopenia, bacteremia, multilobar involvement, extra-pulmonary involvement, circulatory collapse, presence of pre-existing systemic diseases, and occurrence of the disease at the two extremes of life (below 3 years and above 55 years). Infection with type 3 pneumococcus has a higher mortality rate (Tables 37.3 and 37.4).

EXTRA-PULMONARY PNEUMOCOCCAL LESIONS

Pneumococcal meningitis: Pneumococcal meningitis may develop primarily or this may be a complication of pneumococcal pneumonia, otitis media, mastoiditis, or sinusitis. This is a serious illness associated with 20-30% mortality and up to 50% residual morbidity in survivors, if not treated in time.

Over 75% of community acquired meningitis is caused by *S. pneumoniae* and *N. meningitides*.

Early lumbar puncture on clinical suspicion and the promptness with which early specific antimicrobial treatment is started are the most important prognostic factors for recovery.

Pneumococcal peritonitis: This is a rare infection. It is more frequent in girls, patients with nephrotic syndrome, cirrhosis of liver, and abdominal malignancies.

TREATMENT OF PNEUMOCOCCAL INFECTIONS

Pneumococci are generally susceptible to penicillin, but resistant strains are being reported. It is advisable to send

TABLE 37.3

Assessment of severity index in community acquired pneumonias - algorithm

Parameter	Risk points
Clinical points	
Age, men	age in years
Age, women	age minus 10
Co-existent disease	+10
Neoplasms	+30
Liver disease	+20
Congestive heart failure	+10
Cerebrovascular accident	+10
Renal disease	+10
Mental clouding	+20
Respiratory rate	+20
>30/minute	
Systolic BP < 90 mm Hg	+20
Temperature < 35 C or	+15
>40 C	+15
Pulse > 125/minute	+10
Pleural effusion	+10
Laboratory parameters	
Arterial PH < 7.35	+30
Blood urea nitrogen	+20
>30 mg/dL	
Serum sodium <130 m mol/L	+20
Blood glucose > 250 mg/dL -	+10
PCV < 30%	+ 10
Arterial pO ₂ < 60 mm Hg	
or Oxygen saturation	+10
< 90 %	

TABLE 37.4

Prognostic significance based on risk factors

Risk class	Risk	Score based on algorithm	Mortality
I	Low	< 70	0.1%
II	Low	< 70	0.6%
III	Low	71 – 90	0.9%
IV	Moderate	91 – 130	9.3%
V	High	> 130	27%

Ref: Fine M.J et al. N Eng J.Med 1997 – 336 – 243-250

the sputum for sensitivity tests before starting specific therapy. Benzyl penicillin is the drug of choice for pneumococcal infections.

Pneumonia: Crystalline penicillin is given intramuscularly in a dose of 0.5 mega units/8 h till the temperature comes down to normal and then procaine penicillin in a dose of 0.5 to 1 mega unit daily is substituted and continued till the patient is well on the road to recovery. In the ordinary case the antibiotic has to be administered for a total duration of 7-10 days. When resolution is delayed, the cause should be detected by investigations.

An alternative to penicillin is ampicillin 250 mg 6 h for 7-10 days.

The abnormal physical findings in the chest clear in 2-3 weeks. The skiagram may show abnormalities for up to 2 weeks after the temperature comes down to normal. Delay in resolution is due to bronchial obstruction or other underlying lung diseases.

Multiple-drug-resistant pneumococci respond to vancomycin 2 g/day in divided doses or cephalexin or ceftazidime. Levofloxacin is also effective.

Symptomatic treatment includes analgesics (aspirin) for chest pain, oxygen inhalation, non-narcotic sedatives (diazepam), and expectorants for clearing the respiratory passages. Medicated steam inhalations containing tincture benzoin or eucalyptus oil provide symptomatic relief and assist expectoration. It is important to ensure adequate convalescence (at least 2 weeks) after lobar pneumonia and this helps in reducing the sequelae.

Note: See section 14, ch. 134.

Since *S. pneumoniae* has acquired resistance to penicillin, other antibiotics may have to be used. These include vancomycin and third generation cephalosporins.

Susceptibility Rates of Respiratory Pathogens to Antimicrobials

Percentage susceptibility to various antibiotics using NCCLS (National Committee for Clinical Laboratory Standards) breakpoints (Table 37.5).

Prevention

Specific prophylaxis is by vaccinations. Pneumococcal vaccine contains a mixture of 23 polysaccharide serotypes giving protection against 90% of the infecting strains. The vaccine has to be given by SC or IM injection. A single dose gives protection about 3 to 5 years or longer. Vaccination may have to be repeated after 5 years if exposed to the risk of infection. Mass vaccination of children in a community produces herd immunity in the population, in

TABLE 37.5

Susceptibility of respiratory pathogens to antibiotics

	<i>S. pneumoniae</i>	<i>H. influenzae</i>	<i>M. catarrhalis</i>
Penicillin	76	-	8
Ampicillin	78	87	18
Amox-clavulanate	84	98	100
Ceftriaxone	85	100	100
Erythromycin	78	-	100
Clarithromycin	78	95	100
Azithromycin	78	100	100
Chloramphenicol	88	98	100
Doxycycline	78	100	100
TMP-SMX	69	88	100
Ofloxacin	96	100	100

% susceptible using NCCLS breakpoints

Diseases Caused by Infections

addition to the individual benefits. This phenomenon is being studied further. It has been observed that individuals immunized against pneumococcus may be predisposed to colonization of the nasopharynx by *Staph. aureus*.

Indications for vaccination: Asplenia, nephrotic syndrome, sickle cell disease, lymphomas and other immunodeficiency states. In children below 2 years of age and in immunocompromised individuals vaccination is not effective. They have to be given orally phenoxymethyl penicillin on a long-term basis. Protein conjugate pneumococcal vaccine may be given to children > 2 years for protection. Multiple doses may have to be given.

General Measures to Increase Resistance

Studies from Dhaka, Bangladesh have shown that malnutrition predisposes to pneumonia. Oral supplementation of 70 mg of zinc acetate in 10 mL of syrupy base once a week was associated with substantial protection against pneumonia and suppurative otitis media. Mortality from pneumonia was also reduced.

(W. Abdulla et al. The Lancet. 2005. 366-999-1004).

Meningococcal Infections

GENERAL CONSIDERATIONS

Neisseria meningitidis (meningococcus) is pathogenic exclusively to man. The clinical syndromes include meningitis, meningococcal septicemia, and rarely lesions in the joints, ears, eyes, adrenal glands, lungs and heart.

Meningococci are gram-negative diplococci. Based on the capsular polysaccharide antigens, these are divisible into three main serogroups A, B, and C. Group A commonly produces epidemics and Group C, localized outbreaks of meningitis. Other serogroups W₁₃₅ and Y are also pathogenic.

Epidemiology: The organisms are found in the nasopharynx of 5-10% of humans who act as carriers. Before the onset of epidemics carrier rate among the local population goes up above 20% and during an epidemic 90% of subjects may carry the organisms. Outbreaks usually occur in close-knit communities such as inmates of jails, ships, army camps, or dormitories. Sporadic cases may also occur. In India a clear seasonal prevalence is not seen. The organism commonly spreads through droplet infection and to some extent through fomites. In the majority of cases the infection is asymptomatic. In some, the only manifestation is an upper respiratory tract catarrh.

PATHOGENESIS AND PATHOLOGY

The major lesions are cerebrospinal meningitis and meningococcal septicemia. Bacteremia precedes the meningitis. The organism may reach the central nervous

system directly along the perineural sheath of the olfactory nerves or through the bloodstream. Bacteremia leads to endothelial damage and the organisms enter the CSF. Serogroups B and C account for the majority of cases in the west. Serogroups W₁₃₅ and Y account for a smaller proportion. Group C produces more serious disease.

Once the CSF is reached further multiplication is rapid since the humoral defences are absent. Cytokines promote inflammatory processes and increase vascular permeability. Leukocytes adhere to endothelium. Vasogenic cerebral edema occurs which itself may lead to brain herniation. In the central nervous system meningococci produce suppurative lesions of the pia arachnoid. Inflammatory lesions are seen on the surfaces of the brain and spinal cord and the ependymal lining of the ventricles. The whole of CSF becomes turbid and purulent. The base of the brain and the surface of the cerebral hemispheres show thick pus. This exudate may block the foramina leading to internal hydrocephalus and also compress the cranial nerves emerging from the base of the brain. Meningococci may invade the underlying cerebral cortex as well and cause encephalitis.

Histologically the lesions show perivascular cuffing with polymorphs. Thrombosis of small blood vessels may occur. In severe cases, subdural effusions containing blood or exudate may occur.

Clinical pattern of meningococcal infections		
Site of infection	Clinical syndrome	Outcome
Blood and CSF	Septicemia and meningitis with rash	Fatal in 14-50%
	Septicemia and meningitis without rash	Fatal in 2-6%
Blood	Fulminant septicemia Waterhouse-Friderichsen syndrome	Fatal
Blood	Septicemia purpuric rash	Fatal 14-50%
Blood	Chronic septicemia	Recovery with treatment
Metastatic lesions	Arthritis, osteomyelitis, pericarditis, endocarditis, local lesions, pneumonia	Recover with treatment
Eye	Purulent conjunctivitis	Clears with treatment

Meningococcal septicemia (meningococcemia) is characterized by hemorrhagic manifestations. The organisms can be demonstrated in the small blood vessels from all organs. Vascular damage occurs as an allergic

phenomenon (*Schwartzman phenomenon*) caused by the endotoxin of meningococci. In fulminant meningococemia, hemorrhage occurs into the adrenal glands leading to adrenal failure and profound shock. Generalized hemorrhagic tendency may develop due to disseminated intravascular coagulation. Metastatic lesions occur in the joints, ears, eyes, and lungs.

MENINGOCOCCAL MENINGITIS

Syn: Cerebrospinal fever

Infection of the leptomeninges by *N meningitidis* leads to meningococcal meningitis. This may occur in epidemic and sporadic forms. The most common age group is from 6 months of life to adolescence. Incubation period varies from 3-5 days and there may be a preceding upper respiratory tract infection. Onset is acute with fever and other constitutional features like severe headache, neck rigidity, vomiting, and photophobia. Fever is usually high grade, intermittent, and associated with rigor and chills. The pulse is slow. Herpes labialis may develop. The patient is irritable and prefers to lie curled in bed. Drowsiness, confusion, delirium, and coma supervene. Convulsions are common at the onset, especially in children. In children, early signs such as leg pain, coldness of the extremities and abnormal skin colour may develop even before the classic signs of meningitis. Recognition of the disease at this stage and institution of specific therapy are more beneficial.

In a large proportion features of meningococcal septicemia are seen. These include maculopapular and purpuric skin rashes appearing over the axilla, flanks, wrists, and buttocks, and ecchymosis and peripheral gangrene (Fig. 37.2). Signs of meningeal irritation are evident from an early stage. These include neck rigidity, Kernig's sign, and Brudzinski's signs. There is pain over the hamstrings when the knee is extended passively with the hip flexed to 90°, and the extension is restricted (*Kernig's sign*). *Brudzinski's leg sign* is the flexion of the opposite knee when Kernig's sign is elicited on one side. Brudzinski's neck sign is flexion of both legs when the neck is passively flexed. In severe cases, especially in

children, the spasm of neck muscles may be so severe as to produce head retraction and opisthotonus.

Rise in intracranial tension may lead to papilledema. In a small proportion of cases blindness, deafness, and hemiplegia may be found in the acute phase. Some of the patients recover within a month. A toxic encephalopathy may develop in some patients and this is probably due to diffusion of toxins or bacterial invasion.

It is characterized by the development of deep coma within a few days of onset. This condition is associated with a mortality up to 50%. The development of subdural effusion, internal hydrocephalus, or brain abscess should be suspected from the development of localizing signs and progressive deterioration, despite adequate therapy. Most of the untreated patients die in a stage of deep coma within days or weeks, but a few may proceed to a chronic phase characterized by progressive emaciation, opisthotonus, paralysis, bedsores, and hydrocephalus.

Meningococemia

Meningococemia may be fulminant or chronic. The fulminant form is characterized by abrupt onset, severe constitutional disturbances, peripheral vascular collapse, shock, and sometimes myocarditis. The skin rashes are extensive and may even ulcerate. Though in many cases there is associated meningitis, the signs of meningeal irritation may be absent due to shock. In some cases the illness may progress rapidly so that toxemia and shock may occur within hours. These features are collectively called *Waterhouse-Friderichsen syndrome*. This syndrome is caused by hemorrhage into the adrenal glands resulting in acute adrenal failure. Toxic vasculitis aggravates the hypotension. Complications include endocarditis, allergic polyarthritis, pneumonia and osteomyelitis.

Chronic meningococemia is characterized by intermittent fever lasting for several weeks, maculopapular rashes, erythema nodosum, arthralgia or arthritis, and splenomegaly in 20%. If left untreated, the infection may either subside or progress to meningitis.

Other rare meningococcal lesions include *pneumonia*, *genitourinary infection*, *endocarditis*, *osteomyelitis* and *purulent conjunctivitis*. In acute meningococcal infections polymorphonuclear leucocytosis with total counts going up to 12,000 to 40,000/cu mm is common. In chronic meningococemia the leucocyte count may be normal.

Diagnosis

Clinically meningitis is diagnosed when there is fever, severe headache, and signs of meningeal irritation. This has to be distinguished from meningism which is seen in toxic febrile states where the signs of meningeal irritation are present but the CSF is normal. Meningitis has to be distinguished from encephalitis, subarachnoid



Fig. 37.2: Boy meningococemia. Note: blotchy ecchymosis

hemorrhage, and other causes of coma. Meningococcal meningitis has to be distinguished from other causes of purulent meningitis. At the slightest suspicion of meningitis lumbar puncture should be done and the CSF should be examined to establish the diagnosis. **Since early diagnosis and institution of specific antibacterial treatment is the most important single factor in determining the outcome, lumbar puncture should not be delayed.**

Differential diagnosis includes other bacterial meningitis, mainly caused by *H. influenzae* and pneumococci.

Laboratory diagnosis: Diagnosis of meningitis is confirmed by examination of CSF. Lumbar puncture should be done at the earliest if there are no contra indications. Conditions which resemble meningitis include subdural empyema, brain abscess, or necrotic temporal lobe in *Herpes simplex* encephalitis. In patients with onset of seizures, signs of raised intracranial tension and moderate or severe impairment of consciousness, CT or MRI should be done to assess the intracranial pathology before performing LP. Repetition of Lumbar puncture is indicated when the progress with treatment is not satisfactory.

CSF findings confirm the diagnosis of meningitis. These include:

1. Rise in pressure	Opening pressure may exceed even 400 mm CSF
2. Physical appearance	Turbid or purulent
3. Pleocytosis	Leucocyte count is usually 500-10000/cmm or even more. Over 95% are neutrophils. Rarely lymphocytes may be the predominant cells. In 5-10% of cases cell count may be only mildly elevated or be normal. This is associated with poor prognosis.
4. Demonstration of organism	Gram staining of CSF shows meningococci in 60-90% of cases. PCR of CSF can detect the organism early.
5. CSF glucose	It is less than 40% of the level of blood glucose estimated simultaneously
6. Culture of organism	Positive in a variable proportion. Organisms disappear rapidly on starting specific therapy.
7. Detection of meningococcal antigen in CSF	Counterimmunoelectrophoresis

In patients with persistent elevation of intracranial tension lumbar puncture and release of CSF may lead to trans-tentorial herniation of the temporal lobe of the brain and coning of the brainstem which can be fatal if unrecognized. In such cases LP should be done with

precaution to monitor the patient and institute life saving measures if coning occurs. Coning of the brain stem leads to drowsiness, coma and slowing of respiration and death. Emergency management consists of intravenous administration of 200 mL of 20% mannitol, elevation of the foot end of the bed and release of supra tentorial pressure by surgical means. If in any case the LP is likely to be delayed and the clinical suspicion is strong, antibiotic therapy should be started straight away, empirically.

Identification of the infecting agent:

1. Meningococci may be seen in gram stained CSF preparations. This is the most rapid method for diagnosis.
2. The organism can be cultured from CSF, blood or material taken from skin rashes.
3. Meningococcal antigen can be identified in CSF by counterimmunoelectrophoresis.
4. Sera of convalescent patients show antibodies to meningococci and these can be demonstrated by complement fixation test, passive hemagglutination, or by radioactive antigen binding tests. These tests are helpful in retrospective diagnosis.
5. Carrier state is diagnosed by isolating the organisms from material collected from the nasopharynx using a West's postnasal swab. The swab has to be transported to the laboratory in a special medium (Sturt's medium).

Treatment

As early as possible, specific treatment should be started. Penicillin G is the antibiotic of choice and should be administered intravenously in a dose of 24 million units daily in divided doses. In children the dose is 16 million units/m². Dexamethasone 10 mg IV should be started with the first dose of antibiotic and repeated 6 h for 4 days. Further doses should be determined, based on the patient's progress. Addition of glucocorticoids early in treatment favours prompt recovery and prevents complications considerably.

Treatment should be continued for several days. Ampicillin in a dose of 200-400 mg/kg body weight daily is also equally effective. Since penicillin and ampicillin enter the CSF through the inflamed meninges, intrathecal administration is not necessary. In penicillin-allergic patients, chloramphenicol in a dose of 4-6 g daily in divided doses can be used intravenously. The third generation cephalosporins, especially cefotaxime is quite effective when given in doses of 6-8 g/day. The exact dose can be calculated from the weight of the patient. 150-200 mg/kg IV daily in 6 hourly doses to a total of up to 12 g. An alternative is ceftriaxone in a daily dose of 75-100 mg/kg (up to 5 g) given in two divided doses.

The administration of antibiotics is continued at high doses till the CSF becomes clear and cell count comes

down. Thereafter the drug is continued at a lower dose till all symptoms subside and the CSF returns to normal. Return of the CSF sugar level to normal indicates full recovery.

Supportive treatment consists of the maintenance of nutrition, fluid and electrolyte balance, treatment of shock and the management of convulsions. Adrenal crisis should be managed with large doses of hydrocortisone.

Course and prognosis: The disease was invariably fatal before the advent of specific antimicrobial therapy. At present the mortality is reduced to 10%. *Prognosis for full recovery and avoidance of complications depends directly on the early institution of specific antimicrobial therapy with glucocorticoids and therefore it is of utmost importance to make the diagnosis and start treatment without delay.* Other poor prognostic factors include extremes of age, presence of rash, tachycardia (>120 /minute), diastolic BP < 60 mm Hg, total leucocyte count < 1000 / cmm and platelet count below 180,000 / cmm. Long-term sequelae include cranial nerve palsies, seizure

disorders, various forms of paralysis and cognitive impairment.

Prevention

During epidemics it should be the aim to reduce the carrier state among the susceptible population. Rifampicin is given in a dose of 10 mg/kg once in 12 hours for 2 days for adults and children above 1 year. For children below 1 year the dose is 5 mg/kg bw 12 hourly for 2 days.

Alternate drugs include ciprofloxacin 500 mg oral or ofloxacin 400 mg oral single dose daily for four days. For pregnant women ceftriaxone 250 mg in single dose daily for a few days is the drug of choice.

Vaccination: Vaccines containing pure group specific capsular polysaccharides of meningococci A, C, Y and W135 groups are available. The vaccine is given subcutaneously. Immunity lasts for three years. At present this vaccine is available for persons going for Haj pilgrimage.

38

Common Bacterial Infections of Childhood

Diphtheria, Pertussis and *Haemophilus Influenzae*

K.V. Krishna Das

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Diphtheria

General Considerations

Definition: Diphtheria is an acute infectious disease caused by *Corynebacterium diphtheriae*, clinically characterized by a membranous inflammation at the site of infection and deleterious effects on several tissues particularly on the myocardium and nervous system due to the exotoxin.

C. diphtheriae are gram-positive rods $3 \times 0.3 \mu\text{m}$ in size, pleomorphic, non-motile, non-sporing, non-capsulate, generally aerobic and facultatively anaerobic. Based on the colony morphology on tellurite medium, biochemical reactions and hemolytic property, *C. diphtheriae* is classified into three main types—gravis, intermedius and mitis. Virulent strains produce an exotoxin which is responsible for producing remote effects. Around 90-95% of the gravis and intermedius strains are toxigenic while only 80-85% of mitis strains are so. The toxin is a labile protein of molecular weight 62,000 and it is inactive when released by the bacterium. Action of proteases present in infected tissue is necessary for its activation. Treatment with 0.2-0.4% formalin converts the toxin into toxoid. The toxoid is not harmful to the tissues, still it possesses antigenicity and hence is used for immunization.

Epidemiology: The disease has been almost wiped out from developed countries, but in India it is still prevalent. Diphtheria is more common in children, though all ages may be affected. The organism is harboured by carriers and cases. The disease is spread by droplets, contaminated vessels shared by children, or by direct inoculation into skin abrasions or eyes. Unimmunized children in a partially immunized community are highly susceptible. Relaxation of immunization schedule has led to resurgence of outbreaks of diphtheria in some Asian countries. Untreated cases are infective for more than two weeks. Antibiotic therapy reduces the communicability to 2-3 days. During outbreaks susceptible individuals can be identified by the Schick intradermal test, but this method is seldom used in practice.

Pathogenesis and Pathology

The organisms gain entry through the respiratory passage, eyes, middle ear, genitalia, and skin. Incubation period is 3-4 days but it may vary from 2-7 days. The exotoxin causes tissue necrosis, which favours further growth of the organism and toxin production. The epithelium degenerates and a serofibrinous exudate develops which contains inflammatory cells and fibrin. This forms a bluish white membrane over the involved area. The membrane is adherent and when removed forcibly it leaves a raw bleeding surface. Site of predilection for the primary lesions is the respiratory tract. Other sites of infection are the nose, ears, conjunctiva, genitalia, and skin. Around the membrane there may be necrosis, ulceration or hemorrhage. Sometimes, the membrane may not be evident, but the pharynx may show hyperemia and edema.

Regional lymph nodes are markedly enlarged. The toxin is absorbed from the primary site and it causes damage to the myocardium, kidneys, adrenal glands, and the cranial and peripheral nerves. Myocardium shows

cloudy swelling, fatty change, minute hemorrhages and round cell infiltration. This may lead to cardiomegaly and conduction disturbances. Kidneys show cloudy swelling of the tubular epithelium and interstitial nephritis. The adrenal glands are enlarged with hemorrhages in the cortex. Liver cells show degenerative changes with scattered areas of focal necrosis.

Peripheral nerves may show degeneration of the myelin sheaths and axis cylinders, motor fibers being more affected. The posterior column of the spinal cord may be involved. Rarely cerebral hemorrhage, meningitis, and encephalitis have been described. Respiratory obstruction by the membrane or toxic myocarditis may lead to death.

Clinical Features

These depend on the primary site of involvement, duration of the illness, systemic effects of the toxin, and resistance of the host. The disease starts with sore throat, low grade fever, headache, malaise, vague aches and pains and catarrhal symptoms. As the disease progresses, tachycardia, nausea, vomiting, pallor and weakness follow.

Pharyngeal diphtheria: It is the most common form and the membrane is present over the tonsils and pharynx. Gross cervical lymphadenopathy (described as bull neck) is evident and respiratory obstruction may develop, especially in children. In severe cases circulatory collapse occurs. Local effects of the toxin lead to paralysis of the palate and pharynx. The term “malignant diphtheria” is given to the condition characterized by marked edema of the submandibular areas and anterior part of neck. There is moderate leukocytosis (14,000-16,000/cu mm) with polymorphs forming 60-80%.

Laryngeal diphtheria: This forms 25% of the cases. It produces respiratory obstruction early, which may be fatal. The clinical features include barking cough, hoarseness, dyspnea, stridor and cyanosis. Infants with laryngeal diphtheria may refuse to suck the breasts due to choking.

Nasal diphtheria: It occurs in 2-3% of cases. The membrane is limited to the septum or turbinates and it is usually unilateral. The condition may present with a foul smelling serosanguinous nasal discharge or frank epistaxis.

Cutaneous diphtheria: *Corynebacterium diphtheriae* cannot penetrate the intact skin and it gains entry through wounds, burns, or abrasions. It causes ulceration. The typical ulcer is usually punched out and 0.5 cm or more in size. Sometimes, it may resemble a nonspecific ulcer. In the early stage the ulcer is covered by a greyish yellow or brownish membrane. There may be coexistent pharyngeal diphtheria in 20% of cases.

Other sites of lesion are the conjunctiva, vulva, vagina, uterine cervix, bladder, urethra, penis, middle ear, buccal mucous membrane and esophagus.

Complications: Mechanical obstruction of airway by the spreading membrane is a dreaded complication. The other complications are due to the systemic effects of the toxin. The incidence and severity of toxic manifestations increase in proportion to the extent of the membrane.

Toxic complications are most pronounced in the heart and motor nerves. Though 60% of patients have pathological lesions in the heart, only 10 to 12% manifest clinically. Myocarditis should be suspected if there is variation in the intensity of heart sounds, systolic murmurs, conduction defects, atrial fibrillation, ventricular ectopic beats, or ventricular tachycardia. Sudden death may occur due to ventricular fibrillation. Congestive failure and cardiac dilatation are less common. In infants and young children vomiting may be an early symptom of cardiac involvement. Though electrocardiographic changes are nonspecific, the presence of abnormalities strongly suggests myocarditis.

Toxic peripheral neuritis develops 2-6 weeks after the primary lesion. Third, sixth, seventh, ninth, and tenth cranial nerves are commonly affected. Palatal and pharyngeal paralysis may occur as early as the third day. External ophthalmoplegia and paralysis of accommodation are frequent. The autonomic neuropathy leads to paralysis of accommodation with preservation of light reflex. This pattern distinguishes diphtheritic paralysis from other conditions like botulism. Autonomic neuropathy involves the heart, vasomotor tone, urinary bladder and bowel. Motor weakness may involve the limbs or respiratory muscles. Ascending polyneuritic type of lesions may follow 2-3 months after the acute attack of diphtheria. Though there are pathological lesions demonstrable in the adrenals, most cases do not manifest clinically.

Diagnosis

The diagnosis of diphtheria is essentially clinical. Confirmation of the diagnosis depends on the demonstration of the organism in stained smears made from the membrane and by culture using Loeffler's medium. Fluorescent antitoxin staining provides a method for rapid diagnosis. Toxigenicity can be assessed by guinea pig inoculation, passive agar gel diffusion (Elek plate method), or counter immunoelectrophoresis.

Differential diagnosis: Acute follicular tonsillitis with exudate over the tonsils may resemble diphtheria. In follicular tonsillitis the exudate is confined to the tonsils, it is yellowish and can be wiped off without being adherent. The fever is high in acute tonsillitis whereas it is only mild in diphtheria. Regional lymphadenopathy is more marked in diphtheria than in acute tonsillitis.

Agranulocytosis and acute leukemia may lead to necrotic ulceration of the tonsils. In these there is no true membrane. The tonsils are red, enlarged, and necrotic or

hemorrhagic. Hematological examination establishes the diagnosis. In all cases of reasonable clinical suspicion, the antitoxin should be given without delay.

Treatment

The aims of treatment are to neutralize the formed toxins and eradicate the organisms from the primary site to prevent further production of toxin. The formed toxin is neutralized by the administration of diphtheria antitoxin (**anti-diphtheritic serum-ADS**) in adequate quantities. It can be given intramuscularly or intravenously. The dose can be roughly estimated from the extent of the membrane.

Only one tonsil involved	20,000 units
Both tonsils	40,000 units
Laryngeal and pharyngeal forms	80,000 units
Severe cases	120,000 units

The anti-diphtheritic serum is prepared in horses and so sensitivity to horse serum has to be tested by appropriate intradermal test using 0.1 mL of 1/100 solution. One centimeter erythema developing within 20 min indicates allergy. In allergic cases ADS should be administered only after desensitization or after taking appropriate measures to combat anaphylactic shock. Usually one dose of ADS is sufficient.

Corynebacterium diphtheriae is sensitive to penicillin and erythromycin. Procaine penicillin 600,000 units IM bd or erythromycin 40 mg/kg body weight in four divided doses, for 6 to 7 days is adequate to eliminate the organisms. Since there is the possibility of developing carrier state and spread of the infection, the child should be allowed to mix with other children only after ensuring that three repeated throat cultures are negative. General measures of treatment include rest in bed for two weeks and soft liquid feeds. Tetracycline, rifampicin and clindamycin are also effective against *C. diphtheriae*.

Since an attack of diphtheria may not lead to solid immunity, all cases should be followed up with regular vaccination with diphtheria toxoid, during convalescence.

Treatment of complications: Myocarditis is managed with strict bed rest, use of antiarrhythmic drugs, and supportive measures. Corticosteroids (betamethasone 8 mg four times daily) have been employed with beneficial results in some. Artificial pacing may be required if heart block develops.

Neuritis is usually self-limiting and does not respond to any specific treatment. Supportive care and physiotherapy are indicated. Nasogastric tube may be required to aid feeding, if there is palatal and pharyngeal paralysis.

Respiratory obstruction due to the presence of the membrane is an emergency indication for tracheostomy and maintenance of the airway. Respiratory paralysis is managed by artificial ventilation.

TABLE 38.1

Pathogenic non-diphtheria corynebacteria

Immunocompetent hosts	
<i>C. ulcerans</i>	Acute pharyngitis
<i>C. hemolyticum</i>	
<i>C. pseudotuberculosis</i> (<i>C. bovis</i>)	Lymphadenopathy
<i>C. minutissimum</i>	Erythrasma
Immunocompromised hosts	
Opportunistic infections	
<i>C. jeikeium</i>	Infective endocarditis
<i>C. xerosis</i>	Infection of intravascular prosthesis
<i>C. pseudodiphtheriticum</i>	
<i>C. equi</i>	Necrotising pneumonia

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Prevention

Prevention includes general active immunization and management of contacts. Active immunization is done with diphtheria, pertussis, tetanus (DPT) vaccine which is also known as triple antigen. The first dose should be given at two months and thereafter two more doses at four week intervals. Booster doses must be given at the second and fifth years. The DPT vaccine gives substantial immunity, but rarely the disease may occur even in immunized children. *Hemophilus influenzae* type b (Hib) vaccine can be combined with DPT vaccination for primary vaccination.

Immediate contacts should be given 2000 units of ADS. Throat swab culture should be done to identify the carrier state. Carriers should be given treatment. Penicillin or erythromycin is used to eradicate the infection. An alternative is rifampicin in a dose of 600 mg daily orally for 7 days.

A booster dose of DPT is required in previously immunized persons on fresh exposure.

Non-diphtheria corynebacteria: At times, corynebacteria other than C-diphtheriae may cause lesions as given in Table 38.1.

Whooping Cough

Syn: Pertussis

Introduction

The term pertussis, which means intensive cough, is an acute respiratory infection, seen more commonly in young children. The disease is also more serious in them. The term “whooping cough” is derived from the occurrence of progressive repetitive paroxysms of cough followed by inspiratory whoop. Natural pertussis infection and vaccination do not produce life-long immunity. The immunity wanes over a few decades. Since there is almost

complete coverage of DPT vaccination in children, adolescents and adults may become susceptible to infection increasingly. It is therefore possible that adults develop pertussis infection.

Pertussis is caused by *Bordetella pertussis* which is highly infective. *Bordetella parapertussis* and *B. bronchi-septica* are members of the same genus, rarely causing disease in man. Maximum incidence is seen in children below five years and the mortality is highest for children below 1 year of age. The organisms are spread by droplet infection and the route of entry is the respiratory tract. The infectious period is the catarrhal prodrome and for three weeks after the onset of illness. *Bordetella* are small gram-negative coccobacilli, exclusively pathogenic to humans. The genome of *B.pertussis* has been sequenced.

Pathology

The mucosal lining of the respiratory tract shows inflammation. Peribronchial lymphoid hyperplasia occurs initially and this is followed by necrosis of the midzonal and basilar layers of the bronchial epithelium. This leads to the accumulation of tenacious mucus, atelectasis and eventually bronchiectasis.

Clinical Manifestations

The incubation period is usually 7-14 days but may be prolonged to 20 days. Three stages can be distinguished—*catarrhal*, *paroxysmal* and *convalescent*—each lasting up to 2 weeks so that the course of the disease extends to 6-8 weeks.

The **catarrhal stage** manifests with rhinorrhea, mild fever, and cough. During this stage, clinical recognition of the disease is difficult. This is the most infective stage.

In the **paroxysmal stage** cough starts, increases in severity, and becomes repetitive and explosive. Each paroxysm is followed by a whoop produced by a sudden massive inspiratory effort through a narrowed glottis. During the paroxysms of cough the infant develops facial congestion, distension of neck and scalp veins, lacrimation, cyanosis, and clouding of consciousness. The paroxysm ends with the onset of vomiting. The whoop may not be distinctly made out in younger infants, but they may become asphyxiated and develop anoxic convulsions. Physical examination may reveal periorbital edema. In the uncomplicated cases lung signs are usually absent. Pertussis occurring in adults causes prolonged cough. With increasing age the manifestations also become more severe.

Convalescence is marked by the decrease in frequency and severity of the paroxysms. Vomiting subsides and the patient’s appetite improves. At this stage the child is very susceptible to develop superinfections by other respiratory pathogens and this may lead to recurrence of the paroxysms of cough. When this occurs it may last for several months.

Complications

Complications are common to develop

A. Respiratory:

Otitis media, especially in infants

Bronchitis

Bronchopneumonia

Atelectasis (segmental or lobar)

Interstitial or subcutaneous emphysema or pneumothorax due to rupture of alveoli.

Bronchiectasis

Flare-up of tuberculosis.

Sudden death of the infant may occur

B. Central nervous system:

Convulsions may occur due to anoxia, encephalopathy or rarely intracranial hemorrhage.

C. Gastrointestinal:

Severe vomiting with dehydration, tetany, ulceration of the frenum of the tongue (due to biting during a paroxysm), prolapse rectum, hernia.

D. Hemorrhages:

Epistaxis

Subconjunctival hemorrhage

Hemoptysis, hematemesis

E. Malnutrition:

Severe emaciation occurs in most of the affected children. In poor communities it is the starting point for marasmus and kwashiorkor.

Diagnosis

The disease has to be suspected clinically, particularly in an unimmunized child with known contact with the disease. Total leucocyte count is elevated to 20,000 to 50,000/cmm with absolute lymphocytosis. A leukemoid reaction may sometimes occur. Chest X-ray may show perihilar infiltrates or segmental collapse. Bacteriological diagnosis is established by culturing the organism obtained from nasopharyngeal swabs. Fluorescent antibody staining of pharyngeal specimens provides a rapid and specific diagnosis. PCR using nasopharyngeal aspirate reveals the organisms. In cases with duration above two weeks IgG antitoxic antibody can be demonstrated in serum.

Differential diagnosis: Whooping cough has to be differentiated from other conditions in childhood causing spasmodic cough. These are acute bronchitis, bronchopneumonia, aspiration of foreign bodies; extrinsic compression of the trachea and bronchi by tuberculous glands or other masses, obstructive airway disease, cystic fibrosis, and congenital malformations of the upper respiratory tract. Infections with *B. parapertussis*, *B. bronchiseptica* and adenovirus types 1, 2, 3 and 5 closely resemble whooping cough and cannot be clinically differentiated. Respiratory syncytial virus infection is becoming more widespread, accounting for a high proportion of respiratory morbidity

in children. This has to be borne in mind. Postnasal drip caused by dripping of exudate from the nasopharynx may lead to spasmodic cough when the child lies in bed. This may mimic whooping cough.

Treatment

Supportive care is important to maintain nutrition, prevent aspiration into the respiratory tract and maintain the airway. The airway is cleared by suction of the exudates. Anoxic convulsions are managed by administration of oxygen and anti-convulsants. Small, frequent feeds are tolerated if given soon after a paroxysm of cough. Intravenous fluids may be required if the child is dehydrated. In general, administration of antibiotics does not shorten the paroxysmal stage, once it is established. Erythromycin 50 mg/kg/day given for 5-7 days will reduce the period of communicability. It may even abort or prevent the progress of the disease if given in the catarrhal stage. Ampicillin, chloramphenicol and cotrimoxazole may also be used as alternative drugs. Azithromycin 250-500 mg po, od for 7-10 days is effective in controlling the infection if started early. Clarithromycin is a suitable alternative.

Antibodies are not transferred transplacentally in the case of whooping cough. In most patients, a single attack confers life-long immunity.

Prevention

Active immunization is achieved by the administration of the pertussis vaccine, usually given in combination with diphtheria and tetanus toxoids (DPT). The vaccine contains killed *B. pertussis*. The initial dose is given at 2 months, with 2 more doses at 4 week intervals. The first booster is given 1 year later and the next one at school entry. Adverse reactions may develop after vaccination. These are local reactions, fever developing within 12 to 24 hours of injection and rarely post-vaccination encephalitis. The reported risk of encephalitis is 1 in 10^5 to 10^6 vaccinations. At present the benefits of vaccination far outweigh the risks and, hence vaccination should be recommended for all infants. Contraindication to vaccination is severe adverse reaction to a previous dose. If a child has missed pertussis vaccination at the ideal period, it is better to start the course as early as possible. Conventional pertussis vaccine produced in India contains products of whole organisms. It is cheap, but it is likely to cause more adverse reactions. With whole cell vaccines the immunity begins to diminish after 3-5 years and possibly vanishes by 10-12 years.

(Scott A Halperin. N Eng J Med 2007;356:110-113).

Acellular vaccines containing up to five specific antigens of *B. pertussis* are available in other countries. They produce less of adverse reactions, but are more

costly. Adults exposed to risk of infection, such as doctors and nurses can also be protected by vaccination.

Haemophilus Influenzae Infections

General Considerations

Haemophilus are pleomorphic gram-negative rods, which are generally aerobic, but can be facultatively anaerobic. *H. influenzae* is an exclusively human parasite, residing principally in the upper respiratory tract.

Haemophilus influenzae exists in coccobacillary form in cultures but shows bacillary morphology in cerebrospinal fluid of patients with meningitis. It is mainly aerobic but can also grow anaerobically. Culture yields capsulated and non-capsulated colonies. The capsulated forms are more virulent. The organisms have been classified into six types designated a to f based on the capsular polysaccharide. The polysaccharide capsule-polyribosyl ribitol phosphate (PRP) is an important determinant of virulence and the major target for specific immunity. Type b is responsible for most of the serious infections. Around 60-80% of children below three years harbor the organism in the upper respiratory tract. Maternal antibodies confer passive immunity to the child upto the age of two months. Children aged two months to three years are more susceptible to infection. Natural immunity develops due to subclinical infections after the age of three years.

Pathogenesis and Pathology

Haemophilus influenzae may act as the primary pathogen to cause meningitis in children, laryngoepiglottitis, otitis media, pneumonia, arthritis, endocarditis, and pericarditis. It acts as a secondary pathogen in bronchitis, bronchiectasis and sinusitis in adults. Secondary infection is caused by noncapsulated strains.

CLINICAL SYNDROMES

***Haemophilus influenzae* meningitis** follows an acute course and is fatal in 90% of cases, if left untreated. Laryngoepiglottitis causes considerable edema and airway obstruction. Emergency tracheostomy may be necessary to save life. Infection of the lung and pleura lead to lobar pneumonia with empysema.

***Haemophilus influenzae* frequently causes pharyngitis** in children. In adults during prolonged antibiotic therapy superinfection by *H. influenzae* may develop. The

mucosa is red and may be covered by a soft yellow exudate. The local pain and discomfort are out of proportion to the appearance of the lesion. Systemic complications such as septicemia with arthritis, endocarditis, and pericarditis may occur, especially in children.

Secondary infection by *H. influenzae* causes bronchopneumonia, exacerbation of chronic bronchitis and other suppurative pulmonary lesions.

Laboratory Diagnosis

The organism can be identified by Gram stain and can be cultured from materials such as CSF, sputum, pus, etc. Since the organism is highly susceptible to low temperatures, refrigeration during transit should be avoided. The capsulated strain shows Quellung phenomenon when added to type B antiserum.

Treatment

The common antibiotics such as chloramphenicol, ampicillin, and cotrimoxazole are effective. Resistant strains have emerged. Tetracycline or chloramphenicol can be used for treating exacerbations of chronic bronchitis and emphysema. In milder nonfatal infections these drugs can be tried. Meningitis and epiglottitis are rapidly fatal if untreated. Ampicillin does not cross the blood brain barrier in adequate concentration. Third generation cephalosporins are the drugs of choice. For children cephalexin 200 mg/kg bw in divided doses IV has to be administered. For adults the daily dosage may reach up to 12 g. Ceftriaxone in a dose of 100-150 mg/kg bw/day is an effective alternative.

Active Prophylaxis

In many parts of the world a purified capsular polysaccharide vaccine is used. Vaccines have been developed through covalent linkage of the PRP to carrier protein. Four different types of vaccines are available. Hib polysaccharide tetanus protein conjugate vaccine (PRP-T) contains tetanus toxoid as the carrier protein. This can be given along with DTP vaccination in the second, third and fourth months. A booster dose may be required after two years. Routine vaccination has almost eliminated the infection in many countries.

In household contacts, children below the age of five years run the risk of acquiring infection. Rifampicin in a dose of 20 mg/kg daily given orally for 4 days eradicates the carriage of *H. influenzae*.

39

Salmonella Infections

S. Bhasi, K.V. Krishna Das

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General Considerations

Salmonella are members of enterobacteriaceae. They are gram-negative motile rods, commonly found in the intestinal tract of humans, several animals and many arthropods. More than 2000 serotypes have been identified.

Clinical syndromes caused by *Salmonella* include:

1. Typhoid fever and paratyphoid fevers caused by *S. typhi*, *S. paratyphi A*, *B* and *C* – collectively known as enteric fevers.
2. Gastroenteritis (*Salmonella* food poisoning)
3. Bacteremia with or without metastatic infection
4. Asymptomatic carrier state.

Typhoid Fever

Typhoid fever is an acute febrile systemic infection caused by *Salmonella typhi* with initial lesion in the bowel, bacteremia and subsequent affection of many tissues.

Etiology

Salmonella typhi is an exclusive pathogen of humans. 3 antigens have been demonstrated

1. Somatic antigen (called 'O' antigen) – a lipopolysaccharide cell wall antigen

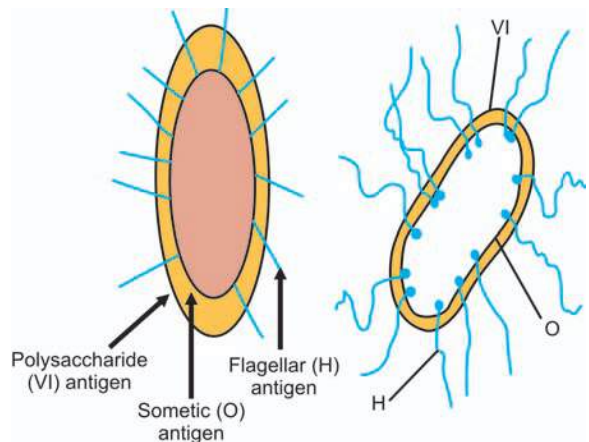


Fig. 39.1: Schema of the antigens on salmonellae
O – somatic antigen H-flagellar antigen VI- virulence antigens

2. Flagellar antigen (called 'H' antigen) – formed from the structural proteins making up the flagella
3. The polysaccharide envelope VI antigen which confers virulence by masking the 'O' antigen from immunological attack (Fig. 39.1).

Epidemiology

The global incidence is around 15 to 30 million cases annually with half million deaths. The disease remains a serious public health problem in developing countries. The incidence in India is about 100 to 1000 cases per 100000 persons per year and enteric fevers continue to be a major infection throughout the country.

The organisms are excreted in feces and urine of cases of typhoid fever in the acute phase and upto 9 weeks during convalescence. Healthy carriers pass the organism in feces and urine without themselves suffering from the disease for indefinite periods. Disease is spread by fecal-oral route, infection getting in by contaminated water sources, milk, ice creams, processed meat, shell fish, food contaminated by infective food handlers and flies. The bacilli remain viable in water or food for considerable periods.

Pathogenesis

Several factors determine the establishment of infection. They are

1. *Size of the infective dose.* The average infective dose in immunocompetent subjects is 10^7 organisms. Higher infective doses are required to transmit paratyphoid.
2. Normal gastric acid rapidly kills the bacilli. Susceptibility is increased by diluting gastric acid by the ingestion of large quantities of fluids with and before meals, antacids, acid suppressant drugs, vagotomy and prior infection with *H.pylori*.
3. Virulence of the infecting strain – multi drug resistant organisms and isolates from fatal cases might vary in their virulence. Highly virulent strains are more invasive.
4. Immune status of the host and the status of bacteria in the upper part of the duodenum and jejunum.

Bacilli enter the epithelial lining of the distal ileum and reach the submucosa where they are phagocytosed by macrophages and polymorphs and reach mesenteric lymph nodes. There, they multiply and enter the blood stream via thoracic duct to produce transient bacteremia. This primary bacteremia results in the organisms reaching the liver, gallbladder, spleen, bone marrow, lymph nodes and other parts of the reticuloendothelial system where further intracellular multiplication occurs inside mononuclear cells throughout the 7 to 14 day incubation period. A second bacteremia follows accompanied by symptoms as the infection spreads throughout liver, gallbladder, spleen, Peyer's patches and bone marrow.

The organism produces endotoxins, which stimulate release of cytokines from macrophages and neutrophils responsible for inflammatory changes in various organs and production of constitutional symptoms and fever.

Pathology

Inflammatory changes mainly occur in the liver, spleen, lymph node, bone marrow and Peyer's patches consisting of mononuclear cell infiltration, hyperplasia and focal necrosis. Focal collections of mononuclear leukocytes are called **typhoid nodules**. The liver is enlarged and shows cloudy swelling. The Peyer's patches in the terminal ileum becomes swollen and surface undergoes necrosis with formation of ulcers. Blood vessels here may be eroded leading to intestinal hemorrhage. Ulceration may extend to the muscularis mucosa and serosa and may result in intestinal perforation. The rectus abdominis muscle may show Zenker's degeneration.

Clinical Features

The usual incubation period is 7-14 days (range from 3-60 days) Typhoid predominantly affects children and

young adults especially in endemic areas because of acquired immunity. It affects both sexes equally. The clinical manifestations are very variable ranging from fever with little other morbidity to marked toxemia and associated complications involving many systems. In a classical case onset is slow with fever, headache, lethargy, anorexia and malaise. The fever is continuous or remittent; it rises in a step ladder pattern in the first week. Chills and rigor do not occur if antipyretics are not used. Abdominal symptoms such as vague discomfort, pain, constipation in the first week, and diarrhea in the second and third weeks occur commonly in the majority of cases. Diarrhea is more common in children. Epistaxis may occur occasionally. Nonproductive cough may be prominent in a few and this may be mistaken for a primary respiratory disease.

Physical examination *in the first week* reveals relative bradycardia (slow pulse fever) and mild tenderness in the right iliac fossa. Erythematous 2-3 mm diameter maculopapular lesions called '*rose spots*' may appear over the upper abdomen and chest by the 5th or 6th day and fade off after varying periods. They are best made out in fair skinned people. They are rare in the local population. They fade after 2-3 days. They are caused by local vasodilatation; probably due to bacterial emboli. *In the second week* temperature reaches around 40°C and remains so for a few days. The tongue is coated in the center. Spleen is palpable 2-4 cm and soft in about 70% of cases. Abdomen is moderately distended (tumidity) with vague tenderness especially over the right iliac fossa. Palpation may also reveal gurgling due to distended ileal loops. Mild scattered wheeze in the chest is not uncommon. Malena or streaks of blood in feces may be present in a few. This should not be mistaken for typhoid hemorrhage in which bleeding is more pronounced.

Patients with advanced disease and toxemia may show "typhoid facies" (**typhoid state**). – a thin flushed face with staring apathetic expression. Typhoid encephalopathy may develop in severe cases in the second to fourth week and may present as muttering delirium, tremulousness of the fingers and wrist (**subsultus tendinum**), picking movement of the hands- example picking at the bed clothes (**carphology**) and a staring unarousable stupor – unconscious but eyes open (**coma vigil**) In uncomplicated untreated cases fever lasts for about 4 weeks and subsides by lysis.

Typhoid in children – It is a milder illness with diarrhea, vomiting and jaundice more commonly.

Neonatal typhoid may occur due to vertical transmission from infected mother during late pregnancy. It is rare but could be life threatening if it occurs.

Uncommon presentations

1. Gastroenteritis – acute presentation with vomiting and diarrhea. More common in children especially in paratyphoid

2. Acute bronchitis—fever cough and bilateral wheeze.
3. Acute abdominal pain mimicking acute appendicitis.
4. Jaundice from beginning – seen in about 1-5% cases. This may mimic viral hepatitis, leptospirosis or malaria
5. Lobar pneumonia caused by *S. typhi* (pneumotyphoid) may occur in 1-2%, *S. typhi* may be isolated from sputum culture. The chest lesion may resemble pneumococcal pneumonia.
6. Acute right upper abdominal pain may be mistaken for acute cholecystitis
7. Acute glomerulonephritis (nephrotyphoid) is seen in upto 3% cases – more common in children,
8. Fever with joint pain may resemble rheumatic fever. This occurs rarely.

Complications may develop quite frequently. These may be general or may be confined to the various organ systems. General complications include dehydration, typhoid state, coma vigil, convulsions in children, delirium and septic shock. Systemic complication are listed below:

Gastrointestinal system: Perforation of ileum with peritonitis, intestinal hemorrhage, paralytic ileus, cholecystitis

Respiratory: Pneumonia

Neuropsychiatric: Typhoid encephalopathy, typhoid meningitis, transverse myelitis, peripheral neuropathy

Hematological: Disseminated intravascular coagulation (DIC), thrombocytopenia

Genitourinary: Glomerulonephritis, pyelonephritis, urinary retention

Cardiovascular: Myocarditis, endocarditis, deep vein thrombosis, thrombophlebitis

Miscellaneous: Focal sepsis, abscess in liver, spleen, breast, typhoid osteomyelitis, parotitis, arthritis, bone abscess (Brodie's abscess)

Relapse

Intestinal hemorrhage occurs during the second or more commonly, the third week of illness. Mild bleeding manifesting as occult blood or malena is seen in about 20% of cases. Severe bleeding from the ulcerated Peyer's patches occurs in about 2% of cases. Unexplained tachycardia, fall in BP, sudden drop in temperature and pallor indicate the onset of intestinal hemorrhage. Patient passes fresh blood and clotted blood with feces in large quantities. If not treated, hypovolemic shock sets in and death follows.

Intestinal perforation occurs in 1-3 % of cases. Terminal 50 cm of the ileum is the site of perforation. The onset of perforation may be heralded by abdominal pain, tenderness and rigidity and features of shock including sudden fall of temperature. Signs of perforation such as abdominal rigidity tenderness and absence of peristaltic

sounds develop from the right iliac fossa and later become generalized. Due to escape of gas into the peritoneal cavity the liver dullness may be obliterated. The temperature may fall. Signs of free fluid in the peritoneal cavity and general peritonitis develop later. Severely ill patients may present without classical features and may show only restlessness, tachycardia and hypotension,

Presence of gas under the diaphragm can be demonstrated by X-ray chest taken in the erect position. Ultrasonography helps to confirm the diagnosis. Secondary infection of the peritoneal cavity leads to increasing toxemia. In untreated cases mortality exceeds 80%. With prompt treatment mortality can be reduced to less than 10%. In those who survive peritonitis may become localized to form an abscess palpable as a mass in the right iliac fossa.

Relapse In 5-10% cases one to three weeks after recovery, fever and other symptoms return. Blood culture often becomes positive again. Relapse rate is lower in those treated with fluoroquinolones and ceftriaxone, compared to those treated with chloramphenicol, cotrimoxazole, ampicillin or amoxicillin. Relapses are generally milder than the initial illness. They respond to the same antimicrobials. Usually only one relapse occurs but rarely several relapses may occur in succession, extending the febrile episode to even a few months.

Chronic carriers are those who continue to excrete *Salmonella* in feces or urine for more than one year. Fecal carriage is more frequent in women above 40 years and those with gallbladder disease. Urinary carriage may be seen more commonly in people with nephrolithiasis or schistosomiasis. Chronic carriers act as source of infection to others especially if they are working as cooks or food handlers.

Immunity: Infection confers partial immunity, which is unrelated to titer of antibodies against O, H, or Vi antigen.

Diagnosis

Clinical: Typhoid fever has to be considered in the differential diagnosis of all prolonged febrile illnesses seen in tropical countries. These include hepatic amebiasis, tuberculosis, infective endocarditis, brucellosis, leptospirosis, typhus, viral hepatitis, malaria, lymphoma, infectious mononucleosis, and prolonged viral fever.

Clinical clues to suspect typhoid

- Fever more than 5-7 days especially in children and young adults
- Gastrointestinal symptoms- vague abdominal pain altered bowel habits ± melena or hematochezia
- Relative bradycardia
- Palpable soft spleen
- Palpable liver ± tenderness

- Central coating of the tongue
- Perforation or peritonitis
- Major GI bleed
- Severe toxemia
- Myocarditis
- And peripheral circulatory failure

Laboratory Diagnosis

A. Isolation of *Salmonella typhi*

1. **Blood culture is the** mainstay of definite diagnosis. Blood is taken directly into 10 times its volume of culture media and incubated. Blood clot treated with streptokinase can also be used. Blood culture is usually positive in 72 hours. Sometimes incubation for up to 7 days may be needed. Positivity of blood cultures progressively diminishes from 90% to 75%, 60% and 25% or less respectively from the first week to the fourth week of the illness. Culture becomes negative soon after starting specific antibiotics.
2. **Bone marrow culture:** This gives the highest positivity. It is especially useful when blood culture is negative. It may remain positive even after starting antimicrobials. 1 to 2 mL of bone marrow aspirate is sufficient.
3. **Bile culture:** Culture of bile aspirated from the duodenum also yields better results.
4. **Feces culture:** This gives higher yield in the third week up to 75 %. Specificity is limited because of the positive results in carriers.
5. **Skin snip from rose spots:** This is not commonly done. It is reported to be positive in 75% of cases, and it may remain positive even for a few days after starting antibiotics.
6. **Urine culture:** This is positive in only 25 to 35% of cases, since bacteriuria may be intermittent. Specificity is limited since carrier state is known to exist. Both in the case of feces and urine culture positive results associated with rise in antibody titre is diagnostic.

B. Widal test: This identifies the agglutinating antibodies against the O and H antigens for *S. typhi* and *S. paratyphi* A and B.

It is a time honoured test in vogue for over eight decades introduced by Fernand Widal (French physician, 1862-1929) for the diagnosis of enteric fevers.

Antibody generally appears by the end of first week, steadily increases upto 3rd or 4th week and then gradually declines after varying periods, often months. Patients in endemic areas who are exposed to *Salmonella* antigen earlier (clinical/subclinical infection or TAB vaccination) may give a rapid and stronger antibody response.

The O antigen is shared by other *Salmonella* and other members of enterobacteriaceae, this sharing being only

partial. Both O and H antibodies increase but the O antibody rises earlier than H antibody. The O antibodies are more specific than H antibody and therefore they are diagnostically more important. The antibodies fall rapidly, reaching low values after 6-12 months. A four fold rise in antibody titre in paired samples collected 5 – 7 days apart is a fairly reliable evidence for diagnosis. The result of a single acute sample should be interpreted taking into account the locally prevalent-widal titer in the general population. Titers of 1/200 or more are suggestive. In the general population of south India 10% show H antibody titre upto 1 : 100 dilution and 2% upto 1: 200 dilution. Prevalence of O antibody in the general population is much less.

O antigen of paratyphoid A and B show cross reaction with that of *S. typhi* and hence O antibody titer is not commonly taken into consideration in the diagnosis of paratyphoid fevers. Widal test is simple and cheap compared to blood culture, but fraught with pitfalls.

The Widal test has a few disadvantages. These include delay or blunting of the antibody response, rise of only the O or H antibody, pre-existing high titers of antibody, false positive response and anamnestic reaction.

Anamnestic reaction: This is the rise in antibody levels in patients who have been exposed to antigen in the past, often by TAB vaccination, when they get any non-specific febrile illness. Hence information about previous vaccination is necessary to assess the diagnostic reliability. This rise in titer involves antibodies of all the *Salmonellae* and it is transient. More over a four-fold rise in titer may not occur on repeating the test.

Early antibiotic treatment may blunt the antibody response. False positive Widal may occur in malaria, rheumatoid arthritis, chronic liver disease and others.

Other Serological Tests

Many other tests for detection of antibodies, *S. typhi* antigen and *Salmonella* DNA in the body fluids have been described. These include passive hemagglutination, counter immunoelectrophoresis, latex agglutination and PCR.

Other laboratory findings include mild normocytic normochromic anemia mild thrombocytopenia and leukopenia with relative lymphocytosis. Leukocytosis may occur when typhoid is complicated by perforation, peritonitis, secondary sepsis or major bleed. The ESR is generally not elevated in uncomplicated typhoid. Mild to moderate elevation of transaminases (ALT and AST) is common.

MANAGEMENT

1. Supportive
2. Symptomatic

- 3. Specific – antimicrobial
- 4. Prevention

General Supportive Care

Rest in bed, proper nursing care, measures to avoid bed sores and maintenance of oral hygiene are to be instituted. A nutritious diet helps in recovery. The diet must be easily digestible and of low residue type. At least 1200-1500 Calories should be supplied as diet. Fluid and electrolyte balance have to be looked after. Generally 2-3 L of fluid should be given orally if patient tolerates. If not I V fluids are indicated. In places where IV fluids cannot be given and the patients cannot accept oral fluids due to vomiting, about 1-1.5L of saline can be given in 3-4 hours as a rectal drip through a urinary catheter introduced high up into the rectum, if the patient can tolerate.

Symptomatic Treatment

Paracetamol is useful for treating fever and headache in doses of 0.5 g 6.h. Tepid sponging, ice caps and physical methods of cooling may be given to lower the temperature when indicated and to give comfort and relief.

Abdominal discomfort and bloated feeling can be reduced by dietary adjustment-low residue easily digestible articles of food given in small quantities at 2-3 hours intervals. Antacid and anti-flatulent drugs such as magnesium hydroxide (250 mg) and activated dimethicone 50 mg given 6 h are effective. Constipation can be relived by drugs like milk of magnesia 11.25 mL as emulsion or sodium picosulphate 10 mg as tablets or syrup. Diarrhea can be controlled by avoiding milk and fatty foods in the diet and an opiod such as codeine phosphate 10-20 mg orally.

Specific Antimicrobial Drugs

The initial choice of antimicrobial drugs depends on the sensitivity pattern of *S.typhi* and *S. paratyphi* isolates in the local area. The following drugs are commonly used.

Fluoroquinolones- ciprofloxacin and ofloxacin

Cephalosporins-ceftriaxone (IM/IV), cefixime(oral) chloramphenicol, ampicillin / amoxicillin, cotrimoxazole in the usual doses. Except in resistant cases all these drugs produce fall in temperature to normal in 3-5 days, reduction of toxemia and cure in more than 90% of cases within 7-10 days (Table 39.1).

Antimicrobial Resistance of Salmonellae

This is mediated by plasmids. Chloramphenicol resistance was initially described in 1972 from Kozhikode by Jayaram Panicker et al. Several reports from Calcutta, Chandigarh and many parts of India and other countries of the world followed soon. The late 1980s witnessed widespread emergence of multidrug resistant *Salmonellae*, particularly *S. typhi*, resistant to chloramphenicol, cotrimoxazole and amoxicillin/ampicillin. This phenomenon continued till the 1990s. Fluoroquinolones, particularly ciprofloxacin and ofloxacin, and ceftriaxone became the drugs of first choice for typhoid. With the drastic reduction in the usage of chloramphenicol, resistance to this drug fell to less than 20% by 2000. Resistance to quinolones started appearing in the mid '90s at many centers in India and abroad and reached upto 50%. Ciprofloxacin- resistant cases may still be sensitive to ofloxacin. Resistance to nalidixic acid is a standard criterion used to assess the drug sensitivity of Salmonella. Resistance to nalidixic acid warrants the use of higher doses of quinolones. Cephalosporin resistance has also been reported but it is not widespread.

S.Typhi and paratyphi isolates can be classified into

- 1. Sensitive to 1st line antimicrobials like chloramphenicol, cotrimoxazole, and amoxycillin/ampicillin
- 2. Multi drug resistant but quinolone sensitive
- 3. Multi drug resistant including quinolone resistance

Fluoroquinolones -ciprofloxacin and ofloxacin- are very effective drugs for treatment of quinolone- sensitive typhoid fever with low relapse rate and chronic carrier

Commonly used antimicrobials in typhoid				
Antibiotics	Dose mg/kg/day	No of doses	Route	Duration days
Chloramphenicol	50 - 75	4	Oral/IV	14
Cotrimoxazole	6.5-10 trimethoprim	2	Oral/	14
Amoxicillin	75-100	3	Oral/IM/IV	14
Ciprofloxacin	1.5 g/day oral/400 mg IV bd	2/2	Oral/IV	7-14
Ofloxacin	800 mg/day	2	Oral/	7-14
Ceftriaxone	60 mg/kg	-2	IV/IM	7-14
Cefotaxime	80 mg/kg	3	IV	7-14
Cefixime	20mg/kg	2	Oral	7-14
Azithromycin	8-10mg/kg	1	Oral/IV	7

state (< 2 %). Chloramphenicol, which used to be the traditional first line drug of choice is less effective in this regard. Ceftriaxone and azithromycin (oral or parenteral) are useful for treating MDR typhoid including quinolone resistance.

Unless there are definite contraindications the drugs and fluids can be given orally. Indications for parenteral administration include severe toxemia, vomiting, and complications such as perforation and peritonitis, hemorrhage, paralytic ileus, meningitis, encephalopathy and toxic shock.

Drugs should be started in full dosage and administered regularly. If the organisms are sensitive, temperature starts coming down in 48-72 hours after starting the drug. Failure to achieve fall of temperature may be due to drug resistance of the organism or other coexisting complications. The drugs have to be continued at full dose for 5-7 days after the temperature has touched normal and remained so. Premature withdrawal of antibiotic therapy predisposes to relapse especially when bacteriostatic drugs like chloramphenicol are used. Toxicity of the drug should be look for.

Role of Glucocorticoids in Typhoid

Short course of oral or parenteral corticosteroids for 3-5 days has been found to be beneficial in patients with severe toxemia who are acutely ill or have encephalopathy and hypotension. Different regimens have been tried, eg. hydrocortisone 300 mg IV daily in divided doses for 3 days or prednisolone 30-40 mg (1 mg/kg bw) for 3-5 days or other preparations in equipotent dosage.

Prognosis. With early diagnosis and proper treatment, prognosis is good with full recovery in the vast majority. In uncomplicated cases, the mortality is 1-2%. Complications such as toxemia, hemorrhage, perforation and meningitis increase the mortality. Septic shock and multi-organ failure are serious with higher mortality.

TREATMENT OF COMPLICATIONS

Intestinal perforation: If the perforation is recent (within 12 hours) and the general condition satisfactory, emergency surgical closure with broad spectrum antibiotic coverage is indicated. If perforation is more than several hours old and the general condition poor, conservative treatment with IV broad spectrum antimicrobial combinations, IV fluids and other supportive measures should be instituted. With proper care the vast majority of these patients can be saved.

Intestinal hemorrhage: Blood loss has to be corrected with blood transfusion if there are signs of hypovolemia such as increasing pulse rate and fall in blood pressure, with continuance of active bleeding. In a severe case rapid quantitative replacement of several units of fresh blood may be required.

Treatment of chronic carriers: Most chronic carriers without gallstone disease can be cured by prolonged course of antimicrobials. Useful regimens are

1. Cotrimoxazole – 6.5 to 10 mg/kg of trimethoprim in two divided doses for 2 months
2. Ciprofloxacin 750 mg twice daily for 4 weeks
3. Amoxycillin/ampicillin 100 mg/kg with probenecid in 4 divided doses for 3 months

For patients with gallstone disease cholecystectomy is indicated in addition.

Treatment of Relapse

Usually relapse also responds to the same antibiotics which are effective for the primary disease. Hence the same medication should be continued, preferably for a longer period, with bacteriological monitoring.

PARATYPHOID FEVER

These are produced by *Salmonella paratyphi* A, B and C. Incubation period is shorter. The illness generally resembles typhoid in clinical pattern but toxemia and complications are less in the majority of cases. The duration of illness is shorter and mortality is less. At present more severe cases are being reported from south Asian countries. There is also disproportionate increase in paratyphoid fever. Gastroenteritis like presentation is more common, especially in children with *Paratyphi* A infection. In some cases paratyphoid may equal typhoid in severity and complications. Diagnosis is confirmed by isolating the organism and serological tests. Treatment is on lines similar to that of typhoid.

Prevention of Salmonella Infections

Personal hygiene, environmental sanitation and eradication of carriers help to prevent salmonella infection. Vaccination is indicated for persons travelling into endemic areas and for contacts and neighbors around index cases.

Vaccines

1. TAB vaccine: This is the most time-tested vaccine. It is a parenteral, killed, whole cell typhoid-paratyphoid A and B vaccine. It is effective, but largely discontinued in many countries because of side effects. In adults 2 doses of 0.5 mL given IM 1-2 weeks apart followed by booster doses every year is the recommended schedule. Adverse side effects include local pain and fever.
2. Vi polysaccharide vaccine – This can be used above the age of 2 years. A single IM or SC injection of 25 mcg gives 70-80% protection for 3 years. Revaccination is recommended every three years.
3. Ty 21a vaccine – This is a Swiss, live attenuated oral vaccine recommended for persons above 6 years of

age. Three doses are to be given on alternate days. Moderate protection occurs for three years.

None of the vaccines produces absolute protection and typhoid can occur if the infecting dose is very high.

A new Vi conjugate vaccine has been developed recently and preliminary data shows efficacy.

Disinfection of water sources with bleaching powder, boiling drinking water, anti-house fly measures and regular washing of hands before eating help to prevent spread of infection and contain the outbreak of typhoid.

Non-typhoid *Salmonella* Infections

These are produced by *Salmonella enteritidis* and *Salmonella typhimurium*. They lead to enterocolitis, bacteremia and localized infections.

Epidemiology : Infection is spread through food and water. Many animals such as chicken, ducks, cattle, sheep, horses, dogs, cats and rodents harbor these organisms as commensals in the intestines. Chicken and duck eggs constitute the largest reservoir of infection. Fish and mussels grown in contaminated water may act as sources for localized outbreaks. Humans develop convalescent or healthy carrier state and excrete the organisms for long periods.

Pathology: After gaining entry through food or drinks the organisms multiply in the small intestine and colon to produce inflammation of the lamina propria of the villi of both the small and large intestines. The lymphoid follicles are enlarged and become swollen. Diarrhea is produced by the production of enterotoxin and direct epithelial invasion. Organisms enter the blood stream to produce bacteremia and metastatic lesions. Conditions like sickle cell anemia and other hemoglobinopathies predispose to

the development of recurrent *Salmonella* infections. Osteomyelitis is common in them.

Clinical Features

Enterocolitis: This is also known as *Salmonella* food poisoning. Lesions occur both in the large and small intestines. Incubation period is usually 8-24 hours but can go up to 3 days. Patients present with fever, abdominal pain and diarrhea. Diarrhea is produced by production of enterotoxin and direct epithelial invasion. The nature of stool varies from profuse watery, to frank dysentery. In healthy young adults *Salmonella* gastroenteritis is usually a benign self-limiting illness, but in young children and elderly, severe dehydration may develop. Spontaneous resolution usually occurs in three to four days. Bacteremia occurs in 1-2%, more commonly in elderly and immunocompromised subjects. Microscopy of the feces shows cellular exudates and organisms can be cultured from feces.

Treatment Mainstay is replacement of fluid and electrolytes. Antibiotics do not alter the outcome. In severe cases ciprofloxacin may be useful.

Salmonella Bacteremia

This is characterized by prolonged or intermittent fever associated with rigor and chills and positive blood culture. Gastrointestinal symptoms may or may not precede bacteremia. Diagnosis is established by positive blood culture. Localized lesions develop in 25% of cases. This includes bronchopneumonia, lung abscess, pleurisy, empyema, pericarditis, endocarditis, nephritis, arthritis, osteomyelitis and meningitis. WBC count is usually normal but may be elevated when localized suppuration develops. Treatment is with systemic antibiotics on lines similar to that of typhoid.

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Gram-negative Bacterial Infections *Shigella*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas* and *Proteus* Infection

S. Bhasi

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Shigella Infections

GENERAL CONSIDERATIONS

Bacillary dysentery is caused by organisms belonging to the genus *Shigella*. Clinically dysentery is characterized by diarrhea with blood and mucus in the stool. Fever and abdominal pain may be present in the majority. *Shigella* dysentery is common in the tropics where environmental sanitation is poor and food hygiene is low.

Shigella are gram -ve non-motile, non-capsulated bacilli belonging to the family enterobacteriaceae. They are classified into 4 species on the basis of antigenic and biochemical features.

1. ***Shigella dysenteriae*** – Types 1 and 11 (*S. shigae* and *S. schimittii*) Type 1 is responsible for the most severe form of dysentery. They account for 8–25% of cases in India.
2. ***Shigella flexneri*** – Most common pathogen responsible for dysentery in developing countries – accounts for 50–85% of cases in India.
3. ***Shigella sonnei*** – Typically causes mild watery diarrhea – commonest cause in the west, responsible for 2–24% cases in India.
4. ***Shigella boydii*** – Least common isolate, usually produces mild disease.

S. shigae is very virulent pathogen, the infective dose can be as low as 10 to 100 organisms.

Epidemiology

Man is the main host. Infection is transmitted by fecal – oral route. Contaminated water supply, low personal hygiene, overcrowding, inadequate sewage facilities and proliferation of house flies contribute to the spread of disease. Apart from contamination of food and water, disease can be acquired through fomites, lavatory seats, door handles and others. During clinical illness and for upto 6 weeks after recovery organisms are excreted in the feces. These may survive for several months in food and water. *Shigellae* are relatively resistant to gastric acid.

PATHOGENESIS AND PATHOLOGY

Reaching the colon, organisms adhere to the mucosal surface and penetrate the epithelial cell lining where they

multiply intracellularly. Maximum involvement is usually in the rectosigmoid region. The entire colon may be affected. Mucosa is inflamed. Shallow ulcers are formed due to necrosis of mucosa. Biopsy specimen shows ulcers and crypt abscess. In severe cases necrosis of the mucosa may occur. The necrosed mucosa may be passed as intestinal casts.

Shigella dysenteriae type 1 produces a powerful exotoxin with enterotoxic and cytotoxic effects which are responsible for the colonic lesions and general toxemia. The toxin may act on the small intestine and lead to secretory diarrhea. Shiga toxin can also cause hemolytic uremic syndrome (HUS) as a complication. *Escherichia coli* 0157:H7 can also produce Shiga toxin and lead on to HUS. This toxin is known as *verotoxin*. HUS is more often caused by *E. coli* than *S. shigae*.

CLINICAL MANIFESTATIONS

Incubation period varies from 1–7 days and in severe cases, it may be as short as few hours. The illness usually starts with fever, colicky abdominal pain and diarrhea with blood and mucus in feces. The stool passed early in the illness contains fecal material, but subsequently it changes into mucus and blood with only small parts of fecal matter. Urgency and tenesmus are marked. Abdominal tenderness is usually prominent in the lower quadrant. The number of stools may exceed 28–30 times per day. In ordinary cases, the symptoms subside within a week. Some cases may be mild and ambulatory.

Fulminant dysentery is characterized by toxemia, electrolyte loss with hyponatremia, prostration and severe bloody diarrhea. In this type mortality may be high especially in children.

Complications

1. General – dehydration, electrolyte imbalance, circulatory failure
2. Renal failure – either due to hypotension or rarely hemolytic uremic syndrome, especially in children
3. Sepsis and septic shock – either primarily due to *Shigella dysenteriae* or due to polymicrobial bacteremia due to other coliforms.
4. Portal pyemia and multiple abscesses in the liver may occur rarely.
5. Intestinal perforation, paralytic ileus and intussusception may occur rarely.
6. Post dysentery complications – 1-3 weeks after resolution of the dysentery, arthritis or full fledged Reiter's syndrome with arthritis, conjunctivitis and urethritis may develop. Presence of HLA B-27 predisposes to this complication.

Diagnosis

Clinically the disease should be suspected when dysentery occurs with fever and signs of toxemia. Diagnosis of

TABLE 40.1

Differentiating features between bacillary and amebic dysentery		
Clinical features	Bacillary dysentery	Amebic dysentery
Onset	Sudden	Slow
Incubation period	Few days	Weeks to months
Number of stools/ day	Over 20	Below 15
Nature of feces blood+feces	Mucus and blood	Mucus,
Reaction of feces	Alkaline	Acid
Clinical course	Acute	Subacute
Microscopy of feces	Cellular exudate	RBCs and <i>E. histolytica</i>
Culture of feces	Shigella	Special methods for isolating ameba
Note: With the improvement in sanitation and the economic progress, amebic dysentery has become uncommon.		

dysentery is confirmed by observing blood and mucus in feces macroscopically and further by microscopy.

1. Microscopic examination of feces reveals large number of erythrocytes, pus cells and macrophages, collectively called *cellular exudates*.
2. *Shigella* can be isolated by culture of rectal swab or fresh feces transported to the laboratory in special medium.
3. Blood count usually reveals neutrophil leukocytosis
4. Sigmoidoscopy reveals superficial ulcers all along the rectal mucosa with intervening areas also showing hyperemia.

Differential Diagnosis

The common conditions to be differentiated include amebic dysentery, fulminant ulcerative colitis, staphylococcal food poisoning, or salmonellosis *Campylobacter jejuni* infection, viral enteritis cholera, necrotizing enterocolitis, antibiotic induced diarrheas rectal carcinoma and other ulcerating lesions. Sometimes amebic dysentery and bacillary dysentery may coexist (Table 40.1).

Enteritis caused by *Vitrio cholerae* and other forms of gastroenteritis show watery stools without blood and mucus.

Surgical conditions such as diverticulitis and carcinoma should be excluded if the clinical picture is atypical and response to treatment is unsatisfactory.

TREATMENT

1. *General and supportive measure include* correction of fluid and electrolyte losses. Potassium loss may be severe since the mucus is rich in potassium. Majority need oral fluids and electrolytes including potassium. Severe cases should be hospitalized. They may need

- intravenous fluids. Diet should be of high calories and low residue, frequently given, and in small quantities.
2. Antidiarrheal agents that reduce intestinal motility such as diphenoxylate or loperamide should be avoided as they may retard intestinal clearance of the organism. Abdominal pain may require antispasmodics such as hyoscine butyl bromide 10 mg oral or 20 mg IM or IV or dextropropoxyphene HCl 65mg with paracetamol 500 mg oral 8 h.
 3. *Antimicrobial therapy* Mild cases, especially produced by *S.sonnei* are self limiting and antibiotics are not needed. Severe cases, especially those produced by *S.dysenteriae* benefit from early treatment with 3-5 days course of antimicrobials which decrease the duration of symptoms by 50% and improve the outcome. Ciprofloxacin 500 mg twice daily is the drug of choice in adults. Ampicillin and cotrimoxazole were the preferred agents in the past. Azithromycin is also effective. Multidrug resistant strains are now common and hence local sensitivity patterns are also to be considered in selecting the drug.

Prevention

Personal and environmental hygiene is important. Hand washing with soap and water after defecation and before handling food helps to avoid spread of infection. Oral vaccines are in the process of development.

Escherichia coli Infections

GENERAL CONSIDERATIONS

Escherichia coli (*E.coli*) belongs to the group enterobacteriaceae and is found as a commensal in the intestine of normal man.

E.coli are aerobic gram-negative motile rods. Classification of strains of *E.coli* is based on three antigens—somatic(O) antigen, flagellar (H) antigen and capsular (K) antigen

Three main types are identified. These are

1. Commensal strains
2. Intestinal pathogenic strains(Enterovirulent *E.coli*) and
3. Extraintestinal pathogenic strains

Commensal strains are present as normal flora of intestinal tract – they generally lack virulence trait. Occasionally they produce infections in the urinary tract in the presence of urinary catheter, urinary obstruction, immunocompromised situations and the like.

CLINICAL FEATURES

Intestinal pathogenic strains These are not commonly present in the fecal flora of healthy humans. They may produce enteritis, enterocolitis or colitis. Five different types are described. These include:

1. **Enterotoxigenic *E. coli* (ETEC)** It is the major cause of endemic diarrhea in tropical and developing countries and also the common cause of traveller's diarrhea. Infections occur by taking contaminated food or fluids. Organism produces a heat labile or heat stable enterotoxin producing secretory diarrhea and vomiting. Incubation period is 1-2 days. Illness is usually mild and self limiting, improving in 3-4 days. Occasionally life threatening cholera- like illness may occur. Antibiotics limit the duration of illness.
2. **Enteroinvasive *E. coli* (EIEC)** – This may either produce watery diarrhea or an illness similar to Shigella dysentery due to invasion of colonic mucosa leading to inflammatory colitis. The disease is usually self limiting.
3. **Enteropathogenic *E. coli* (EPEC)** – which most commonly produces acute diarrheal disease in children. Organisms show characteristic affinity to attach to intestinal cell membrane producing effacement of microvilli (attachment and effacement lesion). This interferes with normal intestinal absorption. These cases present with mild or severe diarrhea with or without vomiting. Fever may be present.
4. **Enteraggregative *E. coli* (EAEC)** – This causes prolonged diarrhea in children and is also responsible for traveller's diarrhea. These strains have genetic codes for adhering to small bowel mucosa and produce a locally active enterotoxin, which causes diarrhea without blood in stools.
5. **Enterohemorrhagic *E. coli* (EHEC)** This strain particularly serotype 0157:H7 produces distinct enterotoxin called verocytotoxin similar to Shiga toxin produced by Shigella. EHEC produces hemorrhagic colitis. The reservoir of infection is herbivores such as cattle. The source of infection is contaminated meat products, milk, unwashed or uncooked contaminated vegetables and others. Small infective doses are sufficient to produce illness. Incubation period is 1-7 days. Initial watery diarrhea is followed by bloody diarrhea with abdominal pain. Fever and vomiting are not common.

Shiga toxin producing *E. coli*, also known as STEC, produce toxins similar to Shiga toxins 1 and 2. These have genes encoding 1 or 2 Shiga toxins. They are the more common causes of HUS. 10-15% of the affected persons may develop HUS, 5-7 days after the onset of symptoms. *E. coli* are common to produce traveller's diarrhea in new immigrants and traveller's.

EXTRAIESTINAL INFECTION BY *E. COLI*

E. coli producing infection outside the gastrointestinal tract are different from commensal and intestinal pathogens. They are more common in hospital settings.

The common infections are:

1. **Urinary tract infection (UTI)** *E. coli* is the single most common pathogen for all UTI syndromes
 2. **Abdominal and pelvic infections:** e.g. peritonitis due to fecal contamination, or spontaneous bacterial peritonitis, appendicitis, diverticulitis, cholangitis and cholecystitis. Rarely septic thrombophlebitis of the portal veins (pyelophlebitis) and pyogenic abscess in the liver may occur
 3. **Neonatal infections,** bacteremia and meningitis
 4. **Pneumonia:** *E. coli* is rare to cause community acquired pneumonia, However *E. coli* and other gram-negative bacilli are common etiological agents for hospital acquired pneumonia, especially in general postoperative and intensive care patients.
- Bacteremia and sepsis:** *E. coli* bacteremia may occur due to
- a. Infections in intravascular devices.
 - b. Primary infections at any other site, commonest being UTI followed by intra-abdominal infections-
 - c. Increased permeability of intestines in situations like chemotherapy-associated mucositis, enteritis, colitis and in neonates. Gut flora cross the natural mucosal barrier of the intestines and reach the peritoneum and bloodstream.
5. **Bone and soft tissue infections:** *E. coli* may cause infections and decubitus ulcers, cellulitis of the leg especially in diabetes, burn site infections and osteomyelitis.

Diagnosis

Culture of *E. coli* from appropriate samples will confirm the diagnosis.

TREATMENT

In the past, most strains of *E. coli* were sensitive to common antibiotics like ampicillin/amoxycillin, tetracyclines, cotrimoxazole and first generation cephalosporins. Now many isolates are resistant to these drugs. Other drugs which are effective include quinolones, third generation cephalosporins, aminoglycosides and extended spectrum penicillins like piperacillin and carbapenams. *E. coli* resistant to multiple drugs especially quinolones and cephalosporins are common in hospital acquired infections. Strains resistant to ampicillin/amoxycillin may still respond to ampicillin – sulbactam or amoxycillin-clavulanic acid.

Prevention

Infection rate can be reduced by restricting the use of indwelling catheters, proper care of the parts and isolates of infected patients. Drug resistance can be reduced by judicious use of antimicrobial agents. *E. coli* transfers its antibiotic resistance to other enteric bacteria like

Salmonella. Hence indiscriminate use of antibiotics without proper indication should be avoided.

Klebsiella pneumoniae Infections

Klebsiella are capsulated gram-negative bacilli found normally in the throat and intestines in healthy humans. The colonization rate ranges from 5 to 35 % in the colon and 1.5% in the oropharynx in the community. Colonization rate increases with wide antibiotic use and hospitalization.

The most frequent serotype found in humans is *Klebsiella pneumoniae* (Friedlander's bacillus) which is 1-2 mm long and 0.5 to 0.8 mm broad. Person to person spread is the predominant mode of transmission.

Lesions Produced by *K. pneumoniae*

1. ***K. pneumoniae* produces pneumonia** commonly in diabetics, alcoholics, persons having chronic lung disease and hospitalized patients (Fig. 40.1).
2. **Urinary tract infection** commonly in complicated UTI including those on indwelling catheters.
3. **Abdominal infections:** biliary tract infections, peritonitis
4. **Other infections** usually occur in devitalized tissues or immunocompromised individuals. Examples includes decubitus ulcers, cellulitis in diabetes, burn site infections, nosocomial sinusitis, meningitis associated with neurosurgery and others.
5. **Bacteremia:** usually spread from primary sites of infection or from intravascular catheters.

Diagnosis

Culture of the organism and determination of the antibiotics sensitivity from appropriate material confirms the diagnosis.

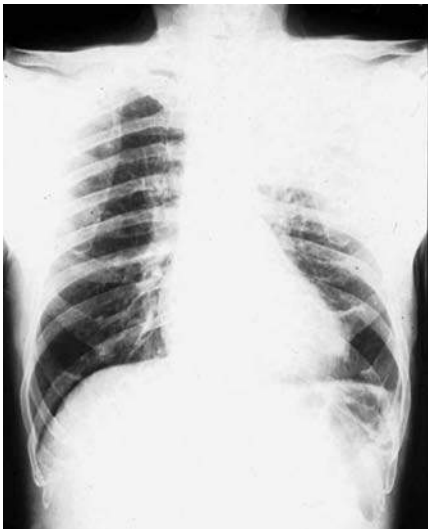


Fig. 40.1: *Klebsiella pneumoniae* left upper lobe

Treatment

Klebsiella are intrinsically resistant to ampicillin/ amoxycillin. Effective antibiotics are third and fourth generation cephalosporins, aminoglycosides, quinolones and carbapenam. Treatment with effective antibiotics has to be continued for 10-14 days.

Pseudomonas Infections

GENERAL CONSIDERATIONS

Pseudomonas aeruginosa is the most common human pathogen among the *Pseudomonas* species. They are opportunistic gram-negative bacilli. Most strains of *P. aeruginosa* produce a characteristic bluish green pigment called pyocyanin which helps in the identification of the organism. The organism has affinity for moist areas, and occasionally it colonises the skin, external ear, upper respiratory tract, perineum or colon of healthy human beings. The organism may contaminate medical devices like ventilators, endoscopes or pressure monitors. Health care workers in hospital may transmit the infection from patient to patient.

P. aeruginosa infection is rare in healthy individuals. Infections occur in immunocompromised persons who are predisposed. Most of the infections are acquired in hospitals especially from intensive care units. Prolonged use of broad spectrum antibiotics favour colonization by the organism and subsequent infection.

Conditions predisposing to infection are

1. Neutropenia – due to disease, chemotherapy or both
2. Mucosal damage – cancer chemotherapy
3. Cystic fibrosis with progressive respiratory tract changes
4. Respiratory assist devices directly inoculating the organism into the tracheo bronchial tree
5. Indwelling urinary catheters
6. Extensive burns
7. Prolonged broad spectrum antibiotic use
8. AIDS

The organisms enter through the breach in the skin or through urinary, respiratory or gastrointestinal tracts. In addition to infection at local site hematogenous spread may also occur.

CLINICAL FEATURES

1. Pneumonia commonly occurs in hospitalized patients especially in immunocompromised subjects, patient on ventilatory support and those receiving prolonged broad spectrum antibiotics. Organisms reach the lungs in aspirated material from the oropharynx or through the blood stream. The lungs show micro abscesses.
2. Bacteremia – This is common in patients with neutropenia especially those with hematological

malignancies. Bacteremia may be primary or it may result from infection elsewhere. Sepsis and septic shock may develop. Mortality is 50-70%. Meningitis may develop

3. Endocarditis – This may occur in IV drug users, patients after cardiac surgery or those who had suffered from burns.
4. Urinary tract infection – *P. aeruginosa* is a common pathogen of complicated UTI, often it results from urinary tract catheterization, instrumentation or obstruction
5. Skin lesions – Wounds, ulcers and burns may be secondarily infected. Bacteremia may lead to *ecthyma gangrenosum* which appears as indurated purple black areas about 1 cm in diameter with ulcerated centers. Maculo-papular and vesiculo-pustular rashes may occur.
6. Ear infection – It is a common pathogen producing external otitis. In elderly diabetic patients severe otitis may result
7. Other infections – *P. aeruginosa* may also produce osteomyelitis, eye infections, meningitis, *hemorrhagic colitis* and brain abscess.

TREATMENT

The antibiotics effective against

P aeruginosa are shown in Table 40.2.

Combinations such as beta lactam antibiotics with aminoglycosides or betalactams with fluoroquinolones are more effective in systemic infections.

Superficial infections respond to local dressing with polymyxin.

Prophylaxis

Since pseudomonas is a common cause of nosocomial infections , utmost care should be taken to prevent cross infection by proper hand washing and strict aseptic precautions. Indiscriminate use of prophylactic antibiotics is not beneficial.

Proteus Infections

The genus proteus includes 3 species pathogenic to man—*P.mirabilis*, *P.vulgaris*, *P.penneri*. They are gram negative rod- shaped bacilli. *Proteus mirabilis* causes 70-90% of proteus infections.

TABLE 40.2

Antibiotics effective against *P. aeruginosa*

Antibiotic class	Agent
Betalactam drugs	Piperacillin, piperacillin/ tazobactam
Cephalosporins	Ceftazidime, cefaperazone, cefipime
Carbapenams	Imipenam+cilastatin,meropenam
Monobactams	Aztreonam
Aminoglycosides	Tobramycin, gentamicin, amikacin
Fluoroquinolones	Ciprofloxacin, levofloxacin
Others	Polymixin B ,colistin

Common Lesions

1. **Urinary Tract Infection:** Normal urinary tract is seldom infected with *Proteus*, but 10-15 % of cases of complicated UTI in diabetes, urinary tract obstruction and in patients with indwelling catheters are caused by this organism. *Proteus* infection makes the urine alkaline by producing ammonia from urea. Alkalinization may lead to precipitation of organic and inorganic compounds leading to urinary stone formation.
2. **Other lesions:** These include pneumonia, sinusitis, biliary tract infections, intra-abdominal abscesses, surgical site infections, decubitus ulcers and diabetic foot infections. In the newborn, the umbilical stump may be colonized by proteus leading to bacteremia and meningitis.

Bacteremia – This may result from UTI or occasionally due to infection in intravascular devices.

Diagnosis

Culture of organisms from urine or appropriate specimen gives the diagnosis.

Treatment

Proteus mirabilis is usually sensitive to most of the antibiotics. Resistance to ampicillin and first generation cephalosporins are now common. Resistant strains respond to cotrimoxazole, fluoroquinolones, aminoglycosides and third generation cephalosporins in the usual dosage.

Anthrax, Plague, Brucellosis

S. Bhasi, K.V. Krishna Das

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animal products even for several years (10-71 years on record). Boiling for 10 minutes or treatment with potassium permanganate, formaldehyde, glutaraldehyde and hypochlorite kills the spores. The organism grows well aerobically in ordinary laboratory media.

Epidemiology

Anthrax primarily affects animals, it is prevalent in all countries throughout the World, but only rarely seen in India. Animals get the infection by coming into contact with spores persisting in soil. Most of the human cases are zoonotic in origin. Human to human transmission has not been reported except in the respiratory form. Human infection is by:

1. Direct contact with infected animals and consuming contaminated meat – raw or poorly cooked.
2. Contact with anthrax spores containing animal products such as wool, hides, hair, skin, bone and inhalation of spore-containing aerosols which may travel long distances in wind. Contaminating the atmosphere with spores may be a method adopted by bioterrorists or for bio-warfare.

Mode of Entry and Virulence

The organisms enter the body:

1. Through abrasions in skin
2. Gastrointestinal tract – eg – eating infected meat
3. and Inhalation of spores

The aerosol should be 1-5 in size to reach the lungs. The infective dose is 8000 to 50000 spores by inhalation. Virulence of the bacterium is determined by two factors (1) γ -linked poly-D glutamic acid capsule and (2) a three component protein exotoxin-termed anthrax toxin complex comprising of protective antigen (PA), lethal factor (LF) and edema factor (EF). Individually these are nontoxic, but in combination they produce lesions. LF + PA form the lethal toxin.

Pathology

Primary foci of human anthrax occurs

1. Skin

Anthrax

GENERAL CONSIDERATIONS

Anthrax is a zoonotic disease, caused by *Bacillus anthracis*. Anthrax occurs primarily in herbivorous animals, especially cattle, goats, sheep and horses which form the reservoirs. Recent interest in anthrax has been the fear of using anthrax spores as biological weapons either in battle or by terrorists.

Etiology

Bacillus anthracis is a large aerobic gram +ve spore forming bacillus. The organism exist as bacillus in the tissues – spores are not produced in living tissue. Spores are produced outside the body under aerobic conditions. These are very resistant, they remain viable in soil and

Diseases Caused by Infections

2. Gastrointestinal tract
3. Oropharyngeal region and
4. Lungs.

Septicemia and meningitis may occur from any of these primary foci. Changes occur due to tissue invasion by the bacillus multiplying rapidly extracellularly and the effect of the exotoxin. The main pathological changes in the tissue are edema, necrosis and hemorrhage.

CLINICAL FEATURES

The disease may present as the cutaneous pulmonary, gastrointestinal, and the meningeal forms.

Cutaneous Anthrax (Malignant pustule)

This occurs as a result of direct contact with *Bacillus anthracis* and this is the common type. The lesion usually occurs on exposed areas and starts as a small papule after an incubation period of 1-2 days (usually 2-5 days). It vesiculates and contains serosanguineous fluid which is highly infectious. The papules are surrounded by erythema and induration. The vesicle turns into pustule, and ulcerates with a depressed black eschar. The lesion is usually painless. Lymphangitis and regional lymphadenitis commonly occur. Systemic symptoms are mild. With appropriate antibiotic therapy recovery occurs. Bacteremia can occur with clinical features of systemic infection.

Pulmonary Form (Inhalation anthrax/wool sorter's disease) – This occurs as an occupational hazard when spores from wool or hides are inhaled. The spores may also spread from person to person as droplet infection. They reach the mediastinal lymph nodes. The bacilli develop in a few days, but the incubation period can be as long as 60 days.

It is feared that as a part of bioterrorism or bio-warfare, dissemination of spores in the environment may lead to large outbreak of severe and fatal anthrax pneumonia.

Classically a biphasic illness occurs. After an average incubation period of 1–5 days (even up to 6 weeks) symptoms start with malaise, fever, myalgia and non-productive cough mimicking viral respiratory disease. In some, there is transient improvement after 2 – 4 days followed by second stage with severe dyspnea, fever, cyanosis and hemoptysis. About 50% develop meningitis. Edema of the chest wall and neck may occur. Bacteremia is common. X-ray of the chest may show mediastinal widening due to lymphadenopathy and pleural effusion, which is often hemorrhagic. Mortality is high and death usually occurs within 24 hours.

Gastrointestinal form of Anthrax – This develops 2–5 days following consumption of contaminated meat. Deposition of bacteria in oropharynx leads to *oropharyngeal anthrax* with ulcers and lymphadenopathy. Dysphagia is common. In the GIT, organisms are deposited in the

duodenum, terminal ileum and caecum. The patient presents with fever, abdominal pain, vomiting, bloody diarrhea, hematemesis, hemorrhagic ascites and mesenteric lymphadenitis. Disease may progress to toxemia, shock and death.

Meningeal Anthrax

Any form of primary anthrax may be complicated with meningitis. CSF is usually hemorrhagic containing bacilli. Mortality is high.

DIAGNOSIS

Clinical suspicion is absolutely necessary for early diagnosis. Occupational history will be helpful.

1. Gram staining of the vesicular fluid in cutaneous anthrax, ascitic fluid, oro-pharyngeal swab, sputum or CSF and demonstration of gram +ve rods arranged in long chains is suggestive.
 2. Blood culture is positive in cases with bacteremia, if done before starting antibiotics.
 3. The capsular and cell wall antigens and virulence factor genes can be detected by PCR.
 4. Antibodies against anthrax can be demonstrated by ELISA test and other methods.
- Neutrophil leukocytosis is common.

Differential Diagnosis

1. Cutaneous anthrax has to be differentiated from tularemia, lymphogranuloma venereum, cat scratch disease, rat bite fever, bubonic plague, glanders and typhus fever.
2. Pulmonary anthrax should be differentiated from other forms of pneumonia, especially hemorrhagic pneumonias
3. Anthrax meningitis may be mistaken for subarachnoid hemorrhage.

TREATMENT

Specific

Penicillin, amoxycillin, tetracycline, doxycycline, erythromycin and other macrolides, chloramphenicol and ciprofloxacin are all effective.

Drug of choice for cutaneous anthrax is benzyl penicillin – 200,000 units IM 6 h for 5–7 days. Higher doses are needed for meningitis. Penicillin resistant patients may be treated with ciprofloxacin 400 mg bd IV or 500mg bd orally for several days.

Anthrax pneumonia should be treated with ciprofloxacin 400 mg bd IV or 500 mg orally b.d. Amoxycillin 500 mg 8h for periods up to 60 days is an effective alternative *Current recommendation by Centre for Disease control USA, (CDC) is a combination of 2 or 3 antibiotics to be given for upto 8 weeks.*

Supportive Care – Ventilatory support may be required for pneumonia with respiratory distress. Vasopressors and volume repletion are necessary for those in shock.

PREVENTION

Personal protection for at-risk persons is by using protective clothing and masks, and by vaccination.

1. Vaccination is available for individuals at high-risk. The vaccine is an inactivated cell free vaccine. Three subcutaneous injections at 2 weeks intervals and additional 3 doses at 6, 12 and 18 months and annual booster doses give adequate protection.

An attack of anthrax generally produces permanent immunity.

2. Gastrointestinal anthrax can be prevented by public education to avoid consumption of contaminated meat.
3. Post exposure antibiotic prophylaxis should be given for those who are exposed to inhaled spores. Ciprofloxacin 500 mg/day oral is recommended for 60 days.
4. Control of anthrax in animals is by immunization.
5. Carcasses of animals that have died due to anthrax are to be buried or cremated to avoid sporulation and further contamination.

Procedure to be observed when anthrax spores are used for bioterrorism/warfare

1. Suspect anthrax and alert the public and health personnel
2. Early specific therapy
3. Burn all infected cattle carcasses
4. Disinfection of infective material with 5% formalin
5. Vaccination of susceptible population and animals. Protective clothing for those at risk
6. Ciprofloxacin prophylaxis for exposed individuals.

Plague

GENERAL CONSIDERATIONS

Plague used to occur in the form of epidemics up to the early part of the 20th century causing more deaths than many other diseases. Now it is a rare disease still capable of appearing as localized outbreaks. There was an outbreak of plague in Surat in India in 1994. Plague is one of the most virulent and potentially lethal bacterial diseases known.

Etiology

Yersinia pestis, the cause of plague is a gram negative aerobic cocco-bacillus. It shows bipolar staining. The organism remains viable for long periods in human

sputum and dried flea feces when protected from sunlight and heat.

Epidemiology

Plague is a zoonotic infection. The main animal reservoirs are rats, mongooses and rabbits. Among the rodent population plague is spread by transmission from one rodent to another by the bite of the rat flea *Xenopsylla cheopis* (sylvatic plague). The organisms multiply in the alimentary tract of the flea and they regurgitate into the mouth parts. These enter the new host when the flea bites to suck blood. Organisms are also passed in the feces of the flea.

Man is the accidental host. Human epidemics usually arise from infected domestic rodents. Man gets infection

1. When bitten by infected rat flea *Xenopsylla cheopis*. When the rat dies and its body heat is lost, the fleas jump to other warm blooded animals including man and sucks blood. Under suitable conditions the flea lives for 1-2 years and remains infective for long periods.
2. Handling of carcasses of infected animals – Direct inoculation into the skin predisposes to the development of septicemic plague
3. Inhalation of respiratory droplets released from infected animals or from dried flea feces
4. Man to man transmission in the setting of pneumonic plague by droplet infections. This risk is low and requires close contact.

Pathogenesis and Pathology

Organisms are transmitted through the skin by the bite of the infected rat flea. At the site of entry a papule or pustule may form. The bacilli reach the local lymph nodes which enlarge and suppurate. This constitutes the bubo. Bacilli proliferate and enter the blood stream to produce metastatic lesions in other lymph nodes, liver, kidneys, spleen, meninges, brain and lungs.

Organisms can directly reach the lung by inhalation of droplets of respiratory secretions of pneumonic cases. Organisms can also remain in the environment by getting released from dried flea feces. The lesion in the lung is pneumonic consolidation. Hemorrhagic manifestations develop due to endothelial damage and disseminated intravascular coagulation (DIC).

CLINICAL FEATURES

Initial manifestations include abrupt onset of high fever, tachycardia, malaise and backache. The patient is toxic and delirious. Three clinical types are classically described.

1. **Bubonic plague** is the most common type. The incubation period is 2-6 days. Symptoms start with fever and lymphadenopathy. Bubos are seen most

frequently in inguinal or axillary regions depending upon the flea bite. Bubo­es may slowly suppurate and discharge their contents. Death may occur due to peripheral circulatory failure.

- The term ***Pestis minor*** refers to mild cases seen during epidemics. This presents with only the buboes which suppurate and discharge pus in due course or may resolve without significant systemic manifestations.
- Septicemic plague**- primary septicemic plague resembles severe bubonic plague with sudden onset of chills, fever, tachycardia, headache, vomiting and delirium. Several organs may be affected. Death may occur within a few days before localizing lesions are evident. Hemorrhagic manifestations like petechiae, subcutaneous ecchymosis, epistaxis, hematemesi­s or malena may develop. Meningitis may occur.
- Pneumonic plague**: Two types of pneumonia occur in plague—primary and secondary. In the primary form the organism reaches the lung by inhalation and in the secondary form, through the blood stream.

The primary form is more fulminant and rapidly fatal. The onset is abrupt with high fever, tachycardia and dyspnea. In comparison to severity of symptoms and respiratory distress physical signs are less marked. Sputum may be scanty, blood stained or frothy

DIAGNOSIS

High index of suspicion is necessary for early diagnosis. Diagnosis is confirmed by:

- Demonstration of organisms by staining of smear of fluid aspirated from bubo, sputum or buffy coat in blood.
 - Culture of blood, sputum or aspirated materials
 - Animal inoculation studies
- Serological tests are also useful
- Neutrophili leukocytosis with shift to left is common

TREATMENT

Early effective antibiotic treatment is necessary to prevent deterioration and death. Streptomycin is the drug of choice. Alternate effective drugs are tetracycline, doxycycline, and chloramphenicol. In meningitis chloramphenicol is preferable. Gentamicin and cotrimoxazole also have been used successfully. Quinolones are also very effective. The duration of treatment is for 10 days (Table 41.1).

Supportive treatment for circulatory failure, DIC, hyperpyrexia, respiratory distress and fluid and electrolyte imbalance has to be instituted early. Bubos may require surgical drainage, at times.

Prognosis

Overall mortality of untreated plague is 50%. Untreated, primary septicemic and pneumonic plague are invariably

TABLE 41.1

Antimicrobial regimen for plague

Drug	Daily dose	Doses/day	Route
Streptomycin	2 g (30 mg/kg)	2	IM
Tetracycline	2 g (adult)	4	Oral /IV
Doxycycline	200 mg (adult)	1-2	Oral
Chloramphenicol	50 mg/kg	4	Oral/IV

fatal. Modern antibiotic therapy has improved the outcome considerably.

PREVENTION

Plague is a notifiable disease. Rats and fleas are to be controlled. In endemic areas avoid contact with susceptible animals or there products. Rodents found dead should be handed only after application of gammaxane or kerosene to kill the fleas. Patients with pneumonic plague are isolated and attendants must wear masks. Contacts should be protected by tetracycline 2 g daily orally in divided doses or doxycycline 200 mg daily for 7- 10 days.

A heat-killed vaccine is useful for population at risk. Plague vaccine is known as Haffkines vaccine in honour of W.M.Haffkine who was of Russian origin. While working in Grant Medical College Hospital, Mumbai he produced the vaccine and tested it on himself on the 10th of January 1897. The vaccine is not in general use, but can be used under special circumstances. An aerosol vaccine is also available for use in special circumstances.

Brucellosis

GENERAL CONSIDERATIONS

Syn. Undulant fever, Malta fever, abortus fever

Brucellosis is an infectious disease of animals which is transmitted to man by ingestion of contaminated articles of food such as unboiled goat’s milk and milk products and meat and also by handling tissues of infected animals.

Etiology

Brucellosis is produced by one of 4 species of *Brucella* commonly.

- Brucella melitensis* the most common type spread from goats, sheep and camels.
- Brucella abortus* : This spreads from dairy cattle. It produces abortion in cattle
- Brucella suis* – from pigs
- Brucella canis* – from dogs

Brucella organisms are small, non-capsulated non-motile gram negative aerobic rods or cocco-bacilli. They are facultative intracellular parasites.

Epidemiology

The disease is worldwide in distribution. The true incidence is not known, but it is definitely many times more than what is reported. Brucellosis is common in the Middle East, USSR, Mexico and S. America. It occurs less commonly in India, Europe, USA, and other countries. Brucellosis is an occupational disease in veterinarians and farm workers, workers in meat processing industries and slaughter houses, shepherds and laboratory workers. Exposure to the placenta and other products of conception of cattle, swine, sheep, dogs and other animals and contact with sick animals can cause infection.

Mode of Transmission

Infected animals pass the bacillus in their milk for long periods. The placenta, fetus, semen, vaginal discharge and urine of animals are also infective. Human infection occurs by

1. *Ingestion of untreated milk and its products, raw meat, liver or bone marrow.* Organisms enter through the mucous membrane of GIT.
2. *Penetration through the abrasion in skin coming in contact with infected material.* *Brucella* may also enter through the conjunctiva when infected material gets into the eye accidentally.
3. *Inhalation of aerosol particles,* - Close contact with infected animals can lead to droplet infection.
4. Transplacental transmission from mother to fetus may occur. *Brucella* has been isolated from human breast milk. Transmission through sexual contact has been recently reported in humans.

***B. melitensis* can be used as an agent in biological warfare or bioterrorism.**

Pathogenesis and Pathology

After entry the organisms pass through the local lymph nodes to reach bloodstream and localize in reticulo-endothelial system. *Brucellae* are unique in that they have no specific virulence factors like exotoxins or endotoxins. Organism which enter the tissue are phagocytosed by RE cells. 15-30% of the organisms survive in vacuoles within the phagocytes. They are periodically released into the circulation.

In the RE tissues including bone marrow, liver, lymph nodes and spleen, they multiply to produce granulomas made up of epithelioid cells, giant cells, lymphocytes and plasma cells. *Brucella* persists in the tissues through inhibition of apoptosis.

Exposure to infection elicits humoral and cell mediated immunity, which helps to clear the infection.

CLINICAL FEATURES

The incubation period is 1 to 3 weeks but may be as long as several months. The clinical syndromes produced by

different species are similar, but *B. melitensis* produces more aggressive disease often with acute presentation.

The onset is either sudden or gradual with fever, malaise weakness, sweating, chills, arthralgia and backache. The term undulant fever is derived from the characteristic pattern of the temperature. Fever shows wide fluctuation and it persists for long periods, up to several weeks or months.

Bones and joints are commonly affected. Migrating polyarthritis mainly involve major joints like knee, hips, sacroiliac joints shoulder and others. Septic monoarthritis is also known to occur in the knee, hip, shoulder and sacroiliac joints. Spondylitis with back pain is a very common and suggestive symptom. This may affect any vertebra, but the fourth lumbar vertebra is the common site of lesion. *Brucella* osteomyelitis is rare outside the vertebral column.

Cardiovascular lesions include myocarditis, endocarditis, pericarditis and thrombophlebitis.

Liver involvement leads to formation of granulomas. Sometimes suppuration may occur. Mild jaundice may be present in some. Cholecystitis may occur.

Splenomegaly is common

Central nervous system: Neurobrucellosis may take the form of meningo-encephalitis with lymphocytic pleocytosis in the CSF. Other lesions include myelitis, radiculopathy, cranial nerve palsies and vasculitis presenting as strokes.

Genitourinary system: Unilateral or bilateral epididymo-orchitis may occur. Acute nephritis has also been described.

Respiratory system: Pneumonitis, pleural effusion and pulmonary opacities in the skiagram may develop. The pleural fluid shows lymphocytic pleocytosis.

Other less common lesions: These include uveitis and pancytopenia.

The term *chronic brucellosis* is used to denote the chronic febrile illness associated with specific organ involvement.

Chronic brucellosis may present as pyrexia of unknown origin or chronic spondylitis.

DIAGNOSIS

Prolonged fever with arthritis or spondylitis with risk of exposure should suggest the possibility of brucellosis. Residence in endemic areas should be considered a strong point for making the diagnosis.

Confirmation is by isolation of *Brucella* from blood, bone marrow or other tissues such as joint fluid, CSF, or tissue aspirate. This is positive in about 50-70% cases. The organisms are slow -growing and take about 6 weeks. Culture by BACTEC technique yields positive cultures in 7-10 days.

Serology: IgM antibodies appear early followed by IgG and IgA. Serum agglutination tests are employed for diagnosis. A single titer $\geq 1:320$ is considered highly suggestive. A 4 fold rise when repeated after 2-4 weeks is practically diagnostic. Antibodies can be detected also by alternate methods such as complement fixation test, ELISA and Coomb's antiglobulin test.

PCR – This is more sensitive and quicker than blood culture. Mild anemia is common. Non-specific laboratory findings include anemia and leucopenia.

TREATMENT

Antimicrobial therapy - For adults with acute brucellosis without localizing lesions elsewhere like bone CNS, and others, treatment with a combination of two antimicrobials given for six weeks is ideal. Most commonly recommended regimens are

1. Streptomycin 1 g IM daily x 2-3 weeks with doxycycline 100 mg oral 12 hourly for 6 weeks. Relapse rate with this regimen is about 5%. Aminoglycosides show synergistic activity with tetracycline.
2. *Alternate regimen* is doxycycline 100 mg oral 12 h + rifampicin 600-900 mg oral daily for 6 weeks. The relapse rate is higher. Chronic brucellosis with established focal infection needs treatment for 3-6 months

PREVENTION

1. Control of infection in animals by active immunization.
2. Pasteurization of milk will prevent transmission from milk and milk products.
3. Human vaccine is in use in countries like Russia and China. It is given to people who are occupationally exposed to high risk of infection.

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Diarrheal Diseases of Infective Origin

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Cholera

GENERAL CONSIDERATIONS

Word meaning of cholera is “flow of bile”. Cholera is an acute infectious disease caused by *vibrio cholerae* occurring in outbreaks, characterized by watery diarrhea and effortless vomiting, often leading to severe dehydration and shock. *Vibrio cholerae* is a comma-shaped, flagellate, motile, gram-negative organism. It was discovered by Robert Koch in 1884. The somatic (O) antigen is of importance in the identification of the organism. Ninety two serogroups are identified based on the O antigen structure. Of these the strain producing epidemic cholera possesses O1 antigen and hence this vibrio is designated *Vibrio cholerae* O1. *Inaba*, *Ogawa* and *Hikojima* are the most important pathogenic subtypes. The others are collectively designated non-O1 *V. cholerae*. Among these some have been now identified to be

pathogenic. The Eltor biotype is a variant of *V. cholerae* O1, and it is characterized by its hemolytic activity and resistance to polymyxin. Many Eltor vibrios are non-hemolytic at present. Morphologically and antigenically Eltor resembles *V. cholerae*. Differentiation is by phage typing and other tests.

The classic disease is caused by *Vibrio cholerae*, but in the majority of outbreaks occurring in India and neighbouring countries in recent times, the main pathogen is the 'Eltor' biotype. Eltor biotype was first identified in Eltor village in Egypt in 1905, from Indonesian Haj Pilgrims. Cholera has been endemic in the banks of the Ganges and Brahmaputra in India and Bangladesh for several centuries. From these endemic foci the disease used to spread along routes of human communication to other parts during fairs, festivals, floods, and famines, causing outbreaks associated with high mortality. Between 1817 and 1923 the disease swept to other parts of the world including Europe and America as pandemics on at least six occasions. *Eltor vibrio* was identified as the cause of the cholera-like disease during 1937-38 in Celebes island of Indonesia. This was identified as a major pathogen causing diarrheal illness in India, Pakistan, Afghanistan, Iran, Iraq and southern parts of USSR in 1965-66. From this time *Eltor vibrios* are responsible almost exclusively for cases of cholera reported in this subcontinent.

A new strain named *V. cholerae* O 139 was found to produce toxin and this was identified as a cause of clinical cholera in 1992. It rapidly spread to several countries in South East Asia and by 1993 it almost replaced the O1 Eltor strain. By 1995-96 Eltor were considerably eliminated even though occasional cases did occur in India and Bangladesh. Recent outbreaks in Ambajogai region of Maharashtra documented the presence of O139 strain in about 25% of cholera like illness.

Etiology and Epidemiology

Man and environment form the natural reservoir. Spread occurs through the environment. Organisms are eliminated in feces of acute cases and carriers. Convalescent patients become temporary carriers passing the organisms in feces for 4-7 days after an attack. Rarely chronic carrier state may develop and organisms may be present in feces for years. Unlike the explosive outbreaks of classical cholera, Eltor epidemics follow a protracted pattern with a few cases occurring everyday for several weeks. The pathogenic vibrios can survive outside the human host in the environment for varying periods. Freezing infected water does not kill the vibrios. The main vehicles of infection are water, cooked food kept unhygienically exposed to flies, sea foods, fruits and vegetables. Apart from shell fish and plankton, there are no animal reservoirs. Biofilm, formation and conversion into a visible, but non culturable state due to nutrient deprivation, helps the organisms to persist within natural aquatic habitats for long periods.

Cholera is predominantly of the lower socioeconomic groups living in gross insanitary conditions. The organisms are killed in the presence of normal gastric acidity. In different places cholera outbreaks follow seasonal patterns.

Immunity

An attack of classic biotype of *Vibrio cholerae* usually protects against recurrent infection by either type. But, El Tor type cholera does not protect against further attacks. Persons with blood group 'O' are at an increased risk of developing El Tor cholera.

PATHOGENESIS

Vibrio cholerae are ingested in food or drinks and they multiply in jejunum and small intestine and produce an enterotoxin. This toxin causes the enterocytes (intestinal mucosal cells) to secrete large amount of isotonic fluid. The rate of secretion of the fluid exceeds the rate of absorption which also goes on. The result is watery diarrhea which leads to the loss of isotonic fluid. The fluid loss accounts for all the clinical manifestations. Virulence is determined by genetic factors which favour bacterial colonization and attachment to intestinal epithelium.

Cholera enterotoxin is a protein of mol. wt. 84,000, made up of two immunologically distinct regions—A (active) and B (binding). The B region is composed of five subunits of mol. wt. about 11,500. This region of the cholera toxin is responsible for binding to cell membrane receptors containing GM I ganglioside. The binding enables the 28,000 MW 'A' region to penetrate the mucosal cells. This toxin leads to the formation of adenylate cyclase which induces excessive production of cyclic-AMP (cAMP), which in turn is responsible for oversecretion of electrolytes and water by the enterocytes. The exact mechanism of action of cyclic-AMP, however, is not clear. The enterotoxin acts locally and does not invade the intestinal wall, as a result the feces does not show cellular exudates which are characteristic of inflammation. The feces is watery, turbid and often does not contain any visible fecal matter.

The pathophysiological changes result directly from the massive gastrointestinal loss of fluid isotonic with plasma. The feces are low in proteins and chloride, but relatively rich in sodium, potassium, and bicarbonate (sodium 126 ± 9 , potassium 19 ± 9 , bicarbonate 47 ± 10 and chloride 95 ± 9 mmol/liter). Excessive loss of fluid and electrolyte gives rise to hypovolemic shock and metabolic acidosis. Most of the fluid loss is from the small intestine.

CLINICAL FEATURES

Severity of cholera varies from a completely asymptomatic form to fulminant diarrhea and shock. In Eltor cholera

outbreaks the proportion of asymptomatic and mild cases is higher than the severe cases.

In most cases the incubation period varies from less than a day to 5 days. Mild cases of cholera may be asymptomatic and diagnosis has to be established by stool culture. In some only a mild diarrheal illness may be seen.

In moderate and severe cases the onset is abrupt with uncontrollable painless watery diarrhea and effortless vomiting. The excreta may contain fecal material at the onset but soon it assumes the characteristic 'rice-water' appearance due to the presence of flakes of mucus and large number of vibrios. Watery stools are passed in quick succession. In many patients vomiting supervenes either along with the diarrhea or may follow later. Nausea is absent. Vomitus consists of clear, watery fluid. Loss of fluid and electrolytes leads to dehydration, acidosis, and shock. Earliest indication of fluid deficit is thirst with dryness of the mouth and tongue. Decreased renal blood flow produces oliguria and renal shutdown. The patient may be unable to talk due to loss of voice. Painful muscular cramps develop due to hyponatremia.

Mental state remains clear. Restlessness is the forerunner of shock. When dehydration is severe, the eyes are sunken, skin is shrivelled, neck veins are collapsed, and signs of shock supervene. The rectal temperature is usually normal or raised even though the extremities may be cold. The abdomen is scaphoid and nontender. The illness seldom lasts for more than 3-5 days. Rarely large amounts of fluid may collect in the intestinal lumen and severe dehydration, shock, and death may result even before evacuation occurs. The term "*Cholera sicca*" is used to denote such cases.

DIAGNOSIS

Laboratory diagnosis is made by isolating the organisms from proper stool samples collected before the administration of antimicrobial agents. The specimen should be transported to the laboratory without delay. A suitable medium for transporting specimens is Venkatraman and Ramakrishnan (V-R) fluid or Carry and Blair medium. It is very important to make bacteriological diagnosis in all cases of diarrhea since undetected sporadic cases may be starting point of outbreaks. Moreover cholera being a notifiable disease, should be notified to the Public Health Authorities in order to take preventive measures. Vibrios can be identified in fresh microscopic preparation of feces by their characteristic movement.

Other laboratory findings: These are non-specific, but they help to assess the fluid and electrolyte status and to plan definitive management. These include:

elevation of PCV	dehydration
neutrophil leukocytosis	
fall in serum bicarbonate	lactic acidosis
increase in anion gap	
hyponatremia	
Hypokalemia	electrolytic loss

Differential Diagnosis

A clinically indistinguishable picture can be presented by about 25 intestinal pathogens such as enterotoxigenic *E. coli*, other vibrios, *Campylobacter jejuni*, rotavirus, and others. Bacterial and toxin type of food poisoning has to be looked for and excluded. Gastroenteritis may resemble cholera. In gastroenteritis vomiting precedes diarrhea, there is abdominal pain and stools may contain cellular exudates. Fever may be present.

Prognosis

During epidemics mortality may be as high as 30%. Malnutrition, intercurrent illness, and want of proper medical attention are adverse factors. Diarrhea is one of the most common causes of infantile and childhood mortality in developing countries. Adequate and early replacement of fluid and electrolytes reduces mortality considerably. Introduction of the oral rehydration solution (ORS), recommended widely by the WHO and adopted as the first line of treatment in diarrheal diseases, has brought down mortality to a great extent. Many complications can also be prevented by early rehydration.

Complications

Most frequent complication is hypovolemic shock which is fatal if untreated. Hypokalemia may lead to fatal cardiac arrhythmias, abdominal distension, and muscle paralysis. Injudicious administration of electrolyte solutions intravenously without correcting metabolic acidosis may result in acute pulmonary edema. Convulsions may develop in children due to cerebral venous thrombosis. Severe hypoglycemia may also contribute to this symptom. Severe shock leads to renal cortical necrosis and renal failure. Other complications include venous thrombosis, cataract, and prolapse of the rectum in children. Florid malnutrition may develop after diarrheal episodes in children from poor communities.

Diarrheal illnesses precipitate and aggravate malnutrition.

TREATMENT

All cases with moderate or severe diarrhea should be hospitalized and treated properly. Early replacement of gastrointestinal fluid and electrolyte losses, maintenance of nutrition, and institution of antimicrobial drugs form the mainstay of treatment. Fluid replacement is done to correct the existing deficit of water and electrolytes (rehydration therapy) and it is continued to replace losses due to continuing diarrhea (maintenance therapy) (Tables 42.1 and 42.2).

Rehydration therapy: In mild and moderate cases, rehydration can be achieved with oral rehydration salt (ORS) solution. The WHO recommended ORS formula contains:

TABLE 42.1

Assessment of dehydration and fluid deficit			
Signs and symptoms	Mild dehydration	Moderate dehydration	Severe dehydration
General appearance and condition—infants and young children	Thirst, alert, restless	Intense thirst, restless or lethargic but irritable when touched	Drowsy, flaccid, cold sweaty, cyanosis, may be comatose
Older children and adults	Thirst, alert, restless	Intense thirst, alert giddiness with postural hypotension	Usually conscious, apprehensive, cold, sweaty, cyanotic extremities wrinkled skin of fingers and toes, muscle cramps
Radial pulse	Normal rate and volume	Rapid and weak	Rapid, feeble, thready pulse
Respiration	Normal	Deep, may be rapid	Deep and rapid
Anterior fontanelle	Normal	Sunken	Very sunken
Systolic blood pressure	Normal	Normal to low	Less than 80 mm Hg, may be unrecordable
Skin elasticity	Pinch retracts immediately	Pinch retracts slowly	Pinch retracts very slowly (>2 seconds)
Eyes	Normal	Sunken	Deeply sunken
Tears	Present	Absent	Absent
Mucous membrane	Moist	Dry	Very dry
Urine flow	Normal	Reduced amount and dark	Almost stops, empty bladder
Percent body weight loss	4-5%	6-9%	10% or more
Estimated fluid deficit	40-50 mL/kg body wt	60-90 mL/kg body wt	100-110 mL/kg body wt

Note: Material for Tables are taken from the WHO and UNICEF statement 1983.

TABLE 42.2

Guidelines for rehydration therapy				
Severity	Age group	Nature of fluid	Volume of fluid	Duration
Mild	All	ORS solution	50 mL/kg	Within 4 hours
Moderate	All	ORS solution	100 mL/kg	Within 4 hours
		Intravenous ringer lactate	30 mL/kg	Within 1 hours
Severe	Infants	Intravenously Ringer lactate	40 mL/kg	Within next 2 hours
		Followed by oral ORS administration	40 mL/kg	Within next 3 hours
	Older children and adults	Intravenous Ringer lactate	110 mL/kg	Within 4 hours initially as fast as possible until the radial pulse is palpable

Note: In the management of severe cases all the measures described under mild and moderate dehydration have to be started before hospitalisation. Use the largest size needle available for IV drip. A common error is the use small needles for IV drip which will delay fluid administration.

Sodium (90 mmol/L)
Potassium (25 mmol/L)
Chloride (80 mmol/L)
Bicarbonate (30 mmol/L) and
Glucose (111 mmol/L)

Procedure to prepare ORS at home

Sodium chloride 3.5 g
Sodium bicarbonate 2.5 g
Potassium chloride 1.5 g

Glucose 20 g
Water 1 liter

It can be easily prepared in any household by dissolving sodium chloride 3.5 g, sodium bicarbonate 2.5 g, potassium chloride 1.5 g, and glucose 20 g, in one liter of drinking water. Rice based oral rehydration solutions have been devised. These are made by replacing the glucose with 80 g/L of rice powder and boiling the solution. In addition to the carbohydrate, the glycine

liberated by digestion of protein also assists the absorption of sodium and water across the intestinal mucosa.

Mothers are advised to give this fluid at frequent intervals to the children, thirst being the guideline for deciding the quantity and frequency. The efficacy of ORS has been widely tested and accepted. The glucose acts mainly as an agent to favour absorption of sodium. Glucose can be replaced by twice the quantity of sucrose or even other household starches, but they are less efficient. Severe dehydration, with or without hypovolemic shock, should be treated with intravenous fluids to achieve satisfactory rehydration. Ringer's lactate solution is the best commercially available preparation suitable for all age groups. This contains sodium lactate, sodium chloride, potassium chloride and calcium chloride. If Ringer lactate solution is not available, the next best is a solution containing sodium chloride 4 g potassium chloride 1 g, sodium acetate 6.5 g and glucose 10 g per liter. The volume and rate of fluid required depends on the severity.

One of the disturbing aspects which make ORS less acceptable to rural people is the fact that even though it stimulates absorption of electrolytes across the intestinal mucosa, often the stool volume is not reduced abruptly. This disadvantage is partly corrected by rice or cereal based ORS. Amylase resistant starch obtained from several types of cereals reaches the colon without being digested and absorbed in the small intestine. Bacterial action converts this starch into short chain fatty acids which promote the absorption of fluid and electrolytes from the colon and thereby reduce stool volume. 10 g of amylase resistant starch added to 200 mL of conventional ORS was found to be beneficial in studies conducted in Vellore S. India.

Fluid replacement should cover the losses in stools, vomitus, and sweat. In a severe case fluid balance should be checked hourly. Where facilities permit, replacement of electrolytes should be guided by laboratory estimations. As the dehydration is corrected, the child's mental state improves, the acidosis clears, blood pressure comes up and urine is passed. It is ideal to achieve a urine flow of 50-60 mL/h. An intravenous line should be maintained till the child is well on the road to recovery.

Maintenance therapy: Maintenance therapy is intended to replace continuing losses of fluid and electrolytes and this follows the initial intensive regimen. The principle is to match the input to the output. Oral rehydration solution can be relied upon for maintenance therapy in moderate cases without severe diarrhea. The volume of ORS should be 100 mL/kg body weight/day in mild cases. In moderate and severe cases, fluid should be given at the rate of 10-15 mg/kg body weight/h until diarrhea stops. Severe cases should be treated with intravenous fluids. IV: fluids can deliver only up to 4 mmols of potassium/L

whereas ORS contains up to 20 mmol/L. Hence ORS should be started as soon as the severe phase is tided over.

Antimicrobial drugs: Though cholera is a self-limiting disease, it is customary to use antibiotics when a case is diagnosed. Tetracycline, furazolidone, ciprofloxacin and erythromycin shorten the duration of the illness and stop excretion of vibrios in stools. Recent work (Dabashish Saha et al N Eng J med 2006: 354:2452-62) has shown that a single dose of azithromycin 1g given orally at the onset of illness reduces the duration of diarrhea (to 30 hours) and achieves elimination of bacteria in 78% of cases. These results are much better than those achieved with ciprofloxacin.

Dosage of drugs: all given orally

Tetracycline	2g od for 3 days or 500 mg 6h for 3 days
Doxycycline	100 mg b.d for 3 days
Ciprofloxacin	500 mg b.d for 3 days and
Erythromycin	40 mg/ kg daily, 6 h for 3 days
Azithromycin	1 g single dose

Dietetic management: Even during the diarrheal phase, food should be given in accordance with the patient's desire and tolerance. Starvation, in addition to the depletion of calories, also reduces the ability of the small intestine to absorb a variety of nutrients. Infants should be breastfed as they demand. Older children and adults should be given easily digestible food with adequate calories depending on customary practices and local availability. Fruit juices, bananas, coconut water, and cereals are usually well tolerated. Bananas and apple help to reduce diarrhea and form stools of normal consistency.

PREVENTION

Cholera is a notifiable disease. All suspected cases should be fully investigated bacteriologically and notified to the health authorities to prevent an outbreak. Health education of communities during outbreaks, chlorination of water supplies, control of flies, and provision of adequate treatment facilities at the affected areas help to limit the epidemic. Instruction on the use of ORS from the beginning of the diarrheal phase has proved to be of great value in reducing morbidity and mortality.

On a long-term basis, improvement in environmental sanitation, provision of protected water supply, arrangement for proper disposal of excreta, and improvement of food hygiene are absolutely essential to wipe out infective diarrheas. Chlorination of water effectively destroys the organism. Spraying the breeding places of flies with deltamethrin will suppress the fly population. Flyproofing of kitchen and food containers is very effective in arresting the spread of cholera.

Personal prophylaxis Vaccination is protective against cholera. The original vaccine was made from killed

suspension containing 8000 million organisms per mL composed of equal number of Ogawa and Inaba serotypes. Many newer vaccines employ equal numbers of classical cholera and eltor biotypes and the concentration has been raised to 12,000 million organisms per mL. This vaccine is antigenic. The course of immunization consists of 2 subcutaneous injections of 0.5 mL and 1 mL separated by an interval of four weeks. Several well-controlled field trials have shown that conventional cholera vaccines provide only low degree of protection, and that too only for 3-6 months. Improved vaccines with better antigenicity containing aluminium hydroxide and phosphate as adjuvants are under trial. Oral live vaccines are also under way. An attack of cholera confers temporary immunity of 6-12 months after which reinfections may occur.

Newer oral vaccines have been developed which are safe and effective. One type contains inactivated whole vibrio cholera O1 either given alone or in combination with the B subunit of cholera toxin, with a view to promote antitoxic activity as well. The other vaccine consists of attenuated strain of V. cholera O1 depleted of the virulence genes but retaining the protective antigens. This is given as a single dose orally. It also produces antibacterial and antitoxic immunity. Widespread administration of the killed vaccine also confers a herd immunity in the population. Since V. cholera forms a part of the normal flora and ecology of the surface water in many places it cannot be eradicated in toto.

Vaccination is to be given to special groups such as inmates of refugee camps and following natural disasters such as earthquakes and floods.

NON-CHOLERA VIBRIOS

Other vibrios that are at times pathogenic to humans are V. parahemolyticus, V. vulnificus, V. anginolyticus and a few others.

Infective agent	Pathogenicity
V. parahemolyticus	Explosive diarrhea
V. vulnificus	a. rapid onset fulminating septicemia. b. rapidly spreading cellulitis. c. acute diarrhea following consumption of shell fish.
V. anginolyticus	Wound infections, mainly opportunis

Acute Diarrheal Diseases of Children

Acute diarrheal diseases are the major killers of infants and young children, accounting for 30-50% of deaths below the age of 5 years. In India about 1.5 million children die annually from diarrheal diseases other than cholera. Disorders in which three or more watery stools

are passed daily with or without vomiting are included under this group.

Etiologic agents: The most well known pathogens are Shigella, Salmonella, enteropathogenic E. coli. Vibrio cholerae, Eltor vibrios, E. histolytica and G. lamblia and these account for only about 20% of the total, the remaining 80% being due to other agents which number about twenty. Diarrhea results either from enterotoxin or through invasive mechanisms. The clinical picture and management are the same as described under cholera.

Viruses account for the majority of diarrheal episodes in infants and young children in both developed and developing countries. These viruses include rotavirus, Norwalk and Norwalk-like agents, corona virus, adeno virus, calciviruses and others whose causative role is not yet clearly established. Viral gastroenteritis occurs globally in epidemic or endemic outbreaks.

- Epidemic gastroenteritis
- Endemic gastroenteritis
- Norwalk viruses
- Rotavirus, astrovirus and corona virus

Adenovirus and calcivirus cause both endemic and epidemic outbreaks.

ROTAVIRUS

Rotavirus affects mainly infants and young children aged 6 months to 2 years. In many places rotavirus has emerged as a major pathogen causing wide outbreaks. Three groups A, B and C are pathogenic to man and produces diarrhea in local or epidemic outbreaks.

Infection is by fecal-oral route Incubation period ranges from 1 to 7 days but usually it is less than 48 hours. The virus affects the enterocytes of the small intestine and the epithelium overlying the Peyer's patches. Destruction of the villi lead to disaccharidases deficiency and malabsorption of carbohydrates. Recovery of the villi takes 2-3 weeks.

Clinical Features

Vomiting occurs early and it precedes diarrhea. Diarrhea extends over 5-7 days but virus is shed for up to 10 days. Asymptomatic infections and mild disease may occur during outbreaks. Breast milk may have a protective role due to the presence of maternal IgA antibodies.

Diagnosis can be established by demonstrating the organism by electron microscopy or rotavirus antigen by ELISA test, in stool. This is not required in the ordinary case since specific antiviral therapy is not widely available. Rotavirus diarrhea responds to standard rehydration therapy as described under cholera. In developing countries rotavirus accounts for 20-30% of the diarrheal deaths. Nitazoxanide, in a dose of 7.5 mg/kg bw given orally for 3 days controlled rotavirus diarrhea in

hospitalized patients. This drug has been licenced in the USA for treating rotavirus infections.

Vaccination

Two rotavirus vaccines are currently available-Rotarix (Glaxo Smith Kline)

1. Monovalent vaccine made from human rotavirus strain and attenuated.
Dose: 2 oral doses 1st dose 6-14 weeks of age. 2nd dose 4 weeks later.
2. Pentavalent vaccine (Rota Teq. (Merck) made from bovine rotavirus strains and attenuated: dose 3 oral doses 1st dose 6-12 weeks of age 2nd and 3rd doses 4-10 weeks intervals.

Several other vaccines are being produced. The Millennium Development Group has suggested the inclusion of rotavirus vaccine in the routine childhood immunization schedule in order to prevent 5% of the deaths occurring in childhood and 4% of deaths due to diarrhea.

Ref. Roger I Glas et al Rotavirus vaccines. Current prospects and future challenges The Lancet 2006;368:323-32.

NORWALK AND NORWALK-LIKE AGENTS

Since 1972 these viruses have been identified as the cause of outbreaks of generally mild gastroenteritis occurring in school, community, and family settings. Norwalk agent was first isolated from Norwalk in Ohio State (USA). Virus particles resembling Norwalk agent morphologically, but serologically distinct are also identified as causing outbreaks of gastroenteritis. They cause illness in all age groups. Symptoms include vomiting, diarrhea, abdominal pain and myalgia which clear up in a day or two.

The viral antigen can be detected in feces by ELISA test. Treatment is symptomatic.

Management

General measures such as fluid replacement orally and if needed, parenterally should be instituted without delay. The condition is self limiting and the child recovers within a few days.

Probiotics

Since diarrheas lead to severe malnutrition, especially in children with subnormal nutritional status, food supplements-calories, proteins, vitamins, minerals and fluids should be started early. Probiotics help to resume normal bowel function, provide symptom relief and aid recovery. Probiotics are live microbes, many of them being normal intestinal flora. For example, lactobacillus, bifidobacterium, varieties of streptococci saccharomyces

boulardi and others. These help to restore normal microbial environment of the gut and antagonize pathogens. The main probiotic effect is the development, maturation and regulation of mucosa-associated immunological defences. Probiotics are also beneficial in suppressing atopy and food allergies.

Rarer Causes of Viral Diarrheas

Other viral pathogens include adenovirus, astrovirus, calcivirus and minirovirus. These produce diarrheas of varying severity.

CAMPYLOBACTER JEJUNI

Epidemiology: *Campylobacter jejuni* (previously known as vibrio fetus) is found in the intestines of birds, particularly in chicken, turkeys, wild birds, and also in dogs, cats, and calves. The organisms are spread by fecal-oral route. They are acquired from sick puppies, kitten, or infected cases. *Campylobacter jejuni* is ubiquitous and has been isolated as the pathogen in several outbreaks. Normal gastric acidity kills the organisms.

C. jejuni is a slender spirally shaped gram-negative bacillus, rapidly motile, non-sporing and microaerophilic.

Pathogenesis

Campylobacter jejuni invades tissues and produces diffuse bloody exudative enteritis and nonspecific colitis. No enterotoxin has been isolated. Bacteremia and metastatic lesions may complicate the primary lesion.

Clinical Features

Incubation period is 1-7 days. Main symptoms include watery or bloody diarrhea, abdominal pain, malaise, fever, vomiting and constitutional symptoms. The severity may vary. On an average there may be 8-10 bowel movements in a day. Recovery occurs within a week. *Campylobacter* infection cannot be clinically differentiated from other forms of dysenteries. Rarely a prolonged illness resembling typhoid and meningitis may develop.

Complications include reactive arthritis (1-2%) and possible induction of Guillain-Barré syndrome (GBS). Fourteen to thirty eight percent of patients with GBS give a history of recent campylobacter infection.

Treatment

Since the infection is self-limiting, fluid and electrolyte replacement forms the mainstay of therapy. The organisms respond to erythromycin given orally in a dose of 250 mg every 6 h. Resistant cases respond to tetracycline in a dose of 250-500 mg every 6 h. For bacteremia, gentamicin or chloramphenicol are given systemically.

Intestinal hemorrhage, toxic megacolon and hemolytic uremic syndrome may occur rarely. Mortality is very low.

Prevention

The organisms are destroyed by proper cooking and storage of animal foods, pasteurization of milk and provision of protected water supply. Chlorination of water kills the organisms.

CLOSTRIDIUM DIFFICILE: PSEUDOMEMBRANOUS COLITIS

Syn: Antibiotic associated diarrhea

Diarrhea occurs as a common side effect of therapy with many antibiotics. In many cases this is mild and non-specific. In the majority, symptoms subside on withdrawal of the drug.

Pseudomembranous colitis is a more serious and specific infection caused by *Clostridium difficile* which develops following the use of clindamycin and several antibiotics such as ampicillin, cephalosporins and others given for both aerobic and anaerobic sepsis. *Clostridium difficile* is a gram-positive anaerobic spore-forming bacillus that can cause pseudomembranous colitis and other disease manifestations. It produces two toxins A and B. Generally toxin A is enterotoxin and toxin B is a cytotoxin. In addition, about 6% of organisms produce a third toxin known as binary toxin CDT which is similar to the toxin of *C. perfringens*. The toxins account for its virulence. Transmission occurs primarily in health care institutions where exposure to antimicrobial drugs especially clindamycin, erythromycin, tetracycline and

chloramphenicol. The presence of spores favour transmission. Alteration in the intestinal microbial flora contributes to the pathogenicity- which is pseudomembraneous enterocolitis. With the widespread use of antibiotics, pseudomembranous colitis has come into prominence.

Pathologically the lesions consist of disruption of villous tips, infiltration by neutrophils, and the presence of yellow plaque-like lesions on the mucosa, especially in the colon. These are caused by the toxins derived from *Clostridium difficile* which overgrows and become pathogenic.

Clinical Features

A broad spectrum of diseases ranging from mild diarrhea to severe life-threatening illness may occur. The disease is clinically characterized by abdominal pain, fever, leucocytosis, watery diarrhea and rarely toxic megacolon. Sigmoidoscopy reveals erythema with ulceration of the mucosa and patchy adherent membranous plaques. If not diagnosed and treated early, the mortality may go up to 50-60%.

Clinical suspicion should lead to the diagnosis. The organism can be isolated from feces. Presence of toxins can be demonstrated in fecal samples by ELISA.

Drug treatment consists of metronidazole in a dose of 400 mg tid for 10 days. An alternative is vancomycin 250 mg qid for 10 days. On stopping therapy recurrence is common. In them addition of rifampicin to vancomycin helps to control the infection. Probiotics like *Saccharomyces bulardi* or Lactobacillus help to reconstitute the intestinal flora.

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Bartonellosis, Legionellosis, Yaws, Pinta, Relapsing Fevers, Lyme Borreliosis

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Bartonellosis

Syn: Carrion's Disease, Oroya Fever, Verruga Peruana

The genus *Bartonella* consists of three main pathogens affecting man.

Bartonella bacilliformis Cause of Carrion's disease

Bartonella henselae Cause of cat-scratch disease and bacillary angiomatosis in patients with AIDS

Bartonella quintana Cause of trench fever, transmitted by body louse.

CARRION'S DISEASE

This name is given in memory of Daniel A. Carrion a Peruvian student who injected infective blood into himself during studies on the infectivity of *Bartonella bacilliformis*.

Carrion's disease is confined to the valleys of Andes mountains of South America and has not been reported from India. It is caused by *Bartonella bacilliformis*, which is seen inside the erythrocytes. The disease is transmitted by the sandfly *Phlebotomus verrucarum*.

Bartonella bacilliformis is a small gram-negative coccobacillus $0.3-1.5 \times 0.2-0.5 \mu\text{m}$. It is motile and strictly aerobic.

It presents different clinical pictures at different stages of evolution of the disease. After an incubation period of three weeks, the disease develops. It is characterized by two distinct clinical syndromes. The initial illness is characterized by constitutional symptoms like fever, rigors, nausea, diarrhea and headache. This is called Oroya fever and lasts for 3 to 4 weeks. Organisms can be demonstrated in blood smears stained by Giemsa's or Wright's stain. Death may occur at this stage due to severe anemia or superinfection by *Salmonella*.

The second stage, called *Verruga peruana*, is characterized by hemangiomatous tumors of skin and mucous membranes varying in size between 2-15 mm, some of which may ulcerate. Mortality is very low at this stage, since immunity develops.

Specific treatment is with chloramphenicol or tetracyclines in addition to supportive measures.

BACILLARY ANGIOMATOSIS

This is caused by *Bartonella henselae* which is seen in domestic cats. It may produce three clinical syndromes;

1. Chronic bacteremia
2. Bacillary peliosis hepatis and disseminated bacillary angiomatosis. Skin lesions occur as vascular nodules and may reach large sizes. Such lesions may be seen in internal organ such as liver, spleen, lymph nodes and bone marrow. Prolonged fever is common. Treatment is with antimicrobials such as erythromycin, doxycycline or ciprofloxacin given for 3 to 8 weeks.

CAT-SCRATCH DISEASE

This is also caused by *Bartonella henselae*. It is transmitted by bites, licks or scratches by the cat. Local lesion develops as a crusted papule. It is followed by fever and malaise and tender regional lymphadenopathy. The lesion is self limiting and usually benign. Rarely complications may occur, which include meningitis, myelitis, encephalitis hepatitis and osteomyelitis. Treatment is with erythromycin or doxycycline.

TRENCH FEVER

This is caused by *Bartonella Quintana* which is transmitted from person to person by the body louse. It is seen in persons huddled in trenches, refugee camps and similar situations. Treatment is with erythromycin or doxycycline.

Legionellosis

Legionellaceae are gram-negative rods whose natural habitat is water. Man is accidentally infected and human to human transmission is unusual. There are over 36 defined species, among which *L. pneumophila* is the most common human pathogen. Two main clinical syndromes are produced—*Legionnaires disease* and *Pontiac fever*. The former has a low attack rate among those exposed whereas the latter has a high attack rate.

LEGIONNAIRES DISEASE

The first description was given in 1976 following the outbreak of an unusual pneumonic illness among members attending the legion convention at Philadelphia. The organisms have been isolated from air-conditioning systems, water taps, soil, and other environment. It is acquired by inhalation, ingestion, or through the conjunctiva.

At present legionella has been found to be a common cause of community acquired pneumonia in several countries including India. Infection is by inhalation of aerosols containing the organisms or microaspiration of infected water. Legionella exist in water. They can infect and replicate within several protozoa found in the soil, including amoebae. By successive replication its virulence increases.

The incubation period is 2 to 10 days after which the patient presents with fever, anorexia, weight loss,

headache, myalgia and confusion. Severe cases progress to pneumonia and pleurisy.

Lesions: Pneumonia is the commonest presentation followed by gastrointestinal symptoms such as watery diarrhea. Cardiac lesions include myocarditis, pericarditis, post-cardiotomy syndrome and prosthetic valve endocarditis. Neurological manifestation are not uncommon these include confusion, frank encephalopathy, neuropathy, myositis, cranial nerve palsies and cerebellar disturbances. These have been described in Indian patients.

(Kulkarni KH et al. Focal neurological manifestation in legionellosis. J. Ass. Phys. Ind. 53, 2005 731-733).

PONTIAC FEVER

Pontiac fever also occurs in persons exposed to the infective environment. It is a brief febrile illness resembling influenza, caused by other species of legionella. Mortality is nil. Nosocomial legionella infections may lead to wound infection or prosthetic valve endocarditis, rarely.

Diagnosis

1. Culture of the organism from sputum.
 2. Direct fluorescent antibody staining is a quick and ready method, but less sensitive and more non-specific.
 3. Legionella urinary antigen detects legionella in urine.
- RIA assay and ELISA are available. Rapid serological tests are good for epidemiological investigations, but not for case management. Four-fold rise in antibody titre or an antibody titre of 128 or more is suggestive of infection. Sometimes a few weeks may be required for serology to become positive.

Legionella pneumophila responds to erythromycin and rifampicin if given early in the course of the disease.

Dose of erythromycin is 500 mg 6 h oral.

Alternate drugs include:

Roxithromycin	300 mg oral bd
Azithromycin	500 mg oral or IV daily
Ciprofloxacin	500 mg oral—8 h or 750 mg oral bd

In severe cases ciprofloxacin may have to be given IV initially, later to be changed to oral dosage.

The total duration of treatment has to be up to 21 days

The disease carries a mortality ranging from 10-20%.

Immunocompromized subjects suffer more.

Legionella in water tanks can be sterilized by heating to 70°-80°C or chlorination.

Yaws

GENERAL CONSIDERATIONS

Yaws and pinta are nonvenereal diseases caused by spirochetes which resemble *Treponema pallidum* mor-

phologically and serologically, but differ in pathogenesis and epidemiology. Primary infection is usually acquired in childhood. Transplacental transmission of infection does not occur usually. Pathologic lesions are confined to the skin and bones, the other viscera are not affected as in syphilis.

Yaws is widely prevalent in the tropics and subtropics. It is seen sporadically in all parts of India, though the disease is more prevalent in Africa. The causative organism is *Treponema pertenue*. The discharges from the primary and early secondary lesions teem with the organism. Transmission is much more efficient during the wet seasons. Portal of entry is abrasions of the skin. Overcrowding and poor personal hygiene favour transmission.

Three stages—primary, secondary and tertiary can be identified during the course of the disease. With the improvement in living conditions and advent of penicillin therapy the picture of yaws and its prevalence have changed considerably, though there are some suggestions that the disease is also showing signs of resurgence.

The pathological lesions in the early stages within five years of infection take the form of papillomas. Late yaws develops five or more years after the onset. These take the form of gummatous changes with widespread tissue destruction, mutilation and ulceration.

Clinical Features

The primary stage: This shows red maculopapular lesions which develop at the site of inoculation of the organism after three to six weeks. These enlarge and become multiple. They are painless but pruritic. Ordinarily they heal without scarring.

The secondary lesions develop in crops, weeks to months after the healing of the primary lesions. Though they resemble the primary lesions, they are more numerous and widely distributed over circumoral, axillary, perineal, and perianal regions. In the moist areas they assume the appearance of condylomas. Over the palms and soles the lesions become painful and walking may be restricted due to pain (**crab yaws**). Bones are affected in the secondary stage. Multiple long bones are involved. The shaft shows cortical rarefaction and sub periosteal inflammation and new bone formation. The affected part is thickened and painful. Nasal bones show thickening (**gondou**) and the tibial lesion may give rise to sabre tibia.

The tertiary stage develops 5-10 years later with gummatous and destructive lesions. The skin and bones are affected. Deep ulcers develop which show overhanging edges. Chronic destructive lesions in the bone may lead to discharging sinuses. Extensive destruction of the facial tissues with gross mutilation of the nose and mouth leads to the formation of a single open cavity (**gangosa**).

Diagnosis

Clinical suspicion should be strong to diagnose this condition since it occurs sporadically or in families and the condition is likely to be missed by the unwary physician.

Yaws has to be differentiated from other granulomatous lesions involving the skin and bones such as syphilis, tuberculosis, leprosy, and mucocutaneous leishmaniasis all of which may cause lesions similar to gondou. The diagnosis is confirmed by demonstrating the treponemes in the discharges from primary and secondary lesions by dark ground illumination. Serological findings resemble those of syphilis.

Treatment

Dramatic improvement occurs with a single dose of 1.2 mega units of benzathine penicillin given intramuscularly. An alternative regimen is to give tetracycline 1-2 g daily for 5 days. Early cases are cured, whereas, in late cases, mutilation may persist.

Pinta

Pinta, which is also a non-venereal treponemal disease prevalent in South and Central America, is caused by *Treponema carateum*. Transmission occurs by close physical contact and the organism enters through skin abrasions. Exudates from the early skin lesions are highly infective.

Clinical Features

The incubation period is 7-21 days. The primary lesions develop at the site of inoculation as erythematous, pruritic papules, which coalesce to form ulcers, which take a long time to heal. Scarring and depigmentation occur at these sites. The secondary stage develops three to twelve months after the primary stage. Morphologically these lesions resemble the primary lesions. They are smaller but more numerous and widely distributed. Lesions at different stages of development occur simultaneously. Constitutional symptoms may occur at this stage. When the skin lesions heal, atrophy, scarring and depigmentation result.

Diagnosis

The discharges from early skin lesions reveal spirochetes on dark ground illumination. In late lesions organisms may not be demonstrable. Serological tests for syphilis are positive in such cases.

Treatment

Single dose of 1.2 mega units of benzathine penicillin given intramuscularly is curative in most of the cases.

Relapsing Fevers

K.V. Krishna Das, K. Sreekanthan

BORRELIAL INFECTIONS

Borrelia are helical rods 8-30 μm long and 0.2-0.5 μm in diameter with 3-10 loose spirals, actively motile and stainable by aniline dyes. In man they cause relapsing fevers and Lyme borreliosis. Relapsing fevers are further classified into louse-borne and tick-borne varieties depending on the vector which transmits the disease viz. body louse or soft tick. Lyme disease is transmitted by hard tick (Figs 43.1 and 43.2).

LOUSE-BORNE RELAPSING FEVER

This disease is caused by *Borrelia recurrentis*. It affects only man. Epidemics used to follow wars, famines, or natural catastrophes such as floods or earthquakes. Overcrowding, malnutrition, and unhygienic surroundings start off epidemics in the tropics and temperate zones. Severe epidemics have occurred in north Africa, Middle East and Europe following World War II and the mortality was as high as 70%. The vector is the body louse



Fig. 43.1: Hard tick



Fig. 43.2: Soft tick

(*Pediculus humanus corporis*) which is infected by blood meal containing the organism from infected persons. The louse becomes infective in 5-15 days and the organisms are found in its body cavity. It remains infective for its whole lifespan (1 month). Lice leave their host when the temperature is high or when the temperature drops after death, to seek new hosts. Pruritus caused by their bites leads to scratching and the lice are crushed. Smearing of their infected body contents and excreta to the bite wound results in infection of the host. Lice do not transmit the infection transovarially to their progeny.

Pathology

In the early phase of infection bacteremia develops and borreliae can be demonstrated in blood films outside the cells. They invade most of the viscera, especially the spleen, liver, brain, meninges, kidneys, and the heart. Skin, mucous membranes, and serous surfaces show petechial hemorrhages. Consumption coagulopathy may occur resulting in thrombocytopenia. Renal involvement leads to proteinuria and hematuria. Macrophages in the liver, spleen, lymph nodes and bone marrow may show engulfed borreliae. After an attack of fever the spirochetes disappear from the blood to reappear again during relapse. Probably immunological factors are important in producing clearance of these organisms.

Clinical Features

The incubation period varies between 2-12 days, but is usually 7-10 days. Onset is abrupt with high fever, rapid pulse, headache, body pains, conjunctival congestion, epistaxis and sometimes a petechial rash. Herpes labialis may develop. The liver and spleen enlarge and become palpable. Jaundice, meningism, and intestinal hemorrhage may occur. In four to ten days the fever comes down by crisis, but in some cases it returns after 5-7 days. Two or three such relapses may occur in succession. The relapses are generally milder and less prolonged. In epidemics, the mortality used to be as high as 40% especially in children and the elderly. After recovery from the illness immunity lasts for 1-2 years.

Diagnosis

Examination of blood films stained with Giemsa's or Leishman's stain reveal the borreliae. Dark ground or phase contrast microscopy of fresh blood may show the motile organisms.

Treatment

The disease responds well to penicillin and tetracycline in the usual doses, the former is more slow in action. Drug therapy may lead to severe *Jarisch-Herxheimer* reaction with profound fall in temperature, shock and cardiac

failure within a few hours. This potential complication should be expected and supportive measures instituted promptly. Initial administration of procaine penicillin 500,000 units on the first day, followed subsequently by tetracycline 2-4 g/day has been recommended as a safer course.

Prevention

The disease can be prevented by undertaking delousing measures. Use of 10% DDT powder effectively kills the lice. Boiling the clothes and bed linen for 30 minutes destroys the lice and their eggs.

TICK-BORNE RELAPSING FEVER

The causative organism is *Borrelia duttonii* which is transmitted by several species of soft ticks (Argasidae). Several antigenic variants of the same species have been identified in different regions, e.g. *B. novyi*, *B. carteri*, etc. Endemicity in a region is determined by the vector population. In the Middle-East, Iran and Afghanistan, *Ornithodoros tholozoni* is the main vector. In these regions non-human animal reservoirs like rodents or bats exist. The ticks are infected from them and they transmit the infection to humans accidentally. In North India relapsing fever is caused by *B. carteri* spread by *O. tholozoni*, *O. crossi*, *O. lahorensis*, and the fowl tick *Argas persicus*. In Central and East Africa the infection is mainly confined to man and the vector is *O. moubata* which inhabits mud floors, crevices in dwelling places or camp sites. Ticks transmit infection transovarially to the progeny so that a large colony of infected ticks develops which acts as a reservoir of infection. The soft ticks live for 14-21 years and can subsist on blood meals taken at very long intervals. These ticks bite at night, and the bite is painless. They attack several animals and man is only incidentally affected. They insert their mouth parts into the skin and remain attached to the body for a few days taking their blood meal, after which they fall off. The site of attachment shows a pruritic erythematous lesion which develops into an eschar. Both the adults and the larval forms suck blood. The saliva, coxal fluid and excreta of ticks contain the organisms. *Borrelia* enter through the bite wound, abrasions on the skin, and also intact mucous membranes. Pathology resembles that of louse-borne relapsing fever, but neurological involvement is more frequent.

Clinical Features

Tick-borne relapsing fever resembles louse-borne relapsing fever, but the febrile bouts may be shorter, lasting only for 3-5 days, so also the apyrexial intervals. Number of relapses are more and may reach up to ten. Neurological complications occur during relapses. These

Diseases Caused by Infections

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include facial palsy, optic atrophy, spastic paraplegia, and other focal paralysis. Mortality is lower than in louse-borne relapsing fever. Though substantial immunity occurs, it is not permanent.

Diagnosis

The clinical diagnosis is supported by the demonstration of the organisms in stained blood smears or by dark ground microscopy. Compared to the louse-borne disease, the organisms are less numerous. Other diagnostic methods such as animal inoculation studies using rats, mice and guinea pigs are available.

Treatment

The disease responds to tetracycline 1 g given daily for seven days and repeated after a week if necessary. Though *Jarisch-Herxheimer* reaction may develop, it is less pronounced. Doxycycline in a single dose of 200 mg is effective against the borrelia but allergic reactions are more frequent.

Prevention

Ticks can be destroyed by spraying with Lindane 1% (gamma BHC). Visitors to infected areas should be informed of the risk. They should wear protective clothing and use insect repellants. Ticks should be looked for and removed mechanically from the body before going to bed after the day's work.

Lyme Borreliosis

This is caused by the spirochete *Borrelia burgdorferi*, transmitted by hard ticks *Ixodes ricinus* and *Ixodes persulcatus* in Eurasia and *Ixodes dammini*, *I. pacificus* and *I. scapularis* in North America. The organisms are present in the saliva of the ticks. Tick bites are generally painless. Ticks inhabit woods. Various intermediate and small mammals including rodents act as reservoirs. Birds help to transfer infected ticks over great distances during their migratory flights. Maternal-fetal transmission of infection has been recorded.

Borrelia burgdorferi is 10-30 μ long and 0.2-0.25 μ wide. Unlike *T. pallidum*, it can be grown in artificial media, though with difficulty. Three different genospecies and seven serotypes have been identified. This fact possibly accounts for the different organotropism and virulence exhibited in various geographical areas.

Pathology

The disease affects mainly the skin, nervous system, heart and joints. The organisms have been isolated from various specimens such as blood, skin, CSF, eye, joint fluid and myocardium, indicating that the organisms get

disseminated widely. The organisms are present in the lesions extracellularly. Histologically the lesions show inflammatory infiltrate consisting mainly of lymphocytes, histiocytes and plasma cells. The total pathogenesis may be the sum total of direct invasion, stimulation of several inflammatory cytokines and autoimmune mechanisms.

Clinical Features

Incubation period ranges from weeks to months. Three clinical stages are seen. The first two stages are early manifestations, the third is late manifestation.

Stage I: Clinical lesion is erythema migrans which is a rash spreading centrifugally.

Stage II: (Early disseminated infection)

This develops a few weeks to months after infection. Several organs become affected, probably because of hematogenous spread. Lesions include:

Neurological Features (Lyme Neuroborreliosis)

These include meningoradiculitis, meningitis, cranial neuritis involving predominantly facial nerve, plexus neuritis, mononeuritis multiplex and rarely encephalitis, myelitis and cerebral vasculitis.

Meningoradiculitis also known as Bannawarth's syndrome—which is common, is characterized by CSF pleocytosis and severe radicular pain, especially worse at night. Other accompaniments of meningitis such as severe headache and signs of meningeal irritation are not present.

Cardiac manifestations include heart block, arrhythmias and heart failure. **Arthralgias and myofasciitis** can develop at this stage. Localized or generalized lymphadenopathy may occur. Ocular involvement presents as conjunctivitis, iridocyclitis, choroiditis, optic neuropathy with papilloedema and panophthalmitis. Rarely hepatitis and orchitis may occur.

Stage III: This develops months to years after infection. This is characterized by mono or oligoarticular arthritis affecting the large joints, particularly the knees.

Skin lesions develop in the extremities as bluish red edematous areas which go on to atrophy and wrinkles. These are called **acrodermatitis chronica atrophicans**.

Rarely progressive lyme encephalitis and encephalomyelitis characterized by spastic paresis and ataxia may develop. Several other rare manifestations have been described.

Diagnosis

This is based on endemicity, evidence of tick bite and the clinical picture. Only 0.5 to 1% of tick bites in affected regions transmit the infection. Material removed by biopsy from the margins of the erythema can be used to culture the organism and also demonstrate them by PCR.

Serological tests to demonstrate IgG antibodies by ELISA, indirect immunofluorescence assay (IFA) and Western blot are available in specialized laboratories. Both serum and CSF have to be tested to diagnose neuroborreliosis.

The cultivation of the organisms from body fluids is difficult and hence serological tests are used for diagnosis routinely.

Treatment

Stage I: Doxycycline, amoxycillin, cefuroxime and ceftriaxone are the most effective antibiotics.

Stage II: High dose intravenous crystalline penicillin as is given for meningitis leads to fast resolution of radicular pain. Corticosteroids given concurrently accelerate relief. Other alternatives are ceftriaxone and cefotaxime.

Stage III: Arthritis responds to doxycycline and amoxycillin. Resistant cases respond to ceftriaxone, cefotaxime or high dose intravenous penicillin.

TABLE 43.1

Dose of antimicrobials for lyme disease	
Doxycycline	2 × 100 mg/day × 14 days
Amoxycillin	3 × 500-1000 mg/day × 14 days
Cefuroxime	2 × 500 mg/day × 14 days
Ceftriaxone	IV 2 g/day × 21 days
Phenoxy methyl penicillin oral	3 × 1-1.5 million units/day × 14 days

Rarely, Jarisch-Herxheimer reaction may develop during treatment (Table 43.1).

Prevention

Tick bites can be avoided by wearing protective clothing impregnated with permethrin which is a tick repellent. Ticks transmit the disease only if they are attached to the body for several hours. So early removal of ticks with forceps without breaking their mouthparts considerably reduces the risk of infection.

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Leptospirosis

R. Sajith Kumar, K.V. Krishna Das

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General Considerations

Leptospirosis is one of the most common zoonotic disease across the world, caused by pathogenic spiral bacteria belonging to the genus *Leptospira*, the family *Leptospiraceae*, and the order *Spirochetales*. These are finely coiled, thin, motile, obligate, slow-growing anaerobes. Their flagella allow them to burrow into

tissues. The genus *Leptospira* was originally thought to comprise only of 2 species, *L interrogans*, which is pathogenic, and *L biflexa*, which is saprophytic. Recent work has identified seven distinct species of pathogenic leptospira which appear as more than 250 serologic variants (serovars). The classic *L interrogans* species, is divided into 7 named and 5 unnamed species as follows:

L interrogans, *L weilii*, *L santarosai*, *L noguchi*, *L borgpetersenii*, *L inadai*, *L kirschner*, and *Leptospira* species 1, 2, 3, 4, and 5. They infect many types of mammals including rats, dogs, cats, cattle, pigs, squirrels, raccoons, mongooses, and bandicoots. Leptospires are passed in the urine of infected animals, even though many of them do not suffer from the disease. They remain viable and infective in fresh water for varying periods upto 16 days and in soil for upto 24 days. They infect humans by entering through intact mucosal surfaces of the conjunctiva, oro-nasal cavity, genitourinary tract and

others, or disrupted skin, when the person bathes, wades through contaminated puddles and fields or engages in under-water activities. The organisms are killed by even minor changes in the temperature, acidity, salinity, chlorine content and other physical and chemical changes.

Epidemiology

The disease was first recognized as an occupational disease of sewer workers in 1883. In 1886, Adolf Weil described the clinical manifestations in four men who had severe jaundice, fever, and hemorrhage with renal involvement. Inada et al identified the causal agent in Japan in 1916. Almost all published case series focussed on seasonal outbreaks associated with changes in local water levels, flood conditions and increased risk of exposure of the population to infection. In India most outbreaks follow flooding in monsoon seasons. Andamans, Tamil Nadu and Kerala have been witnessing many epidemics from the middle of the twentieth century. Workers employed in paddy, pineapple and sugarcane cultivation and people engaged in underwater occupations like sand mining, inland water fishing and cleaning of contaminated water logged areas are predisposed to get the infection. The disease is also more common among butchers, veterinary staff, and people who handle live cattle, dogs and other pets. Leptospirosis has been encountered in almost all major hospitals all over the country.

Only about 10% of all leptospirosis cases run the classic clinical picture and get diagnosed. The majority may get only a non-specific febrile illness or may be even subclinical. Still all develop antibodies and therefore a large porportion of the population in many endemic regions possess anti-leptospiral antibodies.

Using microagglutination techniques, the major serogroups prevalent in Kerala were grippotyphosa, australis, autumnalis, icterohemorrhagiae and leuisiana. A new serovar *Bharathy type Kolencherry* has also been identified in Kerala.

Pathology

Entry of leptospira through the skin or mucous membrane is followed by extensive proliferation of the organism in blood and many tissues. The resulting leptospiremia causes widespread distribution and further damage in many organs. Leptospiremia stage is followed by disappearance of the organisms from blood, but this is followed later by the appearance of leptospira in urine (leptospiruric phase). Most of the pathological manifestations are due to immunologically mediated injury, even though direct invasion by the organism may also cause damage. The true mechanism of injury is not very clear even though complex interactions involving

endotoxin, hemolysin, and lipase are thought to play major roles.

The pathologic findings in many organs include vasculitis of capillaries causing endothelial edema, necrosis, and lymphocytic infiltration and hemorrhage. Capillary vasculitis leads to loss of red blood cells and fluid through the vascular wall. This causes secondary tissue injury. Platelet count is reduced in a good proportion of patients. Bleeding tendencies such as petechiae and mucosal bleeding (sub-conjunctival bleeding in particular) occur. Bleeding may not always be directly proportional to thrombocytopenia or alterations in coagulation function since it is multifactorial in origin.

The liver shows vascular congestion and disorganization of the liver cell plates on histology. Hyperbilirubinemia occurs in leptospirosis. This is caused by hepatic injury, also contributed to by muscle damage and release of myoglobin, intra- and extravascular hemolysis and hemorrhages.

In the kidneys, the interstitium, renal tubules, and tubular lumen are affected causing interstitial nephritis and tubular necrosis. Renal failure is usually due to tubular damage, but hypovolemia resulting from dehydration and altered capillary permeability are also contributory.

In the lungs either focal or diffuse alveolar capillary injury is common. Interstitial and intra-alveolar edema and bleeding can occur. Fatal adult respiratory distress syndrome (ARDS) may occur without warning.

In the heart, epicardial and endocardial petechiae, interstitial edema and lymphocyte and plasma cell infiltration of the myocardium, myocarditis and coronary arteritis may develop.

Clinical Features

The incubation period is usually 7-12 days, with a range of 2-20 days. Approximately 90% of patients manifest mild anicteric form of the disease. 5-10% have the severe form with jaundice, classically known as *Weil's disease*. The natural course of leptospirosis falls into two distinct phases: leptospiremic and immune phases. During a brief period of 1-3 days between the 2 phases, the patient shows some improvement.

The leptospiremic phase resembles any viral fever with high temperatures, generalized myalgia, sore throat, cough, chest pain, hemoptysis, generalized rash and frontal headache. Conjunctival suffusion and prominent myalgia and tenderness over big muscles are very suggestive of leptospirosis. Many cases recover and the patient may becomes afebrile within a week.

The next phase, also called as immune or leptospiruric phase is associated with the appearance of antibodies in blood and elimination of leptospira in urine. Symptoms may persist for 6 days to more than 4 weeks, with a mean duration of 14 days.

There are two well defined patterns, icteric and non-icteric. The non-icteric illness is more common.

The Non-icteric Illness

The presenting feature is usually headache, attributable to aseptic meningitis, confusion, irritability and occasionally delirium. Calf muscle tenderness and subconjunctival hemorrhages appear early in classic *Weil's disease*. Cutaneous manifestations include hemorrhages and maculopapular eruptions on the trunk. *The involvement of kidneys leads to rapid development of oliguric renal failure, which may necessitate dialysis therapy.* Hyperkalemia and metabolic acidosis are common.

The Icteric Illness

The icteric illness is usually associated with deep jaundice, acalculous cholecystitis, pancreatitis, and GI bleeding. Bilirubin levels may exceed 30 mg/dL. Aspartate (AST) and alanine aminotransferase (ALT) are moderately elevated, the elevation being considerably less compared to the rise in bilirubin. This is in contrast to the picture in viral hepatitis in which the elevation of transaminases is much more prominent.

Cervical, axillary and mediastinal lymph nodes may be enlarged. *Different types of bleeding* can occur ranging from epistaxis and gingival oozing to hematuria, hemoptysis, and pulmonary hemorrhage. Subconjunctival hemorrhage is common. It is not related to platelet count or coagulation abnormalities. Uveitis and iridocyclitis may occur.

Pulmonary manifestations include cough, hemoptysis, and pneumonia. Chest X-ray may show multifocal infiltrates, as well as pleural effusions. *Respiratory symptoms* may progress to acute respiratory distress syndrome (ARDS), requiring intubation and mechanical ventilation. *Myocarditis and coronary arteritis* may occur. These present as first-degree A-V block in 30% of patients early in the disease. It resolves completely with recovery. Atrial fibrillation may occur, this carries a bad prognosis. ECG changes includes T-wave inversion in 18%, ST-segment elevation in 15%, and abnormalities of rhythm in 11%. Renal involvement to produce acute oliguric renal failure is also common.

It is known that clinical features of leptospirosis are not specific to the infecting organism since considerable overlap may occur in the disease manifestation caused by the different serovars. But some clinical manifestations are more frequently seen by infection by particular serotypes. These include:

Hepatorenal lesions	<i>L icterohemorrhagiae</i>
Pretibial skin lesion	<i>L autumnalis</i> (Fort Bragg fever)
Meningeal symptoms	<i>L canicola</i>

Diagnosis

Leptospirosis should be suspected in all cases of febrile jaundice associated with severe myalgia, prostration and conjunctival congestion, especially during local outbreaks.

Laboratory Diagnosis

Polymorphonuclear leucocytosis, occasionally with toxic granules and band forms and elevated ESR are seen in about 90% cases. Mild thrombocytopenia may occur in up to 50% cases. Urine examination reveals proteinuria with leukocytes, erythrocytes, hyaline casts, and granular casts in the sediment. As noted earlier the gross elevation in serum bilirubin is associated with only a mild or moderate elevation in transaminase values. Creatine phosphokinase (CPK) is markedly elevated, particularly in patients with muscle tenderness. Higher values of serum alkaline phosphatase suggests cholestasis.

Demonstration or culture of leptospira from blood or urine samples demand advanced laboratory facilities. Dark field examination and use of immunoflourescent techniques are helpful in early stages. The serologic tests become positive by the end of the first week. These include macroscopic and microscopic agglutination using antigens for identifying the strains, and ELISA tests using monospecific antigens to identify serovars. False positive and false negative results are common. Rising titres are more helpful in diagnosis. More recently, rapid commercial tests such as dipsticks (Dry-dot) which contain antigens and used to detect leptospira antibodies in blood, have been made available. CSF may show moderate lymphocytic pleocytosis (200-300/cm).

Differential Diagnosis

Leptospirosis mimics almost any febrile illness at different stages. These include dengue fever, encephalitis, hantavirus hemorrhagic fever with renal syndrome, hepatitis, cholecystitis, yellow fever, rickettsial diseases, falciparum malaria, meningitis, infectious mononucleosis and even enteric fever.

Prognosis

Leptospirosis is a serious illness with mortality ranging from 10- 30% depending on the stage of disease at which people seek treatment and proper early diagnosis. Serious patients may die within 24 hours of hospitalization. Death is due to renal failure, generalized bleeding, shock, ARDS or myocarditis. Hepatic failure per se is not a common cause of death even in jaundiced patients. Infection acquired in the early months of pregnancy is associated with higher incidence of spontaneous abortion.

Treatment

General measures like correction of fluid balance, inotropic support, platelet transfusions and others must

be instituted as in the case of any serious illness. All patients with oliguria, confusion, irritability and bleeding should be hospitalized. Fluid and nutrient intake-output chart should be meticulously maintained in order to detect renal involvement early. Renal failure requires early dialysis. Myocarditis, hepatic failure and bleeding manifestations demand special management in appropriate facilities.

Antibiotics

Leptospira are sensitive to several antibiotics such as penicillin, tetracyclines, erythromycin, quinolones, third generation cephalosporins doxycycline and others. Penicillin is the drug of choice. Benzyl penicillin G in a dose of 1.5 mega units IV every 6 hours produces dramatic improvement in 24-72 hours. Penicillin is continued in the same dose till the acute symptoms subside, and thereafter in a reduced dose. Rarely Jarisch-Herxheimer reaction develops at the commencement of bactericidal therapy. This has to be managed with antihistamines, supportive measures and corticosteroids. In those patients who are allergic to penicillin, doxycycline erythromycin, chloramphenicol and quinolones are also effective alternative drugs.

Prevention

Prevention of leptospirosis in animals is difficult. Environmental sanitation to avoid contamination of water sources by animal and rodent urine and care during bathing and wading through contaminated water should reduce infection. Proper washing with soap and water and quick drying of the skin after exposure to contaminated water reduce risk of infection. Treatment with bleaching powder kills the organisms.

Vaccination of domestic cattle and dogs has been tried with success. Dogs are regularly vaccinated in many countries including India.

Chemoprophylaxis

Doxycycline administered orally in a dose of 200 mg once weekly during the period of exposure is protective.

Points to remember

- 1. Leptospirosis has become a very common infection in many parts of India
- 2. Several serovars cause the disease
- 3. Brunt of the disease is borne by the liver and kidney, but several other organs may also be affected
- 4. Early diagnosis and treatment with penicillin or other antibiotics ensure cure in the vast majority.
- 5. Prompt dialysis therapy saves life in severe renal involvement

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Rickettsial Diseases and Q Fever

K.V. Krishna Das, V.P. Gopinathan

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General Considerations

242 Rickettsiae are obligate intracellular parasites. These organisms are naturally found in arthropods which act as

active vectors without themselves suffering. Rickettsiae are classified into three genera-**Rickettsia**, **Rochalimea**, and **Coxiella**. Tissue culture or the yolk sac of the embryonated egg has to be employed for growing them. Sulphonamides may enhance the growth of rickettsiae, whereas tetracycline and chloramphenicol inhibit.

All of these organisms except *Coxiella burnetii* are transmitted by insect vectors like the body lice, ticks, mites and fleas.

Serological Diagnosis of Rickettsial Diseases

Agglutination of *Proteus vulgaris* (Weil-Felix reaction): Rickettsiae and *Proteus vulgaris* share common antigenic

TABLE 45.1

Details of rickettsiae pathogenic to man			
Group	Agent	Vector and reservoir	Weil-Felix reaction
A. Typhus group			
1. Epidemic typhus	<i>R. prowazekii</i>	Body louse (man)	+++ for OX-19
2. Endemic typhus	<i>R. typhi</i>	Rat flea (rat) (formerly <i>R. mooseri</i>)	+++ for OX-19
3. Brill-Zinsser disease	<i>R. prowazekii</i>	Body louse (man)	Usually negative
B. Spotted fever group			
1. Rocky mountain spotted fever	<i>R. rickettsii</i>	Ticks (rabbit, dog and rodents)	++OX-19 and ++OX-2
2. Mediterranean fever (fever boutonneuse)	<i>R. conori</i>	Ticks (rodent, dogs)	++OX-19 and ++OX-2
3. Rickettsial pox	<i>R. akari</i>	Gamasid mite (mouse)	Negative
4. North Asian tick borne typhus	<i>R. siberica</i>	Tick (wild animals cattle, birds)	+OX-19 and OX-2
5. Queensland tick typhus	<i>R. siberica</i>	Tick (Bush rodents)	+OX-19 and OX-2
6. Indian tick typhus	<i>R. conori</i>	Tick (rodents)	+OX-19 and OX-2
7. African tick bite fever	<i>R. africae</i>	Tick (cattle and goat)	
C. Scrub typhus (Tsutsugamushi fever)	<i>R. tsutsugamushi</i>	Trombidulid mite (small rodent, birds)	+++ OXK
D. Q.fever	<i>Coxiella burnetii</i> which is a coccobacillus	Ticks transmit diseases In animals, human disease is occupational-cattle, sheep, goat	Negative

components and therefore infection by some rickettsial strains lead to the development of antibodies that agglutinate some strains of *Proteus vulgaris*. Detection of these antibodies by agglutination forms the basis of the Weil-Felix reaction which is a commonly used diagnostic test (Table 45.1).

The diagnosis can be confirmed by serologic, molecular, immunohistochemical and/or culture assays. A monoclonal antibody against a lipopolysaccharide has been shown to react with a stable antigen of *R. Akari*, *R. conori*, *R. rickettsii* that survive fixation with formaldehyde and embedding in paraffin before immunoperoxidase staining of tissue. Skin biopsy in relevant cases yields diagnosis even when serology is negative.

Epidemic Typhus

Syn: Louse borne typhus, Typhus exanthematicus, gaol fever

Epidemic typhus is a severe febrile disease caused by *Rickettsia prowazekii*. Man is the only known host for this parasite. As age advances the disease assumes more serious proportions. Several epidemics have occurred during famine, war, and other natural calamities, when people had to be kept in camps under unhygienic conditions.

Rickettsia prowazekii is transmitted by the body louse (*Pediculus humanus corporis*) and rarely the head louse (*Pediculus humanus capitis*) from man to man. The lice

are infected by the blood meal. An infected louse passes the organisms in feces for the rest of its life (4 weeks) when the patient scratches, the lice are crushed and their body contents are smeared on to the bite wound through which organisms enter the host. Inhalation of the dried lice feces is another possible mode of entry. Lice leave dead bodies to seek new hosts and in this process they spread infection. Persons who suffer from typhus acquire life long immunity. In some cases, relapse occurs after a long latent period and this is referred to as Brill-Zinssers' disease. Occasionally epidemics have followed such sporadic cases.

Pathology

Pathologically, the lesions are characterized by angiitis seen in the small blood vessels of various organs including the skin, heart, skeletal muscles and brain. The blood vessels are thrombosed or they may rupture. Rickettsiae are seen in the proliferated endothelial cells. Various tissues show infiltration by round cells, macrophages, and sometimes lymphocytes and plasma cells. The vascular changes lead to patchy gangrene of the skin, sloughing of skeletal muscles and myocarditis.

Clinical Features

Average incubation period is 7 days (5-21 days). Fever is sudden in onset with malaise and myalgia. Temperature rises to 39–40°C and remains continuous. The face is

flushed, conjunctiva are injected and there is severe sore throat. A macular skin rash appears on the fifth day. It is particularly seen in the axilla, abdomen, chest, back and extremities. The rash starts to fade by about the tenth day. Involvement of the central nervous system leads to headache, stupor, coma, and urinary incontinence. Bleeding from the mucous membranes gives rise to hematemesis, epistaxis, melena, and hematuria. Respiratory involvement leads to bronchitis, bronchopneumonia, lung abscess, or gangrene of the lung. Myocardial involvement is manifested by tachycardia, hypotension, and cardiac failure. In uncomplicated cases the temperature comes down by the twelfth to fourteenth day by lysis.

Complications include patchy gangrene of the skin over the extremities, parotitis, cardiac failure, and renal failure. Death may occur in the latter part of the second week due to complications. Though the disease used to be associated with high mortality during the epidemics, early diagnosis and specific therapy have considerably lowered the mortality rate.

Diagnosis

The disease has to be diagnosed by the clinical features. Epidemic typhus has to be differentiated from typhoid, malaria, tuberculosis, pneumonia, relapsing fever, and other rickettsial diseases. Laboratory diagnosis is by the Weil-Felix reaction and other specific tests including isolation of the organisms. The organisms can be isolated from blood collected during the early phase of the illness. Four-fold rise in titre of Weil-Felix reaction is suggestive. Specific anti-rickettsial antibodies can be demonstrated.

PCR studies, western blot and microimmuno-fluorescence can be done in advanced laboratories for specific diagnosis.

Treatment

Chloramphenicol and tetracyclines are specific and highly effective, when given in a dose of 2 to 4 g daily. They have to be continued for a week after the temperature reaches normal in order to avoid relapse.

Prevention

On admission to the wards the clothes of the patient should be disinfested by heat or 10% DDT or 1% Lindane powder. Any ectoparasite remaining on the patient should be removed manually or, by use of the pesticides such as benzylbenzoate 20% emulsion, permethrin, synergized pyrethrin or malathion.

Personal prophylaxis may be achieved by vaccination. Vaccines containing either killed rickettsiae (Cox vaccine) or live virulent strains are available.

Doxycycline given in a dose of 100 mg oral daily prevents infection in contacts.

Endemic Typhus

Syn: Murine typhus, Flea typhus

This is an acute febrile illness caused by *R.typhi* (*R. mooseri*) transmitted from rat to man by the rat flea *Xenopsylla cheopis*.

Etiology

The rat flea and the rat louse (*Polypax spinulosus*) transmit *R. typhi* among rodents. The insect acquires the infection while feeding on an infected rat. The organisms are passed in the feces of the flea after multiplication in the intestinal cells. Man is infected by the flea when it takes a blood meal. The bite wound is contaminated with flea feces and the organisms get in. Infection may also enter through the respiratory tract or the conjunctiva. Since the urine of infected rats contains the organisms, contamination of food with rat's urine is also a possible source of spread. Rats and mice may harbour the organisms in their brain for long periods. Lice have been incriminated as vectors in some areas in Kashmir and China. Compared to epidemic typhus, endemic typhus is milder.

Clinical Features

After the incubation period of 8-16 days, prodromal symptoms like headache, malaise, backache, and arthralgia develop, followed soon by the onset of fever. Fever may be associated with frequent chills, rigors, nausea, vomiting, photophobia, and congestion of the eyes. The fever persists continuously for 12 days and then comes down by lysis. A morbilliform rash develops in the axillae, arms, abdomen, chest, shoulders and thighs by about the fifth day and it fades away. Bronchitis may develop and this is manifested as cough and the presence of rales on examination. Rare complications include stupor, coma, prostration and renal failure.

Diagnosis

The clinical suspicion should be supported by laboratory investigations.

Treatment

The disease responds to chloramphenicol or tetracycline in doses of 2-4 g/day given orally for 10-14 days.

Scrub Typhus

Syn: Mite typhus, mite fever, Tsutsugamushi fever, Japanese river fever

Infection by *Rickettsia tsutsugamushi* (new name *orientia tsutsugamushi*) leads to a febrile illness, which lasts for about 2 weeks.

Epidemiology

The disease occurs in several states in India including Kerala, south east Asia, including Japan, Soviet Union, Australia and several other countries. It is transmitted by different species of trombiculid mites. In India scrub typhus is endemic in many regions especially the north and the vector is *Trombicula deliensis*. Mites are seen in scrub jungles mainly, but they are also seen in sandy beaches, deserts, and dense forests. Reservoir of infection is formed by wild rodents and birds. Mites are infected when they take their blood meals during the larval stage (chiggers). Only larval mites suck blood and they transmit the disease. The infected mites transmit the organisms transovarially to the offspring. Thus a colony of mites which harbour organisms develops which acts as a reservoir of infection for long periods. Man gets the infection from the bites of mites, which are acquired when engaged in jungle clearing operations, warfare, picnicking, and similar activities. Pathologically the lesions resemble those caused by *Rickettsia prowazekii*.

Clinical Features

The incubation period varies from 6 to 18 days. The onset is abrupt with rigor, severe headache, fever and lymphadenopathy. At the site of bite a necrotic ulcer (eschar) develops with local lymphadenopathy. Fever may go up to 38 to 39.5°C. It is associated with relative bradycardia. The cutaneous rash appears after the fifth day, first on the trunk and then it spreads to the extremities. It may persist for a few days. Fever lasts for about two weeks and comes down by lysis.

Serious complications may occur. These include myocarditis, cardiac failure, renal failure and meningo-encephalitis. The mortality is around 6%. Convalescence tends to be prolonged.

Diagnosis

The diagnosis is made clinically by the presence of eschar rash, high fever, bradycardia, body ache, malaise and/or lymphadenopathy. The disease however is to be differentiated from other febrile conditions relevant to the area/country.

The Weil-Felix reaction is positive for OX-K in 50% of cases by two weeks of illness. Rising titers of antibodies demonstrated at the end of three weeks all more suggestive. More sophisticated tests are available. Micro immunofluorescence is the test of choice. Latex agglutination, indirect hemagglutination, immunoperoxidase assay, ELISA and PCR are the other tests available. A dipstick test has been developed for rapid diagnosis. Nonspecific, but very suggestive laboratory findings include moderate elevation of liver enzyme such as SGOT and SGPT (100-200 IU/L) and elevation of CRP.

Treatment

Doxycycline in the usual dose of 100 mg bid orally for 5-7 days is quite effective and safe. Chloramphenicol and tetracycline are effective against the organisms when given in a dose of 2-4 g/day. Within 24 hours of starting therapy, the temperature falls and recovery starts. Rifampicin in a daily dose of 600 mg given oral is quite effective and clearance of fever and febrile symptoms occurs more rapidly. Azithromycin is also effective in usual doses.

Infection can be avoided in endemic areas by wearing protective clothing and using insect repellants. Hot shower bath with lathering soap will remove most of the mites. Drug prophylaxis consists of chloramphenicol or tetracycline 500 mg given once every five days for 35 days. An alternative is doxycycline 100 mg given once a week for the period of exposure and for 6 weeks after leaving the endemic area.

Tick-borne Typhus – (Spotted Fever Group)

Tick-borne typhus group is characterized by the development of prominent rash. Most of them are transmitted by hard ticks (Ixodidae), except *R. akari* which is transmitted by mite. Rickettsiae of this group possess a common antigen and, therefore, may show serological overlap. These organisms are found in animals and enzootics occur periodically. They constitute the reservoir for infection. In addition, trans-ovarian transmission of rickettsiae by the female tick to its offspring leads to the formation of an insect reservoir, which tends to persist for long periods on account of the long lifespan of the ticks. Man is affected accidentally. The course of the disease is similar to that of epidemic typhus. Mortality differs from place to place, but is around 15-18%. The organisms causing this group of diseases are listed in Table 45.1.

The classic disease in this group is **Rocky Mountain spotted fever**. Hard ticks transmit the diseases. At the site of bite an eschar may develop. Eschar is the necrotic ulcer developing about a week after the bite. The rash occurs around the third day. It is maculo-papular and morbilliform. In severe cases petechiae may develop.

In India spotted fevers are caused by *R. conori*, which is distributed over extensive areas at the foothills of the Himalayas. The main vector is the dog tick *Rhipicephalus sanguineus*, but other species of ticks like *Hemaphysalis leachi*, *Amblyomma* and *Hyalomma* may also take part in transmission. **Rickettsial pox** is caused by *R. akari*. It is seen in the USA.

Q Fever

It is a zoonosis caused by *Coxiella burnetii*. It is a gram negative pleomorphic coccobacillus which is having homology with *Legionella pneumophila*. Two forms exist

Diseases Caused by Infections

1. A small cell variant (SCV) and
2. A large cell variant (LCV)

The SCV exists in nature and it is resistant to environmental factors. The LCV develops in the host's monocytes and multiplies. It is the pathogenic form. The disease exists in Australia, India, USA and other areas. In India the disease has been reported from Delhi, Punjab, South Canara and Rajasthan. Animal reservoirs include cows, goats, sheep, dogs cats and others. Organisms are shed in milk, feces, urine and products of conception. Humans become infected by ingestion of infective material or droplet infection through the respiratory tract. Incubation period is 12 to 30 days.

Acute Q Fever

This resembles influenza clinically, with varying degrees of pneumonia and hepatitis. Fever lasts for an average of 10 days (range 10-57 days).

Chronic Q Fever

This occurs in 60-70% of infected persons. It leads to endocarditis which supervenes on pre-existing valvular

lesions. Untreated, the condition is fatal. Q fever may recrudesce during pregnancy and lead to abortion. Other manifestations include osteo-articular infections and hepatitis.

Diagnosis

Antibodies can be detected by indirect immunofluorescence.

Treatment

Acute Q fever —doxycycline 100 mg bid po for 14 days. *Chronic Q fever*—life long doxycycline therapy may be necessary.

Addition of hydroxychloroquine 200 mg tds po given for 18 months favours recovery. It acts synergistically with doxycycline.

Prevention

Pasteurization of milk is partly protective. Occupational risk can be reduced by vaccination in persons exposed to the risk.

6

46

Anaerobic Infections: Tetanus and Gas Gangrene

K.V. Krishna Das

Chapter Summary

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General Considerations

Many areas in the body such as the mouth, nasopharynx, paranasal sinuses, tonsillar crypts, gastrointestinal tract, and female genital tract harbour anaerobes as commensals

and they far outnumber aerobes. Anaerobes thrive in the anaerobic environment provided by the facultative anaerobes such as *enterobacteriaceae*, *staphylococci*, *streptococci*, *E. coli* and *K. pneumoniae* which use up oxygen. They multiply further and acquire virulence if there is reduction in vascular supply, tissue injury, or presence of dead tissue. Most of the anaerobic infections are mixed. These organisms act to facilitate each other to grow, invade tissues, and resist the action of drugs. Their multiplication is promptly inhibited even by moderate increase in oxygen tension. For the isolation and identification of anaerobes, special microbiological techniques have to be adopted in collecting specimens and culturing the organisms. Since anaerobic infections produce septic venous thrombosis and embolism, pyemic

abscesses are common. They liberate endotoxins from their cell walls which lead to endotoxic shock and disseminated intravascular coagulation. Anaerobes can affect all tissues, especially so, if there is tissue necrosis and presence of foreign material.

Anaerobes which are pathogenic to man:

1. Gram-negative bacilli:
 - a. *Bacteroides*: *B. fragilis*, *B. oralis*, *B. melaninogenicus*, *B. corrodens*
 - b. *Fusobacterium*: *F. nucleatum*, *F. varium*, *F. necrophorum*
2. Spore forming gram-positive bacilli:
 Clostridium: *C. botulinum*, *C. tetani*, *C. perfringens*, *C. histolyticum*, *C. septicum*, *C. novyi*, *C. bifermentans*
3. Non-spore forming gram-positive bacilli:
 Actinomyces, *subacterium*, *bifidobacterium*, *propionobacterium*, *catenabacterium*
4. Anaerobic cocci:
 - a. Gram-positive: *Peptococcus*, *peptostreptococcus*, *microaerophilic streptococci*, *anaerobic pneumococci*.
 - b. Gram-negative: *Veillonella*

Anaerobic infections should be suspected under following situations:

1. Location of lesion, in close proximity to mucosal surfaces.
2. Foul smelling exudates.
3. Presence of gas in the tissues.
4. Black discoloration of exudates, e.g. *B. melaninogenicus*.
5. Infections associated with gut perforation and ulceration.
6. Infections after human or other bites.
7. Aspiration pneumonia and infection associated with the presence of foreign bodies.

Lesions Caused by Anaerobes

Central nervous system: Brain abscess, subdural empyema, septic thrombophlebitis of the cortical veins and venous sinuses.

Head and neck: Chronic sinusitis, mastoiditis, chronic otitis media, dental infection (caries), periodontal disease, Vincent's angina, peritonsillar abscess, cervicofacial actinomycosis and Ludwig's angina.

Female genital tract: Endometritis, myometritis, parametritis, pyometra, pelvic cellulitis, pelvic abscesses, pelvic thrombophlebitis, vulvovaginal abscess, Bartholinitis, Skene's gland infection, salpingitis, tubo-ovarian abscess, vaginal cuff infection, chorioamnionitis, intrauterine or neonatal sepsis and pneumonia, septic abortion, and puerperal sepsis.

Respiratory tract: Aspiration pneumonia, necrotizing pneumonia, lung abscess, empyema, mediastinitis, bronchiectasis, and pulmonary actinomycosis.

Bloodstream spread: Septicemia and endocarditis.

Abdomen: Peritonitis, appendicitis, diverticulitis, pyelephlebitis, intra-abdominal abscess, liver abscess and abdominal actinomycosis.

Soft tissues: Cellulitis, gangrene, infected deep wounds, wound infections after gastrointestinal or gynecologic surgery, infections following human bites, necrotizing fasciitis, decubitus ulcer (perineal or gluteal area), infected sebaceous or pilonidal cysts, diabetic ulcers on the feet.

Musculoskeletal: Pyogenic arthritis, osteomyelitis and gangrene.

Urinary tract: Renal abscess, perirenal abscess, pyelonephritis, wound infection after nephrectomy, cystitis, chronic prostatitis and abscess, and testicular abscess.

Therapeutic principles: The polymicrobial nature of anaerobic lesions demand the use of antibiotic combinations active against anaerobes and aerobes.

Surgical measures should be employed in time and these are most important. They consist of drainage of abscesses, debridement of necrotic tissue, and relief of obstruction to natural passages.

Penicillin is effective against all anaerobes except *Bacteroides fragilis* and it is the drug of choice. It has to be given in very high doses (20-30 mega units in 24 hours). Gentamicin, clindamycin and chloramphenicol act synergistically with penicillin against anaerobes and therefore these antibiotics are combined for therapy. When the organisms are resistant to penicillin these antibiotics are used as the primary drugs. Beta-lactamase-resistant cephalosporins—cephoxitin and cephmandole—are also effective. Metronidazole, given intravenously in a dose of 400 mg 8 h as infusion is a useful drug against many of the anaerobes. It has to be combined with other antibiotics. Oral doses are effective to a lesser degree (Table 46.1).

Other measures include the administration of antitoxins, hyperbaric oxygen, local oxygen therapy, and use of oxygen-releasing agents locally, e.g. hydrogen peroxide.

Major drawbacks of the antibiotics in treating anaerobic infections

Agent	Major disadvantages
Penicillin G	Ineffective against <i>B. fragilis</i>
Chloramphenicol	Hematotoxicity
Clindamycin	Poor penetration into CSF, occurrence of pseudomembranous colitis.
Carbenicillin	upto 5-10% of <i>B. fragilis</i> strains are resistant, sodium overload, bleeding tendency.
Metronidazole	All aerobes are resistant.
Cephmandole	Poor penetration to CSF.
Cephoxitin	Poor penetration CSF.

TABLE 46.1

Effectiveness of antibiotics against the common anaerobes							
Antibiotic	<i>B. fragilis</i>	<i>B. melanino-</i>	<i>Fuso-</i>	<i>Clostridia</i>	<i>Propiono-</i>	<i>Actinomyces</i>	<i>Peptostrepto-</i>
Penicillin G	Variable	Variable, but effective	++	+ to ++	+++	+++	+++
Broad Spectrum							
Penicillins	++	++	++	++	+++	+++	+++
Cephoxitin second generation	++	+++	++	Variable	+++	+++	+++
Chloramphenicol	+++	+++	+++	++	+++	+++	+++
Metronidazole	+++	+++	+++	+++	—	—	+++
Imipenam with cilastin	+++	+++	++	+++	+++	+++	+++
Clindamycin	++	+++	+++	+++	+++	+++	+++
Note: + effective, — not effective							

Diseases Caused by Clostridia

These include tetanus, gas gangrene, food poisoning including botulism and pseudomembranous colitis.

<i>C. tetani</i>	Tetanus
<i>C. perfringens</i>	gas-gangrene
Syn: <i>C. welchii</i>	
<i>C. Septicum</i>	-do-
<i>C. novyi</i>	-do-
Syn <i>C. edematiens</i>	
<i>C. histolyticum</i>	-do-
<i>C. sordelli</i>	-do-
<i>C. botulinum</i>	botulism
<i>C. perfringens</i>	also food poisoning
<i>C. difficile</i>	pseudomembranous colitis

Tetanus

Syn: Lockjaw

Tetanus has been in existence over several millennia, as is seen from descriptions from the ancient texts of Ayurveda (Susruta Samhita) and the writings of Hippocrates.

Definition

Tetanus is an acute infectious disease characterized by rigidity, intermittent spasms of the voluntary muscles and convulsions. Trismus, which is a prominent feature, gives it the name “lockjaw”. The disease is caused by the exotoxin produced by *Clostridium tetani*. *C. tetani* is a gram-positive (also can be gram-negative), obligate anaerobe which is motile and sporing. The spores resist boiling water for three hours and dry heat up to 160°C for one hour.

Etiology

Clostridium tetani is commonly found in the soil and the intestinal tract of animals and man. The organism exists

as vegetative forms and spores. They can remain viable *in vitro* for several years. Spores are destroyed by autoclaving at 121°C for 20 min. After entry into tissues through wounds they germinate and grow. Rarely, they may remain dormant for considerable periods. *Clostridium tetani* produces exotoxins among which two are most important. (1) a powerful neurotoxin tetanospasmin, and (2) a hemolysin-tetanolysin. Tetanospasmin is responsible for the clinical disease.

Clostridium tetani remains strictly localized to the site of multiplication, but the toxin reaches the central nervous system through the peripheral nerves and bloodstream. Tetanus toxin which is a polypeptide with mol. weight 148000 daltons enters the bloodstream and reaches the nerve endings in the muscles. From here it ascends though the nerves to the central nervous system. From the motor cells of the brain and spinal cord the toxin passes retrogradely to bind to the terminals of the inhibitory neurons. Tetanospasmin causes disinhibition of both the alpha and gamma motor systems and thereby leads to generalized muscle rigidity. Spasms occur when external stimuli are applied and also spontaneously. Direct effect of the toxin on the muscle leads to contraction. The toxin acts also on the central sympathetic system and possibly on the cerebral cortex and brainstem. The effects of tetanus toxin are self-limited and they pass off within weeks or months if further absorption of toxin is prevented.

Tetanus is more common after sustaining deep wounds with tissue devitalization and introduction of foreign materials inside. In such sites anaerobic conditions are established and *C. tetani* multiplies. In addition to wounds, chronic otitis media, umbilical sepsis of neonates, parturition, septic abortion, burns, intramuscular injections, and chronic ulcers may be complicated by tetanus. In about a fifth of the cases there may be no obvious focus of entry. This is termed cryptogenic tetanus. Despite all advancements in antimicrobial therapy, and

effective vaccination tetanus still occurs frequently in all parts of the country and accounts for considerable mortality.

Clinical Features

Since it is not essential that infection and injury coincide, it is difficult to ascertain the incubation period exactly in all cases. The incubation period is generally less than 2 weeks, although it may range from 2-60 days. Cases with shorter incubation periods tend to be more severe and are associated with higher mortality.

The disease starts with premonitory symptoms like vague discomfort, pain around the site of injury, and restlessness. The diagnosis becomes evident when lock-jaw sets in. It is painless or only mildly painful. Severe pain should suggest a local cause for trismus.

Within hours to days the abdominal and trunk muscles become spastic. Rigidity of the abdominal muscles may simulate peritonitis. Rigidity and spasm of the back muscles result in hyperextension of the spine and neck (opisthotonus). All muscle groups (both the agonists and antagonists) go into spasm at the same time. Risus sardonicus is the characteristic grinning expression brought about by the sustained contraction of facial muscles. Rarely dysphagia can be the first presenting symptom. Spasm of the sphincters leads to retention of urine and feces.

Spasmodic contractions involving different parts of the body develop at variable intervals after the onset of rigidity. The interval between the first symptom and the first convulsion is called the **onset period**. External stimuli or emotions precipitate these painful spasms which cripple the patient. In severe cases they may develop spontaneously. Asphyxia results from spasm of the laryngeal and respiratory muscles. Regurgitation of gastric contents leads to aspiration into the respiratory tract. With progress of the disease the spasms become frequent and prolonged and this leads to muscular exhaustion, hyperpyrexia, and cardiac failure. Sympathetic overactivity causes hypertension, hyperpyrexia and cardiac arrhythmias. Mind remains alert till the end and in many cases the patient is very anxious. Deep tendon reflexes are generally exaggerated, but the plantar response is flexor.

Course and prognosis: It takes about three days for the disease to manifest fully. If complications are prevented the condition remains stable for the next 5-7 days. Thereafter the spasms gradually subside in frequency and intensity to disappear in 2 weeks. Complete recovery may take 4 weeks or more, though in some cases the rigidity may persist even longer.

Local tetanus: In this form, rigidity and other symptoms are confined to a part near the site of injury. This generally runs a mild course and ends in complete recovery.

Cephalic tetanus: This term is used when local tetanus involves the facial muscles only. It is usually unilateral but can be bilateral.

Tetanus neonatorum: This form of tetanus occurs within 10 days of birth. It is usually severe. It manifests as inability to suck the nipple, irritability, and excessive crying associated with grimacing movements of the face. The muscles of the back, neck, and abdomen may become spastic. In many instances the classical signs may not develop in neonates and premature infants.

Tetanus neonatorum is still an important cause of infant mortality in many developing countries including India.

Complications: Respiratory obstruction and aspiration pneumonia are the most frequent complications accounting for death in many cases. Peripheral venous thrombosis may develop and lead to pulmonary embolism. Myocarditis gives rise to cardiac failure and hypotension. Hyperpyrexia is the result of excessive muscular activity and the effect of the toxin on the hypothalamus. Decubitus ulcers and urinary tract infection result from prolonged immobility. Fractures of the spine and other bones are seen at times. Sudden death due to laryngeal spasm, cardiac arrhythmias, or massive aspiration of gastric contents may occur and these have to be anticipated.

Diagnosis

The disease has to be diagnosed clinically. Repeated observations may be required to make the diagnosis in doubtful cases.

Tetanus has to be differentiated from meningo-encephalitis, strychnine poisoning, local causes of trismus, dystonia due to phenothiazines, tetany and hysteria. Cerebrospinal fluid is normal in tetanus.

Treatment

The outcome depends on proper therapy based on the severity of this disease (Tables 46.2 and 46.3).

All cases should be hospitalized. An apparently simple case may rapidly deteriorate and demand specialized care. Best results are obtained if tetanus is managed in institutions where specially trained teams are available. Depending on the severity, treatment has to be planned from the beginning.

General measures: The patient is nursed in an environment where external stimuli such as drafts of air, cold winds, noises, and vibrations are minimal. Nutrition is provided by giving adequate calories in the form of glucose and cereals. Fluid and electrolyte balance should be maintained. *The main aim of treatment is to arrest the growth of C. tetani in the local lesion, prevent further production of toxin, neutralize the toxin already in*

TABLE 46.2

Prognostic factors

1. Age	Neonates and older patients fare badly.
2. Type of injury	Large wounds contaminated with soil, lacerated wounds, compound fractures, and septic abortions are associated with severe tetanus. Though rare, tetanus following intramuscular injections tends to be serious.
3. Incubation period	Short incubation periods indicate greater severity. Apparently long incubation period does not necessarily mean that the case is mild.
4. Interval between the onset of trismus and at all the first spasm	Shorter this period, more severe is the disease. In mild cases spasms may not occur
5. Frequency of spasms	More frequent and more prolonged spasms are poor prognostic signs.
6. Autonomic disturbances	Dysphagia, hypertension, hyperpyrexia, and cardiac arrhythmias indicate poor prognosis.
7. Treatment	Early administration of antitoxin, proper surgical toilet, institution of antibiotics, proper anticonvulsive therapy, availability of a team of physicians, surgeons, and anaesthetists, and proper nursing care are the most important factors determining a successful outcome. Inadequacy of treatment is a common cause of death in many cases.

circulation and to abolish the excitatory effect of the toxin on the muscles. Since the toxin attached to nerve endings cannot be neutralized, antitoxin should be administered without delay to neutralize circulating toxin.

Tetanus antitoxin (anti-tetanus serum—ATS): The best available preparation is human tetanus immunoglobulin (TIG) which is to be given in a dose of 2000-5000 units intravenously or intramuscularly. If the wound is heavily contaminated and in severe cases, up to 10000 units may be required. This is more potent and free from risk of anaphylaxis. Human TIG can also be given intrathecally in a dose of 250-500 units. This measure may help in controlling convulsions more effectively when other measures fail.

The other preparation is ATS prepared from the horse. It may cause anaphylactic shock in allergic individuals and hence it should be administered only after testing for allergy (skin test and later intravenous test) and if human immunoglobulin is not available.

All measures to combat anaphylactic shock should be available ready at hand. The dose is 10,000 to 25,000 units given intravenously or intramuscularly. Ordinarily, there is no need to repeat the antiserum.

Surgical toilet of the wound: It aims at debridement and removal of necrotic material and foreign bodies, with a view to removing the anaerobic environment. Surgical toilet should be done only after giving the antitoxin.

Antibiotics: *Clostridium tetani* is sensitive to penicillin and benzyl penicillin in a dose of 0.5 mega unit 6 hourly administered intravenously helps in preventing the multiplication of the organism and further toxin production. When the infection is controlled, procaine penicillin can be used in a dose of 0.5 mega unit daily. Metronidazole given in doses of 400 mg IV bd has also been found to be effective.

Control of convulsions: Diazepam in adequate doses controls the muscle spasms; 50 mg is added to 600 mL of 5% glucose and it is run as an intravenous drip, at a

TABLE 46.3

A working classification of the severity of tetanus

	Mild	Moderately severe	Severe
Incubation	Above 14 days	7-14 days	Less than 7 days
Onset time	6 days	3-6 days	Less than 3 days
Trismus	Present	Marked	Severe
Dysphagia	Absent	Present	Present
Rigidity	Absent	Mild	Severe
Spasms	Brief and mild	Present, frequent	Frequent, prolonged and generalized convulsions
Ventilation	Not affected	Inadequate ventilation during spasm	Often ventilatory insufficiency
Mortality	Up to 5%	25%	80-90%
Treatment intravenous	ATS, oral medications, intramuscular diazepam	ATS, intravenous drip and medication, Ryle's tube, elective tracheostomy	Early tracheostomy, drips and medication, muscle relaxant, artificial ventilation

Practical clues to determine immune status and administer TIG

	<i>Immune if:</i>	<i>non-immune if:</i>
Injection of tetanus toxoid	Within 6 months of injection 2 doses; for 5-10 years after full course with booster	No vaccination more than 6 months after a course of 2 doses or 10 years after a course of 3 doses without booster
Equine ATS Human TIG	Within 2 weeks within 6 weeks	after 2 weeks after 6 weeks any doubt about vaccination status
Procedure to be followed	Boost up immune status with a shot of TT	Human TIG 250-500 units stat. Start 3 injection TT schedule, the first injection given simultaneously at a different site.

rate required to control the spasms. Even up to 200 mg may be required in 24 hours. Paraldehyde 7 mL every 6 h given orally, chlorpromazine 50 mg every 6 h given intramuscularly and phenobarbitone 200 mg twice daily given intramuscularly are effective in controlling the spasms and producing the required sedation when used in combination with diazepam. A combination of anticonvulsants can be used. Midazolam given IV as a continuous drip in a dose of 5-15 mg/hour is an effective alternative.

In severe tetanus that cannot be controlled effectively by drugs, curarization and assisted ventilation are essential and this regimen has to be undertaken by a team trained for ventilatory assistance (Table 46.4).

Tracheostomy: It maintains patency of the airway and helps in giving effective tracheal toilet. A cuffed endotracheal tube protects against aspiration of gastric contents. In moderate and severe tetanus tracheostomy is indicated which should be performed without delay.

In severe sympathetic overactivity beta adrenergic blockers like propranolol have to be used.

Prevention

Tetanus is an easily preventable disease. Clinical tetanus does not confer immunity and, therefore, the patient should be actively immunized when he recovers. Three subcutaneous injections of adsorbed toxoid in a dose of 0.5 mL at monthly intervals produces lasting immunity. As a part of the total immunization program for children the first dose may be given as the DPT vaccine at the fourth month of life and two further doses at monthly

TABLE 46.4

Procedure to be followed in the management of severe convulsing tetanus

1. Sedation	Diazepam 5 mg I V given at 5 minutes intervals until muscle relaxation is achieved.
2. Airway	Preferably tracheostomy and cuffed tracheostomy tube.
3. Nutrition	Naso-gastric tube feeding, 2500 cal with 70 g proteins in 24 hrs. Fluids adequate to maintain urine output of 60 mL/hour
4. Control of spasms	Diazepam in large doses 10-18 mg or more in 24 hours may be required.
5. Attention to fatal complications such as respiratory arrest, appropriate life saving measures cardiac arrest and shock	
6. Antitoxin	Human tetanus immunoglobulin 1500 units I M injection or administration equine ATS 10000 units I V.
7. Wound toilet	Surgical debridement
8. Immunization	Tetanus toxoid to start early.
9. Severe cases	Management in intensive care room-paralysis by pancuronium 2-6 mg I V and ventilatory support.

intervals. If the full course of DPT vaccine is given, the child gets life-long immunity. Boosters are needed once every 5-10 years. When severe injuries are sustained, one dose of 0.5 mL of toxoid may be given as a precautionary measure. Passive immunization can be achieved in nonimmunized subjects by the administration of 250 IU of TIG or 3000 IU of ATS after test dose. The immunity lasts for about two weeks. Passive immunization is given along with a booster dose of toxoid in separate syringes at different sites to non-immunized individuals who sustain injury. Active immunization of pregnant women ensures adequate antibodies in the neonate and prevents tetanus neonatorum.

Primary care of the wound like surgical toilet and penicillin therapy considerably reduce the risk of tetanus.

Points to remember

1. Tetanus is a life-threatening infection occurring widely in India.
2. It is preventable by suitable vaccination starting during pregnancy of the mother.
3. Diagnosis is clinical.
4. Early treatment using appropriate measures depending on prognostic factors saves lives.

Gas Gangrene

Syn: Clostridial myonecrosis

Gas gangrene is caused by *Clostridium perfringens* (*C. welchii*), *C. septicum*, *C. novyi* (*C. oedematiens*) *C. histolyticum* and *C. sordelli*. These clostridia are commensals in human gut and soil. They produce local necrosis and distant lethal effects.

Pathogenesis

Necrosis of tissue brought about by anoxia, ischemia or injury is complicated by clostridial infection which may be exogenous (introduced along with the wounds) or endogenous (derived from the intestinal tract). The organisms multiply locally and produce toxins which diffuse out and lead to generalized toxemia. The affected tissues are avascular and appear as if cooked.

Clinical Features

After an incubation period of 1-4 days the wound becomes swollen and tender and exudes brownish foul-smelling fluid. Due to the presence of gas, crepitus may be felt. Blebs filled with purplish foul-smelling fluid develop. These blebs rupture and ulcerate. General symptoms such as restlessness and fever develop and the patient may rapidly go into shock and anuria.

Diagnosis

The condition has to be diagnosed clinically. The organism can be identified by culture. X-ray of the affected part shows gas in the tissues. Gas in the tissues may occur in other conditions such as surgical emphysema and infections by streptococci, staphylococci and *E. coli*.

Treatment

Early institution of therapy is most important for success. Shock is treated on the lines of septic shock. Penicillin which is the drug of choice is given intravenously in a dose of 2 mega units 2 hourly. Other antibiotics may be tried depending on the sensitivity tests. Metronidazole and gentamicin are effective in most cases. Antitoxin is available for intravenous use (anti-gas gangrene serum—AGGS). It should be given in a dose of 40,000 units initially to be followed by 20,000 to 40,000 units repeatedly till the condition improves. Keeping the patient under hyperbaric oxygen (3 atmosphere pressure) remarkably improves the result of therapy and this should be instituted wherever it is available. Surgical excision of dead tissue and removal of foreign bodies should be undertaken after administration of AGGS. Gas gangrene can be prevented by taking proper care of the wound and early recognition of the condition.

47

Sexually Transmitted Diseases

K.V. Krishna Das, Usha Vaidhyathan

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General Considerations

Infectious diseases which are transmitted by heterosexual or homosexual intercourse and contacts are included under this group. In many developed countries this group constitutes the main bulk of infectious diseases in adults and the incidence is increasing. Increase in promiscuity, change in sex practices, asymptomatic infections, facilities for intercontinental travel, failure to trace sources of infection and lack of awareness of healthy sex practices have contributed to the increase in prevalence.

The present tendency is to include several other diseases like viral hepatitis B which can also be transmitted sexually in the group of STD.

Syphilis

(Syn: Lues venerea)

GENERAL CONSIDERATIONS

This chronic infection is caused by the spirochete, *Treponema pallidum*. Syphilis is present in all parts of the world. Though the incidence of primary infection continues to be steady, late complications are distinctly rare at present.

Treponema pallidum is aerobic, very susceptible to antiseptics, and is killed by exposure to light in 1-2 hours. It may survive in stored blood for 72 hours. Infection is acquired by the entry of the organism through abrasions in the skin and mucous membranes. In the vast majority of cases, infection is acquired by sexual intercourse. Rarely skin abrasions may be contaminated by infective discharges. The disease can also be transmitted occasionally by needle pricks, blood transfusion or by the transplacental route. *T. pallidum ssp pallidum* (syphilis), *T. pallidum ssp pertenue* (yaws) and *T. pallidum ssp endemicum* (endemic syphilis or bejel) and *T. carateum* (Pinta) are all morphologically identical. They are tightly coiled helical rods 5-15 µm long and 0.1-0.5 µm in diameter, motile and demonstrable by dark ground illumination or special staining methods.

Classification

Based on its course, syphilis can be described in 3 stages—primary, secondary, and tertiary.

Primary stage: In the primary stage, local lesions occur at the site of inoculation.

Secondary stage: The secondary stage is characterized by generalized lesions, most obviously seen in the skin and mucous membranes.

Tertiary stage: In the tertiary stage, which develops 3-10 years after the initial infection, gummatous and destructive lesions develop in many tissues.

For practical therapeutic purposes, the disease can be conveniently considered in two phases—the early and the late. The early phase extends over the first two years after infection and this includes the primary, secondary, early recurrent and early latent stages. This phase is more contagious. Syphilis of more than 2 years duration is called late phase.

Latent syphilis: Latent syphilis is that stage in which there are no abnormal clinical features. Blood serology is positive, but the CSF does not show any abnormality. History of primary or secondary lesions and abortion during the earlier pregnancies help in identifying this stage.

Clinical types of syphilis

1. **Congenital syphilis** (prenatal infection):
 - a. *Infantile form* which manifests within two years of birth
 - b. *Tardive congenital syphilis* (late congenital syphilis)—manifests 2 years or more after birth
2. **Acquired syphilis:**
 - a. Primary
 - b. Secondary
 - c. Latent
 - i. early phase—within 2 years of infection
 - ii. late phase—2 years later
 - d. Late manifestations.

PATHOLOGY

The lesions show a chronic granulomatous inflammation and are histologically characterized by epithelioid cells, plasma cells, lymphocytes, and giant cells. The small vessels are occluded by obliterative endarteritis. This results in necrosis and scar formation. Inflammation, vascular occlusion and probably immunological factors are contributory to the production of gummata. During the primary and secondary stages the lesions teem with the organisms. In the late phases, the number of organisms comes down and infectivity diminishes. Syphilitic lesions show a propensity to attract activated CD4-T lymphocytes. This makes the syphilitic lesions more efficient in disseminating HIV infection as well.

CLINICAL FEATURES—ACQUIRED SYPHILIS

Primary stage of syphilis: The incubation period varies from 1-3 weeks in most cases, though it may extend up to 90 days. A small macule develops at the site of inoculation which later becomes a papule and ulcerates. This is the primary chancre. It presents a characteristic appearance; a punched out ulcer with a dull red areola and a clear granular base exuding colorless serum which teems with the spirochetes. The regional lymph nodes enlarge a few days later. They are discrete, rubbery in consistency, and are generally described as ‘shotty’. Even without treatment the chancre heals in 8-10 weeks leaving



Fig. 47.1: Syphilis primary chancre

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behind a thin scar. Even after the healing of the chancre the lymph node enlargement persists. Generalized lymphadenopathy may develop at this stage before the secondary stage sets in Figure 47.1.

Other ulcers occurring in the genitalia such as Herpes genitalis, traumatic ulcers, chancroid, lymphogranuloma venereum, scabies, and carcinoma, have to be differentiated from syphilitic chancre.

Secondary stage of syphilis: This stage develops 6-8 weeks after the appearance of the chancre. General symptoms such as malaise, fever, headache, anorexia, hoarseness of voice, arthralgia, nocturnal pains, generalized lymphadenopathy, jaundice, and anemia develop.

The *skin lesions of the second stage* have certain common characteristics, though some degree of variability is evident. The distinguishing features of secondary syphilitic lesions are:

1. generalized and symmetrical distribution,
2. pink, coppery, or dusky red color,
3. absence of pruritus,
4. induration, and
5. polymorphic (macular, papular, or pustular) presentation.

Mucous membrane lesions: Condylomata lata are seen in the mucocutaneous junctions. Basically they are papules which are modified due to the constant moisture and rubbing. They are flat topped, hypertrophic fleshy masses with broad bases. They exude serum rich in treponemes. Mucous patches and snail track ulcers occur in the oral cavity and genitalia. Systemic manifestations of secondary syphilis include acute uveitis which may be unilateral or bilateral, meningitis and hepatitis.

Late syphilis: About 3-12 months after the primary and secondary stages, which are easily distinguishable, the disease enters the latent phase. The first two year period of the latent phase is termed the “*early latent phase*”. The organisms are present deep in the tissues and the only evidence of infection is the positive serology. Syphilis may



Fig. 47.2: Syphilis tertiary stage Gumma

of the patient's life. In the early part of the latent phase the patient may be infective, but the infectivity diminishes with time.

Tertiary stage: During this stage typical destructive lesions called “*gummata*” develop. These are granulomas which may be single or multiple. Histologically the lesions show perivascular infiltration by lymphocytes and plasma cells, followed later by fibrosis. Gummata may occur on the skin, mucous membranes, subcutaneous tissue, bones or viscera. These are asymmetric, small to large in size and indolent with a tendency for healing in the center and spreading at the periphery (Fig. 47.2).

Bone lesions: Bony lesions occur more commonly in men than in women and the symptoms are very variable and are likely to be missed if clinical suspicion is not strong. The tibia, skull, clavicle and femur are affected most, but any bone may be involved. Two types of lesions may develop—granulomatous periostitis and gummatous osteitis. Periostitis leads to bony proliferation and deposition of new bone beneath the periosteum. Gummatous osteitis produces circumscribed areas of osteolysis surrounded by areas of sclerosis. Syphilitic osteitis and periostitis may occur in the same *bone*.

Visceral Syphilis: Liver is affected most commonly, and it is enlarged by multiple gummata. As the lesions heal, sheets of fibrous tissue are formed and the liver is shrunk and distorted. The surface of the liver becomes lobular and this is termed “*hepar lobatum*”. Stomach, intestines, lungs and reproductive organs are affected less commonly.

Cardiovascular and central nervous system lesions occur 10-40 years after the initial infection. Cardiovascular lesions include syphilitic aortitis, aortic regurgitation and aneurysms of the aorta. Neurological involvement is more varied and this may be meningovascular or parenchymal. Meningitis occurs in the secondary stage, but in the tertiary

stage meningovascular involvement leads to *meningo-myelitis*, *transverse myelitis*, *syphilitic pachymeningitis*, *Erb's syphilitic paraplegia*, and *occlusive vascular lesions*. *Parenchymal lesions* are *tabes dorsalis*, *general paralysis of the insane (GPI)*, *taboparesis*, and *optic atrophy* (See also Chapters 120 and 188).

CONGENITAL SYPHILIS

Treponema pallidum can pass from the infected mother to the fetus through the placenta. An infected mother can transmit the disease to her child even in the late stages, but in the late latent phase there is less infectivity to the fetus. Since *T. pallidum* is transmitted only through the fully formed placenta which develops by the fourth month of pregnancy, the fetus is unaffected in the early period. Abortions occurring earlier during pregnancy are not attributable to syphilis. Birth of a syphilitic baby is often preceded by repeated abortions occurring at progressively later months.

The primary stage is not evident in congenital syphilis. The early manifestations are similar to those of secondary acquired syphilis. Sometimes, a syphilitic infant may be clinically normal at birth. The skin lesions consist of dusky red papules with bullae containing serum or pus, most prominent in the palms and soles ("*syphilitic pemphigus*"). The discharge contains a large number of *T. pallidum*. Generalized widespread papular skin rashes are seen at times. At the mucocutaneous junctions the papules develop into condylomata. The infant has a wasted and dehydrated appearance which is described as "*old man facies*". The baby fails to thrive and becomes marasmic. Alopecia may occur. Occasionally there may be growth of black hair called the "*syphilitic wig*". Mucous patches may be seen on the nose, mouth, throat and larynx. Radiating fissures may form at the angles of the mouth (*rhagades*). Bloodstained, thick, purulent nasal discharge may block the nostrils and produce a bubbling sound during breathing termed as "*syphilitic snuffle*". Feeding problems may develop due to blockage of the nose.

Bony lesions develop within 6 months of birth. The ends of long bones are swollen and tender due to osteochondritis. The restriction of movement is sometimes referred to as *syphilitic pseudoparalysis*. Osteochondritis clears up by six months of age, but syphilitic periostitis persists and tends to become more marked. Subperiosteal new bone is laid down irregularly over the shaft of bones leading to thickening and deformity, e.g., *sabre tibia*. Due to concentric layering of new bone, the skiagram may reveal a characteristic onion peel appearance. Painless effusions in one or both knee joints ('*Clutton's joints*') develop between the ages of 10 and 20 years.

Eye lesions include choroiditis and retinitis which develop after the first two years of life. Invasion of the

nervous system by *T. pallidum* during intrauterine life may lead to arrest of development of the brain.

Late non-infectious congenital syphilis: This stage sets in after the second year of life. Lesions are more common between 7 and 15 years of age but may occur at any age. Gumma may develop in the skin, mucous membranes, or viscera. The lesions resemble those of acquired syphilis.

Interstitial keratitis is one of the common lesions occurring in late congenital syphilis. This may develop at any age between 3 and 30 years or even later.

Neurological lesions: Nerve deafness develops due to involvement of the 8th cranial nerve endings and this lesion is suggestive of congenital syphilis. It presents as bilateral progressive loss of hearing which may become total. Congenital neurosyphilis leads either to general paralysis of insane or tabes dorsalis, but these patients develop the disease at a younger age. Meningovascular neurosyphilis is rare. When it occurs it presents as cranial nerve palsies, hemianopia, and hemi- or monoplegia.

Stigmata of congenital syphilis: Damage to the developing organs *in utero* leads to the permanent stigmata of congenital syphilis. These include localized thickening of the frontal and parietal bones of the skull due to periostitis giving rise to frontal bossing, *hot cross bun skull* and *Parrot's nodes*. *Saddle nose* develops due to the destruction of nasal bones. *High arched palate* and *bulldog facies* are all characteristic. The permanent teeth show diagnostic abnormalities. Peg-like incisors (*Hutchinson's teeth*) are diagnostic. *Hutchinson's triad* is a combination of *interstitial keratitis*, *Hutchinson's teeth* and *nerve deafness* (Fig. 47.3).

DIAGNOSIS

Serodiagnosis of syphilis: Two types of serological tests have been developed; the nonspecific tests using cardiolipin from beef heart and specific tests using live or killed laboratory strains of treponemes or their

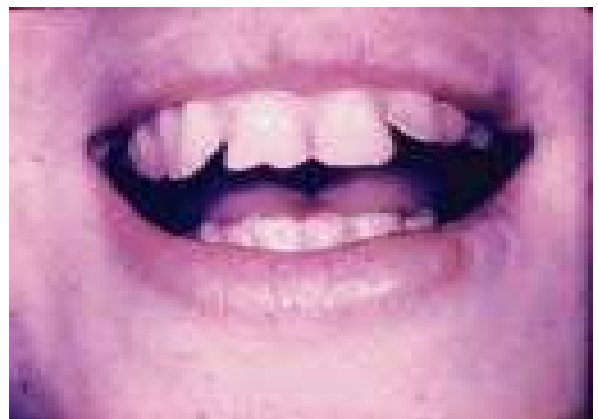


Fig. 47.3: Congenital syphilis Hutchinson's teeth

components. The commonly used nonspecific tests are the *rapid plasma reagin* test (RPR) and the *venereal disease reference laboratory* (VDRL) test. Among the specific tests the commonly used one is *treponema pallidum* hemagglutination test (TPHA). *Fluorescent treponemal antibody-absorption* (FTA-ABS) test and the *treponema pallidum immobilization* (TPI) test are done usually for research purposes. There are several other tests used in different laboratories.

Interpretation of serological tests: The nonspecific serological tests become positive about 4 weeks after infection and the titer progressively increases in the secondary stage. If the disease is treated and cured at this stage the titers fall and the test may become negative in 4-6 months. Treatment instituted late in the disease may not eliminate seropositivity. False positive reactions not due to any technical error are known as biological false positive reactions. This may occur in connective tissue disorders like SLE and rheumatoid disease, malaria, leprosy, hepatitis, infectious mononucleosis, and tuberculosis.

The FTA-ABS test becomes positive early after infection. The TPI test becomes positive only later than the FTA-ABS test. Once positive, they remain so for life. Early treatment in primary stage prevents the development of seropositivity. Nonspecific tests are useful to determine cure since they decline in titer if the disease is treated sufficiently early.

Frequency of serological tests			
Tests	Primary stage	Secondary stage	Tertiary stage
Non specific	50-70 %	98-100 %	70%
Specific	70-85 %	100%	98-100%

In the primary and secondary stages diagnosis is established by demonstration of the organism by dark ground microscopy and serological tests. All genital ulcers should be investigated for syphilis irrespective of their appearance. Treatment should always be given only after an accurate diagnosis has been made. All suspected cases should be kept under observation for a minimum period of three months and serological tests for syphilis should be performed at regular intervals. All sexual contacts of the patient during the past six months should be traced and examined.

Latent syphilis is diagnosed when the standard serological tests for syphilis are positive in the blood without any clinical evidence of the disease.

Late syphilis: It is essential to confirm the diagnosis by serological examination before starting the treatment. The cerebrospinal fluid should be examined in all cases of secondary syphilis to exclude meningeal involvement.

Diagnosis of Congenital syphilis: The disease should be suspected in children born to mothers who are syphilitic. In the early infectious stage diagnosis can be established by finding *T. pallidum* on dark ground examination of the discharge from the lesions of the skin, mucous membrane and nose. Serological tests have to be interpreted with caution in the early weeks of life. Maternal reaginic antibodies of IgG class may be passively transferred across the placenta and these may lead to positive serology in the infant even though the baby is not suffering from syphilis. These disappear with time. If the baby is really affected, IgM antibodies develop and the rise in titers can be demonstrated by specific tests (IgM-FTA-ABS).

TREATMENT

The principal aim of therapy is to make the patient non-infectious within the shortest time and to achieve cure. A treponemicidal level of penicillin (0.018 mg/L) has to be maintained in the serum and cerebrospinal fluid for 7-10 days or more to achieve cure.

Treatment regimen for syphilis:

Early syphilis (primary, secondary, and early latent) Benzathine benzyl penicillin, 2.4 million IU by IM injection, given as two injections at separate sites in a single session.

Alternative regimen: Procaine benzyl penicillin, 1.2 million IU, IM injection for 10 consecutive days.

Treatment of patients allergic to penicillin:

Non pregnant patients: Doxycycline 100 mg orally twice daily for 14 days or tetracycline 500 mg orally 4 times daily for 14 days. A single dose of Azithromycin 2 g orally is also effective.

Pregnant patients: Erythromycin 500 mg qid p.o for 14 days.

Late latent syphilis The dose and choice of the drugs is the same as for early syphilis but the duration is longer. Benzathine penicillin is given once weekly for 3 consecutive weeks, procaine penicillin for 20 days, doxycycline, tetracycline and erythromycin for 30 days.

Neuro syphilis Aqueous benzyl penicillin (crystalline penicillin) 12-24 million IU by IV injection, administered daily in doses of 2-4 million IU every 4 hours for 14 days.

Alternative regimen: Procaine benzyl penicillin 1.2 million IU IM once daily and probenecid 500 mg qid po, both for 10- 14 days.

Congenital syphilis Congenital syphilis (up to 2 years of age) and infants with abnormal CSF: Aqueous benzyl penicillin 100 000 – 150 000 IU/kg/day administered as 50000 IU/kg/dose, IV, every 12 hours, during the first 7 days of life and every 8 hours thereafter for a total of 10 days. Alternative regimen is procaine penicillin, 50 000 IU/kg, IM, as a single daily dose for 10 days.

Congenital syphilis of 2 or more years: Aqueous benzyl penicillin, 200000–300000 IU/kg/day, IV or IM, administered as 50000 IU/kg/dose every 4–6 hours for 10–14 days.

Penicillin allergic children: Erythromycin 7.5–12.5 mg/kg qid p.o for 30 days.

Adverse effects of penicillin: In addition to all the adverse side effects of penicillin, syphilitic subjects receiving the drugs may develop *Jarisch-Herxheimer reaction* caused by rapid destruction of spirochetes. In addition to the products of spirochete disintegration, cytokines such as tumour necrosis factor (TNF) and others may also play a role. It may develop in up to 50% of cases of secondary syphilis and in a smaller proportion of late syphilis. 2–3 hours after receiving penicillin the patient becomes restless and apprehensive and develops severe rigor, fever, tachypnea and rise in blood pressure. In a few hours sweating starts, becomes profuse and the blood pressure drops. The reaction subsides within a few hours with symptomatic management. However, in patients with general paresis or high CSF cell counts further neurological damage may develop and lead to extension of paralysis. The lesions of syphilitic aortitis may extend and lead to coronary occlusion which can be fatal. Administration of 20 mg prednisolone starting 24 hours prior to penicillin injections and continued for two days prevents Herxheimer reaction. If Herxheimer reaction occurs, management is the same as for anaphylactic shock. Antibody to TNF which blocks its action has been employed with benefit in severe cases where other routine measures are inadequate.

Follow-up: Patients should be followed up at the end of 3 months, 6 months and 12 months, clinically and serologically, using a non-treponemal test like VDRL or RPR to assess the results of therapy and to detect possible reinfection.

At all stages of the disease, repeat treatment should be considered when clinical signs or symptoms of active syphilis persist or recur or there is confirmed increase in the titre of a non-treponemal test. Examination of CSF should be undertaken before repeat treatment, unless reinfection and a diagnosis of early syphilis can be established. Retreatment is with schedules as for late syphilis.

When congenital syphilis is detected, the mother also should be investigated serologically. Surveillance plan is the same as for late syphilis. The baby should be followed up late into adult life. *Interstitial keratitis* should be treated with local corticosteroids and atropine drops in addition.

PREVENTION

Congenital syphilis is preventable if the mother is treated before the fourth month of pregnancy. Treatment

administered later in pregnancy usually cures both the mother and the fetus, though residual stigmata may be seen in the baby. If syphilis is detected in the pregnant woman, the course of treatment is the same as for primary syphilis. Tetracycline should be avoided in pregnancy. Azithromycin in a dose of 1.8 g orally given on two occasions within six days has been found to prevent the development of syphilis in persons who had infective exposure. This may serve as a short term measure.

Social measures: When primary or latent syphilis is detected, all sexual contacts should be traced out and examined. Since a social stigma has been attached to the sexually transmitted diseases, patients tend to conceal the infection and do not come up for treatment. Hence, great care is required to avoid psychological trauma to the patient and his contacts. The doctor should not take an admonishing attitude. *Proper instruction on healthy sexual practices, avoidance of direct contact by the use of condoms, and periodic examination of prostitutes and other personnel engaged in similar practices help to limit to some extent the incidence of sexually transmitted diseases.*

Syphilis and HIV: There is increased interest in syphilis at present since it often coexists with AIDS, and each aggravates the manifestation of the other. Genital ulceration facilitates sexual transmission of HIV. All patients with syphilis should be screened for HIV and vice versa. Clinical manifestation of syphilis in HIV may be atypical. A rapid progression from early to late disease is reported. Progression to neuro syphilis occurs more frequently. The diagnosis of syphilis by serologic means become unreliable. Serological tests like VDRL and TPHA may be false negative or quantitatively higher or lower than expected. Dark field microscopy, histology and clinical acumen have to be relied upon. Failure to respond to treatment is also common. Treatment with higher and more prolonged doses is required.

Points to remember

- The primary chancre on the genitalia appears 3 weeks after the sexual contact.
- The generalized symmetrical, non-pruritic papules of the secondary stage develops 6–8 weeks following the chancre
- Tertiary stage develops years later.
- Serological diagnosis includes VDRL and TPHA and demonstration of treponema by dark ground microscopy.
- Treatment is with benzathine benzyl penicillin or procaine penicillin.

Gonorrhea

Gonorrhea is one of the most common sexually transmitted diseases all over the world. This is caused by *Neisseria gonorrhoeae*, which is present throughout the

world. Several strains of *N. gonorrhoeae* produce *betalactamase* and this helps them to develop resistance to penicillin to which they were sensitive. At present occurrence of penicillin-resistant gonorrhea is widespread. The lesions also occur over a wider area, depending on the sexual practices.

Gonococci attach themselves to cells with the help of pili before initiating infection. The organisms are ingested by polymorphs and they survive within the cells for variable periods, being protected from adverse environment. Four types can be distinguished by cultural characteristics. Types T1 and T2 are virulent whereas T3 and T4 are not. Gonococci are gram-negative diplococci seen intracellularly and also free in the exudate.

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Pathology

Gonococci affect columnar and transitional epithelium mainly and infection is initiated in the urethra, anal canal, conjunctiva, pharynx, and endocervix. Pus is produced locally. Direct extension from the site of infection leads to complications such as endometritis, salpingitis, peritonitis, and Bartholinitis in the female, and periurethral abscess, epididymo-orchitis, and prostatitis in the male. Ocular conjunctiva is affected. Metastatic spread of the organisms leads to arthritis, dermatitis, endocarditis, meningitis, myopericarditis, and hepatitis.

CLINICAL FEATURES

In men the onset of the disease is more acute than in women. Incubation period is usually 3 to 5 days.

Gonorrhea in the male: In over 90% of cases urethritis presents with a constant burning sensation in the penis and discharge of infective pus which teems with the organisms. Meatal inflammation and penile edema may be obvious. Variable amounts of pus can be milked from the urethra. Micturition is painful and the patient is severely distressed. Other adnexal structures like epididymis, testes, and spermatic cord become inflamed. Rarely the Tyson's glands and the median raphe of the scrotum may be inflamed. Gonococcal prostatitis and seminal vesiculitis are seen but they are rare. If left alone, the acute manifestations subside over a period of weeks or months even-without treatment. Exacerbations occur frequently as a result of sexual indulgence, alcoholism, or undue exertion. Ultimately, the anterior and posterior urethra develop stricture. Periurethral abscesses may develop at times. Extension of suppuration into the periurethral tissues and scrotum result in fistulous openings discharging urine from multiple sites ("water-can scrotum"). In 10% of subjects the lesion may be asymptomatic and has to be detected by examination.

The rectum is an important site of ulceration in persons who are habitual catamites in homosexual

relationship. The rectum and anal canal are ulcerated and show blood-stained mucopurulent discharge. The condition may present as proctitis and may be mistaken for other ulcerating lesions of this region.

Gonorrhea in the female: In a good number of women gonorrhea may remain asymptomatic. Symptoms include leucorrhea, dysuria, menstrual abnormalities and features of pelvic inflammation. Rectal lesions develop in about 40% of affected women due to contamination by cervical discharges.

The gonococci may pass up from the endocervix leading to acute salpingitis and oophoritis. Chronic salpingo-oophoritis and tubo-ovarian masses may develop. Exacerbations occur during menstrual periods or one or two weeks thereafter. Gonococcal salpingo-oophoritis is a common cause of sterility.

Gonococcal infection in the newborn: Inoculation of gonococci into the baby's eyes from the maternal genital passages leads to ophthalmia neonatorum. This presents with purulent conjunctivitis which may result in blindness. The infection can also disseminate to other tissues and result in arthritis in the newborn.

Disseminated gonococcal infection: This occurs in up to 30% of infected patients, 80% of them being females. Bacteremic spread occurs. Manifestations include cutaneous lesions, septic arthritis, septicemia, endocarditis, myocarditis and rarely, pericarditis and meningitis. Risk of dissemination depends on the type and virulence of the organism. Dissemination is more common from silent foci in the pharynx, rectum, or endocervix. The cutaneous lesions take the form of vesicles and pustules which do not usually ulcerate.

Oropharyngeal infections: Pharyngitis and tonsillitis result from oral sex and may affect both sexes. In the majority of cases symptoms are not severe enough to seek medical care. Strong clinical suspicion and microbiological investigations are required to make the diagnosis. Gonococcal pharyngitis may give rise to dissemination.

DIAGNOSIS

Gonorrhea should be suspected in all clinical situations where there is purulent urethral discharge, leucorrhea in women, atypical oropharyngeal ulceration, proctocolitis and ophthalmia neonatorum. Bacteriological diagnosis is established by demonstrating gram-negative diplococci inside polymorphonuclear cells in the exudates. The organism can be identified by culture and further studies. Culture of cervical discharge is required in women with late manifestations to establish the diagnosis. On rare occasions purulent material may have to be collected by culdocentesis or laparoscopy. Fluorescent antibody techniques help in making quick diagnosis where such

facilities exist. Complement fixation test is useful in selected cases of chronic gonorrhea with systemic manifestations.

TREATMENT OF GONORRHEA

The sheet anchor of the treatment of gonorrhea upto the 1970’s used to be penicillin to which the organisms were invariably sensitive. A large proportion of gonococcal isolates world wide are now resistant to penicillins, tetracyclines and other older antimicrobial agents. Therefore, these drugs can no longer be relied upon for the cure of gonorrhea. Since dual infections with gonococcus and chlamydia are common it is recommended that concurrent anti-chlamydia therapy may also be given.

Recommended regimens (WHO and CDC guide lines 2003)

Ceftriaxone 125 mg IM injection or cefixime 400 mg orally or spectinomycin 2 g by IM injection, as a single dose, is curative. These drugs are also effective in adult gonococcal conjunctivitis.

Ciprofloxacin 500 mg or ofloxacin 400 mg as a single dose.

Neonatal gonococcal conjunctivitis:

Ceftriaxone 50 mg/kg IM as a single dose to a maximum of 125 mg. Alternative regimen includes kanamycin or spectinomycin 25 mg/kg IM single dose, to a maximum of 75 mg.

Disseminated gonococcal infection:

Ceftriaxone 1 g IM or IV injection, once daily for 7 days or spectinomycin 2 g IM twice daily for 7 days.

Gonococcal endocarditis: same dosages of ceftriaxone or spectinomycin for 4 weeks.

Prophylactic treatment: Instillation of 1 to 2% silver nitrate solution or 1% tetracycline ointment into the eyes of newborn babies effectively prevents all forms of ophthalmia neonatorum whether it is of bacterial, viral, or chlamydial origin. Use of condoms helps to reduce transmission of STDs.

Follow up: Patients should be reviewed after 48 hours for subsidence of acute symptoms and at longer intervals for recurrence.

Points to remember

- Males present with dysuria, frequency and urethral discharge
- Females complain of vaginal discharge, dysuria and abdominal pain
- Pelvic inflammatory disease and infertility are late sequelae
- Treatment is with ciprofloxacin or ceftriaxone
- Concurrent antichlamydia therapy should be given to all patients with gonorrhea.

Non-Gonococcal Urethritis
(Syn: Nonspecific Urethritis)

Definition

Urethritis, from which gonococci cannot be isolated, is termed as non-gonococcal urethritis (NGU). While in men the condition is well defined, in women it is not so. The possible causative organisms are *Chlamydia trachomatis* in 60% cases. Other organisms include mycoplasma such as *Ureaplasma urealyticum*, *Mycoplasma hominis*, *M fermentans* and *M genitalis*. Other pathogens such as *Herpes simplex virus*, *Trichomonas vaginalis* and *Candida albicans* may rarely produce the picture of NGU. In a proportion of patients organisms may not be identified.

Human Chlamydial Infections	
Diseases	Organisms
Trachoma	<i>C. trachomatis</i> A, B, Ba, C
Inclusion conjunctivitis	<i>C. trachomatis</i> D-K Ophthalmia neonatorum -do-
<i>Genital tract</i>	
<i>Male</i>	
Urethritis, epididymitis	<i>C. trachomatis</i> D-K
<i>Female</i>	
Urethritis, cervicitis proctitis, salpingitis, perihepatitis, periappendicitis, infertility abortion, stillbirth	<i>C.trachomatis</i> D-K
Lymphogranuloma venereum	<i>C. trachomatis</i> L1-L3
<i>Respiratory tract</i>	
Pneumonitis of infants	<i>C. trachomatis</i> D-K
Pharyngitis, pneumonia	<i>C. pneumoniae</i>
Psittacosis	<i>C. psittaci</i> (avian strains)
Pneumonia	<i>C. psittaci</i> (ovine strains)

Note: Ovine-pertaining to sheep.

Epidemiology

Non-gonococcal urethritis occurs worldwide and it is common in India. Infection is initially acquired by sexual intercourse, though relapses may occur without such contact. The chain of transmission is not as clear cut as in gonorrhea. This infection develops only in a few of the sexual partners of patients in both sexes. The reason for this phenomenon is not known. In many centers NGU outnumber gonorrhea.

Clinical Features

NGU in men: The incubation period ranges from a few days to two months. This wide range may suggest the possibility of different pathogens. Clinical features resemble a mild attack of gonorrhea with a subacute onset and a watery, mucoid, mucopurulent, or rarely frankly purulent urethral discharge. Gram staining shows the absence of gonococci. Even in untreated cases the urethritis subsides, but mild exacerbations occur from time to time. Treatment with tetracycline, which is the drug of choice, rapidly clears the condition in 90% of cases. Non-gonococcal proctitis may occur in homosexual individuals.

Post-gonococcal urethritis (PGU): This term is used for patients with gonococcal urethritis who develop non-gonococcal urethritis after successful treatment with penicillin. It is possible that these patients harbor the organisms of gonorrhea and NGU simultaneously.

Local complications of NGU and PGU: Local abscesses may develop in some cases. Acute unilateral epididymitis develops rarely. *Chronic prostatitis* is the most common complication. Identification of this condition may not be easy. The most significant symptom is prostatic pain which is felt in the perineal region as a vague discomfort and this may be referred to the groins, thighs, and suprapubic region. Presence of pus cells and numerous prostatic threads in the first sample of urine collected after prostatic massage suggests prostatitis. Around 1-2% of males who develop NGU may suffer from Reiter's syndrome later.

Non-gonococcal genital infections in women: This infection is much less clear cut in women than in men. Some women may complain of vaginal discharge. The most important manifestation is salpingitis, which may extend to pelvic tissues to produce pelvic inflammatory disease. Perihepatitis, bartholinitis, postpartum and post-abortion fever, ascending pyelonephritis, infertility and birth of underweight babies have all been recorded as complications.

Non-gonococcal infections in infants and children: Infections may be acquired by the baby during birth, from the maternal genital passages. The newborn may develop non-gonococcal ophthalmia neonatorum and infantile pneumonia caused by *C. trachomatis*.

Diagnosis is by culture of discharges, cervical swab or urethral discharge, in both sexes. Other methods include PCR for *C. trachomatis*.

Treatment of Non-gonococcal Genital Infections

Doxycycline 100 mg orally bd for 7 days or
Azithromycin 1 g orally in a single dose

Alternative regimen (7 days treatment)

Amoxycillin 500 mg tid or

Erythromycin 500 mg qid or

Ofloxacin 300 mg bd or

Tetracycline 500 mg qid

Epididymitis responds to ceftriaxone 250 mg IM bd with doxycycline 100 mg bd for 10 days. Azithromycin 1 g, single dose is a suitable alternative.

Points to remember

- NGU presents as urethral discharge which is watery, mucoid or mucopurulent
- Some patients harbor organisms of gonorrhea and NGU simultaneously and their urethritis persists if gonorrhea alone is treated.
- Treatment is with doxycycline or azithromycin

Lymphogranuloma venereum

Syn: Climatic bubo, Lymphogranuloma Inguinale

Definition

Lymphogranuloma venereum is a common sexually transmitted disease caused by *Chlamydia trachomatis* strains L1, L2 and L3, manifesting as inguinal buboes, pseudo-elephantiasis of the genitals and anorectal involvement in the late stages.

It is present all over the world, more frequently in developing countries. The incubation period ranges from 2 weeks to several weeks.

Clinical Features

The organisms enter by sexual intercourse and a small herpetiform ulcer develops under the prepuce or the labia. This ulcer disappears within 24 to 48 hours. Rarely it may become secondarily infected and persistent.

The manifestations are different in the two sexes. In **males** the prominent feature is development of inguinal buboes since lymphatics from the prepuce and penis drain into the inguinal group of lymph nodes. On the other hand, in the females they drain into the anorectal lymph nodes or directly into the hypogastric lymph nodes. The buboes are usually unilateral, painful, matted, firm or fluctuant, and tender. The overlying skin is indurated. If the femoral and inguinal nodes are enlarged, they are separated by Poupart's ligament producing a groove called *Groove sign of Greenblatt*, which is pathognomonic. Buboes may be bilateral at times. Sooner or later, the bubo suppurates and multiple sinuses develop and discharge pus. Some buboes may remain indolent for a long time.

In **females** mild constitutional symptoms like fever, malaise and lower abdominal pain on the side of the bubo, are fairly common. Local peritonitis may develop through peritoneal lymphatics. Other lesions in the female include stricture of the urethra, destruction of the floor of urethra and rectovaginal, urethro-vaginal, or vesico-vaginal fistulae. In debilitated patients extensive tissue damage may develop. Pelvic inflammation may follow.

Esthiomene: This is a pseudo-elephantoid condition of the genitalia caused by lymphatic obstruction, due to extensive involvement of deeper pelvic lymph nodes and lymphatics. It is more common in women. Hypertrophy involves the labia, prepuce of the clitoris, and sometimes the clitoris. They enlarge to big sizes and the surface is warty, mammilated, verrucous or ulcerated.

Anorectal lesions: These develop late in the disease and are more common in women and in male passive homosexuals. Initial lesion is ano-proctitis which may resemble dysentery, but does not respond to usual treatment. Finally it leads to rectal stricture. Rarely, stricture may develop without evidence of preceding anoproctitis. Below the stricture extensive polyposis and cock's comb like condylomatous masses may develop in the perianal region.

Extragenital manifestations are rare in LGV. These are meningitis, cutaneous eruptions, episcleritis, iridocyclitis, and arthritis.

Diagnosis

Diagnosis is clinical. The causative organism can be grown in chick embryo or tissue culture, where facilities exist. The *LGV complement fixation test* becomes positive in 1-3 weeks in 90 to 95% cases. This test is nonspecific since other chlamydiae may give rise to positive reactions, though not in the same titers as seen in LGV. A four-fold rise in the titer can be taken as diagnostic of LGV. Other more specific tests are the *immunofluorescent tests* and *radio-isotope precipitation tests* (RIP).

Treatment

The recommended regimen is

Doxycycline 100 mg orally bd for 14 days or
Erythromycin 500 mg orally qid for 14 days.

Alternative regime is to treat with oral tetracycline in doses of 500 mg qid for 14 days. The suppurating buboes should be aspirated through healthy skin and not incised. Some patients with advanced disease may require prolonged treatment.

Surgery is required for excising elephantoid lesions and dilating strictures after treating adequately with tetracycline. Sometimes, even established strictures resolve with simple medical treatment.

Points to remember

- Caused by L1, L2 and L3 strains of *Chlamydia trachomatis*.
- Primary asymptomatic ulcer that develops two weeks after the sexual contact is usually unnoticed.
- Males present with tender, unilateral inguinal bubo.
- Complications are more common in females.
- LGV responds to doxycycline or erythromycin

Granuloma inguinale

(Syn: Granuloma Venereum, Donovanosis)

Definition

Granuloma inguinale is a specific chronic granulomatous disease affecting primarily genitalia in both sexes. It is particularly prevalent in the tropical and subtropical regions. It constitutes 1.5 to 6% of the total number of STD cases seen in clinics in India. There is a higher incidence of this disease in the eastern coastal states particularly in the states of Orissa, Andhra Pradesh, and Tamil Nadu. It has been reported from all regions.

The disease is caused by *Donovania granulomatis* (syn: *Calymmatobacterium granulomatis*) which is seen either as bacillary forms inside phagocytes in discharges or biopsy specimens. The organism can be cultured *in vitro*.

Clinical Features

The incubation period ranges from a few days to a few months. The disease starts as a subcutaneous papule or vesicle which ulcerates to give rise to a granuloma. The lesion extends by contiguity. Draining lymph glands are not affected and this helps to differentiate the lesion from a primary chancre. Rarely it can present as a subcutaneous swelling in the inguinal region which bursts open to produce a granulomatous ulcer. This is called "pseudo bubo". The initial lesion may be in the genitalia, groin, thigh, perineum, or oral mucosa depending on the sex practices. It may extend to the buttocks or anterior abdominal wall. In most of the cases extragenital lesions on the tongue, cheek, or oral cavity are accompanied by a primary lesion in the genitalia. Fusospirochetal infection supervenes as secondary invader and this result in tissue destruction. The ulcers show pouting granulation tissue. Healing leads to scarring and local elephantiasis of the genitalia. Epidermoid carcinoma may develop in 0.5% of cases.

Diagnosis

Granuloma inguinale has to be differentiated from syphilitic chancre and carcinoma. Diagnosis is confirmed by biopsy and demonstration of the organism in tissue spreads obtained from the margins of the ulcer.

Treatment

Recommended regimen: Azithromycin 1 g orally on first day, then 500 mg orally once a day or doxycycline 100 mg orally bid until all lesions have completely epithelialized. Alternatives are erythromycin or tetracycline 500 mg q.i.d or trimethoprim 80 mg/sulfamethoxazole 400 mg, 2 tablets orally b.d for a minimum of 14 days. Patients

Diseases Caused by Infections

should be followed up clinically until signs and symptoms have resolved.

Points to remember

- Granulomatous lesion in the genitalia and neighboring sites.
- Lymph nodes are not affected.
- Treatment is with azithromycin or doxycycline till the lesions heal.

Chancroid

(Syn: Soft Chancre, Soft Sore, Ulcus Molle)

Chancroid is caused by *Hemophilus ducreyi*. The organism is seen in clusters or singly in smears from ulcers and can be grown in special media. The disease is seen more in the poor with bad personal hygiene. Incubation period is 5 days.

Clinical Features

Multiple, superficial, non-indurated, painful ulcers which bleed easily develop along the corona glandis or inner aspect of the labia. Inguinal glands may be enlarged and in many cases they suppurate to form inguinal buboes called (inflammatory bubo). Secondary infection with *Vincent's spirochetes* may develop. In such cases balanoposthitis with offensive discharge may be prominent.

Diagnosis

Diagnosis is confirmed by demonstrating *H. ducreyi* in gram stained smears from ulcers or by culture. Other ulcerating lesions have to be excluded.

Treatment

Ciprofloxacin 500 mg bd for 3 days or erythromycin 500 mg qid for 7 days or azithromycin 1 g orally as a single dose is recommended. Alternatively ceftriaxone 250 mg IM as a single dose can be given.

Trichomoniasis

Trichomoniasis is infection by the flagellate protozoan *Trichomonas vaginalis* that causes vaginitis in women and

rarely urethritis in men. In women the condition is localized to the vagina. In most of the cases infection is acquired by sexual intercourse.

Pathology

The infection is most common in the second and third decades of life and may be associated with gonorrhea. The superficial layers of the vagina are affected. There is marked polymorphonuclear infiltration and changes in the epithelium of the vagina.

Clinical Features

Females: In young women there is a florid, profuse, irritating, offensive, yellow vaginal discharge. Severe cases may show vulval swelling with excoriation of the adjacent skin. The vaginal pH tends to become more alkaline (pH 5-8) than normal (pH 4-5). Symptoms are milder in older women.

Males: Many are asymptomatic carriers. Some may suffer from true trichomonal urethritis or they may harbour *T. vaginalis* in addition to non-gonococcal urethritis. Occasionally frank purulent urethritis may occur due to this flagellate.

Laboratory diagnosis is established by demonstrating the active flagellates in fresh exudates.

Treatment

Metronidazole or tinidazole, 2 g orally in a single dose is recommended. Alternatively, metronidazole 400 mg or 500 mg orally b.d for 7 days or tinidazole 500 mg orally b.d for 5 days can be used. Patient should be followed up after 7 days. If not cured, the treatment is repeated with the 7 day regimen. If there is no response to repeat treatment, metronidazole 2 g orally daily together with 500 mg applied intravaginally at night for 3-7 days is recommended. Vaginal preparations are advised only in refractory infections. Relapse is prevented by treating both sexual partners simultaneously. Relapses of trichomoniasis are unusual. Recurrence of symptoms is usually due to reinfection.

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Sexually Transmitted Viral Diseases Including AIDS

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Several viruses may be transmitted by sexual contact. Important among them are herpes simplex, human papilloma virus, molluscum contagiosum, hepatitis B virus, cytomegalovirus, Marburg virus, and AIDS.

Herpes Genitalis

Herpes genitalis is caused by *herpes simplex virus (HSV) type 2 and less frequently by HSV type 1*. It is moderately infectious. The virus remains dormant in the presacral sensory ganglion cells. Periodically it moves into the skin through the axons of sensory nerves to produce recurrent attacks of herpes simplex locally. Factors which produce the reappearance of herpes are not clear. In many western countries herpes genitalis is emerging as the commonest among the STD. The disease is transmitted by sexual intercourse. The virus is shed from the lesions for up to 2 weeks after apparent healing. Infection of the baby during birth leads to neonatal herpes.

Clinical Features

The incubation period is 2-4 days or rarely longer. The onset of local lesions may be preceded by burning pain in the S1 to S5 dermatomes.

The lesions occur in the external genitalia of men and in the anal canal of homosexuals. Over the penis, it starts with erythema followed by the appearance of papules or vesicles which soon rupture to form shallow painful ulcers. Ultimately, crusts form which dry up and fall off leaving healed scars which fade. Tender inguinal adenopathy develops in the primary attack but not with recurrences. The lesions are infective throughout. Recurrences are generally much milder (Fig. 48.1).

In women the primary lesion and recurrent attacks differ from each other considerably. Primary attack is severe, whereas, subsequent attacks are milder. Lesions occur usually in the vulva and adjacent skin areas. Morphology of the lesion is the same as in men. During the primary attack retention of urine may develop due to extreme pain on micturition. Herpes virus infection is directly or indirectly related to the development of carcinoma of the cervix, vagina, or vulva in later life as the virus is oncogenic. HSV 2 can also act as a cofactor with human papilloma virus for invasive cervical cancer.



Fig. 48.1: Herpes genitalis male

Diseases Caused by Infections

Dissemination of the infection is rare in adults, but if it occurs it can be fatal. The skin, the central nervous system, and other internal organs may be affected. HSV2 can also act as a cofactor with human papilloma virus for invasive cervical cancer.

The newborn may acquire herpes during delivery if the mother has active lesions in the genitalia. Lesions develop in the baby usually within two weeks after birth. These occur more commonly with primary maternal herpes than with recurrent attacks. Both HSV-1 and HSV-2 may be responsible but the latter is more common. The lesions in the newborn include meningoencephalitis or generalized herpetic lesions involving several organs. If not treated, mortality and morbidity are very high.

Laboratory diagnosis is established by isolation of the virus from the lesions. Serological tests using blood include complement fixation test which becomes positive about a week after infections. In primary infection, the first sample is seronegative, the second sample shows a marked rise in titer. In recurrent herpes both samples give the same low titer. Herpes virus can be demonstrated by electron microscopy of vesicle fluid or tissue specimens. In herpes simplex encephalitis the CSF shows antibodies.

Cytology

Papanicolaou's stained smears from vesicles show multinucleated giant cells with eosinophilic inclusions. In meningoencephalitis CSF shows changes. CT scan, MRI imaging and brain biopsy are employed to diagnose herpetic encephalitis.

Treatment and Prophylaxis

Treatment options for genital herpes:

First clinical episode: Treatment duration-7 days

Acyclovir 200 mg orally 5 times daily or
400 mg t.i.d or

Valacyclovir 1 g orally b.i.d or

Famciclovir 250 mg t.i.d.

Recurrent infection: Treatment duration-5 days.

Acyclovir (oral) 200 mg 5 times daily or
400 mg t.i.d or

800 mg b.d or

Valacyclovir 500 mg b.d or 1g once daily or

Famciclovir 125 mg twice daily.

Suppressive therapy: The condition tends to recur often on cessation of treatment. If the recurrence is too frequent, >6 times a year, suppressive therapy is indicated for prolonged periods.

Acyclovir 400 mg bid or

Valacyclovir 500 mg or 1 g or

Famciclovir 250 mg bid continuously.

Recommended regimen for *severe disease* is acyclovir 5-10 mg/kg IV every 8 hours for 5-7 days or until clinical resolution is attained.

Severe herpes with *coinfection with HIV*: Acyclovir 400 mg orally 3-5 times daily until clinical resolution is attained.

Neonatal infection: Acyclovir 10 mg/kg IV 3 times daily for 10-21 days.

If the mother develops primary attack of herpes genitalis after the 36th week of pregnancy, caesarean section is indicated before the rupture of the membranes to avoid infection of the baby and the baby has to be watched for 2-4 weeks for the development of generalized herpes.

Points to remember

- Commonest STD.
- Primary herpes is severe and is characterized by shallow painful ulcers on the genitalia.
- Recurrent attacks are milder
- Acyclovir is effective.

Genital Warts

(Syn: Condyloma Acuminata)

Genital warts are benign growths of the skin and adjacent mucous membrane, caused by the *human papilloma virus*. More than 100 types exist. They can be broadly classified into 1) low risk non-oncogenic types e.g types 6 and 11 which cause benign anogenital warts, condyloma acuminata and 2) high risk oncogenic types e.g types 16, 18, 31, and 45 which occasionally lead to cancer. Majority of cases of genital warts are sexually transmitted. Though usually the incubation period is two to three months, it may be up to a year in some cases.

Clinical Features

Warts are commonly seen on the moist surfaces of the male and female genitalia, especially the coronal sulcus, glans penis, frenum, and shaft of the penis in the male and posterior part of the introitus, labia majora, labia minora, and clitoris in the female. Warts may develop in the urethral meatus and the cervix uteri. The wart virus is always present in the cervix, even if warts are not seen there. In females the genital warts enlarge during pregnancy and regress during the puerperium (Fig. 48.2).

Treatment

No specific treatment is effective in eliminating the virus and, therefore, recurrences are frequent.

Recommended treatment: Podophyllin resin 10-25% in spirit or tincture of benzoin should be applied carefully to the warts avoiding normal tissue at weekly intervals. It should be washed thoroughly after 1-4 hours of application. Podophyllin is teratogenic and should not be used during pregnancy. Podophyllotoxin 0.5 %, one of the active constituents of podophyllin can be self applied



Fig. 48.2: Condyloma acuminata. Note the warty growth on the labia minora. Other large lesions on the neighbouring skin were removed by electrosurgery

and it is less toxic. It is used twice daily for 3 days followed by 4 days of no treatment, the cycle repeated up to 4 times. Imiquimod 5 % cream applied with a finger at bed time, left on overnight, 3 times a week for as long as 16 weeks can be self applied by the patient. The treatment area should be washed after 6-10 hours of application.

The warts can be cauterized under local anesthesia, using electrocoagulation. Cryotherapy with liquid nitrogen, solid carbon dioxide, or a cryoprobe has been used. Large warts are removed surgically.

Molluscum Contagiosum

Molluscum contagiosum is a viral disease which can be transmitted from person to person by sexual or nonsexual contact, the latter is more common. The infective agent is a virus belonging to the pox group. Cellular proliferation occurs in the deeper layers of the skin in the stratum malpighii. Many cells contain ovoid eosinophilic intracytoplasmic inclusions which can be demonstrated by Romanovski's stains. These are called *molluscum bodies* and they are diagnostic. The cheesy material exuding when the lesion is squeezed is taken up for demonstrating the molluscum bodies. Lesions may develop on any part of the skin. The incubation period varies from 3 weeks to several months. The sexually transmitted lesion develops on the genitalia. The lesions are papular, ranging in size from 2 mm to 1 cm, waxy and pale pink with central depression.

Treatment

Local application of pure phenol or concentrated trichloroacetic acid by a sharpened match stick will destroy the virus. Electrocoagulation is also useful.

Human Immunodeficiency Virus (HIV) Infection and Acquired Immunodeficiency Syndrome (AIDS)

R. Sajith Kumar, K.V. Krishna Das

AIDS is the name given to a group of disorders related to immunodeficiency produced as a result of the infection by the *Human Immunodeficiency Virus (HIV)*. The syndrome was first described in 1981 in Los Angeles in male homosexuals. In a short span of twentyfour years, it has spread all across the globe, affecting various spheres of human life. AIDS is the final consequence of various changes that take place in the immune status of the individual and is characterized by the occurrence of opportunistic infections and specific malignancies.

It is estimated that there are about 40 million cases of HIV infection worldwide as of end 2005. Five million people have been infected with the virus last year itself. Three million AIDS patients have died in one year. As a continent, Africa has maximum number of cases (26 million). The current estimates put India as the second largest country with 5.3 million infected persons. As per the statistics released by the National AIDS Control Organisation (NACO), Govt of India, the maximum number of cases have been identified in the state of Tamil Nadu, even though states like Maharashtra, Andhra Pradesh, Manipur and Karnataka also have increasing number of cases. Serosurveillance studies in different states have brought out the prevalence of the infection- 44.7% of all female sex workers in Mumbai, 17.6% of all STD clinic attendees in AP, 22% of IV drug users (IVDUs) in Manipur and 2.2% of all expectant mothers in AP. Maharashtra, Tamil Nadu, Manipur, Andhra Pradesh, Karnataka and Nagaland have been identified as high prevalence states with the HIV prevalence exceeding 5 % among high-risk groups and 1 percent among antenatal women. Gujarat, Goa and Pondicherry which are adjacent to the high prevalence states report HIV prevalence exceeding 5 percent among high-risk groups, but only less than 1 % among antenatal women. All other Indian states are classified as low prevalent states.

The present situation in India reveals the following:

1. 87.7% are in the age group of 15-44 years.
2. The predominant mode of transmission of infection is through heterosexual contact in 85.7%. Other sources include injecting drug use in 2.2%, blood and blood components transfusion in 2.6% , perinatal transmission in 2.7% and various other causes in 6.8%.

3. The HIV sentinel surveillance of 2003, show that males accounted for 73.5% and females, 26.5% of the total, the ratio being 3:1.

Further reading: Steinbrook R. HIV in India—A complex epidemic. *NE J Med* 2007;356:1089-93.

The Causative Organism

The disease is caused by infection with HIV which is a retrovirus and belongs to the family of lentiviruses. Infections with lentiviruses typically show a chronic course of disease, a long period of clinical latency, persistent viral replication and involvement of the central nervous system. There are many viruses which are classified under this name. HIV-1 and HIV-2 are the major ones. Using electron microscopy, HIV-1 and HIV-2 are almost similar. However, they differ with regard to the molecular weight of their proteins, as well as having differences in their accessory genes. Both HIV-1 and HIV-2 replicate in CD4⁺ T cells and are regarded as pathogenic, HIV-2 being less pathogenic. HIV-1 is subdivided into groups: M (for main) and O (for outlier), antigenically. Within group M are the vast majority of HIV-1 strains subdivided into subtypes (currently 10: A-J) based on genetic variation. HIV-1 subtype B is more prevalent in homosexuals and IV drug users. However most of the ongoing HIV-1 epidemic around the world is due to non-B subtypes, especially subtype C in sub-Saharan Africa and India. But almost all subtypes have been identified in all parts of the world.

HIV viruses are RNA viruses. HIV-1 viral particles have a diameter of 100 nm and are surrounded by a lipoprotein membrane.

During the process of budding, the virus may incorporate, different host proteins, such as HLA class I and II proteins, or adhesion proteins from the membrane of the host cell into its lipoprotein layer.

HIV has greatest affinity towards CD4 receptor bearing T helper lymphocyte group. Two newly identified proteins found on immune cells, CCR5 and fusin (also known as CXCR4) are considered as co-receptors. Certain chemokines are also considered important in modulating the entry of virus into the CD4 cell. After HIV successfully attaches and fuses with the cell, the RNA strands are transcribed to DNA by the timely activation of reverse transcriptase, a viral enzyme. The DNA strands thus formed in the cytoplasm migrate to the nucleus and integrate with the human DNA (with the help of enzyme integrase). This is an irreversible bonding and leads to the beginning of a permanent HIV infection.

The integrated human CD4 cell may take various routes. Some of them are detected by the person's immune system and are eliminated promptly. Some of them get activated against other antigens or allergens and start producing chemical mediators. When parts of the DNA

correspond to that of the virus, the proteins so produced will contain the amino acid sequences needed for the virus replication too. These 'viral' proteins are cleaved into correct sequence by the enzyme protease. The newly synthesized viral proteins acquire their coating from the CD4 cell surface and 'bud out' damaging the cell membrane. This leads to significant damage to the cells and they are destroyed in large numbers. Some of the cells undergo fusion and form syncytia. Some may be destroyed by cell mediated, complement mediated or antibody dependent cytotoxic mechanisms. Some CD4 cells undergo apoptosis (programmed and premature cell death). Thus the virus infection over a period of years leads to fall in the number of CD4 cells. The virus can also produce direct effects on cells in the brain, heart and bowel and reticulo endothelial system. HIV can replicate aggressively and upto 10 billion virus particles may be produced in a day with an average half life of 6 days.

The CD4 count in a normal person is between 800 and 1200 cells per cmm in peripheral blood. The CD4 cell is responsible for the smooth and coordinated function of all arms of the immune system. Once the CD4 function is compromised, various abnormalities occur. Both physiologic and dysregulated activation contribute to the profound immune activation and accelerated cell death that characterizes HIV infection. In early HIV infection, CD8⁺ T-cell numbers tend to increase, reflecting expansion of memory CD8⁺ T cells, particularly HIV-reactive cells. CD8 cell expansion persists until far advanced stages of HIV disease, when all T-cell numbers tend to fall. A number of immunological abnormalities have been described including:

1. leukopenia and lymphopenia.
2. loss of T4 lymphocytes from the peripheral blood.
3. hypergammaglobulinemia.
4. skin anergy.
5. decrease in lymphocyte proliferation, cytotoxic T cell response and antibody production to new antigens.
6. elevated levels of immune complexes, interferon and β_2 microglobulin

Immunodeficiency manifest in three different patterns:

- a. reactivation of dormant infections like tuberculosis and herpes infections
- b. infections by opportunistic pathogens
- c. atypical manifestations of common infections.

The immune dysregulation also leads to development of specific malignancies such as Kaposi's sarcoma related to HHV 8 infection

Route of Transmission

HIV is susceptible to destruction by many physical and chemical agents. Close contact and exchange of blood or body fluids is necessary for transmission. The most rampant route is sexual intercourse. Male homosexuals

practicing anal sex have the highest risk. Heterosexual anal sex, heterosexual vaginal sex, oral sex and sex using condoms have been stratified in the decreasing order of risk involved. The infection is common amongst IV drug users in whom sharing of contaminated needles, syringes and drugs is the risky factor. The infection can also be transmitted from the mother to the child during pregnancy, at the time of labor or during breast feeding. The transmission is most effective following transfusion of infected blood. Occasionally needles and sharps used in hospitals can act as sources of infection to health care professionals if proper precautions are not taken. HIV does not spread through casual contact, furniture, touching, sharing the food, utensils, toilet or through air or water.

Route	Percentage	Efficiency (%)
Sexual	85.96	0.1-1
Perinatal transmission	3.64	14-45%
Blood and blood products	2.00	~100%
Injecting Drug users	2.39	0.5%
Others (not specified)	6.01	

Transmission by sexual intercourse is increased in the presence of other sexually transmitted diseases leading to ulcerative or inflammatory lesions in the genitalia. HIV infected mothers transmit the disease to their babies. Efficiency of transmission depends upon the viral load and clinical stage of the mother, the nature of delivery and time spent in labor. It can vary from 14 to 40%. The risk of transmission by accidental needle pricks in hospitals is around 0.3%.

Definition and Diagnosis

HIV infection is a laboratory diagnosis and is made by demonstration of

- HIV antibodies by ELISA or solid state card/spot tests
- Circulating antigens (p24) or
- The viral RNA itself by PCR –qualitative and quantitative- in peripheral blood.

Since false positive tests are not uncommon, it is advisable to repeat the tests using different types of ELISAs or different antigens before labelling an asymptomatic person as positive. If clinical symptoms have manifested two positive tests are considered enough.

Fallacies of the tests:

- The test become positive only after the ‘window’ period i.e. 4-6 weeks or more after infection, by which time only the antibodies appear.
- In the late stage when antibodies are too low, the tests may be only weakly positive or even negative.

Note: Testing for HIV should be done after counselling the patient and getting his permission.

AIDS is defined as the presence of one of the AIDS defining conditions or a decline of CD4 cells to less than 200 per cmm in an HIV infected person.

Clinical Features

The spectrum of diseases caused by HIV is quite wide. The clinical patterns are grouped into four stages.

- Acute Retroviral syndrome
- Asymptomatic stage
- Early symptomatic stage
- Advanced immunodeficiency

AIDS Indicator Conditions

- Candidiasis, of esophagus, trachea, bronchi or lungs
- Cervical cancer, invasive*
- Coccidioidomycosis, extrapulmonary*
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis with diarrhea longer than 1 month
- Cytomegalovirus of any organ other than liver, spleen, or lymph nodes
- Herpes simplex with mucocutaneous ulcer for more than 1 month duration or bronchitis, pneumonitis, esophagitis
- Histoplasmosis, extrapulmonary*
- HIV-associated dementia: disabling cognitive and/or motor dysfunction interfering with activities of daily living*
- HIV-associated wasting: involuntary weight loss >10% of baseline plus chronic diarrhea (2 loose stools/day 30 days) or chronic weakness and documented enigmatic fever 30 days*
- Isosporiasis with diarrhea greater than 1 month*
- Kaposi's sarcoma in patient under 60 years (or over 60 years*)
- Lymphoma of brain in patient under 60 years (or over 60 years*)
- Lymphoma, non-Hodgkin's of B-cell or unknown immunologic phenotype and histology showing small, noncleaved lymphoma or immunoblastic sarcoma
- Mycobacterium avium complex or *M. kansasii* disseminated tuberculosis*
- Nocardiosis*
- Pneumocystis carinii* pneumonia
- Pneumonia, recurrent-bacterial (2 episodes in 12 months)*
- Progressive multifocal leukoencephalopathy
- Salmonella septicemia* (non-typhoid), recurrent*
- Strongyloidiasis, extraintestinal
- Toxoplasmosis of internal organs

* Requires positive HIV serology

Note: Criteria of Center for Disease Control (CDC) Atlanta



Fig. 48.3: AIDS persistent lymphadenopathy neck



Fig. 48.4: AIDS oral candidiasis

Acute retroviral syndrome (also called Primary HIV infection or seroconversion illness) occurs 2-6 weeks after the entry of HIV into human body. The illness is associated with fever, papular eruptions, arthralgia, lymph node swelling and oral ulcers (Figs 48.3 and 48.4).

The CD4 count falls and viral load increases during this period. The symptomatic phase of acute HIV-1 infection lasts between 7 and 10 days, and rarely longer than 14 days. The severity and duration of symptoms have prognostic implications. Severe and prolonged symptoms are associated with more rapid disease progression, which may be unnoticed in the majority of cases (Fig. 48.5). The infected person recovers completely to an asymptomatic



Fig. 48.5: AIDS cachexia diarrhea

stage with the return of CD4 count to normal but becomes HIV antibody positive thereafter.

In the next few years many changes take place in the immune system even though the person is grossly asymptomatic. Immune mediated events like lymph node enlargement, thrombocytopenia, demyelinating disorders of central nervous system, occur with increasing frequency. Most of these are because of misdirected immunologic activity. The occurrence of persistent generalized lymphadenopathy (defined as enlargement of two or more extra inguinal lymph nodes of size 2-3 cm persisting for more than a month) is common at some time in this stage.

As the CD4 count drops to below 500 cells per cmm the person experiences reactivation of dormant organisms like tuberculosis (pulmonary and extra pulmonary), herpes zoster, disseminated herpes, molluscum contagiosum etc. Fungal infections of the genital tract, extensive non genital warts, exaggerated insect bite reactions on the exposed skin etc. are seen in this stage (Fig. 48.6).



Fig. 48.6: Severe herpes zoster

Pulmonary complications in patients with HIV infection		
Infections	Neoplasia	Others
<i>Pneumocystis jiroveci</i>	Kaposi's sarcoma	Lymphocytic interstitial pneumonia
Bacterial pneumonia		Non-specific interstitial pneumonia
<i>S. pneumoniae</i>	Non-Hodgkin's lymphoma	Pulmonary hypertension
<i>S. aureus</i>		COPD
<i>H. influenzae</i>	Hodgkin's lymphoma	Bronchial hyperreactivity
<i>B. catarrhalis</i>	Bronchial carcinoma	
<i>P. aeruginosa</i>		
<i>Rhodococcus equi</i>		
<i>Nocardia asteroides</i>		
Mycobacteria		
<i>M. tuberculosis</i>		
Atypical mycobacteria		
Other		
Cytomegalovirus		
Aspergillus spp.		
Cryptococcus		
neoformans		
<i>Histoplasma capsulatum</i>		
<i>Toxoplasma gondii</i>		

As the CD4 count drops below 200 cells per cmm, the opportunistic infections appear. This is also the time when neoplasms like high grade B cell lymphoma, Kaposi's sarcoma, cervical intra-epithelial neoplasia and primary CNS lymphoma appear. Many infections which remain localized in immunocompetent subjects tend to become disseminated (e.g. *M.tuberculosis*, *Toxoplasma gondii*, *Cytomegalovirus*, *Cryptococcus neoformans* and *Histoplasma capsulatum*).

Respiratory System in AIDS

Respiratory system gets involved in almost all patients at some stage.

The most important among these are *Pneumocystis carinii* *Pneumonia* (now re-named as *P. jiroveci*) and tuberculosis (Fig. 48.7).

***Pneumocystis Carinii* *Pneumonia* (PCP):** The organism is an unusual type of fungus. PCP gives rise to interstitial pneumonia with the classic triad of symptoms:- dry cough, without fever and gradual onset of dyspnea on exertion. The diagnosis may be delayed weeks or months. Diagnosis is clinched by a chest X-ray and, if possible, high resolution computed tomography (HRCT) of the lungs. The chest X-ray often shows relatively characteristic findings with a butterfly-shaped (perihilar) interstitial infiltrate. In the early stages, the focus is on the mid and lower fields (Fig. 48.7). Cystic changes may also occur. Indistinct, diffuse changes are more easily visible on HRCT than on chest X-ray. There is almost always partial respiratory insufficiency, which should be confirmed by arterial blood gas analysis. Lactate dehydrogenase (LDH) is often elevated. High levels of LDH reflect the severity



Fig. 48.7: X-ray chest pneumocystis pneumonia

of the PCP. Sputum specimens are generally not useful for identification of the organism. Bronchoalveolar lavage (BAL) aspirate is usually necessary. Methenamine silver staining and PCR demonstrate the fungus. The organism may be demonstrable for a few days more after starting treatment.

Treatment should be initiated immediately if there is clinical suspicion. In cases of mild PCP with arterial PO₂ > 70-80 mm Hg, ambulatory treatment can be attempted; oral medication is effective. Respiratory insufficiency is an indication for hospitalisation. **Therapy** with cotrimoxazole (2 DS tablet three times daily for adults) should be given for 21 days. Prednisolone 20-80 mg bid should always be co-administered initially for

5-10 days. In patients who cannot tolerate cotrimoxazole intravenous pentamidine is the drug of second choice. Induction therapy consists of 200-300 mg pentamidine in 500 ml 5 % glucose or normal saline, as IV trip. Half this dose is given from days 6 to 21.

Prevention Patients with CD4 T cell count less than 200 / μ l are at risk and should therefore receive prophylaxis, ideally with cotrimoxazole daily or three times weekly. Monthly inhalation of pentamidine is a well-tolerated alternative. PCP prophylaxis regimens can be discontinued safely when the CD4 T cell count rises above 200 /cmm and remain so for at least for three months.

Tuberculosis and HIV disease are closely linked. This is described in Chapter 49.

6

Cutaneous Manifestations

Cutaneous manifestations these are quite common in AIDS. A broad spectrum of cutaneous infections caused by viruses, bacteria, fungi, protozoa, and parasites as well as many unusual manifestations of common dermatoses is seen.

Acute primary HIV infection may lead to a transient, generalized, morbilliform eruption on the trunk and the arms. With the person developing immunosuppression, nonspecific skin changes occur. These include common disorders with atypical clinical features, including recurrent varicella zoster, numerous hyperkeratotic warts, treatment-resistant seborrheic dermatitis, and oral hairy leukoplakia.

Chronic *Herpes simplex virus* (HSV) and *Cytomegalovirus* (CMV) infections, mycobacterial infections and mucocutaneous candidiasis occur in late stages.

Kaposi's sarcoma (KS). This was the first malignancy detected to be associated with HIV infection. The worldwide prevalence of KS in patients with AIDS may approach 34%. Most of the patients are homosexual men. KS is due to proliferation of endothelial cells induced by *Human herpesvirus type 8*. KS begins as pink macules that become disseminated and palpable. Purplish or brown macules and plaques may become nodular. Mucosal involvement is common. The clinical progression of KS in patients infected with HIV is more aggressive than the other clinical types of KS (Fig. 48.8).

Other malignancies can also occur more commonly with HIV infection. AIDS-related B-cell non-Hodgkin's lymphomas may lead to skin nodules. Anal carcinoma and cervical intraepithelial neoplasia are papillomavirus-associated tumours. These tumours tend to be more progressive and aggressive. An increase in squamous cell carcinoma of the anal mucosa has been reported, especially in young homosexual men. Intraoral or multiple squamous cell carcinoma, Bowen disease, and metastatic basal cell carcinoma have occasionally been reported.

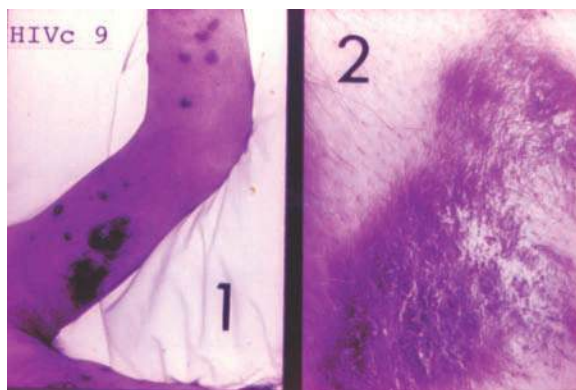


Fig. 48.8: Kaposi's sarcoma. Note (1) General appearance—pigmented lesions (2) Enlarged view $\times 100$

Malignant melanoma occurring in patients with HIV is more aggressive than in individuals without HIV. Children with AIDS have a higher risk of developing leiomyosarcoma, although the incidence is still low in this population.

Fungal infections occur extensively on the skin and mucous membranes. Recurrent and persistent mucocutaneous candidiasis is common. Recurrent vaginal candidiasis can occur in any stage of the disease. In adults, generalized dermatophytosis, or tinea capitis, which is typically caused by *Trichophyton rubrum* is common. Onychomycosis in HIV infected may continue for many years.

Deep fungal infections like cryptococcosis, histoplasmosis and coccidioidomycosis may disseminate to the skin, usually as hemorrhagic papules or nodules.

Other infections: *Mycobacterium tuberculosis*; *Mycobacterium avium-intracellulare* complex; and, rarely, *Mycobacterium kansasii* may present as acneiform papules and indurated crusted plaques. Impetigo and folliculitis may be recurrent and persistent in HIV disease, particularly in children. Disseminated furunculosis, gingivitis, gangrenous stomatitis, and abscess formation can occur. Bacillary angiomatosis, which is caused by *Bartonella henselae* and rarely by *Bartonella quintana*, usually manifests as red papules and nodules. Atypical or Norwegian scabies, which is characterized by widespread hyperkeratotic, scaly maculopapular eruptions or crusted plaques, can occur. Seborrheic dermatitis like eruptions are observed in 83% of patients with AIDS. Seborrheic dermatitis may be the initial cutaneous manifestation of HIV disease. The eruption, which is characterized by widespread inflammatory and hyperkeratotic lesions, may progress to erythroderma in some patients.

Pruritic papular eruption and eosinophilic folliculitis also presents with papular eruptions.

Nail and hair changes (graying and other pigmentary changes), photosensitive eruptions, and diffuse alopecia are noticed.

Among sexually transmitted diseases, chancroid, syphilis in homosexual men, and lymphogranuloma venereum, are more commonly associated with AIDS. Syphilis coexisting with HIV creates special problems. (refer Chapter 47).

Treatment: Almost all cutaneous manifestations in HIV can be managed by the same modalities as in seronegative persons.

Neurological Manifestations

1. **AIDS encephalopathy** Infection of the CNS by HIV leads to encephalopathy (HIVE) which is also known by terms such as *AIDS dementia complex*, *AIDS dementia*, and *HIV associated cognitive motor complex*. HIVE is a late manifestation when there is a profound immune suppression with CD4 counts below 200 per cmm. HIVE is a subcortical dementia, caused by leukoencephalopathy typically emerging over the course of weeks and months. Typical complaints are slowing of reasoning, forgetfulness, difficulties concentrating, lack of energy and drive, mild depressive symptoms and emotional blunting. Magnetic resonance imaging often shows patchy, diffuse, hyperintense and relatively symmetrical lesions in the white matter. These changes indicate leukoencephalopathy. HIV-associated myelopathy whose histopathological hallmarks are vacuoles, most prominent in the cervical and thoracic parts of the spinal cord, hence called *vacuolar myelopathy*.
2. **Progressive multifocal leukoencephalopathy (PML)** is a severe demyelinating disease of the central nervous system predisposed to by AIDS. It is caused by JC virus (JCV), which is a polyoma virus found worldwide. The main focus of disease is the white matter of the cerebral hemispheres, but the cerebellum and in some cases the grey matter may also be affected. The median interval between the onset of the first symptoms and death was between 3 and 6 months. Patients usually die of secondary complications after being bedridden for many weeks. In addition to cognitive disorders, which may range from mild impairment of concentration to dementia, focal neurological deficits are very typical of PML. Mono- and hemiparesis are observed most frequently, as well as defects of speech and vision. MRI usually shows asymmetrical high signal intensity lesions in T2-weighted imaging, hypointense in T1-weighted images. Usually they do not show gadolinium enhancement or mass effect. Non-involvement of the grey matter is characteristic. The lesions are almost always asymmetrical.
3. **Cerebral toxoplasmosis** almost always results from the reactivation of a latent infection with *Toxoplasma gondii*. Patients may present with seizure, headache or focal neurological deficits. Cerebral toxoplasmosis is extremely rare above a CD4 T cell count of 100/cmm. It should always be expected when the CD4 T cell counts fall below 100/cmm. A CT or MRI scan of the head should be performed promptly in all cases of focal neurological deficit. Ring enhancing lesions and solitary or multiple abscesses should suggest the infection. Up to 97 % of patients with cerebral toxoplasmosis have IgG antibodies, and therefore absence of these antibodies help to rule out toxoplasmosis. Treatment is described in page 389.
4. **Cryptococcal meningitis** is more common in advanced immunodeficiency when the CD4 count is less than 200 cells per cmm. *C. neoformans* is transmitted by droplet infection.
5. **Primary CNS lymphomas** are late complications of HIV infection, occurring in up to 10 % of AIDS patients. Almost all cases are EBV- associated. Neurological deficits occur depending on their location.
6. **Peripheral neuropathy** may complicate all stages of HIV infection. Acute inflammatory demyelinating polyneuropathy (AIDP) and Guillain-Barré syndrome (GBS) usually occur during seroconversion or during the latent stages of HIV infection. Chronic inflammatory demyelinating neuropathy, vasculitic neuropathy, distal symmetrical sensory polyneuropathy and drug induced neuropathies may occur are all reported.
7. **Reactivation of CMV infection:** When the CD4 count falls below 50/cmm reactivation of CMV infection can lead to retinitis. Any visual impairment occurring subacutely or acutely, such as blurred vision or floaters especially unilaterally should prompt immediate ophthalmological examination. Oral and/or intravitreal gancyclovir or valacyclovir will be useful if started early. Primary prophylaxis is not effective against CMV retinitis.

Cardiovascular System Involvement

Cardiovascular involvement is common in HIV-infected patients.

Pericardial diseases: Pericardial effusion, Pericarditis (viral, bacterial, fungal), neoplasms (Kaposi's sarcoma, lymphoma).

Myocardial involvement: HIV-associated dilated cardiomyopathy, acute or chronic myocarditis, Kaposi's sarcoma or lymphoma and adverse effects of antiretroviral drugs.

Endocardial involvement: Infective endocarditis—bacterial or fungal and nonbacterial thrombotic endocarditis.

Vascular diseases: Arteriosclerosis, vasculitis, perivascularitis, pulmonary artery hypertension.

Other Miscellaneous Infections

Oroesophageal candidiasis: Candidiasis takes the form of extensive and persistent superficial lesions over the oropharynx, the buccal mucosa, tonsillar ring, tongue and the oesophagus. Candida esophagitis usually occurs with oropharyngeal involvement, but in about one third of the cases there may not be oral lesions. Esophagitis presents with odynophagia and retrosternal pain. Fluconazole therapy rapidly clears the infection.

Atypical Mycobacterial Infections: *M. avium* complex infection supervenes when the CD4 cell count falls below 50/cmm. The symptoms of disseminated MAC infection are usually nonspecific. Fever, weight loss and diarrhea in a patient with CD4 count less than 100/cmm should always raise the possibility of atypical mycobacteriosis. Elevation of serum alkaline phosphatase is a strong evidence for the diagnosis of MAC infection. Similarly development of anemia with constitutional symptoms may be due to bone marrow involvement by MAC. Hepatosplenomegaly and lymphadenopathy may occur. Atypical mycobacteria grow more readily in blood culture compared to *M. tuberculosis*. MAC infection responds to treatment with a macrolide, clarithromycin or azithromycin with ethambutol and rifabutin given for a period of six months or more.

Cryptosporidiosis: Cryptosporidiosis, caused by *Cryptosporidium parvum* may occur as a complication in AIDS. It presents as severe diarrhea (refer chapter 65).

Penicilliosis: Most fungi belonging to the *Penicillium* species are not pathogenic. One exception is *Penicillium marneffei*, which seems to be a problem mainly for HIV patients in south east Asia including parts of Manipur state in India. The clinical symptoms consist of prolonged high fever, lymphadenopathy, hepatosplenomegaly, weight loss, malaise, cough and hemoptysis, diverse cutaneous and mucocutaneous lesions resembling molluscum and abnormal increase in liver enzymes. Amphotericin B and itraconazole are effective in control in the infection.

HBV and HCV infections: Co-infection of hepatitis B and/or C viruses with HIV occurs frequently, since they share the same modes of transmission. Parenteral drug users and recipients of blood products are particularly susceptible. Primary HBV infection leads to chronic hepatitis in 2-5 % of immunocompetent adults, whereas in HIV-infected patients the chance for the disease to become chronic is five times more. Viral replication of HBV is more active in AIDS patients. In general, patients with chronic hepatitis B should be screened for hepatocellular carcinoma (HCC) every 6 to 12 months.

The progress of hepatitis C is also more rapid, particularly in patients with CD4 counts below 100/cmm. The unfavorable course of hepatitis C in HIV infection can be improved by treatment of HIV infection by HAART. In addition, the development of liver failure can also be delayed. Hepatitis C infection can aggravate the potential hepatotoxicity of several drugs used in HAART regimens, especially nevirapone. Up to 10 % of patients have to discontinue HAART due to severe hepatotoxicity. The response to treatment of HCV infection is less satisfactory due to lower clearance rates and adverse side effects of drugs which prevent continuation of therapy. Results are better if HCV RNA is < 2 million copies/mL, HCV genotype is 2 or 3 and the age of the patient is < 50 years. Histologically low grade fibrosis of the liver, normal γ -glutamyl transferase and stable HIV infection are good prognostic factors. Treatment is given in chapter 55.

MANAGEMENT OF HIV INFECTION

General measures: HIV infection should be confirmed beyond doubt by appropriate investigations. The immunological status is assessed by CD4 estimation. Severity of infection can be assessed by estimating the viral load using PCR test or other methods. The co-existence of opportunistic infections should be confirmed by investigations. Regular repetition of CD4 T-cell count and RNA viral load helps to assess the progress of the disease.

The interventions in HIV disease can be grouped into three major headings.

- nonpharmacologic modifications,
- prophylaxis and treatment of opportunistic infections and
- antiretroviral therapy. Specific guidelines for all these aspects have been laid down by the Association of Physician of India

(API consensus guidelines for use of antiretroviral therapy in adults

(Ref: JAPI. 2006;54:57-74).

Antiretroviral therapy aims at bringing down the virus levels to undetectable levels, i.e. below 20 copies per mL with the presently available tests. This will ensure immune reconstitution with the return of CD4 counts above 200 per cmm. Symptom free survival is also prolonged. Different groups of drugs are used. These include reverse transcriptase inhibitors, (RTIs) protease inhibitors (PIs) and entry inhibitors. The RTIs belong to two groups, the nucleotide and nucleoside RTIs (NtRTIs and NRTIs) and nonnucleoside RTIs (NNRTIs). The reverse transcriptase inhibitors block the transcription of DNA from viral RNA, without which the genetic material cannot be incorporated into the human DNA. The Protease inhibitors block the protease enzyme, effectively preventing the formation and

TABLE 48.1

List of currently available antiretroviral drugs. Several new drugs are in the process of development

Nucleoside reverse transcriptase inhibitors (NRTIs)

Zidovudine (AZT, ZDV)
Didanosine (DDI)
Zalcitabine (DDC)
Stavudine (D4T)
Lamivudine (3TC)
Abacavir (ABC)
Emtricitabine

Non Nucleoside RTIs (NNRTI)

Nevirapine
Delavirdine
Efavirenz

Nucleotide (Nt RTI)

Tenofovir

Protease Inhibitors (PI)

Saquinavir
Ritonavir
Indinavir
Nelfinavir
Amprenavir
Lopinavir
Atazanavir
Fosamprenavir

Entry (Fusion) inhibitors

Enfuvirtide (T-20)

release of new virions. The newly added class of fusion inhibitors blocks the virus fusion with the CD4 and other receptors on the cell membrane, thus preventing the entry of the virus into a new cell (Table 48.1).

The principle of treatment is to use a combination of three or more synergistic drugs belonging to the different groups. Several protocols are under trial. The current protocols use two NRTI + one NNRTI or one PI. Three NRTI based regimes are also considered. Monotherapy should be avoided due to the risk of developing resistance by HIV. The importance of adherence with regard to dosage and relationship with food must be stress in a therapeutic counselling setting. More than 95% adherence to the schedule is needed for the desirable result. There is no consensus at present about the duration of therapy. Therefore, once started, the drugs have to be continued for long except when the person living with HIV/AIDS (PLWHA) develops drug intolerance, adverse effects or failure.

Indications for Starting Therapy

The major indications to start therapy are (i) symptomatic stage of AIDS (ii) CD4 count less than 200 cells per cmm (iii) asymptomatic person with a CD4 count of 200-350 with a viral load of more than 1,00,000 copies per mL. In other cases, treatment must be started after considering

the long life span of the PLWHA and individual considerations.

Out come of therapy The desired outcome of therapy will be a rise in CD4 count in 6-8 weeks and a fall in viral load to 'undetectable' range in 3-6 months. Following initiation of therapy, viral load should fall below 5,000 copies/mL within one month. Fall in viral load is measured in logs and one log reduction (ten times fall) is to be expected in 6-8 weeks. At present it is possible to arrest the multiplication of HIV and reduce the chances for opportunistic infections by judicious drug combinations. This highly active retroviral therapy (HAART) is the goal initiated by the WHO and accepted by several countries.

Adverse side effects All ARV drugs are associated with adverse side effects.

Drug	Major side effects
Zidovudine	Bone marrow suppression
Nevirapine	Skin rash
Protease inhibitors	Mitochondrial toxicity and lipodystrophy
Stavudine	Lactic acidosis and lipodystrophy

Severe toxic effects warrant change of drug schedule. Failure of response can also happen when the virus acquires resistance. This is due to the changes in the nucleoside sequence of the new viruses occurring during reverse transcription and other stages of viral multiplication. Development of resistance can be identified by two types of tests. (a) Genotypic resistance: This is detected by testing for the occurrence of alterations in the nucleotide chains. This gives an indirect clue to resistance of the virus. (b) Phenotypic resistance: Studies look for the survival patterns of growth of the virus in a cell culture medium in the presence of ARV drugs.

With the introduction of HAART death rates have come down and the quality of life of AIDS patients has improved considerably. Review of the therapy in developing and developed countries has shown very encouraging results.

Pregnancy complicating AIDS: The foetus may be infected by the virus. Infection rate is higher in mothers who have HIV RNA levels exceeding 1000 copies /mL. Viral loads are higher if the baby is infected early in pregnancy. Most of the antiretroviral drugs cross the placenta if administered during pregnancy. Treatment reduces the transmission rate to $\pm 2\%$ if started early. HIV infection during pregnancy does not produce congenital birth defects in the baby.

Prevention

AIDS, though a dreaded disease, is preventable too. Sex with a regular uninfected partner is the safest way to

prevent HIV infection through sex. However condoms, if properly used offer almost complete protection against acquiring infection during natural sexual intercourse. Strict screening of blood products for transfusion reduces the risk considerably. Transmission in parenteral drug abuse groups is tackled by supply of sterile syringes by governmental and other agencies. Other measures to reduce illicit use of habituating drugs include counselling, group therapy and legal measures to prevent drug trafficking. Transmission in hospital settings can be reduced by proper practice of universal (standard) precautions.

Post exposure prophylaxis protocols in health care personnel are mandatory. These consist of the administration of basic antiretroviral regimen as early as possible after exposure to the risk, ideally within 2 hours. The standard regimen is to give zidovudine 300 mg and lamivudine 150 mg twice daily for a period of four weeks. In the expanded regimen a protease inhibitor is also added.

Prevention of parent to child transmission (PPTCT) protocols (e.g. ACTG 076, Thai Harward, HIVNET012, PeTRa) are available, which includes the use of Zidovudine and nevirapine in the expectant mother, during labour and to the newborn child after delivery. Administration of single drugs to the mother for preventing transmission to the child should be avoided due to the risk of developing drug resistance in the child later. Caesarean delivery without trial of labour reduces the risk of transmission to the baby from 10.5 to 1.8%. Women with HIV RNA loads above 1000 copies / mL should be offer Caesarean delivery.

Vaccines: Several attempts to produce anti-HIV vaccines for prevention and therapy are taking place under the International AIDS Vaccine Initiative (IAVI). National

AIDS Research Institute (NARI) Pune also has developed a vaccine which is undergoing field trials. The need for proper health education and awareness are promoted as the major preventive strategy.

Global measures: Provision of regular supply of anti-retroviral drug to patients in developing countries has been taken up by the WHO aided agencies and several philanthropic non governmental funding sources. At present the government of India and State Governments have made primary anti-HIV drugs available free of cost in major government hospitals. Several international governmental and non governmental organizations have come forward to help needy nations with funds, manpower and drugs. Several Indian drug manufacturers have contributed to this global venture.

Male circumcision has been found to reduce the rate of acquisition of HIV infection by several studies in African countries.

Ref: Newell Marie-Looise The Lancet 2007;369:617-9.

Points to remember

1. India has the potential to become one of the most heavily affected countries by AIDS if the medical fraternity government and non-governmental organizations take steps to arrest the spread of infection
2. AIDS involves directly or indirectly almost all systems in the body
3. Morbidity caused by AIDS and the heavy cost of treatment and rehabilitation of bereaved families cause heavy financial burden to the country
4. Several drugs have been introduced to arrest progress of the disease, if started early.
5. Primary treatment for AIDS patients is available in several centers in the country free of charge.
6. This devastating illness is preventable by adopting safe sex habits, especially meticulous use of the condom.

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Mycobacterial Infections:

Tuberculosis, Non-tuberculous Mycobacteria and Leprosy

K.V. Krishna Das

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Tuberculosis

K.V. Krishna Das

GENERAL CONSIDERATIONS

Tuberculosis is one of the most widely prevalent chronic infectious diseases affecting mankind. The global incidence of tuberculosis (TB) is gradually coming down at the rate of 0.5 to 1% per annum but in parts of Russia and sub Saharan Africa this trend is not seen. Though the developed countries have brought down its prevalence and incidence, in developing countries it is still a major cause of ill-health and mortality. Tuberculosis is caused by *Mycobacterium tuberculosis* which may involve all organs in the body, but lungs are the most common sites. Robert

Koch discovered the organism in 1882. Man is affected most commonly by the human strain and less commonly by the bovine strain. With the availability of pasteurized milk and improved animal husbandry practices, the frequency of the bovine tubercle bacillus infection has fallen considerably. Phage typing helps to sub-classify the strains further. *Mycobacterium tuberculosis* can survive in dark moist environment for very long periods (up to years). In sputum it remains viable for 20-30 hours. In droplet nuclei and dust the viability is much longer.

Tubercle bacilli are non-motile, non-spore-forming non-capsulate straight or curved rods about $3 \times 0.3 \mu\text{m}$ in size. They grow only in special enriched media. They are obligate aerobes. Ultraviolet light and pasteurization of milk destroy the bacillus. Genotyping of *M. tuberculosis* has been completed and the fingerprint is available. Genetic studies employing *restriction fragments length polymorphism* (RFLP) help to make accurate epidemiological observations. Genetic studies also help to distinguish relapse from re-infection. In many countries shelters, workplaces, healthcare facilities and bars are common sites for transmitting the disease. Infection in teachers spreads readily to the children at school.

Epidemiology

All over the world, tuberculosis was in the forefront as a major cause of morbidity and mortality before the middle of this century. The present estimate of the World Health Organisation (WHO) is that there are about 15-20 million infectious cases in the world at any one time and that three million deaths occur annually. The three major killers in the developing world are HIV disease, tuberculosis and malaria. In India TB still remains as a major cause of death from a curable infection. In the study launched by Indian Council of Medical Research (ICMR) in 1955-58 the prevalence of sputum positive pulmonary tuberculosis was 4/1000. Such nationwide surveys have not been performed subsequently. Only limited data is available.

Tuberculin surveys are employed to detect infection in the community. A limited study conducted in

Trivandrum (South India) in 1980 showed that by the age of 14 years 7.4% of school children was tuberculin positive. The WHO has suggested that the tuberculin positivity rates in children below 14 years has to be brought down below 1% to achieve control of this disease. It is evident that India has still a long way to go in achieving this goal. Despite the vigorous measures to control the disease undertaken by the *National Tuberculosis Control Program*, the disease tends to persist because of the poor socioeconomic and educational levels of the population, reluctance to accept treatment and non-compliance with the prolonged drug regimen.

Immunodeficiency states—both iatrogenic and AIDS led to a resurgence of the disease in several parts of India. Vitamin D deficiency impairs the ability of monocytes to inhibit growth of *M. tuberculosis*. HIV predisposes to tuberculosis infection because of the reduction of Th1 lymphocytes which produce gamma interferon. Tuberculosis accelerates the progression of AIDS and thereby hasten death. Both pulmonary and extrapulmonary lesions are more frequent.

Susceptibility to Tuberculosis Conferred by Other Disease State

The lifetime risk of developing overt tuberculosis in an infected child is 10%. Among such children 50% develop TB within 2 years of infection. There is a genetic predisposition to develop TB in some individuals.

Human immunodeficiency virus (HIV) infection increases the susceptibility to get primary infection as well as reactivation of acquired TB lesion by 10-folds. In HIV negative individuals who develop TB, over 80% manifest as pulmonary tuberculosis (PT). In HIV positive individuals the occurrence of non-pulmonary manifestations is relatively higher. In India co-infection of HIV and TB is seen in 10-11% of TB cases. Co-infection by the two diseases decreases the cure rate with treatment and also increases mortality. Susceptibility to develop TB is increased 2.4 times in patients with chronic renal failure. In persons receiving corticosteroid therapy for immunosuppression the risk is twice the normal. Tuberculosis remains predominantly a disease of the poor. 22 countries where the per-capita income is < \$ 760 contain more than 80% of the total global burden of TB patients.

PATHOGENESIS AND PATHOLOGY

The portal of entry of the organisms is inhalation, ingestion, or inoculation. Inhalation is the most common route. Droplets containing MTB are released when a PT patient coughs. Larger droplets fall to the ground. Medium sized droplets are trapped in the mucosa of the upper respiratory tract from where they are cleared without causing infection. Tiny droplets < 25 µm in diameter

evaporate immediately leaving particulate organisms to float in the air. These particles escape the trapping mechanisms and reach the lungs, where even a single bacterium can initiate infection. Given adequate exposure, tuberculosis is highly contagious. 45-60% of children of parents with sputum positive PT gets the infection. One open case may infect at least 20 persons of whom 10%, i.e. 2 persons develop overt disease—one will be infectious and the other non-infectious. Smoking may increase the incidence of TB.

Ref: Vendhan, Ajalekshmy, et al. The Lancet 2003;362: 507-15.

The primary site of infection depends on the mode of entry. It may be in the lungs, tonsils, mucous membranes, intestines or skin. The development of hypersensitivity plays a major role in determining further events. The pathological process occurring in an individual who has not been sensitized to the organisms, i.e. occurring for the first time, is known as *primary tuberculosis*. Subsequent infection occurring in the sensitized individual who possesses immunity gives rise to a different course of events. This is known as *post-primary tuberculosis*. T-lymphocytes play a major role in conferring immunity against *M. tuberculosis*. Tuberculosis bacillus circulates in blood and the number of circulating bacteria may reach high counts in immunocompromised hosts. They can be detected by PCR.

The host's reaction to the bacilli which enter is initially exudative, and later proliferative. Initially the exudate is composed mainly of neutrophils. Later, lymphokine activated macrophages accumulate and these engulf the organisms. These phagocytes are derived from the fixed tissue macrophages, the alveolar macrophages of the lungs, and the monocytes from blood. Macrophages with engulfed organisms get transformed into epithelioid cells. Multi-nucleated foreign body type of giant cells (*Langhan's giant cells*) are formed by the fusion of epithelioid cells. These are surrounded by lymphocytes and fibroblasts. At the centre of the lesion caseation necrosis occurs. The secret of the organism's success is its ability to evade the immune system by penetrating into macrophages without being destroyed by them. Activated macrophages prevent replication of the tubercle bacillus, but may not kill them altogether. The pathological hallmark of tuberculosis is the tubercle which consists of an area of central caseation, around which there is infiltration by epithelioid cells, giant cells, round cells and peripherally by fibroblasts. Several such microscopic tubercles form the macroscopic tubercles which are seen in affected tissues.

Granuloma formation is usually adequate to limit the infection. The lesion becomes quiescent and surrounding fibroblasts produce scar tissue which may become calcified. Some bacilli remain in this tissue as "*persisters*" which, when reactivated produce postprimary disease.

In a minority of cases the infection progresses without being localized and gives rise to serious manifestations of the primary infection such as progressive primary lesion in infants, pleurisy, renal lesion, bone tuberculosis, meningitis and so on. If a primary focus ruptures into a blood vessel, miliary tuberculosis develops, with affection of all organs, particularly the meninges and brain.

Immunity against tuberculosis: Organisms possess non-specific and specific immunity against tuberculosis. Nonspecific immunity is present in people living in areas of high prevalence. Depression of the general immune mechanism in diseases such as diabetes, malnutrition, immunosuppressed states, and therapy with corticosteroids predispose fresh infection by *M. tuberculosis* and reactivation of quiescent lesions.

Specific immunity in tuberculosis is T-lymphocyte mediated. Though humoral antibodies are demonstrable, they do not play any protective role. *M. tuberculosis* can survive and replicate within macrophages thereby evading the immune defences of the host. The infection also suppresses the reaction of macrophages to activating cytokines. One attack of tuberculosis does not confer solid immunity so that both reactivation of a quiescent focus and reinfection are possible. Abdominal tuberculosis occurring in HIV +ve subjects is characterized by visceral involvement with necrosis, best made out on CT scans. Abdominal tuberculosis in HIV –ve subjects leads to omental thickening, ascites and peritonitis more often. Though the T-lymphocyte function is demonstrable as tuberculin sensitivity (Mantoux testing), sensitivity and immunity are not identical. Tuberculin sensitive individuals possess a degree of resistance to further infection by tuberculosis, but this immunity is not absolute.

Pulmonary Tuberculosis

In man, lungs are the most frequently affected organs. All those who develop the disease for the first time manifest primary tuberculosis irrespective of their age. The pathological lesions in primary tuberculosis show prominent lymph nodular enlargement (usually hilar) with only minimal parenchymal lesions. Post-primary tuberculosis presents mainly as parenchymal disease with only minimal lymph node enlargement.

In primary tuberculosis the bacilli multiply rapidly in the lesions and dissemination by lymphatics and bloodstream is frequent. Extensive tissue necrosis is rare.

PRIMARY PULMONARY TUBERCULOSIS

Lung is the commonest site for primary tuberculosis. Children are affected most, though no age is immune. The initial lesion is a subpleural tubercle located in the lower part of the upper lobe, upper part of the lower lobe, or middle lobe. This parenchymal lesion (*Ghon's lesion*)



Fig. 49.1: X-ray chest tuberculosis—middle lobe consolidation right

with its enlarged regional lymph nodes and interconnecting lymphangitis is known as the primary complex (*Ghon's complex*). More than 80 per cent of cases of primary tuberculosis do not produce systemic disturbances and the lesions heal spontaneously. These remain undetected. The tuberculin test becomes positive within 4 to 6 weeks of infection. Once it becomes positive, it usually remains so for life.

In 10-15% of children the primary lesion goes on to progressive disease. This may be due to poor general resistance, immunosuppression, high infective dose, or virulent strains of bacilli. AIDS, measles and whooping cough lower the resistance and favour progression. The hilar lymph nodes enlarge progressively and undergo caseation. Compression of the neighbouring bronchi, especially of the middle lobe, leads to collapse-consolidation and bronchiectatic changes. This may present later as the 'middle lobe syndrome' (Fig. 49.1). When a caseated node ruptures into a bronchus, spread occurs to other parts of the lungs and tuberculous bronchopneumonia develops. Erosion of a vessel and discharge of the caseous material into the bloodstream lead to wide dissemination and the development of miliary tuberculosis. Rarely the pulmonary lesion may increase in size to produce cavitation. It may also spread to the other regions of the lung parenchyma. Spread to the pleura results in pleurisy with effusion.

CLINICAL FEATURES

Progressive primary tuberculosis is invariably symptomatic. Onset may be acute or insidious. Fever, loss of **277**

appetite, loss of weight and cough are early symptoms. Lethargy, vague ill-health, failure to thrive and delay in the milestones may be the presenting features in children. At this stage the disease can be diagnosed only if the clinical suspicion is strong. Allergic manifestations like **phlyctenular conjunctivitis** or **erythema nodosum** may herald primary tuberculosis in some cases. Erythema nodosum manifests as reddish, indurated, painful, swellings usually seen in front of the tibia. These persist for varying periods. Occasionally the disease predisposes to recurrent respiratory infection. Acute pleural effusion may develop in some. Other presentations in children include tuberculous pneumonia, hemoptysis, or *asthma*. Miliary tuberculosis may manifest as meningitis in many.

Physical examination may not give any positive finding in many patients and the diagnosis has to be based on investigations. In some, the signs of pulmonary consolidation, collapse, or pleural effusion may be present. Tuberculin skin test is positive in the vast majority. Blood examination shows raised ESR and lymphocytosis.

If the parenchymal lesion is small, expectoration may not be present. Chest X-ray reveals hilar lymphadenopathy and on careful examination the pulmonary lesion may be detectable. The diagnosis of primary tuberculosis is based on the history of tuberculous contact, clinical symptomatology, X-ray findings, and recent tuberculin positivity. Bacteriological confirmation is usually difficult to get.

POST-PRIMARY TUBERCULOSIS

Pathogenesis and Pathology

Post-primary tuberculosis occurs in one of four ways:

- 1. Direct progression of primary lesion,
- 2. Reactivation of a quiescent primary focus,
- 3. Hematogenous infection of lung from lymph nodes, tonsils, etc., and
- 4. Re-infection or superinfection.

Post-primary pulmonary tuberculosis is characterized by tendency for early cavitation, limitation of the disease process and healing. The upper lobes are more commonly affected, unlike as in primary tuberculosis. Depending upon the resistance two pathological forms are seen.

- 1. Slowly progressive nodular form in individuals who possess resistance, and
- 2. Fibrocaceous form with tendency for cavitation if the resistance is low.

In the nodular form the sputum shows only less number of tubercle bacilli, whereas the reverse is true in the latter.

Mainly the lung parenchyma shows lesions, the lymph nodular changes are minimal. The initial lesion is an exudative pneumonia. Subsequently tubercles form. They coalesce to give rise to large macroscopic lesions. The caseous material is discharged into a bronchus and

coughed out, leaving behind a cavity. The wall of the cavity teems with the bacilli and its surroundings show many tubercles. Blood vessels in the cavity become unsupported. Many of them are occluded by thrombosis, but those that remain patent become aneurysmal (*Rassmussen's aneurysms*). They may rupture and give rise to massive haemoptysis. Healing, occurs with replacement fibrosis.

Clinical Features

Adolescents and young adults are more frequently affected, though no age group is spared. The disease manifests insidiously with respiratory symptoms such as mild and persistent cough, low-grade evening fever, anorexia, loss of weight, and general weakness. The fever is moderate and comes on in the evening to subside with sweating by midnight. In a few cases the onset may be acute with high fever, cough and hemoptysis, and the lesion may resemble lobar pneumonia. The nodular type is generally silent and in many cases it is detected radiologically. Sputum is mucoid or mucopurulent, initially scanty, later it is more copious. Mild streaky hemoptysis may occur initially, but later, profuse hemoptysis occurs due to erosion of blood vessels. The larynx is affected and laryngitis results in hoarseness of voice. In some cases pleural effusion, empyema or pneumothorax may be the initial presentation.

Physical examination of the chest may reveal signs of consolidation, cavitation, collapse, fibrosis, pleural effusion, or pneumothorax. As the condition proceeds, the patient becomes emaciated. Cough with expectoration is pronounced and extreme cachexia develops (Phthisis). If left untreated, death occurs due to extensive disease, cachexia, intercurrent infection, or any of the complications. The classic picture of well-established lesion is rarely only encountered at present. Due to the free availability of X-ray chest and strong clinical suspicion, cases are diagnosed at earlier stages.

COMPLICATIONS

Several complications may develop during different stages of the disease. These may occur in the early part of the disease or much later. Some may be delayed by several years.

COMPLICATIONS OF PULMONARY TUBERCULOSIS

These are listed below

Early: Occurring within months

- 1. Mild hemoptysis
- 2. Pneumothorax
- 3. Pleural effusion
- 4. Poncet's syndrome

Intermediate: Occurring within several months or a few years

1. Massive hemoptysis
2. Secondary infection of cavities
3. Pneumothorax, pleural effusion, empyema
4. Progressive fibrosis with dyspnea
5. Spread to other organs such as larynx, pericardium and others
6. Non-healing of lesion due to drug resistance of organisms.

Late: Occurring after several years.

1. Pulmonary fibrosis with compensatory emphysema, cor pulmonale, pleuropulmonary fibrosis.
2. Bronchiectasis
3. Persistence of open cavities without healing
4. Aspergilloma i.e., growth of *Aspergillus fumigatus* in the cavities in the form of a fungus ball
5. Coexistence of apical tuberculosis with carcinoma
6. Secondary amyloidosis.

Diagnosis

Tuberculosis should be suspected in all patients suffering from chronic respiratory disease, especially if associated with night sweats, fever, emaciation, and hemoptysis. Other conditions which should be differentiated are bronchiectasis, lung abscess, cystic disease of the lung, chronic pneumonias, malignancy and tropical eosinophilia. Cough persisting for more than two weeks without other obvious causes should alert the physician to investigate for pulmonary tuberculosis.

Differential Diagnosis

In bronchiectasis, the lesions are often bilateral, involving usually the lower lobes. The condition is more chronic extending over several years. Finger clubbing and history of postural cough with copious sputum may be present. In the majority of cases of pulmonary tuberculosis finger clubbing does not occur, except in the bronchiectatic form and in the chronic fibrotic stage. Tuberculous bronchiectasis is usually confined to the affected part, unlike as in primary bronchiectasis.

Lung abscess usually affects the lower lobes. Postural coughing is prominent, symptoms are more pronounced, and finger clubbing occurs early. History of pneumonia or aspiration into the respiratory tract may be elicitable in some cases.

Congenital cystic disease manifests in adolescence or adulthood. Lesions are more widespread, clubbing is only minimal, and radiographs show thin walled multiple cysts, more in the lower zones.

Some types of pneumonias may become recurrent or chronic, especially if there are underlying conditions such as bronchial obstruction or malignancy.

Carcinoma of the lung has to be considered when lesions are unilateral. Carcinoma is more common in heavy

smokers. It affects persons in the fourth and fifth decades. Males are affected more. The lesion is more around the hilum. Signs of consolidation, collapse, pressure effects like Horner's syndrome or diaphragmatic paralysis should suggest this possibility. Clubbing of fingers occurs early and supraclavicular or pretracheal lymph nodes are palpably enlarged in most cases.

Tropical eosinophilia may present with cough, fever, and loss of weight, especially in adolescents and young adults. Physical examination may reveal signs of bronchospasm and scattered rales. There may not be evidence of any localized lesions. Blood eosinophil count is high (often above 3000/cmm). The sputum shows numerous eosinophils.

Tuberculosis should be considered as a probable underlying cause in all cases presenting with asthma of recent onset, prolonged fever, and pneumonias which tend to persist even after administering a standard therapy. Onset of tuberculosis in otherwise apparently healthy persons should raise the possibility of diabetes mellitus or AIDS as possible predisposing factors.

Poncet's syndrome is a hypersensitivity reaction to the infection, manifesting as arthritis, which may resemble rheumatoid or other forms of arthritis.

Investigations

Sputum examination: The most important diagnostic investigations are the demonstration of acid-fast organisms in sputum by Ziehl-Neelsen method and radiology. Positivity of smears and cultures depends on the bacterial count in the sputum. While examining a sputum smear, at least 100 fields should be seen for 10 minutes before declaring it as negative. At least 3 bacilli should be seen before the smear is declared positive (Fig. 49.2). Concentration methods are available using 24-hr collection of sputum to detect AFB when direct smears are negative. Fluorescence microscopy is being employed to identify tubercle bacilli. It is more rapid and this method has the advantage of better coverage of the smear. Modern techniques using polymerase chain reaction (PCR) have

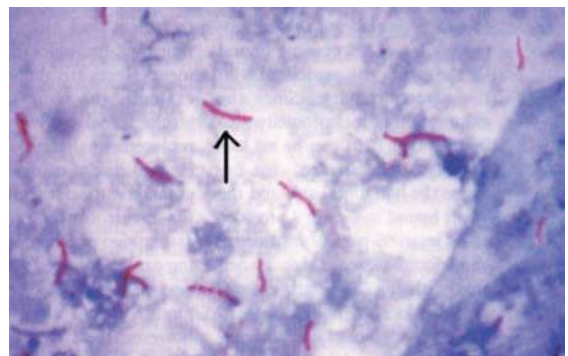


Fig. 49.2: Sputum Zeihl-Neelsen stain

been found to be very useful in making early specific diagnosis.

Further confirmation is obtained by identification of *M. tuberculosis* in sputum culture. In high prevalence areas, it may not be practicable to do culture in all cases. For all practical purposes, two consecutive morning sputum examinations can be accepted as confirmatory of the diagnosis. When the sputum is difficult to get, as in children and psychiatric patients, laryngeal swab or material collected by gastric aspiration may be used. Laryngeal swab is 25% and gastric aspirate about 50% as efficient as sputum examination in identifying the organism. Sputum may be collected by transtracheal aspiration in comatose patients. Bronchoscopic aspiration is resorted to in exceptional cases. In high prevalence areas, sputum culture and animal inoculation studies should be reserved for cases with negative sputum smears, but with suggestive radiological features and in whom drug resistance is suspected.

Radiology

In day to day practice, radiology is the easiest and most readily available investigation to visualize the pulmonary lesion. Early cases show infiltration in the upper zones (Fig. 49.3). Later the lesions coalesce to produce consolidation. When cavitation occurs thin-walled cavities are seen, often multiple, with intervening fibrosis. As the lesion becomes fibrotic, the opacities become dense, with reduction in pulmonary volume and shifting of the trachea and mediastinum towards the side of lesion. Such lesions occupying the upper zones, especially if bilateral, should raise the strong suspicion of tuberculosis and the diagnosis has to be confirmed or excluded by appropriate tests. In



Fig. 49.3: X-ray chest tuberculosis. Infiltration bilateral

untreated cases sputum examination is invariably positive for acid-fast bacilli. A common cause for sputum-negativity in India is partial treatment with anti-tuberculosis drugs.

With treatment, infiltration, consolidation and even early cavitation may heal completely leading to full resolution of the radiological abnormality. Once cavitation is chronic and fibrosis has set in, the radiological abnormalities do not clear up with further treatment even though the disease becomes arrested. In such cases, it is essential to distinguish residual radiological abnormalities from active disease.

Blood examination shows mild lymphocytosis and raised ESR in most cases. Since these findings are non-specific, they have only a limited diagnostic value. Progressive fall of ESR and clearance of radiological abnormalities are fairly reliable and simple practical methods to follow up the progress of the disease with treatment.

Presence of organisms in blood can be detected by PCR. PCR is a highly sensitive and specific test taking only a few hours for diagnosis. Sputum, blood, CSF, pleural fluid and other tissues may be subjected to PCR. Different kits containing appropriate probes are available. DNA detected by PCR may remain so for long periods even after the infection is cured or suppressed.

Amplified mycobacterium tuberculosis detection (AMTD) test uses the principles of transcription mediated amplification of ribosomal RNA of MTB. The detection of t-RNA indicates the presence of actively multiplying MTB. RNA is a much more short-lived molecule compared to DNA which persists for long periods. Specimens such as sputum, aspirated fluid, CSF, bone marrow and FNAC tissue can be used for the test. It takes 24 hours to get the result and costs approximately Rs. 1000/-.

Enzyme linked immunospot assays (ELLISPOT technique) have been developed and different commercial kits are available. These are based on detection of interferon- γ produced by T-cells in response to antigens specific to *M. tuberculosis* (T-SPOT.TB, QuantiFERON-TB Gold) which have been tested in children and approved by the FDA. It has sensitivity of 83% to detect TB in children whereas Mantoux test has sensitivity of only 63%.

Moreover, unlike Mantoux test which may be influenced by immunosuppressed conditions, the ELLISPOT test is unaffected. Non-TB mycobacteria and BCG vaccination does not interfere with the ELLISPOT test.

(Ref. Susan Liebeschuetz et al The Lancet 2004. 364: 2196-2203).

Proteomic finger printing methods are being developed to detect tuberculosis early, by identifying serum markers.

Tuberculin skin test (Mantoux Test): This test is usually done by injecting one unit of purified protein derivative (PPD) in the volar surface of the forearm intradermally.



Fig. 49.4: Forearm showing accelerated reaction to Mantoux test in a male having active tuberculous lymphadenopathy

The result is read after 48 h and the area of induration is recorded. In a positive test, the diameter of the induration exceeds 12 mm. Negative results do not always rule out tuberculous infection since conditions like malnutrition, immunosuppression therapy and Hodgkin's disease, suppress the test. Patients suffering from active tuberculosis show an accelerated Arthus reaction with necrosis. Though the occurrence of '*accelerated reaction*' is not a wholly reliable parameter, invariably it points to active tuberculosis.

The diagnostic value of tuberculin test is in those individuals who are '*recent converters*'. This should suggest the occurrence of infection by mycobacteria. In infants below the age of one year, tuberculin positivity should be taken as recent infection and therefore it is an indication for starting anti-tuberculosis treatment.

Tuberculin testing is widely employed to assess the prevalence of the disease in the community. Prevalence of tuberculin positivity in the young subjects is related to the number of infective cases. This is of help in planning tuberculosis control programs. BCG vaccination if successful, gives rise to tuberculin-positivity.

Other methods to test tuberculin-sensitivity include Heaf multiple puncture test and tuberculin Tine test. Infection by non-tuberculosis mycobacteria may give rise to positive tuberculin test. Differential tuberculin testing using PPD prepared from these mycobacteria helps to identify such infections.

TREATMENT

The goals of treatment are

1. To ensure cure without relapse
2. To prevent death
3. To prevent spread and
4. Prevent the development of resistance. Since MTB can remain dormant for long periods, all anti-tuberculosis treatment programmes have two phases.

- a. An active phase intended to kill actively growing and a proportion of the dormant organisms and
- b. The second phase intended to eliminate the persisting bacilli.

Modern therapy is mainly dependent on the powerful antituberculosis drugs currently available. With judicious combinations, virtually all lesions can be rendered bacteria-free and allowed to heal. Early lesions heal without any residual damage, whereas late lesions heal with fibrosis and calcification in some cases. It is important to institute treatment without delay after establishing the diagnosis. The drugs are always given in combination to avoid the development of resistance and for synergistic effect. A strict schedule should be instituted. Patient compliance is absolutely necessary to ensure cure and prevent the development of resistance. Lack of motivation of the patient and the long course of treatment are the most important factors which account for many drop-outs after receiving incomplete therapy. Since most of the cases can be treated at home with excellent results, domiciliary treatment is preferable. Moreover, it is now well understood that once the case is notified, the risk of spread to contacts is only slight. Simple precautions like isolation at home, use of separate utensils and disinfection of the sputum are advised to the patient and his family members. Since there is likelihood of other cases occurring in the family and other contacts, detection of all fresh cases should be followed up with a survey of the family members and other immediate contacts. Hospitalization is required for cases with high fever and toxemia, hemoptysis, pleural effusion, pneumothorax, extreme cachexia and coexistence of other diseases like uncontrolled diabetes mellitus. Rendering the patient sputum-negative is the most effective method to control spread to others.

Drug schedules: Adequate chemotherapy administered without interruption for the optimal duration is the cornerstone of success. The available drugs are classified into standard or first line drugs and reserve or second line drugs based on their efficacy, cost, availability and toxicity (Table 49.1).

Short Course Chemotherapy

At present short course chemotherapy using INH, rifampicin, ethambutol and pyrazinamide is the preferred method, on account of its efficacy, ease for supervision and better patient compliance. Though the drugs are expensive, the Government supplies the drugs free of cost from the TB control centres. Short course chemotherapy extending over 6-9 months is adequate to cure 95-98% of all forms of tuberculosis, and in all age groups. Alternate drugs or longer period of treatment are indicated when drug resistance or intolerance of the primary drugs exists. Among the anti-tuberculosis drugs INH, rifampicin,

TABLE 49.1

Drugs used in the treatment of tuberculosis, dosage, route or administration and toxicity

Name of drug	Daily dose for adults	Children	Route of administration	Diffusion in CSF	Main toxic effects
A. First line drugs					
1. Isoniazid	5 mg/kg bw for ordinary cases 12 mg/kg bw in miliary TB and meningitis	10 mg/kg bw	Oral	Good	Hypersensitivity hepatitis, peripheral neuropathy
2. Rifampicin	Persons weighing below 50 kg 450 mg above 50 kg 600 mg	10-20 mg/kg	Oral	Good	GI toxicity, hepatitis, elevation of hepatic enzymes, hypersensitivity, flu-like syndrome, blood dyscrasia esp. thrombocytopenia.
3. Pyrazinamide	Persons weighing up to 50 kg 1.5 g 51-74 kg 2 g above 75 kg 2.5 g (i.e.) 20-35 mg/kg bw	40 mg/kg maximum 2 g	Oral	Good	Arthralgia hepatitis, hyperuricemia
4. Ethambutol	800 mg/day (24 mg/kg bw) for 2 months thereafter 15 mg/kg bw		Oral	Good	Retrobulbar neuritis, rare if dose is kept below 15 mg/kg.
5. Streptomycin	below 30 kg bw or above the age of 60 years, 0.75 g above 30 kg bw lg (20 mg/kg bw)	20 mg/kg bw	I.M inj.	Fair	Deafness, nephrotoxicity vestibular dysfunction
B. Second line drugs					
1. Thiacetazone	150 mg	4 mg/kg bw	Oral	±	Gastrointestinal hepatitis, exfoliative dermatitis.
2. Ethionamide	500-750 mg	—	Oral	±	Gastrointestinal, metallic taste in the mouth, hepatitis.
3. Cycloserine	0.5-1.0 g	—	Oral	Good	Confusion, slurring of speech, convulsions, psychosis.
4. Kanamycin	15 mg/kg bw	—	I.M inj.		Ototoxicity and nephrotoxicity
5. Capreomycin	30 mg/kg bw, up to 1 g/daily for 4 months, followed by 1 g 2-3 times a week.	—	I.M inj.		Nephrotoxicity vestibulotoxicity.
6. Viomycin	3-4 g weekly	—	I.M inj.		Nephrotoxic and vestibulotoxic.
7. Amikacin	15 mg/kg bw	—	I.M inj.		Ototoxicity, nephrotoxicity
8. Rifabutin is an analogue of rifampicin—used for treatment of rifampicin resistant mycobacteria.					
9. Rifapentine	600 mg once a week	oral	serum half-life 10-15 hours suitable for once-a-week schedules		
C. Reserve drugs					
Ofloxacin	400 mg b.i.d		Oral		Abdominal distress, headache, anxiety, tremor, thrush, druginteraction Allergy
Ciprofloxacin	750 mg b.i.d or t.i.d		Oral		
Clarithromycin	500 mg b.i.d		Oral		

Morphazinamide is a derivative of pyrazinamide given orally in a dose of 40 mg/kg bw which is less toxic. Prothionamide is a derivative of ethionamide, given in the same dosage. Its toxicity is possibly less. Both these drugs are only seldom used. Para-aminosalicylic acid (PAS) is not used in regular therapy, but at times it is used as a second line drug.

pyrazinamide and streptomycin are bactericidal, the other drugs are bacteriostatic.

Response to therapy occurs in three stages.

1. Within the first two weeks of starting therapy the majority of actively replicating bacteria in cavity walls are killed, mainly by INH, but also by rifampicin and pyrazinamide.
2. In the succeeding few weeks, rifampicin and pyrazinamide kill the less active bacteria lurking within macrophages, caseous material and exudates.
3. With maintenance therapy, the dormant bacilli are killed by rifampicin during their short bursts of activity.

Emergence of drug resistant bacilli is uncommon if the short-course therapy is given properly under supervision. Relapses, if they occur, are still caused by drug-sensitive bacilli, though rarely it may be by drug-resistant strains. Several regimens for short course chemotherapy are recommended.

Domiciliary Treatment

Success of domiciliary treatment has been established by several studies. Contacts of a notified case naturally maintain isolation and therefore spread from such cases is less common. Open cases of TB should maintain restricted isolation so that they do not transmit the disease to others. They may be advised to confine to home till the sputum becomes AFB- negative. Separate utensils for eating and drinking are preferable. Infective materials like sputum should be disinfected by burning or burying deep in soil. All contacts with an infective case of TB should be followed up with a view to detect infection early.

DIRECTLY OBSERVED THERAPY (DOT) SCHEDULE

Standard therapy

Drugs

Initial phase first 2 months

Rifampicin	450 mg	
INH	600 mg	given under observation
Ethambutol	1200 mg	thrice a week
Pyrazinamide	1500 mg	

Maintenance treatment 4 months

Rifampicin	450 mg	given under observation
INH	600 mg	thrice a week

Modifications are done under special circumstances

Category I	Severe forms of pulmonary TB with sputum positivity
Category II	Defaulters of past treatment and failed cases from category I

To the standard regimen add streptomycin 0.75 g IM thrice a week for 3 months. This period is extended to 4 months if clearance of lesion is not satisfactory.

Maintenance with three drugs INH 600 mg, rifampicin 450 mg and ethambutol 1200 mg thrice a week for 4 months. Total 8 months.

Category III Extrapulmonary tuberculosis and sputum negative cases—regimen is the same as for standard therapy.

Note: Some regimen do not include ethambutol in the initial phase. Only three drugs are used.

India has launched the **Revised National Tuberculosis Control Programme (RNTCP)** in 1993 based on directly observed treatment schedule (DOTS). This has been very successful. RNTCP has achieved cure rates of 80%.

All the anti-TB drugs are given together in full dosage on an empty stomach in the morning since absorption is best at this time. Any food is allowed only at least 30 minutes later.

Since *M. tuberculosis* develops drug resistance rapidly when exposed to a single drug, combination therapy should always be insisted upon. Late relapses are more likely to occur if the full duration of treatment is not completed. INH which is still the most popular anti-tuberculosis drug behaves differently in slow acetylators and fast acetylators. Fast acetylators are persons who have high levels of acetyl transferase activity in the liver. This enzyme metabolizes INH much faster and so fast acetylators require higher doses. In slow acetylators the half-life of INH is over 2 hours, whereas in fast acetylators it is 0.5-1.5 hours. Above 70% of Indian subjects are slow acetylators.

The standard regimen is adequate for all forms of tuberculosis, both for human and bovine strains of mycobacteria.

Patients with uncomplicated tuberculosis, receiving uninterrupted treatment for the entire period, should be considered cured, unless proved otherwise. Upto 2% cases relapse after successful chemotherapy. The risk of relapse is more in the first three years after completing treatment. The DOTS programme launched in 1993 has achieved the following results in India. More than 200000 health workers have been trained. 40% of the population has access to DOTS regimen 800000 received treatment. The World Bank, Danish and UK National Agencies and the Government of India have funded the programme.

Course and prognosis: With successful regimen the lesions become sterile and the vast majority heal by fibrosis. Surgery is indicated only under exceptional situations. These include open healed cavities with aspergilloma, grossly destroyed lung with secondary infection, bronchiectasis and persistence of tubercle bacilli resistant to all drugs, especially in cavitory lesions.

Common causes for failure of therapy are:

- i. inadequate drug dosage,
- ii. noncompliance with the schedule,
- iii. early stopping of therapy,

- iv. drug toxicity, and
- v. initial drug resistance.

DRUG RESISTANCE AND RESERVE DRUGS

Resistance to drugs may be of different types:

1. Some strains of *M. tuberculosis* are naturally resistant to drugs. This is extremely rare.
2. **Primary drug resistance:** Bacilli which are initially resistant to drugs may be the infecting organism.
3. **Secondary drug resistance:** This is drug resistance acquired by initially sensitive bacilli, due to irregular and inadequate chemotherapy.
4. In some cases initial resistance may be *either primary or secondary*, especially when a patient conceals the history of earlier chemotherapy.
5. **Transient resistance:** This is a bacteriological phenomenon which occurs sometimes during successful chemotherapy. One or two cultures may be reported as resistant but later these cases may also become sensitive. This is not an indication to change the drugs.

Patients with cavitory lesion in which the bacterial population is very high, are more likely to develop drug resistance. Resistance should be suspected when a lesion fails to become sputum negative and heal, despite adequate chemotherapy.

Alternate drugs: These are used when the organisms are resistant to one or more of the standard drugs, or toxicity is severe. The regimen consists of 3 to 4 drugs administered for a period of 2 years or more. The drugs include rifampicin, ethambutol, pyrazinamide or morphazinamide, ethionamide or prothionamide, cycloserine, kanamycin, viomycin, and capreomycin. There should be at least two bactericidal drugs. Life-long follow-up is necessary in cases where reserve drugs have been used.

Multidrug resistant TB (MDRTB) is increasing due to noncompliance and poorly supervised treatment programmes. Resistance to INH and rifampicin in MDRTB is highly dangerous. In HIV –ve individuals it causes 22% mortality. In HIV +ve case it is about 50%. Concurrent MDRTB and HIV infection carries a high mortality. Early detection and treatment of this combination is needed for successful outcome. Prevalence of MDRTB in some surveys in India give the following figures

Mahjan et al Delhi 1996	Tiwari et al Pune 1994
Resistance against INH- 26-48%	Resistance to 1 drug-38%
Resistance to SM 18-63%	Resistance to 2 drugs-28%
	Resistance to 3 drugs-13%

MDR TB may be classified as **basic MDR TB** in which the resistance is only to INH and rifampicin and **MDR TB plus** in which there is resistance to several other drugs as well. The molecular basis for resistance has been

elucidated. Even with combination drug regimen the cure rates for MDR TB is only 50-60%.

Treatment of MDRTB

1. Start treatment with at least three drugs to which the organisms is sensitive *in vitro*.
2. Use bactericidal drugs as far as possible.
3. Avoid drugs that impair absorption of anti TB drugs e.g. antacids.
4. Never add a single agent to a failing regimen.
5. Malabsorption is common in AIDS and therefore check the serum levels.
6. Always use directly observed therapy.
7. Surgical measures should be considered early so as to eradicate infection.
8. Consider treatment as successful only if two sputum cultures done at least two weeks apart are negative.
9. Continue treatment for at least 18-24 month after bacteriological clearance.
10. Strict isolation of the patients.

X-DR tuberculosis: This newly coined term denotes extensive resistance to drugs in the first and second line also. X-DR tuberculosis is classified as cases resistant to three or more of the second line drugs. The reason for developing.

X-DR tuberculosis is misuse and mismanagement of second line drugs. This problem is widespread in many countries. In India also this is cropping up. The mortality is $\pm 80\%$.

Special Points in Anti-tuberculosis Treatment

1. **Pregnancy and lactation** are not contraindications to standard anti-tuberculosis treatment. The drugs are not embryotoxic. If a sputum-positive mother gives birth, the baby should be removed, given BCG and preferably brought back to the mother only after it becomes Mantoux-positive. The baby should be observed for the development of primary tuberculosis. INH therapy is advocated as prophylaxis after BCG vaccination has taken effect.
2. **Hepatic disease:** It is better to avoid rifampicin, INH and thiacetazone since these drugs are metabolized in the liver.
3. **Renal failure:** Streptomycin and ethambutol are to be avoided. Rifampicin, INH and pyrazinamide are well tolerated.

TREATMENT OF TUBERCULOSIS (TB) IN HIV POSITIVE PATIENTS

Co-infection with the two diseases presents special problems. Primarily the resistance against TB is considerably reduced. So also the progression of AIDS is

also accelerated. The special problems include drug-drug interactions, overlapping toxicities, additional pill burden, problems of compliance and development of immune reconstitution inflammatory syndrome (IRIS). All HIV-TB patients should be treated with standard four-drug anti-TB therapy. Intermittent (once a week or twice a week) therapies should be avoided. The exact duration of treatment is not well defined, but drug susceptible TB should be treated for 6 months. Those with slow response i.e. sputum cultures positive even at 2 months should receive treatment at least for 9 months. Tuberculosis involving the central nervous system should receive treatment at least for one year.

In those with HIV and TB, the treatment has to be instituted against both diseases simultaneously. Despite starting treatment for TB, the death in the subsequent one month may still be mostly attributable to TB, whereas deaths occurring later may be due to other causes as well.

When should anti-retroviral therapy (ART) be started along with anti-TB therapy?

The CD4 T cell count provides an answer. In those with CD4 counts > 200/cmm. ART can be delayed till anti TB treatment is completed. In those with CD4 T cell counts < 200/cmm, ART should be started concurrently since progression of AIDS may lead to death.

What drug regimen should be given to treat HIV in the presence of TB? Rifampicin causes enzyme induction in the liver and this may lead to reduction in the blood level of nevirapine and other anti-retroviral drugs. It also predisposes to nevirapine induced hepatitis, especially in women with CD4-T cell counts > 250/cmm. Therefore the treatment of HIV should consist of two non-nucleoside reverse transcriptase inhibitors (NNRTI) with efavirenz in a daily dose of 600-800 mg. After completion anti-TB therapy, a cheaper NNRTI drug like nevirapine can be substituted.

Immune Reconstitution Inflammatory Syndrome (IRIS)

This phenomenon is not uncommon. This condition arises when anti-retroviral therapy partially restores the immunosuppression in AIDS. This manifest as exacerbation of tuberculous lesion such as lymphadenopathy, hepatosplenomegaly, fever, aches and pains, granulomas, suppuration, necrosis of tissues, rise in intracranial tension, flare up of pulmonary lesions and several others. Similar exacerbation may occur in other. AIDS- related infections as well. This may mimic drug reactions and it may even be life threatening IRIS is more likely to occur in patients where CD4 T cell counts are < 100/ cmm and in whom HAART is started within the first 2 months of starting anti TB therapy. The usual time for manifestation is 3 months after starting the therapy.

Treatment

Some cases clear up spontaneously on continuing the combination therapy. At times if IRIS is life threatening, such as worsening of lesions, the HAART has to be temporally withdrawn. Non-steroidal anti inflammatory drugs and prednisolone in adequate doses may have to be used. In any case development of IRIS is not a reason for abandoning specific treatment for both conditions.

PREVENTION OF TUBERCULOSIS

Improvement in economic and social factors and education of the community are associated with reduction in incidence of tuberculosis. Specific immunization is by Bacillus Calmette Guerin (BCG) vaccination. BCG mounts up CD4 T cell mediated immunity. Recent trials conducted in south India have thrown doubts on the full efficacy of BCG vaccination. However, the World Health Organization still recommends BCG vaccination as a protective measure against tuberculosis especially in children. BCG vaccination prevents severe disease and reduces the mortality in children, but protection against the development of pulmonary tuberculosis in children and adults is doubtful. As at present it is included in the primary vaccination programme of infants. There are attempts to modify BCG vaccine to improve its immunogenicity.

The vaccination is given intradermally over the left shoulder just below the insertion of the deltoid with 0.1 mL of the liquid or reconstituted dry vaccine. For infants below 4 weeks 0.05 mL is the recommended dose. Ideal time is to give BCG at the third month of life but in practice the vaccine is given in the neonatal period in many centers, for administrative convenience. A nodule develops which ulcerates and heals in 8-12 weeks, leaving a scar. Though BCG was given only to tuberculin negative subjects previously, it is now given routinely even without routine tuberculin testing. Relative immunity starts to appear in 4-6 weeks which wears off with the passage of time and disappears in 5-7 years. In some countries revaccination is done at 7 years intervals in high risk groups till the age of 21 years. Rare complications include non-healing of the ulcer, abscess formation in the axillary lymph node, and keloid formation. Dissemination may occur in immunosuppressed individuals. Nonhealing ulcers or troublesome lymphadenopathy responds promptly to local or systemic isoniazid therapy, but chemotherapy also eliminates the protective role of the vaccine.

Chemoprophylaxis: INH has been found to offer effective prophylaxis against tuberculosis in high risk groups. Chemoprophylaxis may either be primary or secondary depending on whether prophylaxis is given to a person who is tuberculin negative or tuberculin positive

respectively. Primary prophylaxis is given to the contacts of sputum-positive tuberculosis patients, before they develop the disease, e.g., newborns of infective parents.

Secondary chemoprophylaxis is employed only rarely. When corticosteroids or immunosuppressants have to be administered, INH may be given to prevent exacerbation of healed tuberculous lesion.

Surveillance: Persons who are at high risk of developing tuberculosis occupationally (danger group) such as hospital staff, school teachers, bus conductors, barbers, hotel employees, and others should have periodic medical examination.

WHO has developed the stop TB strategy with the following targets: Year 2015—reduce prevalence of TB and deaths due to TB by 50% relative to the levels that existed in 1990.

Year 2050—eliminate TB as a public health problem that is < 1 case per million population.

24th March of every year is designated the **World TB day** by the WHO.

MILIARY TUBERCULOSIS

Syn: Acute hematogenous tuberculosis

Tubercle bacilli entering the bloodstream are diffusely disseminated and results in miliary tuberculosis. This is more common in young children in whom it is seen as a complication of primary tuberculosis. Post-primary tuberculosis may also lead to hematogenous spread when the general resistance is low.

Pathogenesis and Pathology

Entry of the bacilli into the blood stream is through lymphatics or by erosion of blood vessels by caseating lesions. Areas of caseous vasculitis (Weigert's foci) occurring in veins or arteries may result in the discharge of bacilli into the circulation. Numerous tubercles develop in the affected tissues. These coalesce to form multiple lesions of the size of millet seeds. All organs are affected, especially the lungs, liver, spleen, kidneys, meninges, brain, bones and joints, intestines, skin, choroid of the eye, and serous membranes. The lesions may become confluent with the progress of the disease.

Clinical Features and Diagnosis

Majority of cases present varying grades of pyrexia. Localizing signs may not be evident in the beginning. In some cases meningitis and in a few others pneumothorax or pneumomediastinum may be the presenting manifestation. About one-third of the cases show enlargement of the liver and spleen. Generalized lymphadenopathy may occur. The lymph nodes are small or moderately enlarged in size, and discrete. Choroid tubercles may occur rarely.

Evidence of an underlying tuberculous lesion may be present in a few cases, but this is more an exception than the rule.

Diagnosis

Clinically the diagnosis of miliary tuberculosis should be considered in the differential diagnosis of fevers, especially so in children. Skiagrams of the chest are most helpful. This shows numerous, small rounded shadows—the miliary mottling. The upper lobes are more affected and this helps to distinguish miliary tuberculosis from other conditions such as pulmonary hemosiderosis, eosinophilia, disseminated carcinoma, pneumoconiosis, sarcoidosis, and histoplasmosis in which mottling of the lungs is more prominent in the lower zones. There is no characteristic abnormality on blood examination. Sputum examination is often unrewarding. Tuberculin test may be positive only in some cases. Histologically, the diagnosis may be made through biopsy of tissues like the liver, lungs or bone marrow (trephine biopsy). Choroid tubercles are diagnostic if they occur, but in Indian subjects they are only rarely found.

Treatment

Standard chemotherapy has to be started early and in most cases the condition dramatically improves within weeks. Corticosteroids may be given along with full anti-tuberculosis treatment to reduce toxemia in severe cases. Results of treatment, if started early, are excellent and complete resolution is the rule.

TUBERCULOUS MENINGITIS

About 25 to 30% of the total number of cases of meningitis seen in many hospitals in India were presumed to be due to tuberculosis. Children suffer from this disease most, but all age groups can be affected. The proportion of tuberculous meningitis is coming down (See also Chapter 188).

Pathogenesis and Pathology

Tuberculous meningitis develops commonly as a complication of miliary tuberculosis. The organisms reach the central nervous system in the blood stream. The other source of infection is rupture of a subcortical caseous focus. Small granulomas are formed in the superficial layers of the brain (*'Rich foci'*). Bacilli reach the subarachnoid space from these lesions and set up leptomeningitis. Tubercles are formed most commonly at the base of the brain and along the cerebral vessels. There is increased production of CSF. Adhesions develop in the base of the brain and these block the foramina. The CSF pressure is increased. Autopsy reveals thickening and cloudiness of the pia and arachnoid. The surface shows a

creamy white exudate. In advanced disease the whole of the base of the brain may be covered by thick granulation tissue, which envelops the cranial nerves and the major arteries. The cerebral vessels may develop endarteritis obliterans and thrombosis. This may lead to cerebral infarcts. Surfaces of the cerebral hemispheres and the choroid plexuses may show tubercles. The inflammation spreads to the inner lining of the cerebral ventricles as well.

Clinical Features

The onset is generally insidious with vague ill-health. The child may show nonspecific symptoms like fever, restlessness, irritability, vomiting and loss of appetite. In others, the onset may be acute with convulsions, high fever and signs of intracranial tension. A few cases develop abnormality of behaviour which may progress to stupor and coma. Death occurs in 4 to 8 weeks in untreated cases.

Physical findings depend on the stage at which the patient is first seen. Signs of meningeal irritation may not be evident in very early stages, but soon these become obvious. Neck stiffness is less prominent in younger children. Complications such as cranial nerve palsies, hemiplegia or monoplegia may be evident. Papilledema may be present in some. An acute presentation resembling purulent or aseptic meningitis is not rare. In a few cases the onset may be with brainstem involvement and acute pulmonary edema. Other features of miliary tuberculosis may be evident, especially in children.

Complications

Complications are invariably present in those cases which are seen late in the disease. Acute complications include internal hydrocephalus, cerebral infarction, cranial nerve palsies, convulsions, fluid and electrolyte disturbances and bed sores. The chronic complications are obstructive hydrocephalus, optic atrophy, subdural effusions, diffuse or localized spinal arachnoiditis, spinal cord compression and the development of tuberculoma in the brain and spinal cord (Fig. 49.5). In cases where treatment is delayed for four weeks or more, focal paralysis, intellectual impairment, epilepsy, hypothalamic disturbances and intracranial calcification may persist as sequelae. The overall mortality in large series varies from 10-15%.

Diagnosis

Early diagnosis is possible only if the clinical suspicion is strong. History of contact with tuberculous cases, evidence of miliary tuberculosis and the presence of choroidal tubercles should suggest the underlying cause. The clinical picture of advanced disease is that of a child, dehydrated, lying in opisthotonus with the typical

meningitic cry. This picture is rarely seen now. Differential diagnosis includes other forms of meningitis, encephalitis, acute or subacute demyelinating lesions, cerebral space occupying lesions such as brain abscess, subdural hematoma or tumors, leukemic and carcinomatous meningitis, and all other conditions causing coma.

Meningitis is diagnosed by examination of the CSF. **Lumbar puncture** should be done as early as possible on suspecting the diagnosis. If lumbar puncture fails due to spinal block, CSF should be obtained by cisternal puncture or ventricular puncture. Examination of the CSF shows rise in pressure, turbidity, and a rise in lymphocytes upto 500-1000 cells/cmm. A mixed pleocytosis may occur in some rare cases. A Fine coagulum ('cobweb') forms in the CSF when kept at room temperature for 6-24 hrs. Though this is highly suggestive of tuberculous meningitis, it may rarely be seen in other types of meningitis as well. Proteins are moderately increased up to 200-300 mg/dL. Sugar is reduced to less than 50% of the blood sugar. In severe cases the depression of CSF sugar is even more marked. The chlorides are diminished, as a part of generalized hypochloremia due to electrolyte losses. With meticulous care, *M. tuberculosis* may be demonstrable by culture and animal inoculation in up to 50% of cases. Acid fast bacilli (AFB) may be demonstrable in the cobweb in about 15-20% of cases.

Tuberculous meningitis has to be distinguished from other forms of meningitis. In purulent meningitis the CSF shows neutrophil predominance and the organism may be demonstrable by Gram stain. Cryptococcal meningitis may closely resemble tuberculous meningitis. The fungus is demonstrable in CSF by India ink staining.

In partially-treated purulent meningitis the CSF picture shows mainly lymphocytes. This should not be mistaken for tuberculous meningitis. Leptospirae, viruses, leukemic infiltration and carcinomatosis may all give rise to CSF pleocytosis and biochemical abnormalities. These should be kept in mind.

Treatment

The most important factor deciding a favourable outcome is early institution of chemotherapy. General treatment includes the correction of dehydration and electrolyte imbalance, maintenance of nutrition, good nursing care with special attention to the skin, bladder and bowels, analgesics to relieve headache and anticonvulsants to stop convulsions.

Standard antituberculosis chemotherapy is instituted as early as possible. INH is administered at a higher dose of 12-15 mg per kg (600 mg for an average adult). **Systemic corticosteroids** help to reduce morbidity, especially those due to adhesions and fibrosis and speed up recovery. They are employed after establishing specific chemotherapy. Prednisolone is started at a dose of 0.5 to

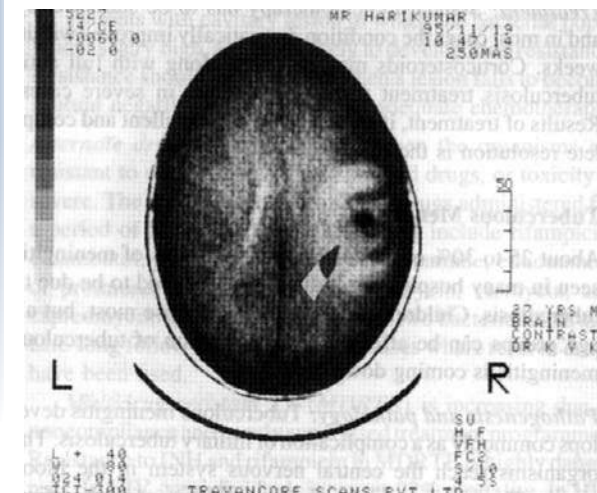


Fig. 49.5: CT scan. Tuberculoma right parietal lobe (see arrowhead). Male aged 26 with epilepsy. Completely cleared with therapy

1 mg/kg and is tapered off in 4-8 weeks. In severe cases dexamethasone in doses of 4-8 mg should be given twice or thrice daily IM or IV till the patient can tolerate oral medication for children the dose is 200-500 mcg/kg bw daily.

The progress is monitored by clinical assessment and also repetition of CSF studies at weekly intervals. When the cell count reaches normal levels, dosage of INH is reduced to 6 mg/kg bw. Thereafter, standard chemotherapy is continued as for pulmonary tuberculosis. The sugar content of CSF is the last to return to normal. Ambulation should be permitted only after the CSF sugar returns to normal.

CT scanning is an excellent method to demonstrate meningitis, obstructive hydrocephalus, presence of tuberculomata and for excluding conditions such as subarachnoid or subdural hemorrhage and primary space occupying lesions. Wherever possible, this facility should be employed for diagnosis, as well as follow-up (Fig. 49.5).

Prognosis

Specific therapy given within two weeks of onset of symptoms gives complete recovery. If treatment is delayed for 4-6 weeks, complications and sequelae may develop. Treatment started beyond six weeks is unrewarding in many cases.

Points to remember

- 1. Despite prolonged efforts over half century, tuberculosis still continues as a major cause of death in India and several other developing countries.
- 2. The main reasons are the high infectivity of the organism, its capacity to remain dormant, need for prolonged multi-drug therapy and the development of drug resistance.

- 3. The HIV epidemic has caused a boost to the incidence and complications of TB all over the world.
- 4. Development of drug resistance is a serum problem which has to be avoided at all costs.
- 5. The government of India has accepted the Revised National Tuberculosis Control Programme (RNTCP) with collaboration from international agencies. The DOTS programme which was developed by WHO with active participation of Indian scientists is the mainstay of TB control.

Further reading API consensus Guidelines 2006. Management of pulmonary tuberculosis, extra pulmonary tuberculosis and tuberculosis in special situations (JAPI 2006;54:219-34).

Non-tuberculous Mycobacteria

Several mycobacteria other than *M. tuberculosis* affect man as opportunistic invaders. These are known by several names such as opportunist mycobacteria, atypical mycobacteria, anonymous mycobacteria and unclassified mycobacteria. Some of these cause pulmonary lesions indistinguishable from tuberculosis, while others involve the lymph nodes, skin or subcutaneous tissues. Superinfection in cystic fibrosis cases is more common

Non tuberculous mycobacteria (NTM) are free living organisms that are widespread in nature (Table 49.2).

Based on their rate of growth and pigment production they are divided into four groups.

Group I—Photochromogenic: The colonies produce a yellow or orange pigment on exposure to light, e.g., *M. kansasii*, *M. marinum*. These have been described from the USA and European countries.

Group II—Scotochromogenic: This group produces yellow, orange or reddish pigment in the dark, e.g., *M. scrofulaceum*. It may give rise to cervical lymphadenitis in children.

TABLE 49.2

Lesions caused by nontuberculous mycobacteria

<i>M. marinum</i> (swimming pool bacillus, fish tank bacillus)	Ulceration of skin
<i>M. ulcerans</i>	Extensive ulceration of skin and subcutaneous tissue (Buruli ulcer)
<i>M. kansasii</i>	Pulmonary disease, local abscesses
<i>M. scrofulaceum</i>	Bone and joint lesions, lymphadenopathy
<i>M. chelonae</i>	Pulmonary disease, local abscesses
<i>M. fortuitum</i>	Furunculosis
<i>M. avium intracellulare</i>	Lymphadenopathy, pulmonary lesions, AIDS related and non-AIDS related disseminated lesions

Group III—Nonchromogenic: This group does not produce pigment on exposure to light, e.g., *M. avium intracellulare*, *M. ulcerans*.

Group IV—Rapidly growing mycobacteria: These organisms grow rapidly at 25°C, e.g., *M. fortuitum*, *M. chelonae*.

***Mycobacterium avium intracellulare* complex** consists of two distinct, but closely related mycobacteria.

Mycobacterium avium was described in chickens in 1890 referred to as avium tubercle bacillus. *M. intracellulare* was first cultured in 1969 from the sputum of tuberculosis patients at the Battey state hospital in Rome, Georgia USA. *M. avium intracellulare* complex is ubiquitous, isolated from all parts of the world from soil, house dust, fresh water plants, animal foods, bedding, chickens and other birds. *M. avium* complex grows slowly. They are nonphotochromogenic, smooth, cream coloured colonies unlike *M. tuberculosis* which produces rough flat dry colonies. In AIDS patients, *M. avium* complex organisms may show plasmid induced virulence and the colonies may be rough.

Treatment

Mycobacterium avium complex are very common pathogens in advanced AIDS and they produce infection and bacteremia. Clarithromycin 500 mg b.d. oral is an excellent drug to treat *M. avium* complex.

A three drug combination using rifabutin 600 mg/day, ethambutol 15 mg/kg/bw/day and clarithromycin 1000 mg has been found to be effective in producing resolution of lesions in 70% of cases. Rifabutin produces uveitis in high doses. Adverse effects of clarithromycin include taste perversion and rectal problems. Clarithromycin is effective as prophylactic in AIDS patients with CD4+ below 50/cmm.

Infection by these bacteria also leads to tuberculin sensitivity. Person to person spread of organisms does not generally occur.

In immunocompromised subjects, these mycobacteria cause extensive disseminated lesions. Various regimens based on one or more of the following drugs have given fully or partly successful results. Treatment consists of a combination of a macrolide such as clarithromycin or azithromycin with ethambutol and rifabutin given for six months or longer.

Leprosy

K.V. Krishna Das, Usha Vaidhyathan

Syn: Hansen's disease

GENERAL CONSIDERATIONS

Leprosy is a chronic communicable disease caused by *Mycobacterium leprae*. Mainly the nerves and skin are

affected but it may also involve mucous membranes and other internal organs. Gerhard Henrik Armauer Hansen identified the organism in 1873 and so the disease is named after him.

Leprosy has been known to affect mankind from biblical times. At present it is common in tropical regions of Asia, Africa, and Central and South America. Low standards of living, poverty and overcrowding favor its transmission and prevalence. But the disease is not confined to this group. Persons belonging to all socioeconomic groups may be affected.

By global efforts initiated by WHO, the prevalence and incidence of leprosy has been brought down considerably. Whereas the WHO figures for leprosy patients worldwide was 10-12 million in 1985, it came down to 1.15 million in 1997 with an annual incidence of 5.6 lakhs. The incidence of childhood leprosy cases has not fallen proportional to that of adults. In India, the prevalence has fallen from 57/10000 population in 1981 to 5.8/10000 in 1997. Of the 408000 people diagnosed as leprosy globally, 2 60 000 cases are in India, in 2004. Now 9 countries including India and Nepal have prevalence of 1/10 000. The term elimination is defined as a prevalence of <1/10 000 population. WHO accepted eradication of leprosy by 2000 AD as possible goal which is not achieved yet.

The Organism

Mycobacterium leprae is a rod-shaped, gram-positive, acid-fast bacillus varying in size from 1.8 to 2.5 µm in length. It is less acid fast than *M. tuberculosis*. 5% sulphuric acid is used for decolorization and staining by Ziehl-Neelsen method. The bacterial morphology helps in assessing the viability and the effects of drug therapy. Viable bacilli appear as regular rods. Bacilli which appear irregular and granular are probably dead. *Mycobacterium leprae* is grown experimentally in the foot pads of mice and in the nine-banded armadillo. *M. leprae* multiplies maximally at a temperature of 27-30°C. Consequently, the infection is maximum in the cooler parts of the body (i.e.) 34-35°C. The organisms infect the skin, cutaneous nerves, peripheral and autonomic nerves.

Transmission

Portal of entry is through abrasions in the skin or mucous membranes of the upper respiratory tract. Untreated subjects with lepromatous leprosy shed numerous bacilli in nasal discharges and minor abrasions in the skin even before they are clinically detectable. Other possible sources of spread such as insect vectors have also been incriminated but not proved.

The incubation period is ordinarily 2-7 years, but this may vary from a few months to 30 years. The mean incubation period for tuberculoid leprosy is 4 years and

for lepromatous is about 10 years. Since man has natural immunity against lepra bacilli, lesions do not develop in the majority of cases, or they remain subclinical. The clinical disease manifests in 1/350 of those infected with the organisms in endemic areas. Adults are more resistant, but 30% of children living in intimate contact with infective cases develop early lesions. In most of them the lesions heal spontaneously. Chronic progressive disease develops only in about 8% cases. Majority of the patients initially present with the disease within the first three decades of life. In lepromatous leprosy, males are twice more commonly affected than women, but in tuberculoid leprosy such a predilection is not noted.

Irrespective of the virulence of the infecting organism, the clinical outcome is so varied, depending on the immune status of the individual which is the deciding factor in pathogenesis. Both cellular and humoral immune mechanisms operate. The cellular immunity is protective, whereas the humoral antibodies are not. Cell-mediated immunity (CMI) which develops against the lipid components of *M. leprae* determines the progress of the disease. Based on the immune response, a wide clinical spectrum varying from the well-localized tuberculoid leprosy to the generalized lepromatous leprosy may be encountered.

The two polar forms are the lepromatous and tuberculoid types. Borderline leprosy denotes the variable clinical patterns seen in between the two polar forms.

PATHOLOGY

During the early stages of infection the clinical and histological changes are non-specific. The dermal nerve twigs show infiltration with round cells and histiocytes. *M. leprae* has tropism for laminin 2, a component of Schwann's cells, which are present in peripheral nerves. Mycobacteria may be seen in nerves and muscles of the skin and this is diagnostic. This stage is known as the *indeterminate stage* since it is not possible to predict the clinical outcome at this stage. The lesion heals due to natural resistance in 75% of cases. In those with progression of lesions tuberculoid lesions develop in the presence of good immunity whereas lepromatous lesions develop in its absence.

Tuberculoid Leprosy

This type is characterized by well-localized granulomatous lesions in and around the nerves. The cells are derived by the mobilization of phagocytic macrophages which are transformed into epithelioid and giant cells. These are surrounded by lymphocytic infiltration. This granuloma extends into the epidermis. The dermal nerves are destroyed by the cellular infiltration. Caseation is rarely seen in the nerves. The bacilli are very few and are not

generally demonstrable in these lesions. Such patients are non-infective.

Lepromatous Leprosy

In contrast to tuberculoid leprosy, lepromatous lesions teem with organisms. Mononuclear phagocytes ingest the organisms which multiply within and fill them completely. These bacterial masses are called *globi* and such cells are called *lepra cells*. Their cytoplasm is foamy. Lymphocytes are only a few or absent. There is no attempt at tubercle formation. The dermis is infiltrated throughout its entire thickness. The nerves, erector pili muscles, and endothelial lining of blood vessels also show similar changes. The epidermis is spared and a clear cell-free zone exists below the epidermis. The organisms are disseminated through the blood stream to other parts of the skin and organs such as eyes, respiratory mucosa, testes, liver, kidneys and muscles of the hands, feet and face. As a late complication amyloidosis may develop.

Borderline Leprosy

When the immunity is variable, borderline leprosy develops in which the histological picture tends to vary. With good cell-mediated immunity, the picture resembles tuberculoid leprosy, and this is called '*borderline tuberculoid*' (BT). There is differentiation of mononuclear phagocytes into epithelioid cells, but giant cells are not common. Lymphocytes are usually present but do not show tubercle formation. The subepidermal zone is clear and nerves are infiltrated but are still recognizable.

When the immunity wanes the picture resembles that of lepromatous leprosy and this is called *borderline lepromatous* (BL).

In peripheral neuropathy occurring in leprosy, the nerves are damaged mainly by the cellular reaction to the components of dead bacilli.

The lepromin test: The lepromin skin test detects delayed hypersensitivity. It is positive in tuberculoid and negative in lepromatous type. This test was in vogue for diagnosis and prognosis. This is seldom used now.

CLINICAL FEATURES

Indeterminate Leprosy

The disease starts with a single lesion or a few multiple lesions which appear as small hypopigmented or erythematous macules. Careful testing may reveal hyperesthesia, paresthesia, hypoesthesia or hypoalgesia. At this stage nerve trunks are not thickened. Slit skin smears are usually negative for acid-fast bacilli. Lepromin reaction may be negative or doubtfully positive. Evolution into the polar forms takes a long time after infection. In the early stage, which is known as indeterminate leprosy,

the distinctive features are absent. Though diagnosis is possible, it is difficult to predict the clinical outcome and the type.

Tuberculoid Leprosy (TL)

In this form the skin lesions are only a few (3 or less) and they vary in size. They are hypopigmented or erythematous and the margins are well-defined. The lesions may be flat or raised. Either the entire lesion or only the margins may be elevated. The surface is dry, rough, and anhidrotic. By this time the temperature and pain sensations are impaired. Nerve trunks, especially in the vicinity of the raised lesions, are palpably thickened. Supraorbital and great auricular nerves in the head and neck, ulnar, cutaneous branch of radial, the main radial and median nerve in the upper limb, and lateral popliteal (common peroneal), posterior tibial, musculocutaneous and sural nerve in the lower limbs are the common nerves palpated. Facial palsy manifesting over parts of the face either on one or both sides may develop. Slit skin smear does not show acid-fast bacilli and lepromin test is positive. Early lesions may heal spontaneously without complications. More advanced lesions also heal ultimately, but residual damage to nerves may occur due to reactions, which complicate the illness (Figs 49.7 to 49.11).

Lepromatous Leprosy (LL)

In this form the bacilli spread rapidly from the skin, both by local extension and through the blood stream, to other parts of the body. Extensive involvement of nerves, mucosa of the upper respiratory tract and the internal



Fig. 49.7: Hansen's disease- borderline tuberculoid



Fig. 49.8: Nerve thickening in Hansen's- great auricular nerves



Fig. 49.6: Hansen's disease- Lepromatous leprosy

organs occurs. Eyes, testes, lymph nodes, marrow of the phalanges, superficially placed muscles, liver, spleen and kidney may all be affected in varying degrees.

The morphology of the skin lesions depends upon the stage of the disease. Early lesions are flat, smooth, shiny, hypopigmented or coppery red, with ill-defined margins (Fig. 49.6). Numerous small lesions are distributed symmetrically. The entire body surface may be involved except certain areas like the axilla, groin and the flexor aspects of the limbs. In dark subjects they may be inconspicuous and can be made out only by careful search. Early lesions do not show sensory loss. As the disease progresses, papules and nodules appear especially on the ears and face. The eyebrows are lost. The facies is described as leonine and this is caused by infiltration and thickening of skin of the face. The mucosal lesion leads to ulceration of the nose, mouth, trachea and larynx. Nasal



Fig. 49.9: Ulnar palsy and muscle wasting in Hansen's disease



Fig. 49.10: Plantar ulcer in Hansen's disease due to peripheral neuropathy

(Figs 49.6 to 49.10 were provided by Dr Pradeep S Nair, Assistant Professor, Dermatology, Medical College, Trivandrum)



Fig. 49.11: Ulnar palsy in Hansen's disease

discharge teems with the bacilli. Nasal bones may be destroyed resulting in deformity of the nose. Involvement of the premaxilla leads to loss of the upper incisors.

Clinical evidence of nerve damage occurs late in lepromatous leprosy. The nerve trunks are symmetrically enlarged and soft to feel. Dorsal aspects of the forearms and legs show anesthesia and anhidrosis. Gradually

anesthesia spreads over the whole body except the palms, soles, axillae and groins. Motor weakness follows further nerve damage. Tendon reflexes are preserved till late stages. Paradoxically, the wasted muscles may be hyper-reflexic. In addition to neural damage, muscular dysfunction may result from direct invasion of the muscles by the bacilli. Affection of the testes gives rise to impotence and enlargement of the breasts.

Ocular involvement may occur by extension from the skin or by hematogenous spread. Common lesions include miliary lepromata on the iris and superficial punctate keratitis. All parts of the eye except the retina may be affected.

Lepromatous leprosy progresses relentlessly if left untreated, crippling the victim further and leading to mutilation. Progression of the disease can be arrested with treatment, though complete clearance of bacilli is difficult to achieve.

Lucio Leprosy

This is a special type of diffuse lepromatous leprosy originally described from Mexico, but it is also seen in other areas. The whole skin becomes smooth and stiff with loss of body hair, especially on the eyebrows. Slit skin smears are always positive for the organisms.

Borderline Leprosy

In this form the clinical picture truly reflects the absence of localization seen in histology. Skin lesions are numerous, which are asymmetrical, varying in size and shape. The flat lesions are not as well-defined as in tuberculoid leprosy. The margins may be entire or deficient in places and they slope outwards to the periphery. Satellite lesions may be present. Papules and nodules form only rarely, and would show central dimpling when they occur. The involvement of nerves is more widespread than in tuberculoid disease. Nerve damage is earlier in onset than in lepromatous disease. Bacillary count and the lepromin test are variable. Spontaneous healing is uncommon except in the very early stage. Improvement in the immune status converts the disease into the tuberculoid form with tendency to heal. Loss of immunity downgrades the lesion to the lepromatous type with its characteristic features, but nerve damage is seen in addition. Borderline leprosy can be further subclassified into borderline tuberculoid (BT), mid-spectrum borderline (BB), and borderline lepromatous (BL) based on the bacterial index and lepromin test.

Pure Neuritic Leprosy

Though in all forms of leprosy the nerves are the first targets of attack, sooner or later the lesions extend into the skin. In some patients only nerve involvement is seen

without any perceptible skin lesions. This form is called pure neuritic leprosy. Clinically, the presentation is with the affection of single or multiple large nerve trunks. The nerves are enlarged, firm and tender. Both sensory and motor abnormalities are demonstrable. The affected parts are usually negative for bacilli. Lepromin test is generally positive but it may be doubtful or negative in some. Definite diagnosis of this stage can be made only by nerve biopsy. Autonomic nerves may be affected.

Main causes of tissue damage in leprosy

1. Bacillary infiltration—lepomatous leprosy
2. Peripheral neuritis—loss of sensory, motor and autonomic functions.
3. Reactions in leprosy.

REACTIONS IN LEPROSY (LEPRA REACTION)

Episodes of acute inflammation (called reactions) occur during the course of leprosy. In some patients occurrence of a reaction may be the precipitating event to seek medical help. Immune reactions may be caused either by delayed hypersensitivity (*Jopling type 1 reactions*) or to the formation of antigen antibody complexes—(*Jopling type 2 reactions, erythema nodosum leprosum*).

Type 1 reaction occurs in patients with borderline leprosy cases. There is a sudden change in cellular hypersensitivity. These reactions may be spontaneous or precipitated by therapy occurring within six months.

Existing lesions increase in size and severity and may become erythematous, edematous and tender. New lesions may develop. The nerves become swollen, painful and tender, and nerve abscesses may form. The neurological deficit may increase. Edema of feet, hands and face may occur. Constitutional symptoms like fever are rare.

Type 2 reaction is caused by vasculitis resulting from the deposition of immune complexes, without a shift along the immunological spectrum. This type of reaction is seen in about one half of the patients with lepomatous leprosy and one fourth with borderline leprosy. Commonly this reaction occurs during the second year of treatment. These reactions may be associated with the appearance of tender erythematous nodules, which are called *erythema nodosum leprosum* (ENL). Type 2 reactions are characterized by general inflammatory phenomena such as fever, rigor, pain and tenderness in the skin and nerves, arthritis, lymphadenopathy, iritis and keratitis. Further damage to nerves and eyes may develop and repeated reactions aggravate the disability.

Lucio Phenomenon

This is a severe form of type 2 reaction occurring in lucio leprosy. It is characterized by the formation of erythe-

matous macules which become purpuric or ulcerated. Later they heal with atrophic scarring.

DIAGNOSIS

The diagnosis of leprosy is based on clinical signs and symptoms. A case of leprosy is defined as a person having one or more of the following features, and who has yet to complete a full course of treatment.

1. Hypopigmented or reddish skin lesion(s) with definite loss of sensation.
2. Involvement of the peripheral nerves, as demonstrated by definite thickening with loss of sensation.
3. Demonstration of acid-fast bacilli in skin lesions by standard slit skin smears or histological diagnosis of granuloma affecting the nerves.

Demonstration of *M. leprae* in the skin is by preparing a slit skin smear from the ear lobe or other areas by scraping the subepidermal tissue through a small incision. The material is stained by modified *Ziehl-Neelsen method*. *The disease should not be diagnosed if only nerve thickening is present, without any other accompanying symptoms or signs.*

Quantitative estimation of the bacterial count is obtained by noting the density of the bacilli in the smear which is recorded as the *bacterial index*. Presence of many clumps of bacilli in an average field is recorded as 6+ whereas presence of 1 to 10 bacilli in hundred fields is recorded as 1+. In addition, the morphology of the bacilli enables the observer to assess their viability. This morphological index is used for recording progress with treatment. Nasal mucosa shows organisms and nasal smears give an idea of the infectivity of the patient. In borderline leprosy *M. leprae* are scanty and in tuberculoid leprosy they are not present in skin smears.

None of the cardinal diagnostic criteria like sensory changes, thickened nerves or organisms may be present in indeterminate leprosy. A high index of suspicion and familiarity with the early signs and symptoms are the only factors which help to diagnose this stage. Diagnosis has to be confirmed by the demonstration of *M. leprae* inside nerves or erector pili muscle.

Differential Diagnosis of the Skin Lesions

Many other common skin conditions give rise to macular lesions. These are pityriasis alba, tinea versicolor, nutritional dyschromias, birth marks and early vitiligo. Raised lesions or plaques have to be differentiated from fungus infections, cutaneous tuberculosis, lupus erythematosus, and lichen simplex. Psoriasis and lichen planus do not give rise to problems in diagnosis due to their distinctive features. Post kala-azar dermal leishmaniasis has to be distinguished from lepomatous leprosy. Reaction in leprosy may be mistaken for other

forms of vasculitis as in systemic lupus erythematosus or polyarteritis nodosa. Other conditions that produce localized sensory loss are entrapment neuropathies and injury to peripheral nerves. Rarely nerves may be thickened, in hypertrophic polyneuritis, Refsum's disease, amyloidosis, and traumatic neuromas.

MANAGEMENT

The clinical diagnosis of leprosy should always be confirmed by the laboratory tests, before starting treatment, in view of the socioeconomic and psychological implications. The lepromin test is seldom done for clinical purposes because clinical differentiation along with bacteriological and histological diagnosis is quite satisfactory for management. Education of the patient on the nature of the disease, outcome of treatment, and measures to avoid spread is absolutely essential for success.

General Treatment

This includes measures to improve general health and treatment of intercurrent illness.

Chemotherapy

At present six effective antileprosy drugs are available. Among these, dapsone, rifampicin and clofazimine are used in standard regimens. The others which are used in special situations include minocycline, ofloxacin and clarithromycin. None of these should be used as monotherapy.

Dapsone: The time honored and basic drug for the treatment is dapsone. The drug is inexpensive and relatively non-toxic in the doses used. Delayed hypersensitivity reactions and less commonly agranulocytosis have been reported. Mild hemolytic anemia is common, but severe anemia is rare except in glucose 6 phosphate dehydrogenase deficiency. The drug is cumulative in the system. Dapsone is weakly bactericidal in a dose of 100 mg daily. Dapsone in combination with clofazimine kills more than 99.999% of *M. leprae* within 3 months. This suggests that the rifampicin-resistant mutants in an untreated patient with LL are likely to be eliminated by 3-6 months of treatment with dapsone - clofazimine component of the standard MDT regimen.

Rifampicin: Rifampicin is the most powerful bactericidal drug against *M. leprae* and three monthly doses of 600 mg kills 99.999% of viable *M. leprae*. It is relatively nontoxic, although occasional cases of renal failure, thrombocytopenia, influenza-like syndrome and hepatitis have been reported.

Clofazimine: Clofazimine is bacteriostatic when given in a dose of 50 mg a day. It has also got anti-inflammatory

properties in high doses. Pigmentation of the skin is common but it clears completely after treatment is discontinued. Higher doses may cause gastrointestinal symptoms.

Though most of the patients are rendered non-infectious within a few weeks, clinical improvement may not be apparent for several months. Complete resolution may take a few years.

Clinical Classification for Control Programs

The WHO expert committee concluded that patients could be classified into three groups

Paucibacillary single lesion leprosy (one skin lesion)

Paucibacillary leprosy (2-5 skin lesions)

Multibacillary leprosy (more than five skin lesions)

When classification is in doubt, the patient should be treated as having multibacillary leprosy. All smear positive cases should be treated as multibacillary leprosy.

The bacillary load in paucibacillary cases is of the order of 6 logs whereas in multibacillary cases it is 11 logs or more.

Standard Multi Drug Therapy (MDT) regimens: (Seventh report of the WHO expert committee on leprosy- 1998)

Paucibacillary cases: (for adults)

Rifampicin 600 mg once a month, supervised,

Dapsone 100 mg daily, self administered.

Duration- 6 months

Multibacillary Cases: (for adults)

Rifampicin 600 mg once a month, supervised

Dapsone 100 mg daily self administered

Clofazimine 300 mg once a month, supervised and 50 mg daily self administered.

Duration - 24 months.

Children should receive appropriately reduced doses of the above drugs. Multibacillary patients should complete 24 monthly doses within a 36 month period and paucibacillary patients, 6 monthly doses within a 9-month period. Patients should receive their drugs in monthly, calendar blister packs.

The possibility of further shortening the duration of MDT is being evaluated. On the basis of many large trials, it is possible that the duration of the current MDT regimen for multibacillary leprosy could be further shortened to 12 months without increasing the risk of developing resistance to rifampicin.

A patient who relapses should be treated with a further course of MDT. A defaulter is a patient who started MDT but who has not received treatment for 12 months. If such a patient returns to the health center for treatment, and shows signs of active disease, he should be given a new

course of MDT. In the absence of activity, there is no need to re-start MDT and the patient should be educated to report promptly on the appearance of any of these signs.

Once treatment is started, there is rapid clearance of the organisms from the nose. Therefore isolation is not necessary. Rifampicin, dapsone and clofazimine are safe during pregnancy.

Alternative MDT Regimens

1. A single dose of rifampicin 600 mg, ofloxacin 400 mg and minocycline 100 mg (ROM) is an acceptable and cost effective alternative regimen for the treatment of patients with single lesion paucibacillary leprosy.
2. For patients who do not tolerate clofazimine, ofloxacin or minocycline could be used as substitutes for clofazimine. An alternative regimen is to give monthly doses of ROM for 24 months
3. Patients harbouring rifampicin resistant *M. leprae* are very often resistant to dapsone and their treatment depends on clofazimine. The recommended regimen for adults (multibacillary cases) is daily administration of 50 mg of clofazimine together with ofloxacin and minocycline for 6 months. For at least an additional 18 months, clofazimine with either minocycline or ofloxacin should be administered.

Treatment of Reactions

In reactions the specific anti-leprosy treatment is continued unchanged unless there are compelling reasons to discontinue it.

Because of the high-risk of permanent damage to the peripheral nerve trunks, *type 1 reaction* (reversal reaction) needs to be diagnosed as soon as possible and treated adequately. Prednisolone is the drug of choice. To begin with, 40-60 mg of prednisolone is given daily and gradually tapered (over 12 weeks) weekly or fortnightly and eventually stopped.

Type 2 reactions vary in severity, duration and organ involvement. Mild Erythema Nodosum Leprosum (ENL) can be treated with analgesic or antipyretic drugs such as aspirin, while severe reactions with neuritis should be treated with prednisolone. Thalidomide, 100 mg three to four times daily is also effective for the treatment of severe ENL. It should be used only in male or post menopausal female patients who have become dependent on corticosteroids and must be given only under close medical supervision.

Clofazimine in a dose of 300 mg daily in divided doses is also effective for ENL but is less potent than corticosteroids and often takes 4-6 weeks to develop its full effects. So it should never be started as the sole agent for the treatment of severe ENL. The total duration of high dose clofazimine therapy should not exceed 12 months.

Other Measures

Splinting and physiotherapy help to prevent nerve damage and its sequelae. Care of hands and feet, protective footwear, physiotherapy and rehabilitation are integral parts of patient care in subjects with sensory loss.

PREVENTION AND CONTROL

BCG offers variable protection against leprosy in different countries, ranging from 34-80%. The reliable way to control the spread of leprosy in contacts is regular 6 monthly examinations. Close contacts with high-risk of transmission can be given chemoprophylaxis with 15 mg/kg rifampicin once a month for 6 months.

Early diagnosis and treatment are the sure ways to arrest the disease, prevent spread and avoid disability. Educating the public, increasing the awareness of the problem and eliminating the social stigma through propaganda have helped to implement mass programs and prevent spread.

Rehabilitation of the disabled patient is to be undertaken along with curative measures. This includes surgical correction of deformities, plastic surgery especially of the hand to make the hands more functional, avoidance of burn injuries to hands and feet, protection of the eyes from exposure keratitis and other community measures needed to ensure social rehabilitation.

The national leprosy control program: This was launched in India in 1955. This program emphasized the need for health education. Centers were established for survey, education, and training (SET centers) in areas of high endemicity, for early detection and mass treatment. In addition, training and research centers for leprosy were established at different parts of the country. This program was redesignated *National leprosy eradication program* (NLEP) in 1982. More than 250 non-governmental organizations are active in India working for prevention of leprosy and offering other services to the victims.

Points to remember

1. India still harbours a large number of leprosy patients though, the incidence and prevalence have dropped considerably.
2. Infection is spread by nasal droplets and through cuts in skin and mucous membranes
3. Manifestation depends upon the degree of CMI.
4. Diagnosis is clinical and by demonstration of *M. leprae* by slit skin smears.
5. Treatment is with rifampicin, dapsone and clofazimine.
6. National and international programmes are afoot to eradicate the disease.

Further reading: JI Ind Medical Assn 2006;104(12) special number on Leprosy.

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Psittacosis

K.V. Krishna Das

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Chlamydia—General Considerations

Chlamydiae are small gram-ve organisms which remain intracellular. They have both DNA and RNA. They possess cell wall and divide by binary fission. They have a unique biphasic life cycle with dimorphic forms which are functionally and morphologically distinct.

Life Cycle

The elementary body (EB) is an infectious but metabolically inactive form which attaches to the epithelial cell surface and enters the cell by endocytosis. Once endocytosed it differentiates into a larger pleomorphic form called reticular body (RB) and remains inside a membrane bound vacuole thereby evading phagolysosomal fusion. Once inside the cell they interrupt the metabolic processes of the host cells and utilize them for their own metabolism and replication. These processes are not yet fully understood. Antigenically they are complex, possessing antigens of genus, species and serotype specificity.

The human pathogens include the species *Chlamydia trachomatis*, *Ch. pneumoniae* and *Ch. psittaci*.

Psittacosis

Syn: Parrot fever

Definition

Psittacosis is an infectious disease caused by the organism *Chlamydia psittaci* which is a primary pathogen of birds. *Chlamydia psittaci* is a gram-negative obligate intracellular parasite.

Epidemiology

The disease is present all over the world. Psittacine birds (parrots, parakeets, cockatoots) are commonly affected,

Spectrum of human diseases caused by Chlamydiae

	Acute lesions	Chronic lesions
<i>Chlamydia trachomatis</i> serovar A to C	Conjunctivitis	Trachoma
do—serovar D to K	Urethritis	Proctitis, pelvic inflammatory disease, urethritis, Reiter's syndrome, tubal obstruction epididymoorchitis
do—LGV serovars	Lymphogranuloma venereum	Multiple sinuses esthiomene
<i>C. pneumoniae</i>	Pharyngitis, sinusitis, bronchitis, community acquired pneumonia	Atherosclerosis asthma
<i>C. psittaci</i> derived from parrots, canaries, pigeons, turkeys, ducks chickens, cats, ewes	Atypical pneumonia, hepatic and renal dysfunction, endocarditis, conjunctivitis abortion	

but all types of birds may suffer. Infection in man results from close contact with birds. The organism is present in the feces of infected birds. Humans acquire the infection by inhalation of bird's feces or handling the tissues of infected birds.

Pathology

Chlamydia psittaci reaches the pulmonary alveoli and the reticuloendothelial cells of the spleen and the liver. In the lung patchy consolidation develops. Liver and spleen are enlarged due to congestion. The heart, meninges, and the brain also show congestion. The alveolar exudate is mainly mononuclear.

Clinical Features

The average incubation period is about ten days. The onset is sudden with fever, malaise, sore throat, and intense photophobia. Temperature ranges from 37-39°C. There is relative bradycardia. Tachypnea may occur. There may be cough with scanty mucopurulent sputum. Signs of pulmonary consolidation may be evident. After about 10 days of fever the temperature comes down by lysis. Mortality may reach 20%. Respiratory failure and toxemia are the usual causes of death.

Diagnosis

Psittacosis has to be differentiated from viral pneumonia, typhoid fever, influenza and Q fever. History of contact with birds is the most helpful clue to diagnosis.

In the first few days of the illness the organisms can be isolated from the sputum and blood by inoculation into

mice or into the yolk sac of embryonated eggs or into irradiated cell cultures. Diagnosis can be established by demonstrating antibodies by ELISA or microimmunofluorescence.

Treatment

Tetracycline is very effective. It is given in a dose of 4 g/day for 2 days and then 2 g daily till recovery is complete. Doxycycline 100 po bd up to 3 weeks is a convenient alternative.

Control

Quarantine of birds imported from other countries should be insisted upon and the infected birds should be killed. Carrier state among the birds is reduced by incorporating tetracycline in bird feeds.

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Viral Infections

K.V. Krishna Das

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General Considerations

Most of the viruses are not visible under light microscope. They vary in size from 300 nm to 20 nm. Each virus contains a nucleic acid molecule with either RNA or DNA as its genome. A complete viral particle which contains the genetic material (genome) and the surrounding protective coat which serves as vehicle for its transmission from one cell to another is called a *virion*. Viruses lack enzymes required for the synthesis of their components and for energy metabolism. They are, therefore, dependent on the metabolic pathways and components of their host cells. They are obligate intracellular parasites. They cause lesions in several living organism such as animals, insects,

plants and bacteria. Many viruses may live in their host cells without producing disease but some are pathogenic.

Viral Multiplication

Multiplication of viruses is controlled by the genetic information contained in the viral nucleic acid. Viral multiplication involves six sequential steps. These are: (i) adsorption to the host cell, (ii) entry to the cell, (iii) release of viral nucleic acid into the cell contents, (iv) biosynthesis of viral components, (v) maturation of the virus particles, and (vi) release of numerous virus particles from the host cell.

Viral infection causes demonstrable changes in the host cell such as cytolysis and destruction of the cell. Sometimes the virus may become latent and persist within the cell to be reactivated later. Incorporation of viral nucleic acid into the genome of the host cell may result in malignant transformation. Several cells may fuse together to form giant cells. In the central nervous system demyelination may occur. Many tissues infected by virus

show inclusion bodies within the cytoplasm or the nucleus. These are made up of aggregates of virions at the site of synthesis or these may merely represent products of degeneration caused by virus infection.

Viral Spread

The mechanism of transmission and portal of entry of viruses vary.

Common Routes of Entry

1. Respiratory tract e.g., coryza, influenza, measles and smallpox.
2. Alimentary tract e.g., enteroviruses and hepatitis A and E.
3. Abrasions or wounds on the skin which may be due to animal bites (rabies), arthropod vectors (arboviruses), injection (virus B hepatitis) or abrasions of skin (papilloma virus).
4. Intact conjunctiva (adenovirus and measles).
5. From mother to fetus through the placenta (rubella cytomegalovirus, HIV).
6. From the genital tract, during birth (Herpes simplex virus type II, HIV).

The outcome of infection by a virus depends on its virulence and the resistance of the host. The effects on the host may be divided into specific and nonspecific. Specific response is the production of immunity, while the nonspecific response includes fever and production of interferons. Both humoral and cellular immune responses play their roles in viral infections.

Proteins of the viral capsid stimulate the formation of humoral antibodies which neutralize the virus. They also cause complement mediated lysis of the infected host cells. Although in many cases the antibodies are protective, sometimes these are harmful, causing immune complex type of tissue injury to the renal glomeruli, synovia of joints or the skin. IgA antibodies secreted into the respiratory tract protect against infection by other respiratory viruses. Humoral immunity is vital for recovery from many viral infections, e.g. enterovirus infections. Some viruses like herpes, rubeola and pox stimulate cell-mediated immunity which plays the major role in defence.

Interferons

Interferons are proteid substances produced by the host cells in the early phase of infection. Other stimuli also may stimulate the production of interferons and hence this response is not strictly specific. Interferon protects the cell against the virus by interfering with the translation of viral messenger and thereby inhibiting viral multiplication. The interferons are not virus specific, but they show species specificity. Only interferons produced in human or primate cells have protective effect against human infections.

Viruses show variation in their susceptibility to interferons. Interferons exert their protective role even before humoral antibodies develop. At present interferons are produced commercially by DNA technology.

Laboratory Diagnosis

1. **Isolation of the organism:** Viruses can be isolated by inoculating material removed from the subject at the optimum time, into suitable cell systems like tissue culture media, chick embryos or experimental animals. Specimens include throat swabs, sputum, rectal swabs, blood, urine, CSF or vesicle fluid. Since the virus is present in the host in the early part of illness, specimens have to be collected early to isolate the organism. They have to be transported in sterile screw-capped bottles containing Hank's balanced salt solution. Such specimens can be stored at -70°C without affecting the viability of the virus. These methods are mainly used for research purposes at present.
2. **Demonstration of viral inclusions, viruses and viral antigens:** Viral infection used to be diagnosed by the demonstration of inclusion bodies under light microscopy, e.g., rabies and smallpox. At present the viruses can be identified by electron microscopy, e.g., rotavirus in feces.

The presence of viruses or viral antigens in tissues can be demonstrated by immunofluorescence, immunodiffusion, immunoelectron microscopy, radioimmunoassay, countercurrent immunoelectrophoresis and enzyme-linked immunosorbent assay (ELISA) techniques. These methods are being employed increasingly when viral isolation is difficult or impossible.

3. **PCR and other techniques** employed in molecular biology are widely employed to make specific diagnosis. Apart from identifying the virus, these methods also help to quantitate the viral load.
4. **Antibodies against viruses:** These can be demonstrated in the serum of the patient. Paired samples of sera are collected, the first sample in the acute phase and the second sample after an interval of 12-14 days. Humoral antibodies can be demonstrated by techniques such as virus neutralization, complement fixation, hemagglutination inhibition, indirect hemagglutination, immunofluorescence, radioimmunoassay and ELISA. In the acute phase IgM antibodies are formed, which give place to IgG antibodies as the infection becomes chronic, or with the passage of time.

The diagnosis of the viral infection can be confirmed by isolating the virus and demonstrating a four-fold increase in the specific antibody titers in paired samples of serum.

Prevention of Viral Diseases

At present, protection against many viral infections is possible by specific immunization. Live vaccines or inactivated vaccines are used for this purpose. Live vaccines are used in the cases of poliomyelitis (*Sabin's oral vaccine*), yellow fever, measles, mumps and rubella. Killed virus vaccines are used for prevention of rabies (*human diploid cell vaccine and duck embryo vaccine*), poliomyelitis (*Salk vaccine*), Japanese encephalitis and several others.

Passive immunization against diseases such as measles, mumps, rabies and infective hepatitis can be conferred by the use of human gammaglobulin or convalescent sera, early during the incubation period. Hyperimmune serum, which gives better protection, is used for the prevention of rabies.

Specific identification of the viral infection is important since specific methods for prevention and specific antiviral drugs are available.

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Viral Infections of the Respiratory Tract

Coryza, Influenza, Parainfluenza, RSV, SARS, Nipah Virus, Human Metapneumo Virus

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Coryza

Several viruses cause the clinical picture of coryza. Of these, *rhinoviruses* are the most important and common. The disease spreads by droplet infection and the portal of entry is the upper respiratory tract. Epidemics occur in early autumn, mid-winter and spring. Incubation period varies from a few hours to 3 to 4 days. Hyperemia and edema of the mucosa of the nose and rhinopharynx are the early lesions. Copious amounts of watery fluid rich in glycoproteins exude. After a short course the disease spontaneously subsides completely without any residual damage.

Clinical Features

Onset is abrupt with headache, nasal congestion and obstruction. It is followed by sneezing and watery discharge from the nose, which becomes mucopurulent and tenacious later on. Mild fever (37.5-38°C) and muscle pains set in within a few hours. The whole course lasts for 2-3 days. Coryza predisposes to the development of secondary bacterial infection. Physical examination is negative except for nasal congestion, conjunctival injection and pharyngitis. Complications are sinusitis, infection of the lower respiratory tract and otitis media.

Diagnosis

Clinical diagnosis is easy. Secondary bacterial infection should be looked for. Coryza has to be distinguished from allergic rhinitis in which nasal congestion may be prominent. In this, there may be other signs of allergy like pruritus and asthma extending for long periods. The causative organism of coryza can be cultured from throat washings or nasal swabs.

Treatment

Treatment is symptomatic. Confinement to home and avoidance of contact with others help to shorten the course of the illness and limit its spread. Paracetamol 0.5 g given thrice daily provides symptomatic relief of aches and

pains. Medicated inhalations, throat lozenges and decongestant nasal drops are all helpful. Specific protection using vaccines which contain a few strains of rhinoviruses has been attempted on a limited scale.

Influenza

Influenza is a common viral disease which presents as an acute febrile illness. It is caused by three groups of *myxoviruses*, important among them being *Influenza virus A, B and C* which are antigenically different. Influenza A has occurred in pandemics on several occasions. India experienced influenza pandemics in 1781, 1889, 1918, 1957, 1968 and 1977. The pandemic that took place in 1977 was due to H1N1. During these pandemics the antigenicity of the causative organisms has changed due to the development of new mutants. Influenza A, B and C consist of at least four subgroups each. The virus is spherical (80-120 nm in diameter) or filamentous in shape. The virus has a glycoprotein coat possessing hemagglutinin (H) and neuraminidase (N) activity. The subtypes of influenza viruses differ in their surface proteins-Hemagglutinins (H) and neuraminidase (N). The usual human subtypes are H1N1, H1N2 and H3N2. Influenza viruses undergo re-assortment of their genetic material between different influenza viruses and new strains emerge, so that existing vaccines may be ineffective to protect against newer strains.

During epidemics children and the elderly suffer more. Dissemination of the virus occurs more readily when people are crowded together. Infection is through the respiratory tract. Influenza can also occur as inter-pandemic illness. This takes the form of sporadic illness or local outbreaks.

Influenza B causes localized outbreaks in closed communities such as schools, military camps and dormitories. Influenza C leads to human disease only rarely.

Pathology

Virus spreads by the respiratory route. Viral multiplication reaches its peak in 24-72 hours after the onset of the clinical illness. The virus multiplies in cells lining the respiratory tract including the ciliated epithelium, alveolar cells, mucous gland cells and macrophages. The infected cells show degenerative changes like cytoplasmic granulation, vacuolation and swelling. Ultimately the cells undergo necrosis and they slough away. The mucosa is hyperemic and edematous. Focal hemorrhages are common in these sites. Pneumonia may occur primarily due to viral infection, though it is more common to get secondary bacterial pneumonia. In viral pneumonia intra-alveolar hemorrhage may occur. Secondary bacterial infection occurs in about 25% of cases and it gives rise to suppurative inflammation.



Fig. 52.1: X-ray chest pneumonia

Clinical Manifestations

The incubation period ranges from a few to 48 hours. Onset is sudden with fever, severe generalized myalgia and prostration. There is spasmodic non-productive cough. Conjunctiva is injected. Temperature varies from 38°C to 40°C and may last for 3-4 days. In the uncomplicated case there is relative bradycardia. Severe complications may occur in a few, especially at the extremes of age and in debilitated subjects. Mortality is higher in the age groups below 2 years and above 65 years.

Complications

Pulmonary Complications

These include primary influenza virus pneumonia, influenzal pneumonia with secondary bacterial infections, and bacterial pneumonia with multiple organisms (Fig. 52.1).

1. **Primary influenza virus pneumonia:** This is a serious condition associated with high mortality. These subjects present with high fever, cough with blood stained expectoration, dyspnea and cyanosis. Examination of the chest may reveal bilateral rhonchi and crepitations. Pulmonary involvement is diffuse. Fever and respiratory signs persist despite antibiotic therapy and other symptomatic measures. The course is more acute and serious in those cases with rheumatic heart disease, myocardial infarction, or chronic obstructive airway disease.
2. **Influenzal pneumonia with secondary bacterial infection:** In addition to viral pneumonia, localized consolidation may also develop.
3. **Bacterial pneumonia:** The condition is caused by multiple organisms such as *staphylococci*, *H.*

influenzae, group A streptococci, and pneumococci. This type of pneumonia carries a grave prognosis.

Cardiac Complications

Toxic myocarditis may occur. This gives rise to tachycardia and cardiac failure. The ECG may be abnormal.

Neurological Complications

These include febrile convulsions, meningitis, meningo-encephalitis and encephalitis. A rare complication is the development of Reye's syndrome, which is more frequently seen in children. It presents as hepatic failure with encephalopathy and rise in intracranial tension. Reye's syndrome is associated with ingestion of aspirin. Apart from influenza A and B other viruses may also lead to this syndrome, e.g. varicella. Reye's syndrome develops as a result of serious derangement of mitochondrial function.

Diagnosis

The diagnosis is not difficult during an epidemic. Coryza may be mistaken for a mild attack of influenza. Nasal symptoms predominate in coryza but are less marked in influenza.

Adenovirus infection, which may resemble influenza, can be diagnosed by the prominence of sore throat and pharyngitis. Primary atypical pneumonia has to be differentiated from influenza virus pneumonia. In primary atypical pneumonia the sputum is more purulent. It is of gradual onset and the clinical course is milder.

Streptococcal pharyngitis may present as a short duration fever with sore throat. Its incidence is higher in children. Cervical adenitis is present and blood shows neutrophil leucocytosis. The severe pain and bodyache of influenza may be mistaken for dengue fever and sandfly fever.

Specific diagnosis can be made by isolating the virus from throat washings or sputum and by demonstration of four-fold rise in titre of antibodies in paired sera by hemagglutination inhibition test.

Prognosis

The disease runs a benign course without complications in the majority of cases. Uncomplicated cases recover within a week or two. Complications increase the mortality. In many cases convalescence may be prolonged. Generalized vague ill-health may persist for several weeks.

Treatment

Bed rest is essential during the period of illness and during convalescence. If there is secondary bacterial infection, a course of appropriate antibiotics should be given.

Specific drugs include **amantadine**, **rimantadine**, **zanamivir** and **ostelamivir**. These drugs act on the virus in different ways.

Amantadine in a dose of 100 mg given twice daily for 10 to 14 days offers chemoprophylaxis against influenza A virus, but not B. It protects the host cell from virus invasion. These drugs interfere with viral uncoating within the cell. Amantadine and rimantidine reduce the duration of fever by 1-2 days. These are ineffective against avian influenza. Prolonged administration during outbreaks reduces the incidence of fresh infections by 50% and ameliorates the disease in 70-100% of clinical cases. Side effects of amantadine include nausea, headache and neurological features. **Rimantadine** which is an analogue of amantadine is also effective.

Neuraminidase Inhibitors

Neuraminidase promotes influenza virus release from infected cells and facilitates viral spread within the respiratory tract, two neuraminidase inhibitors have been licenced for human use—zanamivir and oseltamivir. Unlike amantadine and rimantadine that target M2 protein of influenza A virus, these inhibit the replication of both of influenza A and B viruses. Zanamivir is given by inhalation due to its low availability when given orally. Oseltamivir is active when given orally. Both the drugs are good for chemoprophylaxis. When given early during the disease they reduce the severity, complications and duration. Compared to amantadine and rimantidine, development of resistance is also less.

Dose: Zanamivir (manufacturers Biote/Glaxo)

Inhalation: 5 mg Zanamivir + (20 mg lactose). After a single inhalation the drug is detectable in sputum for 2-7 days.

Ostelamivir (Tamifin) given in dose of 75 to 150 mg bd orally early in the disease probably controls the infection. Success is directly correlated with earlier administration of the drug. In children the dose is 30 mg bd oral for 5 days. Resistance of the virus to ostelamivir is being reported.

Specific Prevention

Vaccines containing inactivated viruses are available for use during pandemics or epidemics and these offer 90% protection. Since the viral characteristics change from time to time the composition of the vaccine has also to be different at times.

The general direction for the vaccine is given by the WHO, taking into consideration the most prevalent viral strains. Usually the vaccine contains A and B strains. One dose in previously exposed individuals and two doses in unprimed subjects give a 90% protection rate. Mild local and general side effects may occur in a few. Sensitivity to egg protein is a contraindication for the vaccine. Pregnancy is not a contraindication.

AVIAN FLU (INFLUENZA GROUP A H5N1 VIRUS)

The Threat of a Pandemic by the Avian Influenza Virus

The subtype H5 N1 influenza virus is a natural pathogen of chicken, ducks, turkeys and others. Though it was thought to be pathogenic only to them, the subtype H5N1 has crossed over to infect humans and caused small outbreaks. Hong Kong (1977) Thailand, Cambodia, Indonesia and several other Asian countries have reported outbreaks in poultry by H5N1 virus. In India H5N1 virus has been identified in Nawapur and Jalagon in Maharashtra State. As on 26th April 2006 the WHO cases has reported the occurrence of 205 confirmed cases in humans, with 113 deaths (55%). If human to human transmission of the virus becomes efficient, devastating pandemic more severe than the previous ones is likely to breakout. *Hence this matter is of great concern to all nations.*

Pathologically the lesions resemble those of classic influenza, but hemophagocytic histiocytosis may also be seen.

Clinical Features

The incubation period for human influenza viruses is short-2 to 3 days (range 1-7 days). However with influenza A H5N1 the median time between exposure and onset of illness is 3 days (range 2 to 4 days). Most cases have occurred in previously healthy children and young adults. Symptoms of bird flu in humans include fever, cough, and sore throat, pneumonia, acute respiratory distress, and life-threatening complications. The symptoms of bird flu may vary depending on the type of virus. Primary viral pneumonia and multi-organ failure are common. In the present outbreak, more than half of those infected with the virus have died. Death is due to respiratory failure and multi-organ failure especially respiratory, renal and cardiac failure.

Case Definitions

Criteria for suspecting avian flu. Persons with illness characterized by fever, (temperature > 38°C), cough and/or sore throat, severe respiratory symptoms and one or more of the following:

1. contact with a confirmed case of influenza A H5N1 during the infectious period,
2. recent (less than 1 week) visit to a poultry farm in an area known to have outbreaks of HPAI (highly pathogenic avian influenza), or
3. worked in a laboratory that is processing samples from persons or animals suspected to be having HPAI infection.

Procedure to Establish the Diagnosis

1. Suspect the disease and start investigations. Virus can be isolated from pharyngeal secretions 2-15 days after the onset of illness. Nasal secretions, blood, CSF and feces also contain the virus. Children may continue to shed the virus in nasal discharges for over 2 weeks after recovering from the acute attack.
2. Positive immunofluorescence antibody (IFA) using H5N1 monoclonal antibodies can be demonstrated in serum.

Diagnosis is confirmed by the following tests:

1. positive viral culture for influenza A H5N1.
2. positive real time PCR for influenza A H5N1.
3. and/or four-fold rise in H5N1-specific antibody titer.

Management

Avian influenza virus is resistant to amantadine and rimantadine. Oseltamivir 75 mg orally twice daily for 5 days and zanamivir would probably be useful if started as early as possible. No vaccine is available now to protect against H5N1 virus for general use.

A 2 dose regimen of 90 µg of sub-virion influenza A (H5N1) given IM over the deltoid muscle at 28 days interval generates neutralizing antibody. This vaccine is under trial.

Infection Control Precautions for Hospital Staff

Patients who have visited endemic regions within 10 days and who present with severe febrile illness and respiratory symptoms should be observed for avian influenza, with isolation, barrier nursing and other precautions.

1. Proper hand washing before and after contact with the patient.
2. Use gloves and gowns for all patient contacts. Use separate equipment for individual patients.
3. Protection of the eyes with goggles or face shields.
4. Precautions against droplet infection: Patients should be isolated in monitored negative air pressure ventilation systems. Health care staff should use a fit-tested respirator, or approved N-95 filtering mask when entering the room.
5. Suspected poultry meat and eggs should be properly cooked so that the whole item reaches a minimum temperature 70°C which is needed to destroy the virus.

Parainfluenza

This is caused by para influenza viruses which belong to the group of paramyxoviruses. Other members of the group include mumps measles respiratory syncytial virus and human metapneumovirus. These viruses are 80-120 nm in size. They cause respiratory infection. Based on antigenic differences, para influenza viruses are divided

into four types. Para influenza has nothing in common with influenza virus. Para influenza viruses affect mostly children. Mainly the respiratory tract is involved.

Clinical Manifestations

After an incubation period of 5-6 days, it starts with fever which is a constant feature. Type I infection causes laryngotracheobronchitis or croup. Type II infection causes tracheobronchitis, bronchiolitis and bronchopneumonia in infants and children. Submandibular lymph nodes may become enlarged and tender. **Complications** include secondary bacterial infection leading to otitis media, sinusitis and bronchiectasis.

Treatment

There is no specific drug against this virus. Secondary bacterial infection has to be treated with antibiotics.

Respiratory Syncytial Virus Infection (RSV)

It is a major pathogen of the lower respiratory tract in infants and elderly persons, especially immunocompromised. It belongs to the family Paramyxovirus and the genus Pneumovirus. According to WHO data a third of the deaths in children below 5 years of age is due to respiratory tract infections caused mainly by *Str. pneumoniae*, *H. influenzae* and RSV. There is no clear data of the epidemiology of RSV infection in India. Still it is most likely that the infection is quite prevalent. Route of infection is the upper respiratory tract, especially the nasopharynx and the eyes. Incubation period is 3-5 days. Main pathological lesions are in the bronchiolar epithelial cells leading to inflammation and edema of the peribronchial region. Plugs containing mucus and epithelial debris lead to ball-valve obstruction of distal airways with air trapping. Cellular immunity plays a major role in the recovery from infection.

Clinical Features

Most common manifestations are rhinitis, cough and fever at times. Otitis media, bronchiolitis, pneumonia and croup are common in children. Severe bronchiolitis may lead to respiratory failure.

In adults RSV infection leads to exacerbation of chronic bronchitis and emphysema.

Diagnosis is established by demonstration of RSV antigens in nasopharyngeal washings, by ELISA.

Management

In many cases the disease is self limiting and only supportive measures are needed.

Ribavirin is probably effective as an antiviral agent and this should be employed in severe cases.

Prophylaxis

Vaccines are under trial. In immunocompromised infants a humanized monoclonal antibody may be tried with benefit during epidemics. While attending to cases, handwashing and avoiding contamination by oronasal discharges are important.

Severe Acute Respiratory Syndrome (SARS)

SARS is an emerging infectious disease caused by a novel corona virus first described from China and Hong Kong and reported in 2003, which threatened to assume pandemic dimensions. The disease spreads widely, probably by the respiratory route by droplet infection even by very short periods of exposure. Possibly the secretions from other sites and excreta are also infectious. Direct exposure, closed environment in aircrafts and air travel contributed to the dissemination of the virus in many parts of the world. The disease was effectively contained from spreading, by prompt action directed by the W.H.O and taken up internationally. India did not have proved cases of SARS during this period.

Clinical Features

The cases presented with fever initially with or without chills or rigor, influenza-like symptoms and radiological signs compatible with pneumonia. History of contact with established cases was present. The mean age of the patients were 35-40 years. Presenting symptoms include pyrexia (90%), chills or rigor (71%), cough (52%), vague symptoms (50-60%), dyspnea (30%) and diarrhea (25%).

Common laboratory findings include lymphopenia in 58%, thrombocytopenia in 40% and raised lactate dehydrogenase (LDH) in 70%. Viral RNA can be identified by real time PCR (RTPCR) from nasopharyngeal aspirate, stool and urine. Seroconversion occurs slowly and IgG might be detected by 8-10 weeks.

Radiological abnormalities were present in all cases on admission or follow up. In 70% they were bilateral. The abnormalities include subtle haziness (36%), mild infiltrates and ground glass appearance (57%), denser infiltrates and dense confluent opacities (7%).

The differential diagnosis includes atypical pneumonia, influenza, parainfluenza, respiratory syncytial virus and adenovirus infections, and pneumocystis pneumonia. The disease carries a high mortality exceeding 50%, if unrecognized.

Management

SARS should be suspected in acute febrile illnesses with moderate or severe respiratory embarrassment. Isolation of the patient and protection of health care staff should be instituted as described for avian flu (pp 302).

Environment and contaminated materials are disinfected by domestic bleach (1000 ppm hypochlorite

solution) for non-metallic articles and 70% alcohol for metallic objects.

Specific Therapy

1. Anti bacterial drugs: Treatment with levofloxacin 500 mg once a day IV or oral should be started without delay in patients above 18 years of age. In patients younger than 18 years, pregnant women and patients suspected to have tuberculosis clarithromycin 500 mg orally bd with co-amoxyclav (amoxycillin and clavulanic acid) 375 mg tds is the combination of choice.
2. If chest radiograph shows extensive lesions or clinical features are worsening the antiviral drug ribavarin should be started in doses of 400 mg 8 h (1200 mg/day) IV for 3 days or till the condition becomes stable, and thereafter 1200 mg oral bd (total 2400 mg/day) for 10-14 days.
3. Corticosteroids should be started along with ribavarin. The standard protocol consist of a 21 day regimen as follows:
 - a. Methyl prednisolone 1 mg/kg bw 8 h IV (total 3 mg/kg bw/ day) for 5 days
 - b. Methyl prednisolone 1 mg/kg bw/ day IV for 5 days
 - c. Prednisolone oral 0.5 mg/kg bw/bd daily for 5 days
 - d. Prednisolone oral 0.5 mg/kg bw od daily for 3 days, and
 - e. Prednisolone oral 0.25 mg/kg bw od for 3 days.Ventilation should be assisted in those having ventilatory problems. Success rate of treatment is high, if instituted early.

Points to remember

1. SARS is an emerging, serious life threatening infection by a corona virus which ushered in several parts of the world in 2003.
2. Prompt recognition of the mode of spread and International action helped to prevent the spread of the disease.
3. All health care professionals should be aware of such infections and early reporting to public health authorities is vital, to prevent devastating outbreaks.

Ref. Loletta K.Y.So Development of a standard treatment protocol for severe acute respiratory syndrome. The Lancet 2003, 361 1615-1617.

Other Paramyxoviruses

NIPAH VIRUS

Other paramyxovirus infections are being reported in recent times. Nipah virus is a member of this group which was identified to produce local outbreaks of encephalitis-like illness in persons working in pig farms and abattoir workers handling pigs in Singapore. Further reports are likely to follow.

HUMAN METAPNEUMO VIRUS

Human metapneumovirus is a common respiratory pathogen especially in children. It is a RNA virus. It causes bronchitis in 59%, pneumonia in 8% croup in 18% and exacerbation of asthma in 14%. Nasal wash specimen is used to isolate virus.

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Exanthems and Enanthems

K.V. Krishna Das

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Measles

Syn: Rubeola

Measles or Rubeola (red spots-Arabic) is an acute exanthematous febrile illness caused by a specific virus of the paramyxovirus group affecting children more. It is an RNA virus varying in size from 150-300 nm.

The present day major killers of children globally are measles, diphtheria, whooping cough, tetanus, tuberculosis, polio-like paralysis and to some extent poliomyelitis.

In developing countries 10% of all deaths in children below 5 years of age are measles related.

Pathogenesis and Pathology

Man is the only natural host. The disease may occur in localized or wider outbreaks once in 2-3 years, especially during spring. The virus is present in the nasopharyngeal secretions, and infection is by droplets. Portals of entry are the respiratory mucous membrane and the conjunctiva. The period of infectivity starts 5 days after the exposure to the virus and lasts until 5 days after skin eruptions have appeared. Infants do not generally suffer, presumably because of the persistence of maternal antibodies in them.

The virus multiplies in the epithelium of the respiratory tract and then causes viremia. Hematogenous spread occurs to various tissues. The virus can be isolated from blood, conjunctiva, lymphoid tissues, and secretions of the respiratory tract for a few days before and for 1 or 2 days after the appearance of rashes and from the urine as long as 4 days after the rash. Following the viremic phase the virus localizes in the skin and respiratory tract in addition to several tissues. There is interaction between the virus and the T-cells.

The mucous membrane lesions (enanthem) known as *Koplik's spots* seen in the cheeks, consist of vesicles and necrotic epithelium. Microscopically the lesions show cytoplasmic and intranuclear inclusions, giant cells and intercellular edema. Aggregates of virions in the affected cells can be demonstrated by electron microscopy.

Multinucleated giant cells with acidophilic nuclear and cytoplasmic inclusions (*Warthin Finkelday cells*) may be found in the hyperplastic lymphoid tissues of lymph nodes, tonsils, spleen and thymus. Chromosomal breaks may be seen in leucocytes. Epithelium of the respiratory tract is disrupted and this favours secondary bacterial infection. Lungs show interstitial pneumonia with giant cell infiltration. In patients, who develop encephalomyelitis, the brain shows focal hemorrhage, congestion and perivenous demyelination.

Clinical Features

Incubation period is 9-11 days. The initial manifestations are malaise, irritability, high fever, conjunctivitis with

excessive lacrimation, edema of the eyelids, photophobia, hacking cough and nasal discharge. These symptoms last for 3-4 days (up to 8 days) and then the rashes start. Koplik's spots appear as small, red irregular lesions with bluish-white center on the mucous membrane of mouth 1-2 days before the skin rash. They are best seen in the buccal mucosa opposite the upper molar teeth. Lesions similar to them may occur in the conjunctiva and intestinal mucosa. The rashes are red and maculopapular, first appearing on the forehead and behind the pinna, later on spreading down to the face, neck, trunk and limbs. Maximum affection is on the face and shoulders. These rashes persist for about 3 days and disappear in the order in which they appeared. The disease becomes more severe in adults in whom complications are likely to be more. The general symptoms disappear 1-2 days after the appearance of skin rash. Cough may persist throughout the illness.

Complications

These are common, though in the majority the disease is self-limiting. Respiratory complications include croup, bronchitis, bronchiolitis and rarely interstitial giant cell pneumonia. These are more common in immunocompromised persons and malnourished children. The eye lesion may progress to corneal ulceration, keratitis and blindness. Myocarditis develops in 20% of cases and this causes transient ECG changes, but clinically this may remain silent. Acute abdominal pain may occur due to mesenteric lymphadenitis. In pregnant women, fetal loss may occur in 20% of cases.

Secondary bacterial pneumonia by *Staphylococcus*, *Streptococcus*, *Pneumococcus* and *H. influenzae* is common and may progress to lung abscess and empyema. Otitis media may develop commonly. Stomatitis may develop and progress to cancrum oris, especially in malnourished children. Quiescent tuberculous lesions may flare up or fresh tuberculous infection may develop. Diarrhea may occur as a complication and may prove troublesome.

Neurological complications of measles include;

Acute post infectious measles encephalitis caused by cell mediated autoimmune response to measles virus-frequency 1/1000 cases. *Encephalomyelitis*, another serious complication, occurs in 1/1000 patients, usually occurring 4-7 days after the appearance of the eruption. It is characterized by high fever, headache, drowsiness and coma ending fatally in 10% of cases.

Measles inclusion body encephalitis (MIBE) – This occurs only in immunocompromised subjects.

It is a subacute infection occurring 1-7 years after infection. Measles virus persists in the brain. It presents as alterations in cognition, convulsions and coma. This disease is invariably fatal.

Progressive encephalitis may develop in 1-6 months after measles in immunosuppressed children. Subacute sclerosing panencephalitis (SSPE) is a late complication of measles in which the virus persists in the brain, possibly with alteration of matrix proteins. It is characterized by progressive dementia and motor weakness. In this disorder the measles virus tends to persist for long in neural tissue and bring about slow degenerative lesions and a clinical picture similar to slow virus infections result. SSPE is estimated to occur with a frequency of 1/8000 in children infected with measles.

Laboratory Diagnosis

Laboratory investigations are essential to diagnose atypical cases and also for differentiating measles from rubella. Leucopenia is frequent in the early stages. Leucocytosis occurs with secondary bacterial infection. Cerebrospinal fluid shows raised protein and lymphocytosis in encephalomyelitis.

Demonstration of multinucleated giant cells in Giemsa stained smears of nasal secretions is a simple side room laboratory test. Virus antigen can be detected in the cells by immunofluorescence. Virus can be isolated in human embryonic kidney and amnion cells.

Demonstration of rising antibody levels by complement fixation test, hemagglutination inhibition test and neutralization test in paired sera help to make serological diagnosis.

Differential Diagnosis

Rubella has to be differentiated from measles. Rubella is a milder illness of short duration without significant respiratory complaints. Infectious mononucleosis, toxoplasmosis, secondary syphilis, adenovirus and enterovirus infections, scarlet fever and drug rashes have to be differentiated.

Treatment

There is no specific drug against the virus and, therefore, management is symptomatic. Bacterial infection has to be treated with antibiotics based on clinical and bacteriological findings. Children who continue to be ill after an attack of measles should be investigated for the presence of tuberculosis.

Prevention

Administration of gammaglobulin 0.25 mL/kg within 5 days of exposure effectively prevents or attenuates the attack. Children below three years, pregnant women, immunocompromised persons and those who suffer from tuberculosis should be given gammaglobulin for passive immunization.

Live attenuated measles vaccine, prepared from *Edmonston B strains of measles virus* is used for active immunization. Immunity lasts for a period of over 10 years. Vaccination after 12 months of age is more effective, though earlier vaccination can be done in measles prevalent areas. In those vaccinated before 12 months, a second dose should be given at the age of 15-18 months. The vaccine may be given alone or in combination with rubella and mumps vaccines. Vaccination is contraindicated in pregnancy, tuberculosis, leukemia, lymphoma and immunocompromised patients. Combined vaccines for measles, mumps and rubella are available (MMR vaccine). Adverse effects include fever in 5-15% and rashes. MMR vaccination 2 doses give seroconversion in 98% for measles and only 88% for mumps. So more among the vaccinated persons are susceptible to mumps than measles.

Measles vaccine is supplied free of cost along with the general immunization schedule. MMR vaccine is available at cost for those who prefer to take it. Several reports suggest that supplementation of vitamin A (400000 units or 20 mg once orally) to undernourished children help to reduce mortality during measles outbreaks.

Though the WHO recommended vaccination coverage of 90% of the children by 2000 AD, this target is still to be achieved. Vaccination is very effective in preventing measles and SSPE.

Aerosol vaccines using Schwartz or Edmonston-Zagreb strains of the virus have been compared with the standard subcutaneous injection. The antibody response at one month and one year are reported to be comparable.

Smallpox Syn. Variola

Smallpox is a natural infection in man caused by variola virus and the virus affects only humans. The virus is 200-250 nm in size and belongs to the group of pox viruses which are DNA viruses. The variants of variola virus – variola major and variola minor can be distinguished in the laboratory. Studies to sequence the genome of the virus are in progress.

The virus is transmitted from man-to-man by the respiratory route. There are no animal reservoirs or insect vectors in the transmission of this disease. The transmission may be direct from patient-to-patient or through fomites and other contaminated articles. Nasopharyngeal secretions, vesicle fluid, and dried scabs contain the virus. The virus can remain viable in dried scab for over one year. The patient is infective from the onset of early symptoms till the last scab has fallen off.

Though smallpox was one of the most dreaded diseases and outbreaks occurred in the tropics regularly, at present the disease has been eradicated by worldwide

efforts undertaken by the WHO from 1967 to 1977. The world was declared free of natural infection in October 1977. In India the last case was reported in 1976. Except for the stock cultures of the virus maintained in a few laboratories the virus is believed to have disappeared. This achievement was made possible by an intensive program of mass vaccination and early case reporting. Absence of any non-human reservoir and vector and the solid immunity produced by vaccination have contributed to the achievement. Variola virus proteins modulate the immune system. *Since the virus can be grown easily and modified genetically to evade the vaccination induced immunity, it is a good candidate for bio-terrorism and warfare.*

Pathology

After entry, the virus reaches the lymph nodes, where it multiplies and then enters the circulation. The skin and mucous membranes are affected thereafter. Cellular, humoral and innate immunity influence the course of small pox. The affected epithelial cells show acidophilic cytoplasmic inclusion bodies called *Guarnieri bodies*. These are aggregates of the virus particles which are called *Paschen bodies*.

CLINICAL MANIFESTATIONS

The incubation period is 12 days (8-16 days). Prodromal symptoms occur 2-4 days before the eruption starts. These consist of high fever, myalgia, headache, backache, delirium and abdominal pain. The rash starts on the third day and the fever subsides when the rash appears. Fever reappears after varying intervals, when the rash becomes pustular. The temperature comes down with scabbing. The rashes are characteristic. They are distributed in a centrifugal pattern. The face, arms and legs are more often and more heavily affected. Presence of vesicles in the palms and soles is characteristic (Fig. 53.1). Initial lesions are erythematous macules, which progress successively into papules, vesicles, pustules and scabs at 48-hour

intervals. The vesicles and pustules are deep-set in the skin, multiloculated and the center is umbilicated. Unlike as in chickenpox, all the vesicles are at the same stage of development. When the scab separates, pitted scars are left behind, which tend to remain permanent.

In vaccinated individuals who possess residual immunity, the clinical picture is modified and this is termed varioloid. This is abrupt in onset with the development of only a few rashes. The course is benign. Smallpox may occur without the characteristic rash “*variola sine eruption*”. A less virulent form of the virus capable of producing milder manifestations, “*variola minor*” (*alastrim*), has also been recognized.

Other serious clinical types may occur less commonly. These are hemorrhagic smallpox which is highly fatal, and the flat form in which the papules are velvety, which may become vesicular and lead to peeling off of the whole epidermis.

Complications

Secondary infection by staphylococci occurs during the stage of pustulation. This may lead to septicemia, pneumonia, osteomyelitis, septic arthritis, otitis media and pyelonephritis. Death is due to coagulopathy, hypotension and multi-organ failure. In the eye, vesicles in the cornea may suppurate and lead to panophthalmitis and blindness. Smallpox was a common cause of blindness in India till three decades ago. Neurological complications include demyelinating lesions such as encephalitis, encephalomyelitis and peripheral neuritis. Laryngeal edema may occur, leading to respiratory obstruction.

Osteomyelitis Variolosa

In this form of destructive osteomyelitis, the metaphyses are infected with the virus during the phase of viremia, but symptoms are late to develop. Destruction and detachment of the epiphyses lead to permanent bone and joint deformities which persist in later life (Fig. 53.2).

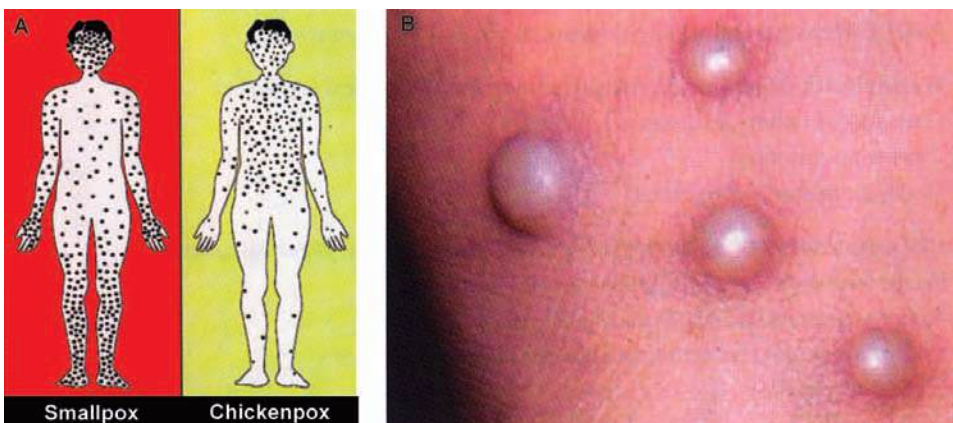


Fig. 53.1: Smallpox (1) Distribution of rash (2) Note the deep seated vessels, all at the same stage of development

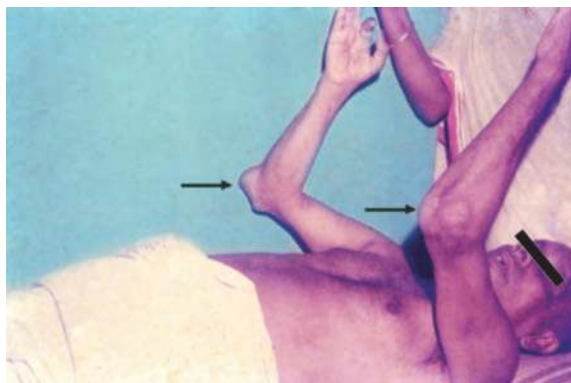


Fig. 53.2: Osteomyelitis variolosa

6

Course and Prognosis

Till the middle of this century smallpox used to be a major killer among children with a mortality of 20-80% among unvaccinated subjects. Death is due to severe toxemia or secondary infection.

DIAGNOSIS

Clinically smallpox should be suspected when an unvaccinated person gets high fever with prodroma and rash occurring on the third day. The distribution and progress of the rash strengthens the diagnosis. Since the world has been declared free of smallpox, physicians have to be alert to detect initial cases and subject them to thorough laboratory investigations. By international agreement reporting of fresh cases to the health authorities carries a cash award. Chickenpox, drug rashes and erythema multiforme are to be differentiated from smallpox. Rickettsial pox and pustular syphilis may resemble mild cases of smallpox.

Laboratory Diagnosis

1. Demonstration of the virus in material from vesicles or crusts by electron microscopy. Characteristic brick-shaped virus can be identified. PCR assays confirm the presence of virus.
2. Identification of Guarnieri bodies from the vesicular material.
3. Isolation of the virus.

Treatment

The treatment is mainly supportive. Antibiotics are used when secondary bacterial infection occurs. After exposure, the attack can be prevented by administering methisazone in a dose of 1.5-3 g twice daily for four days. Methisazone offers protection in unvaccinated individuals but it has no curative effect when the disease is manifest. Vaccinia immunoglobulin can be administered and it has a protective role. Early notification of cases, strict barrier

nursing and large scale immunization of the surrounding population should be undertaken to prevent the spread of the disease. Since the vaccine is not at present available for regular use, vaccination programs have to be undertaken by the appropriate health authorities.

Prevention

Vaccination used to be the most effective method to prevent smallpox. It was introduced by Edward Jenner on May 14, 1796. Since the world is declared free of smallpox, regular vaccination of infants is not insisted upon at present. Several strains of vaccinia of low pathogenicity are used for the vaccine. Single clones are used for vaccine production. Attenuation is achieved by serial passage in non-human tissue. Third generation vaccines are under development. The immunity is solid, the exact duration is not clear. There is evidence that the conventional vaccine diluted ten times still maintains its immunogenicity. Vaccination done within 3-4 days of exposure will prevent or allay the disease manifestations. Due to the fear of bioterrorism, many countries are actively producing smallpox vaccine. Priority is to vaccinate health care workers.

The vaccine contains killed or freeze dried vaccinia virus. Though generally safe, rarely complications occur. These include generalized vaccinia, secondary infection, eczema vaccinatum, progressive vaccinia (vaccinia gangrenosa) and post-vaccinial encephalitis.

The doctor working in India has to keep smallpox in mind and report the first suspicious case to prevent the occurrence of a devastating epidemic in a non-immune population.

WHO website on additional information on small pox are available at <http://www.who.int/topics/smallpox>

Chickenpox

Syn: Varicella

Chickenpox is a common viral infection occurring frequently in children. The disease is highly contagious. It is characterized by fever and disseminated vesicular eruptions. Though in children the disease is benign and self-limiting, as age advances the disease becomes more serious and produces grave complications.

The etiological agents of varicella and herpes zoster are identical in all respects. The varicella zoster (V-Z) virus is a DNA virus measuring 100-150 nm in diameter. It multiplies in the nuclei of infected cells and produces intranuclear inclusions.

It is an exclusively human herpes virus that causes chickenpox (varicella), become latent in cranial nerves and dorsal root ganglia, to be reactivated later to produce shingles (zoster) and post-herpetic neuralgia.

Pathogenesis and Pathology

Cases of chickenpox are most infective in the early stages of illness and virus is present in the lesions and the respiratory discharges. Infection occurs by respiratory route, contacts or nosocomially. After entry there is a period of blood stream dissemination and widespread organ involvement demonstrable in autopsies. Vesicles develop in the skin and mucous membranes. The epidermis undergoes degeneration. The vesicles contain serum, polymorphs and multinucleated giant cells. Virus is present in vesicle fluid for 3-4 days, but not after the onset of crusting.

As a complication, pneumonia may occur. In varicella pneumonia the tracheobronchial mucosa, the alveolar septa and the interstitial tissues of the lungs are edematous and show mononuclear cells with intranuclear inclusions and giant cells. Pneumonia develops as nodular areas of consolidation in the lungs. Ultimately these lesions may become calcified. Encephalomyelitis which resembles that seen in measles may occur as a complication. During the acute phase of the disease infants and children may develop acute encephalopathy with fatty infiltration of the viscera (*Reye's syndrome*).

Epidemiology

The infectious period extends from a day or two before the onset of the rash to six days after the appearance of new skin lesions or until all vesicles have started crusting. Chickenpox develops commonly due to exposure to other cases of chickenpox and rarely in contacts of herpes zoster. Herpes zoster is mainly a disease of adults who have partial immunity to the virus. Though chickenpox produces good immunity, it wanes off after 10 years and second attacks may develop.

CLINICAL FEATURES

The rashes appear 14-16 days after exposure (range 10-23 days). Prodromal symptoms are mild in children, the first manifestation in whom is the appearance of vesicles. Early symptoms in adults include fever, headache, backache, sore throat and malaise which last for 2 or 3 days. Enanthem occurs over the palatal and pharyngeal mucosa even before the skin rash appears. The skin rashes (*exanthem*) come up in crops starting from the first day of fever and these continue for 3-4 days so that lesions at different stages—macule, papule, vesicle, pustule and scab—may be present simultaneously (*polymorphism*). The rashes are centripetal, maximally affecting the trunk and sparing the distal parts of the limbs. Face may be affected variably. The axillae are almost invariably affected. The vesicles are unilocular, *superficial, elliptical in shape and contain clear fluid in the beginning (tear drop vesicles)*. These become pustular in 24 hours. Intense



Fig. 53.3: Chickenpox. Note superficial vesicles; in different stages of development

pruritus may develop and scratching disrupts these vesicles. The pustules dry up to form scabs in a few days. When the scabs fall off, superficial scars are left behind which clear up in due course. Recovery is the rule in the vast majority of healthy subjects. Complications and death may occur in immunosuppressed persons and children receiving glucocorticoids. In them progressive varicella develops and organ involvement is more common (Fig. 53.3).

Complications

1. Thrombocytopenia may develop leading to hemorrhage into the vesicles, conjunctiva and intestines.
2. Staphylococcal infection may supervene leading to bacteremia and delayed healing.
3. Children with impetigo may develop bullous lesions.
4. Superinfection by hemolytic streptococci causes varicella gangrenosa.
5. Around 15% of adults with chickenpox may develop primary varicella pneumonia. This is manifested 1-6 days after the onset of the rash. This may be asymptomatic or it may present with high fever, tachypnea, cough, pleuritic chest pain, cyanosis and hemoptysis. Physical examination may not give evidence of extensive consolidation. It may show only a few rhonchi, scattered rales or rarely pleural effusion. Radiologically extensive nodular lesions are seen in both lungs. As the rashes subside and general condition improves the pulmonary lesions clear up.
6. *Neurological complications* develop more in immunocompromised individuals at all ages. In elderly persons these may occur in immunocompetent individuals as well. The central nervous systems lesions include myelitis, encephalitis, encephalomyelitis, ventriculitis and meningitis. The major pathological change in varicella zoster encephalopathy is a vasculitis affecting the small and large vessels. Clinically the presentations include transient

cerebellar ataxia, encephalomyelitis, polyneuritis cranialis, ascending paralysis, transverse myelitis and optic neuritis.

7. Other systemic complications that may develop rarely are myocarditis, keratitis, iritis, nephritis, arthritis, purpura, orchitis and appendicitis. Quiescent tuberculosis may be reactivated. Chickenpox occurring in the first two trimesters of pregnancy may give rise to congenital malformations in 9%.
8. Varicella during pregnancy: *Congenital varicella syndrome* in the fetus occurs in the 3rd trimester of pregnancy especially between 8-20 weeks. Clinical features include skin lesions, neurological and eye defects, limb hypoplasia, Intra uterine growth retardation (IUGR) and other manifestations due to direct viral invasion. Risk of developing this syndrome is 0.7% in first trimester and 2% in the second. Detailed ultrasound examination is diagnostic. Abnormalities include limb deformities microcephaly, hydrocephalus, polyhydramnios and soft tissue calcification. These are detectable at least 5 weeks after maternal varicella. If the mother develops the rash between four days prior to delivery and two days thereafter, it is highly probable that the newborn is infected. The disease is associated with high mortality in the neonate.

Diagnosis

Clinical diagnosis is not difficult in typical cases. Fever with vesicular rash occurring on the trunk and milder prodromata is suggestive of chickenpox. Smallpox used to be an important differential diagnosis. Though smallpox has been eradicated, it is extremely important to identify any similar illness and subject the patient to full investigation. The clinical differentiation between chickenpox

and smallpox is given in Table 53.1. When the disease is modified by immunization or immunosuppression laboratory confirmation becomes necessary.

Laboratory Diagnosis

Examination of material scraped from the vesicles (Tzanck smear) reveal eosinophilic intranuclear inclusion bodies within epithelial cells and multinucleated giant cells. Virus can be isolated from vesicular fluid. Serological diagnosis can be made by complement fixation, immunoadherence, hemagglutination, indirect immunofluorescent antibody detection tests or ELISA. Presence of the virus in blood vessels can be detected by PCR.

Treatment

In the majority of cases only symptomatic treatment is required, when the illness is mild. Paracetamol in a dose of 0.5 g given thrice daily serves to relieve pain. To prevent secondary infection, local antiseptics like chlorhexidine can be used. Pruritus can be reduced by local application of peanut oil containing 1 % phenol. Antiviral drugs such as acyclovir have to be given parenterally in complicated cases.

For normal hosts acyclovir 20 mg/kg bw orally as tablets up to a maximum of 800 mg 4-5 times a day for 5 days is effective.

In immunocompromised hosts and in normal hosts with pneumonia or meningoencephalitis the dose is 10 mg/kg IV 8 hourly for 7-10 days or more. If started early the results are excellent.

Prophylaxis

Spread of infection can be prevented by isolation of the patient and heat sterilization of contaminated articles.

TABLE 53.1

Clinical differentiation between chickenpox and smallpox		
Signs and symptoms	Chickenpox	Smallpox
1. Prodromal symptoms	Absent or mild	Prodromal symptoms more
2. Rash		
a. Appearance of vesicles	Within 24 hours of onset of fever	3rd or 4th day of illness
b. Distribution	Centripetal rash, i.e. more on the	Centrifugal, i.e. rash more on the face and body and less on the face and limbs extremities and less on the covered parts of the body
c. Nature of eruption	Superficial and more on flexor regions Axilla involved Rash appears in crops for 3-4 days	Deep-set in skin and more on extensor regions and bony prominences Axilla usually free Rash comes out as a single crop during 1-2 days
	Vesicles are oval or elliptical Rash in different stages occur simultaneously Unilocular vesicles without umbilication, which collapse on puncture Superficial scars which fade off	Vesicles are round Rash is in the same stage all over Multilocular and umbilicated vesicles, do not collapse on puncture Deep permanent scarring

Immunosuppressed children who are exposed to chickenpox should be given protective immunoglobulin. Varicella zoster immunoglobulin (VZIG) prepared from pooled human plasma contains antibodies against varicella, and when given in a dose of 12.5 units/kg body weight within 72 hours of exposure it gives passive immunity. Secondary bacterial infection should be treated with antibacterial agents.

Live attenuated varicella zoster virus vaccines are available for use in special situations. The vaccine is prepared by growing the attenuated virus in human diploid cells. It may be given to children after the age of 1 year.

Dose

1 year to 12 years	0.5 mL subcutaneous injection.
Above 12 years	0.5 mL two doses at an interval of 6-10 weeks in between vaccination is indicated for children who are likely to undergo immunosuppressive therapy.

Available commercially as varilrix C (Smith-Kline and Beecham). Vaccination should be avoided during pregnancy and within one month of measles vaccination. Pregnancy has to be avoided for three months after chickenpox vaccination. Immunity persists for two decades or more. A second dose of vaccine boosts up immunity.

Herpes Zoster

Syn: Shingles

Herpes zoster is an acute eruptive disorder characterized by painful radiculitis and vesicular eruptions in the corresponding dermatomes. It is seen more commonly in subjects above the age of forty years. Chickenpox and herpes zoster are caused by the same virus, the latter occurs in persons who have acquired partial immunity. Following the episode of chickenpox the varicella-zoster virus becomes latent in

ganglia along the entire neuraxis, particularly the trigeminal ganglia and the dorsal root ganglia, remaining mainly in the cytoplasm of the neurons. Later the perineural cells of the ganglia are also involved. The virus persists in noninfectious form with intermittent periods of reactivation and shedding. The exact factors leading to reactivation are not fully known. The virus can be isolated from these tissues by appropriate methods. Attacks of herpes zoster are often precipitated by immunodeficiency states, hematological or neurological malignancies or trauma. Involvement of the cerebral arteries by VZV produces unifocal or multifocal vasculopathy (i.e.) granulomatous arteritis. The localized form occurs in immunocompetent and the multifocal form occurs in immunocompromised subjects. This usually occurs after reactivation from the ganglia. This virus travels trans-axonally to involve the cerebral arteries. This leads to vascular occlusion and stroke. Intensive intravenous administration of acyclovir helps to resolve the lesion. When used along with other supportive measures.

CLINICAL FEATURES

The eruption has an abrupt onset after a prodromal illness characterized by malaise, fever and severe pain in the corresponding dermatomes lasting for 3-4 days. The pain may be lancinating, deep-boring, burning or vague, and in many cases it is unbearable. The common sites for the eruptions are the ophthalmic and maxillary divisions of the trigeminal nerve, geniculate ganglion of the facial nerve and thoracic and abdominal nerve roots. After a variable period of pre-eruptive neuralgia, the rash begins as reddish papules which soon develop central vesiculation. The vesicular fluid becomes turbid in three days and crust formation occurs after a week. The rash may involve a whole dermatome or only parts of it. The eruptions seldom cross the midline (Fig. 53.4).

With the formation of pustules the initial pain may subside, but in many elderly patients it may persist in the

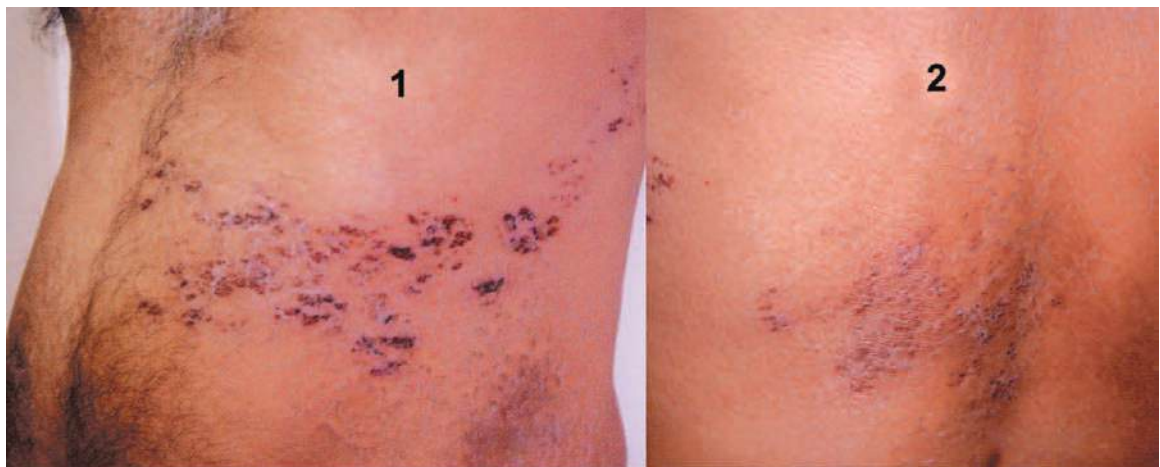


Fig. 53.4: Herpes zoster

same form or in an altered form for months or even years. This is referred to as **post-herpetic neuralgia**. Vague paresthesiae, varying degrees of sensory loss and even lesser degree of motor loss may persist over the affected segments for considerable periods. In general the condition is benign, but the development of neuralgia may lead to severe distress and even suicidal tendencies in susceptible subjects. Incidence of post-herpetic neuralgia is more in elderly subjects (9-34%) with severe prodromal symptoms and painful confluent lesions. VZV involvement of CNS is accompanied by high leukocyte count in the CSF. Presence of virus in CSF detectable by PCR.

Complications

1. Secondary infection: The vesicles may be infected by bacteria, giving rise to fever. Deep scarring may occur.
2. Ophthalmic herpes: In herpes involving ophthalmic division of the trigeminal nerve keratitis may develop. Optic neuritis and oculomotor palsy may occur less commonly.
3. Herpes of the geniculate ganglion presents as facial nerve palsy and vesicles over the ipsilateral external auditory meatus (Ramsay-Hunt syndrome). Generally the facial nerve palsy tends to persist. Zoster occurring in the distribution of the maxillary and mandibular divisions of the trigeminal nerve may lead to osteonecrosis and spontaneous loss of the teeth.
4. Paralysis of muscles corresponding to the involved spinal segment is a rare sequel. Cervical herpes zoster may give rise to weakness of the arm. Encephalitis and myelitis have been reported rarely.
5. In leukemic subjects and those on immunosuppressant therapy extensive vesiculation may develop (generalized herpes).
6. Pregnancy: The fetus may be infected and this may lead to congenital malformations.
7. **Post-herpetic neuralgia.**
8. VZV vasculopathy and strokes.

Diagnosis and Differential Diagnosis

Once the eruption has occurred over the sensory root distribution, diagnosis becomes easy. Before the onset of the eruption, the pre-herpetic neuralgia may be mistaken for other serious conditions depending on its location. These include trigeminal neuralgia, vascular headache, painful ophthalmic problems, myocardial infarction, pleurisy, cholecystitis, appendicitis or any surgical abdominal emergency. Careful examination of the part in bright light may show at least erythematous rashes in many cases and this should suggest the diagnosis. Examination of the serum and CSF may reveal anti VZV IgG in serum and CSF, the levels being relatively higher in CSF. Even in cases with clear-cut diagnosis, an attempt

should be made to bring out an underlying malignancy like lymphoma or carcinoma, especially in the elderly subjects.

Specific Treatment

Immunocompetent individuals—Acyclovir 800 mg orally five times a day for 7-10 days. A new drug famcyclovir is a newer and more effective analogue given in a dose of 250mg t.i.d orally for 5-7 days. If started early it may even prevent the occurrence of post herpetic neuralgia.

Immunocompromised individuals: - Acyclovir 500 mg/m² IV eighth hourly for 7 days. Steroid should be given only under cover of acyclovir.

Local treatment consists of keeping the area dry and clean. Analgesics like aspirin and dextropropoxyphane are required in the eruptive stage. A short course of ACTH or prednisolone has been recommended in the elderly patients with a view to prevent post-herpetic neuralgia. Opinions are divided on this issue. The risk of dissemination of infection is a real danger.

The most troublesome complication of herpes zoster is post-herpetic neuralgia. Age is the most important single factor to predict its occurrence. There is no reliable method to prevent the neuralgia. Treatment consists of the administration of analgesics, tricyclic antidepressants and anticonvulsants. The pain is often refractory to analgesics. Diphenylhydantoin (300-400 mg/day), carbamazepine (200-1000 mg/day), and tricyclic compounds (amitriptyline, imipramine, doxepine) have been used with some benefit. Other therapeutic modalities like transcutaneous nerve stimulation (TNS) have benefitted some patients. Aspirin dissolved in chloroform and allowed to evaporate topically reduces pain. Capsaicin applied as ointment over the affected segment may bring about relief. Early specific treatment of herpes zoster reduced the chance for neuralgia.

Zoster Sine Herpete

1. This condition is characterized by recurrent severe shooting pains, but no vesicular eruptions. The diagnosis can only be made based on rising titers of antibody to V/Z virus.
2. Characteristic localization of pain to a dermatome with serologic evidence of herpes zoster, in the absence of skin lesion is diagnostic.

Pre-herpetic Neuralgia

This develops in herpes zoster before the appearance of the rash. This is due to ganglionitis. The area of pain and site of rash usually coincide in most of the cases, but not always so. Aseptic meningitis and acute meningo-encephalitis may occur with the occurrence of the rash.

Herpes Simplex

Syn: Herpes febrilis, Fever blister, Cold sore

Infection by *Herpes simplex virus (HSV)*, also known as *Herpes virus hominis (HVV)*, produces recurrent crops of vesicles over the mucocutaneous regions. The virus remains in the skin and nerve ganglia in the dormant form to be activated periodically to give rise to recurrent eruptions. Herpes viruses are DNA viruses and the pathogenic types are two different antigenic variants herpes simplex type 1 (HSV 1) and herpes simplex type 2 (HSV 2). The former causes lesions around the mouth, noses, cornea and conjunctiva and around the nails—(herpetic whitlows). This is a non-venereal infection. HSV 2 is a sexually transmitted disease which has assumed great importance since it leads to genital cancers in woman.

Fever, exposure to sunlight, physical or emotional stress, malignancy and immunosuppressant drugs lead to exacerbation. Fevers, especially pneumonia, malaria and meningitis are commonly associated with herpes labialis. Herpes simplex is rare in enteric fevers. A crop of vesicles develop following a short period of tingling pain and paresthesia over the affected region. The vesicles remain for 7-10 days after which they start to heal with the formation of crusts. Healing is complete in 21 days. When the crusts fall off, thin scars persist for some time. Common sites of eruption are around the mouth and external nares. Less commonly herpes simplex keratitis, recurrent gingivostomatitis and vulvovaginitis may occur. Herpes simplex virus can cause mild fever.

Serious complications may occur in susceptible persons and in immunosuppressed subjects. These include herpes simplex encephalitis and *Kaposi's varicelliform eruptions (eczema herpeticum)*. Herpes simplex encephalitis may lead to necrosis of the temporal lobe and rise in intracranial tension. Kaposi's varicelliform eruption develops in infants and adults with eczema. In such subjects the eruptions become generalized and this leads to excessive loss of fluid, electrolytes and proteins. Herpes tends to become generalized in subjects who have sustained burns. Generalized herpes simplex occurring in wrestlers is called *herpes gladiatorum*. Herpes simplex virus pneumonia occurs in immunocompromised hosts.

Diagnosis

Herpes simplex has to be differentiated from pustular or vesicular rashes and herpes zoster; the latter is nonrecurrent. Herpes simplex virus can be isolated from the vesicle fluid. Serological diagnosis is by demonstrating complement fixing antibodies. In herpes simplex encephalitis the virus can be demonstrated in CSF by PCR.

TREATMENT

Local lesions which are benign may be left alone with simple cleaning and application of gentian violet. Topical

idoxuridine (0.1% hourly as drops or 0.5% ointment) is effective in herpetic keratitis. Acyclovir ointment is available for local use over the vesicles. This gives relief of pain and prevents recurrence. In severe cases and complicated cases systemic therapy with acyclovir has to be given. Dose is 800 mg orally 5 times a day for 5 days. In case of HSV encephalitis, acyclovir should be given in a dose of 10 mg/kg bw IV 8 h for 10-14 days. For neonatal herpes simplex infections the dose is 10 mg/kg bw IV for 10-14 days. Fanciclovir 500 mg oral tds for 5 days is a suitable alternative.

Note: HSV2 infection (Genital herpes) is described along with sexually transmitted diseases in chapter 48

Rubella

Syn: German measles—Three days measles

Rubella is an exanthem caused by a RNA virus (50-85 nm in size) belonging to the family of togaviruses. The disease is characterized by mild constitutional symptoms and rash. Its importance is due to the risk of producing fetal abnormalities and abortion if it occurs in women during the early months of pregnancy.

Epidemiology

The infection spreads through droplets and entry is through the nasopharynx. Infective period starts one week before the onset of the rash and it lasts for one week after the rash fades. Virus is present in the nasopharyngeal secretion one week before the onset of the illness. In the early stage, viremia occurs. The virus reaches the fetus through the placenta and causes lesions in the fetus. The baby sheds the virus at birth and continues to be infective for 6 to 31 months. The disease is prevalent in the community and small epidemics may occur from time-to-time. Many cases may be subclinical. An attack confers life-long immunity. In western countries it is estimated that 10-15% of adult women are susceptible to infection. In India the disease is not infrequent, though reliable statistical figures are not available.

Pathogenesis

The virus is present in blood up to two days before the onset of the rash. Lymph nodes are moderately enlarged, showing edema and hyperplasia. When the fetus is affected, the virus multiplies in the liver, spleen, bone marrow and other tissues and leads to various structural malformations in the heart, nervous system, eyes and the limbs.

CLINICAL FEATURES

The incubation period is usually 2-3 weeks. The onset is sudden with malaise, fever, rashes and characteristic

TABLE 53.2

Differential diagnosis between measles and rubella		
	Measles	Rubella
Prodrome	Nasal congestion and cough more severe	Mild
Rash	Confluent reddish and pinkish maculopapular rash—slower progress and clearance	Discrete maculopapular—rapidly progressing and clearing
Temperature	Rises abruptly with rash	Does not rise abruptly with rash
Lymph nodes	Not characteristic	Retroauricular, posterior cervical or posterior occipital are characteristic
Koplik's spots	Pathognomonic	Nil

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enlargement of the occipital, posterior auricular and posterior cervical lymph nodes.

The rash which resembles that of measles begins on the face and neck and spreads to the trunk and limbs, but the rash is less extensive. Enanthem may occur consisting of discrete rose colored spots on the palate and fauces. The rash becomes discrete by the second day and it disappears in 3-4 days.

Compared to measles, constitutional symptoms are mild in children. In addition to fever and malaise, arthralgia, joint stiffness and headache may occur. Rarely serious neurological complications like encephalitis, encephalomyelopathy or polyneuropathy develop 5-10 days after the onset. Thrombocytopenia may develop in a few (Table 53.2).

Diagnosis

Clinically the disease should be suspected when fever, posterior cervical lymphadenopathy and rash occur in a young subject. Rubella has to be distinguished from measles, secondary stage of syphilis, drug rashes, infectious mononucleosis and Echo, Coxsackie and

adenovirus infections. The leukocyte count is normal in rubella. Specific diagnosis is established by finding a four-fold increase in hemagglutination inhibition antibodies in paired sera or by isolating the virus.

Congenital Rubella

Rubella embryopathy results either from inhibition of cell growth or cellular necrosis. Fetal defects include retardation of growth, eye defects like cataract, glaucoma, or retinopathy, congenital heart defects, nerve deafness, mental retardation, hepatosplenomegaly and skeletal abnormalities. Rubella occurring in women in the first 16 weeks of pregnancy leads to fetal malformation in up to 50 to 80% of cases. Risk of fetal affection reduces if the infection is acquired later in pregnancy.

Treatment

As the disease is generally benign, it is desirable to acquire rubella before the child-bearing age. No specific treatment is indicated. Medical termination of pregnancy has to be considered if there is proof of rubella infection in early pregnancy.

Prevention

Vaccination using live attenuated virus confers immunity. Live attenuated rubella virus RA 27/3 grown in human diploid fibroblast cells is effective, when given in a dose of 0.5 ml as a single injection. Vaccination confers solid immunity over 10 years. If facilities are available, vaccination should be considered for girls in the age group of 11-13 years and women in the child-bearing age who are antibody-negative and are desirous of child-bearing. The vaccine virus passes into the fetus and so pregnancy should be avoided for eight weeks following vaccination. Gammaglobulin administered to the mother after exposure aborts an overt -attack, but safety of the fetus cannot be guaranteed. Ideal time for vaccination is after 12 months of age. The combined MMR vaccine takes care of rubella as well.

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Mumps

K.V. Krishna Das

Chapter Summary

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Clinical Features 315

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General Considerations

This common childhood infection is caused by mumps virus which belongs to the group of paramyxoviruses. It is an RNA virus. The infection is worldwide in distribution and spreads through droplets. The disease runs a subclinical course in 30-40% of cases. Man is the only known host and the infection spreads directly from man-to-man. Infectivity rate among contacts is not high. Second attacks do not occur since mumps produces solid life-long immunity.

Pathology

Organisms enter through the respiratory tract. The virus is present in the saliva from 7 days before to 8 days after the onset of parotitis. In susceptible hosts viral multiplication leads to viremia. Thereafter the virus localizes in several organs such as the salivary glands, pancreas, central nervous system, testes, ovaries, thyroid gland and others. The salivary glands are enlarged and histology shows mononuclear infiltration. Neurological lesions take the form of meningoencephalitis or encephalomyelitis. Testicular lesions include intense interstitial edema, perivascular lymphocytic exudate, focal hemorrhages and destruction of germinal epithelium, which may be patchy or generalized.

Clinical Features

Incubation period is 18 days (range 12-21 days). Initial symptoms are fever, pain over the region of the parotid gland, especially on opening the jaw, trismus, dryness of the mouth and headache. Soon the parotids and less



Fig. 54.1: Female mumps

commonly the other salivary glands become tender and enlarged. Unlike suppurative parotitis, redness and edema are absent. Sialoadenitis is usually bilateral, but rarely it may be unilateral (Fig. 54.1).

After 5-7 days the fever and glandular enlargement subside. In the uncomplicated case, there is leukopenia with relative lymphocytosis. A few atypical lymphocytes may be present. When complications occur, neutrophil leukocytosis may develop. Around 50% of cases show CSF pleocytosis.

Complications

In the vast majority, the course is benign and uncomplicated. If the disease occurs in adult males 25% develop uni- or bilateral **orchitis**. The affected testis are red, swollen, tender and painful. Reactive hydrocele may develop. Sterility may follow bilateral involvement. **Oophoritis** may develop in women. Though parotitis is present in most of such cases, rarely gonadal lesions occur without obvious parotitis.

Pancreatitis should be suspected when patients with mumps complain of upper abdominal pain. In a few cases, serum amylase level may be increased. Pancreatitis usually subsides without sequel. Thyroiditis develops in some cases. The occurrence of **meningitis** is heralded by intense headache and signs of meningeal irritation. CSF shows

lymphocytic pleocytosis. Encephalomyelitis is a rare complication. Arthritis follows the acute illness after 2-3 weeks.

Diagnosis

Bilateral enlargement of the parotid and other salivary glands with mild constitutional disturbances should suggest the possibility of mumps. The diagnosis is easy, during outbreaks but it may be difficult when the presentation is atypical such as unilateral parotitis, or meningitis. Mumps virus can be isolated from throat washings obtained 48 hours before to 7 days after parotid swellings develop. Rise in antibody titer can be demonstrated in paired sera by complement fixation, hemagglutination inhibition or Elisa. PCR helps to identify the viral antigens.

Treatment

Symptomatic treatment consists of analgesics and antipyretics in addition to bed rest. This is all that is

required in most of the cases. Troublesome dryness of the mouth can be relieved by frequent sips of water.

When orchitis is present, local dressing with ichthyol glycerine and supportive bandage give relief. Prednisolone 40 mg daily for 4-7 days may help in reducing the inflammation. The meningitis also subsides with symptomatic measures. Corticosteroids produce early clinical improvement though there is no objective benefit demonstrated by controlled studies.

Prevention

Specific prophylactic measures are not generally required, since the infection runs a benign course and produces lasting immunity. A live attenuated vaccine (*Jeryl-Lynn strain*) is available for administration along with measles and rubella vaccines (MMR vaccines). This produces a noncommunicable subclinical infection. The vaccine is administered to children above the age of 13 months. Measles, mumps and rubella vaccines can be given together as a single injection safely between the age of 13-15 months. Booster doses are not required. Rarely fever, rashes and seizures may occur as adverse reactions.

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Viral Hepatitis

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GENERAL CONSIDERATIONS

Several viruses can cause the syndrome of acute viral hepatitis. This is characterized by diffuse inflammation of the liver as the predominant feature. Five viruses are mainly responsible for the vast majority of cases—Hepatitis A Virus (HAV), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), Delta Virus (HDV), and Hepatitis E Virus (HEV).

HAV and HEV are transmitted predominantly feco-orally through the enteric route. The others are transmitted parenterally. Viruses A and E produce acute hepatitis. Chronicity and delayed damage to the liver do not occur. On the other hand HBV and HCV cause both acute and chronic hepatitis, as in many cases the infection tends to persist and lead to chronic hepatitis, cirrhosis liver and carcinoma. HDV is exceptional in that it can exist only in the presence of HBV infection. It acts as a co-infecting agent and modifies the clinical picture and outcome in HBV hepatitis. Recently many workers described a sixth hepatotropic virus and independently named it hepatitis GV virus (HGV-C) and hepatitis GE virus (HGV). Probably they are the same, and are commonly referred to as HGV.

HCV, HEV and other viruses were previously known as non-A non-B viruses because diagnostic markers were not available. At present diagnostic serological markers are available for all hepatitis viruses.

Several other viruses cause hepatic lesions in addition to lesions in other parts of the body. These include cytomegalovirus, *Epstein-Barr virus*, herpes simplex, varicella zoster, dengue, yellow fever, rubella, hemorrhagic fever viruses, human immunodeficiency virus and others (Table 55.1).

Hepatitis A Virus (HAV)

It is a single stranded RNA virus belonging to the genus hepatovirus. There are four genotypes of the virus showing antigenic cross reactivity.

It is present in faeces of cases from 2 weeks before the onset of the symptoms. Infection is by the fecal-oral route. In tropical countries and in communities where food

hygiene is low, this infection is prevalent and the vast majority of sufferers are children. Contamination of drinking water supply with sewage is responsible for several outbreaks from time-to-time. Most of the adults acquire immunity due to subclinical infection or overt disease. They show the presence of specific antibody which is protective. With improvement in hygiene the disease becomes less common in children, and older age groups are affected more. Other methods of transmission include oral-anal sexual contact in homosexual men and rarely the parenteral route if the blood donor incubates the infection. The incubation period varies from 2-6 weeks. This virus has been grown in tissue culture. This infection does not become chronic. HAV used to be known as short-incubation hepatitis. HAV is relatively acid stable, it resists drying and can remain for at least a month under room temperature. The virus multiplies in the liver, and is passed into bile 2-3 weeks before the onset of jaundice, and the feces contains the virus. Maximal infectivity is during the later part of the incubation period. Once jaundice occurs infectivity comes down even though the virus is present in feces. The initial antibody response is IgM anti-HAV. This runs parallel to serum transaminase levels. After the eighth week the levels come down. IgG anti-HAV rises during recovery and this confers life-long immunity. RIA and ELISA tests are available for detecting these antibodies. PCR test can identify the virus specifically and distinguish between the different hepatotropic viruses.

Hepatitis B Virus (HBV)

HBV is the prototype member of the Hepadnaviridae (hepatotropic DNA virus). It is 42 nm in diameter. Chronic

TABLE 55.1 The important features of the viruses primarily causing hepatitis						
	HAV	HBV	HCV	HDV delta virus	HEV	HGV
Type of virus	RNA	DNA	RNA	RNA	RNA	RNA
Source of infection	Feco-oral rarely parenteral	Parenteral, sexual and mother to baby	Parenteral, rarely sexual, and mother to baby	Parenteral	Feco-oral, rarely parenteral	Parenteral
Incubation period weeks	2-6	8-48	2-22	4-8	2-9	"
Onset of clinical illness	Acute	Insidious	Insidious	Acute	Acute	Clinical significance not established
Presence of jaundice	50%	33%	25%		20%	
Diagnostic markers	IgM HAV	HBsAg	Anti-HCV IgM	Anti-HDV IgM	Anti-HEV	HGV RNA
Establishment of chronic carrier state	Nil	5-10%	Upto 60%	Vast majority	Nil	"
Vertical transmission	—	+	+	+	—	"
Chronic hepatitis	Very rare	5%	30-50%	70%	Rare	"
Fulminant hepatitis	0.1%	Upto 1%	Not known	Upto 17%	Upto 10% in pregnant women	
Vaccination	Available	Available	No	—	No	No

hepatitis B affects 350 million people, approximately 5% of the world population. Carrier state of the virus ranges from 0.1-20 % in different parts of the world. Prevalence has been classified as high (> 8% of population affected), intermediate (2-7%) and low (< 2%). Prenatal transmission is high in high prevalence areas. In India the prevalence ranges from 1.2 to 12.2% the average carrier rate is 3.34%. Eight genotypes A-H have been identified and the prevalence in different geographical areas varies. In India A and D genotypes are more prevalent. The different genotypes vary in their pathogenicity, especially in severity, chronicity and oncogenic potential. Mothers who are chronic carriers of infection and those who develop acute hepatitis B in the last trimester transmit the disease to their babies in the perinatal period. If the HBsAg and HBeAg are positive the chances for transmission exceeds 90%. Infection is acquired by the infant during its passage through the vagina and inoculation of mother's blood and liquor amnii. Infection acquired during the neonatal period leads to chronicity in > 90% of cases, whereas infection acquired during adult life leads to chronicity only in 5-10% of cases.

HBV spreads by parenteral introduction of the infective agent along with blood or blood products or through needle pricks. In communities where the carrier rate is low (1 in 1000 or less) HBV infection is seen in special population groups such as newborns of carrier mothers, homosexuals, drug addicts and personnel working in dialysis units and laboratories. The virus can also spread by hetero-or homosexual intercourse. In homosexuals, the transmission rate is high. Risk factors include multiple casual sexual partners, anal intercourse, and a high carrier rate among these subjects. Oral-oral spread occurs by kissing, since the virus is present in saliva. Accidental contamination by infected blood can transmit the disease. In India the main mode of transmission is horizontal-from child to child or adult to adult. Other than the liver and plasma, it may be present in saliva, tears, vaginal secretions, semen, breast milk, sweat and urine. It is highly infectious. Infection is by parenteral route or contact with abraded skin, or mucosal surfaces. Risk of infection from needle stick injuries in health care workers is as high as 30%. This risk can be prevented by immunisation. Gastric acid and pancreatic enzymes destroy the virus. It is demonstrable in sera of patients many weeks before the acute illness, and it may be demonstrable for 3 months or more after clinical recovery.

Viral Morphology

The virus consists of a central core consisting of core antigen (HBcAg), e-antigen (HBeAg), a specific DNA polymerase and a circular DNA (HBV-DNA). Under electron microscope the virus is seen as spherical particles

called Dane particles. The virus consists of a lipoprotein outer coat which is secreted in excess by hepatocytes and released into serum. Presence of excess of envelope antigen HBsAg is a special feature of HBV. This surface antigen circulates in the plasma in the form of rods or spheres with a diameter of 22 nm. This is detectable as hepatitis B surface antigen (HBsAg) 1-10 weeks after infection and 2-8 weeks before onset of symptoms. This is diagnostic of the presence of infection. Some cases of HBV hepatitis do not show HBsAg in blood, even though the viral genome may be demonstrable. HBsAg is itself not infective to others. HBsAg was described in 1965 first by Blumberg in the blood of an Australian aboriginal and was hence termed Australia antigen. HBsAg can be detected by RIA or ELISA tests. Its presence is pathognomonic of recent or chronic HBV infection. With the onset of clinically detectable hepatitis and jaundice, the level of HBsAg falls. Clearance of HBsAg indicates resolution of infection.

Immune Markers of HBV Infection

Antibodies to HBsAg develop (anti-HBs) and these may be IgM and IgG in serum and IgA in secretions. These antibodies provide immunity to future infection by HBV. IgM is short lived, whereas IgG antibody persists. Anti-HBs antibody (anti-HBs Ab) can be estimated to detect protective immunity. These are detectable in patients who recover from the disease and in these who are successfully vaccinated. Antibody levels above 10 m IU/mL are protective.

Antibodies to other HBV components develop in due course. HBcAg (Hepatitis-B core antigen) is not detectable in serum, but with the onset of clinical illness anti-HBc IgM (IgM antibody to core antigen) appears and remains elevated throughout the course of the disease. Detection of anti-HBc IgM is diagnostic of HBV hepatitis. This also helps to rule out superinfection in an HBV carrier by other hepatitis viruses. Anti-HBc IgM is the only serological marker of HBV infection when HBsAg has disappeared and anti-HBsAg has not reached detectable levels. Anti-HBcAb is not a neutralizing antibody and therefore it is not protective. Initial antibody is IgM type later it is replaced by IgG type. Persistence of anti-HBc IgG in high titer indicates continuing infection.

HBe antigen is a circulating peptide derived from the core genome and transported from liver cells. HBe positive mothers transmit the disease more readily to their infants (73%) than HBe negative mothers (13%).

Detection of hepatitis-e antigen (HBeAg) indicates active replication of the virus and presence of infective agent in the liver. HBeAg appears within 1 week of appearance of HBsAg and disappears within 4 weeks of onset of symptoms. Persistence of HBeAg beyond 10 weeks should suggest progression to a carrier state and it

may also portend the development of chronic hepatitis. In those who overcome the infection antibody to HBe- (anti HBe) appears within 4 weeks of onset of symptoms. Presence of anti-HBe suggests good immunological response and chance of recovery.

Presence of virus in blood is demonstrable directly by the presence of circulating viral DNA (HBV-DNA). In India about 25% of HBsAg + subjects show also HCV positivity. Coexistent hepatitis C infection suppresses markers of HBV replication.

HBV DNA and DNA polymerase appear in the serum at the same time as HBeAg. These also are markers of HBV replication and potential infectivity. HBV DNA is detected by polymerase chain reaction (PCR). Levels of HBV DNA correlate with transaminase levels and HBsAg in the serum.

HBV infection is tolerated by the body and once infection occurs, 5-10% become chronic carriers. *Younger the age of getting the infection, greater is the chance of developing carrier state. In vertical transmission from mother to newborn the carrier state may develop in 80-90%, whereas in transmission in adult life the chances are less.* Most of the carriers tolerate the virus which replicates in the liver. They show HBsAg positivity and viremia, but at the same time do not suffer from the disease. They are the main source of spread to others. This state may persist lifelong. Risk of primary carcinoma of the liver is high in them and many of the cases of liver cell cancer occurring in young adults, especially in India and other neighbouring countries are attributable to HBV.

The life cycle of HBV can be divided into four stages:

- Stage 1** Immune tolerance occurs. Viral replication occurs even without elevation of hepatic SGPT. This is the incubation period. HBeAg and HBV DNA levels in serum are high.
- Stage 2** Immunological response develops leading to production of cytokines, direct cell lysis and the inflammatory process. Secretion of HBsAg continues. This is the stage of active sympto-

matic hepatitis. This may last for 2-4 weeks. In those with chronic hepatitis this stage may extend to several years, leading to cirrhosis and its complications. If the host is able to mount an immune response that eliminates the infected hepatocytes, active viral replication ends and this marks the onset of the third stage.

Stage 3 This is the stage at which the bulk of the virus infected cells have been cleared. At this stage HBeAg is no longer detectable but anti-HBeAb becomes demonstrable. Viral DNA levels drop even through PCR may still be able to detect it. In most cases the infection is cleared and the SGPT levels become normal. However HBs positivity may still persist, presumably because of the integration of the viral genome with that of the hepatocyte.

Stage 4 At this stage the virus is cleared and protective antibody is abundant. Most patients eventually become negative for HBsAg and positive for anti-HBsAg (HBsAb). HBV DNA is no longer detectable and the patient is immune to further infection.

The factors affecting the stagewise progression of the infection and the ultimate outcome include.

- 1. genetic predisposition of the host
- 2. co-infection with other virus (hepatitis C and D)
- 3. treatment with immunosuppressant drugs, and
- 4. the appearance of HBV mutants (Table 55.2).

Hepatitis C Virus (HCV)

This was first identified in 1989. It is an RNA virus belonging to the family flaviviridae. At least six genotypes, HCV 1 to HCV 6 are identified and subtypes are denoted by letters a, b, etc. In India HCV3 is more prevalent. In voluntary blood donors in West Bengal the prevalence rate was 1.8%, in Chandigarh it was 2.8% and in Delhi it was 1.85%. The genotypes determine the response to treatment. Types 2 and 3 are more responsive

TABLE 55.2				
The four stages of hepatitis B infections				
	Replicative phase		Integrative phase	
Disease marker	Stage 1	Stage 2	Stage 1	Stage 2
HBsAg	Positive	Positive	Positive	Negative
Antibody to HBsAg	Negative	Negative	Negative	Positive
HBV DNA	Strongly positive	Positive	Negative	Negative
Antibody HBcAg	Positive	Positive	Positive	Positive
HBeAg	Positive	Positive	Negative	Negative
Antibody to HBeAg	Negative	Negative	Positive	Positive
Asparate and alanine aminotransferase levels	Normal	Elevated	Normal	Normal

to pegylated interferon and ribavirin (85%) whereas the others are less so (48%). Genotype 1b is most aggressive in course and least amenable to drugs.

The virus is present in blood, tissue fluids, saliva, vaginal secretions and semen of infected persons. Infection is acquired mainly by parenteral route. Transfusion of blood and blood products and sharing of contaminated needles for injection account for more than 85% of cases. Sexual transmission occurs from unprotected sexual intercourse. Male to female transmission by the sexual route is more efficient and infection rate is 1.6% among sexual partners. Co-infection with HIV enhances the rate of sexual transmission. Health care staff gets infection by entry of the virus through contamination by blood and body fluids coming into contact with cuts and wounds or needle stick injuries. Infection rates among health care workers are 0.6-4.5%. Hemodialysis patients have infection rates ranging from 0.6-4.5%. Perinatal transmission rate is 2-3%. In general HCV is less infectious compared to HBV.

The course of HCV is progressive if untreated. Unlike HBV 50-70% of cases develop chronic hepatitis. Of these 20-50% develops cirrhosis over a period of 10-20 years. Twenty five percent among these cirrhotic patients may develop hepatocellular carcinoma. In contrast to HBV, infection HCV acquired during childhood: runs a more benign course than that in adults. Older age, alcoholism and coinfection with HBV and HIV increase the risk of diseases progression and chance of developing decompensated cirrhosis. In thalassemic children with iron overload HCV runs a more aggressive course.

After infection by HCV, the viral RNA becomes detectable in serum within 1-2 weeks. Thirty percent of cases are anicteric. Eighty-five percent go into chronicity. The natural history of HCV infection is variable. In more than 60%, the infection persists and the virus is demonstrable in blood for over 5 years. Ten percent may recover completely.

Hepatitis Delta Virus (HDV)

Syn: Delta Agent

This is an RNA virus which is incomplete, and therefore, requires prior infection by HBV for establishing and replicating in the host. HDV is transmitted parenterally and sexually. Vertical transmission from mother to offspring is rare. HBV and HDV may enter together or separately and cause co-infection of the recipient or HDV may cause super-infection on a person already suffering from HBV.

HEPATITIS E VIRUS (HEV)

This is an RNA virus transmitted mainly by the enteral route, and is associated with poor sanitation. It can occur

in small or large outbreaks. The virus is shed in feces and so fecal-oral route of infection accounts for most of the cases. HEV antigen has been identified in the cytoplasm of hepatocytes in patients suffering from the disease.

Waterborne outbreaks of HEV hepatitis have been described from several parts of India—Ahmedabad, Kohlapur, Srinagar and others. HEV RNA or anti HEV antibodies have been reported from swine, cows, goats and rodents. Infection by consuming uncooked deer meat has been recorded.

(S. Tei et al. The Lancet 2003. 362. 371-373).

HEPATITIS G VIRUS (HGV)

Two groups of investigators detected a new hepatitis virus independently named hepatitis GB virus (HGBV-C) and hepatitis G virus (HGV). The letter GB stands for the initials of the patient from whom the virus was isolated first. Three viral agents have been identified HGBV-A, HGBV-B and HGBV-C. They belong to the group of tamarin viruses which cause hepatitis in tamarin monkeys.

HGV was cloned from a patient who developed community acquired chronic hepatitis.

Molecular characterization of both HGBV-C and HGV has shown an almost identical pattern. They are single stranded RNA viruses belonging to the family flaviviridae. HGBV-C and HGV share 80% of this nucleotides and 86% of their amino acid sequences. HGV viremia is highly prevalent in persons undergoing hemodialysis and is correlated with the number of transfusions and duration of hemodialysis. In reports from India HGV and HBV coinfection occurred is 6-17% where as HCV and HGV coinfection occurred in 11-19%. GBV closely resembles HCV, but unlike HCV, it does not replicate in the liver cells. It does not cause hepatitis. It replicates in vitro in peripheral blood mononuclear cells, CD4 and CD8 T lymphocytes and also B lymphocytes. Human infection by GBV occurs in 1-8% of blood donations. Clinical significance of HGV still remains uncertain. Its role in the pathogenesis of hepatic lesions remains unsettled. At present it is not found to worsen the course of HCV. Though HGV responds to interferon, at present this treatment is not recommended.

PATHOGENESIS AND PATHOLOGY

Under most circumstances HBV and other viruses by themselves do not kill the hepatocytes. An intact immune system is necessary to cause cell injury as well as ultimate clearance of the virus. For practical purposes the severity of hepatocyte injury also reflects the vigour of the immune response. The most complete immune response is also associated with the chance of viral clearance and full recovery.

The hepatitis viruses cause injury to liver cells by direct invasion and immunological processes. Immune

complexes appear in blood prior to the onset of liver injury. They may account for the serum sickness like syndrome observed in the early phase. Cellular immunity also plays a role in altering the host's response to the virus and the progression to the chronic carrier state.

Pathology

The lesions caused by viruses A, B and others are all similar. In uncomplicated hepatitis the essential lesions are ballooning of hepatocytes, acidophilic degeneration leading to the presence of **Councilman's bodies** and focal necrosis or cell dropouts. Changes are more pronounced in the centrilobular regions. There is infiltration by small lymphocytes, plasma cells and eosinophils, most marked in the portal regions. Kupffer cells undergo hyperplasia. Many large multinucleated hepatocytes are formed. There is also a variable degree of cholestasis. The pathological changes are seen diffusely involving all the lobules.

Necrosis of liver cells is a prominent feature in severe cases. Necrosis involving many adjacent hepatocytes is described as *confluent necrosis*. The term "*submassive*" *necrosis* is used to denote necrosis involving several adjacent lobules. The necrosis may extend between adjacent central zones, portal zones or between adjacent central and portal zones. If the reticulum is intact, full regeneration is possible and recovery is complete. If the reticulum collapses, collagenous tissue is laid down and this leads to fibrosis, which bridges adjacent zones. These cases have a more unfavourable prognosis and many of them progress to subacute necrosis or to chronic hepatitis and cirrhosis. When necrosis is submassive or massive and fulminant, the liver shrinks in size and this carries a grave prognosis. With the onset of recovery, regenerative changes and Kupffer cell activity become evident.

HBV and HCV predispose to cirrhosis and carcinoma. In India post-hepatitic cirrhosis is caused mainly by HBV and also by HCV. In endemic areas with a high carrier rate and chance for vertical transmission of the virus from mother to child, primary carcinoma of the liver occurring in young adults may be a late sequel to these infections.

GENERAL CLINICAL FEATURES

Hepatitis presents a clinical spectrum ranging from mild and inapparent infection to the most serious, fulminant and rarely fatal acute hepatic failure. Subclinical infection is recognized by the rise in antibody titer during epidemics. In many others, clinical illness without jaundice may develop. In these cases of anicteric hepatitis, prodromal symptoms and biochemical abnormalities may develop but jaundice may not occur. Such anicteric cases far outnumber the icteric cases during epidemics. As a general rule the onset of HAV hepatitis is more acute than that of HBV. The onset of the other viral infections is

generally similar, but variable in intensity. The clinical picture is similar, but HBV and HDV hepatitis tends to be more severe.

Prodromal Symptoms

The classic attack of viral hepatitis is heralded by a prodromal phase which lasts for three to five days or longer, before the onset of jaundice.

The prodrome consists of general malaise, headache, fatigue, nausea, vomiting and mild pyrexia. Severe anorexia and aversion for smoking and alcohol are characteristic. Symmetrical non-migrating polyarthritides with or without effusions may occur in 15% of cases. Features like anosmia, dysosmia, hypageusia or dysgeusia, urticaria, maculopapular rashes, polyarteritis and thrombophlebitis may occur less commonly.

The Icteric Phase

The prodromal phase is followed by the icteric phase. Urine becomes deep yellow and the stools pale in colour with the appearance of jaundice. Nausea and vomiting subside and appetite returns. The patient becomes afebrile and feels better. Transient pruritus might appear. Discomfort in the right hypochondrium may be felt. Liver may be moderately enlarged and mildly tender. Spleen is enlarged in 20% of cases. The jaundice deepens over the first one or two weeks, after which it gradually subsides to clear up in three to four weeks. Initially the jaundice is hepatocellular in type, later it becomes obstructive. Convalescence may be prolonged in many cases. HBV and HCV may produce symptoms related to other systems such as arthralgia and arthritis, lymph node enlargement and skin rashes, glomerulonephritis, keratoconjunctivitis and others (Fig. 55.1).

Stage of Recovery

In most of the cases clinical and biochemical recovery is complete within four to six months of the onset of



Fig. 55.1: Obstructive jaundice in viral hepatitis

jaundice. Loss of weight, general weakness and vague illhealth may persist for varying periods in many.

SPECIAL CHARACTERISTICS OF HCV, HDV AND HEV

Hepatitis C

The three types of clinical presentation are:

1. Florid stage with high viremia
2. Symptomless carriage with low viremia
3. Recovery without viremia — this occurs only in a few.

In contrast to HBV—there is no state of immune tolerance. Liver shows subacute or chronic lesions varying in severity. Hepatitis C is a common cause for hepatic transplantation. In many cases, the graft also gets infected by hepatitis C.

Acute HCV infection is asymptomatic in many, except for the presence of elevated transaminase levels in serum within 2-26 weeks (15 times the normal levels). 30% have symptoms such as anorexia, weight loss abdominal pain, myalgia and mild jaundice. These resolve in 1-3 months-PCR detects the virus in serum within a week of exposure. Antibody response occurs in 4-8 weeks and this can be demonstrated by ELISA tests.

Chronic HCV Infection: 60-70% of cases go into chronicity; among which a third are symptomatic. Clinical features include fatigue, right hypochondrial pain, hepatomegaly in 30-70%, splenomegaly in 15% and cirrhosis in a few. Carrier state with normal transaminase levels occur in 70% and with elevated transaminase levels in 30%. Those with elevated transaminase levels follow an unpredictable course. Transition from hepatitis to cirrhosis may take 3-30 years-Hepatocellular carcinoma develops in 20-30 years, the annual risk being 1.4%. Male gender, alcoholism, age above 45 years, host immune factors, viral genotype 1b and co-infection with HIV are adverse prognostic factors.

Extra hepatic manifestations of HCV: These are common in HCV infections. 45-65% show antinuclear antibodies (ANAs), smooth muscle antibodies and antithyroid antibodies is serum as epiphenomena.

Essential mixed cryoglobulinemia is associated with the presence of HCV RNA in serum in up to 84% of cases. The clinical features include the triad of palpable purpura, arthralgias and weakness. The various mixed cryoglobulinemia-related extra hepatic manifestations of HCV infection include the following

1. **Cutaneous leukoclastic vasculitis** This manifests as palpable purpura in the lower limbs, which ulcerate due to plugging of the dermal capillaries by precipitated cryoglobulins containing the virus. Severity of manifestations directly correlates with the viral load. Interferon treatment allays the lesions.

2. **Renal disease:** Membranoproliferative glomerulonephritis (MPGN) is associated with cryoglobulinemia in 20% of cases. The renal lesions confer poorer prognosis.

3. **Locomotor system:** 50% have one or other musculoskeletal manifestations. These include arthralgia, myalgia, polymyositis dermatomyositis Behcet's syndrome, antiphospholipid antibody syndrome, fibromyalgia and others. Joints affected include ankles, wrists, elbows, hands and toes. Response to antiviral therapy is good.

Nervous system—Neuropathies occur in 10-20% of cases. Lesions include cerebral infarction, stupor, mononeuritis multiplex and cranial nerve palsies.

4. **Miscellaneous conditions**

- a. Pulmonary vasculitis and respiratory distress syndrome
- b. **Sjögren's syndrome**
- c. **Porphyria cutanea tarda** (20-50% of cases)
- d. **Lichen planus, polyarteritis nodosa, prurigo, erythema nodosum and immune thrombocytopenic purpura.**

Hepatitis D (HDV)

HDV can lead to acute or chronic liver disease when co-infecting with HBV. This combination is more severe than simple HBV. Clinical presentation of HDV ranges from asymptomatic carrier state, acute and chronic hepatitis, cirrhosis and liver failure. Direct response to interferon, ribavirin and lamivudine is minimal if any. Control of HBV indirectly controls HDV as well.

Hepatitis E (HEV)

Volunteer self-inoculation study published from PGI Chandigarh revealed the following:

Incubation period was 15-20 days. Initial symptoms include anorexia, epigastric pain and high coloured urine. All these were well-established by 30 days post-inoculation. Icteric phase started from day 38 and lasted till day 120 associated with rise in serum bilirubin and transaminases.

HEV was first identified in blood on day 22 and could be detected till day 46. HEV antibodies appeared on day 41 and persisted beyond 2 years. Recovery was complete and follow up for 2 years did not reveal any sequel. Since HAV and HEV appear in blood before the onset of jaundice, there is risk of transmission by blood transfusion during the window period.

Clinical features are similar to those of HAV—jaundice, anorexia, hepatomegaly abdominal pain, nausea, vomiting and fever. Mortality in the general population is 0.5-4%, but in pregnant women the disease is more serious and mortality may go up to 20%. HEV is being reported from developed countries as well. At present there is no vaccine to protect against HEV.

Hepatitis G

The exact pathogenesis role of HGV is yet to be established.

INVESTIGATIONS

Urine

Bilirubin is present early in the disease. This is followed by the appearance of urobilinogen. With the onset of the obstructive phase, urobilinogen temporarily disappears from the urine to reappear during recovery. The feces is clay-coloured during the obstructive phase.

Blood

Initially there is leukopenia with relative lymphocytosis which reverts to normal with the onset of jaundice. Atypical lymphocytes may be present in small numbers. The erythrocyte sedimentation rate is mildly elevated in the pre-icteric phase returning to normal as jaundice appears.

Biochemical Tests

These depend upon the severity of hepatic functional impairment. The prothrombin time may be prolonged. Serum bilirubin increases in the first two weeks to reach levels of 10-15 mg/dL or more. This is a mixture of conjugated and unconjugated pigment, the former predominating. Serum bilirubin levels return to normal in 3 to 4 weeks. Serum transaminase values-alanine and aspartate transaminases (SGPT and SGOT) increase considerably to reach peak levels just before or after the onset of jaundice. In the majority of cases the enzyme levels are in the range of 200-600 IU/L. Raised levels may persist even for a few months after apparent clinical recovery. In some cases the enzyme levels reach much higher values. Apart from the transaminases, alkaline phosphatase, 5-nucleotidase, gamma glutamyl transpeptidase and serum LDH are moderately elevated. Serum alkaline phosphatase level rarely goes above twice the normal value and this helps in differentiating viral hepatitis from extrahepatic obstructive jaundice. Persistent elevation of the enzymes beyond six months would point to the development of chronic liver disease.

Serological markers are diagnostic for the different viruses. Second and third generation ELISA help to demonstrate viral antibodies. Recombinant immunoblot assay detects antibody to HCV and qualitative PCR measures the viral RNA.

Serological Markers for Diagnosis

Hepatitis B virus: Acute hepatitis due to HBV may be associated with HBsAg and IgM HBc. If IgM HBc is negative the hepatitis may be due to other causes as well.

Presence of HBsAg alone indicates the carrier state. Modern tests can detect HBsAg levels as low as 1ng/mL. The usual values in acute hepatitis vary from 10,000 to 100,000 ng/mL.

Presence of HBeAg indicates infectivity. Generally HBsAg and HBeAg are positive in most cases. Routine testing of HBeAg is not indicated. In chronic cases presence of HBeAg is an indication for starting treatment. Favourable response results in the production of antibody to HBeAg. Anti-HBe antibody (anti-HBe ab) appears in the serum and this indicates resolution and success of therapy.

Anti-HBe is found in both acute and resolved cases of HBV hepatitis. In acute hepatitis IgM anti-HBe is elevated in all cases and its presence is diagnostic. In chronic infections it is the IgG antibody.

Anti HBs antibody is not a reliable test to determine the prevalence of HBV infection in the population, but it is a good test to determine the success of vaccination against HBV.

Hepatitis C is diagnosed by demonstrating anti HCV antibodies and PCR tests to detect the viral RNA. Genotyping helps to characterize the virus, assess the prognosis and plan treatment.

Liver biopsy: Liver biopsy is not indicated in the ordinary case. Biopsy is indicated to differentiate viral hepatitis from extra hepatic obstruction and confirm the presence of chronic hepatitis if the condition does not resolve and diagnostic parameters are not clearcut. It is advisable to have biopsy confirmation of the persistent hepatic lesion before starting on interferon therapy.

COMPLICATIONS AND SEQUELAE

Complications occur in a small proportion of cases whereas the vast majority of cases recover uneventfully.

1. **Relapse:** About 15% of patients may get relapse after initial clearance of jaundice. Premature resumption of physical activity favours relapse. With proper management this also subsides completely.
2. **Prolonged cholestasis:** Cholestasis may persist due to the development of intrahepatic obstruction. This is more frequently seen with acute HAV and HEV infections. With rest and supportive measures these patients usually recover completely within weeks or months.
3. **Fulminant hepatitis:** This is a serious complication occurring in 1 to 2% of patients, more so in type B hepatitis. Hepatic function deteriorates rapidly with the onset of hepatocellular failure. When hepatic encephalopathy occurs within 8 weeks of onset of jaundice it is called fulminant hepatic failure. If this occurs between 8 weeks and 28 weeks it is called subacute hepatic failure. Hepatitis B is responsible for 30-60% of cases of acute hepatic failure. The liver

shrinks progressively. The condition is fatal in 80% of patients, irrespective of the treatment. Death is due to cerebral edema, brainstem damage, gastrointestinal hemorrhage, infections or renal failure. The overall mortality is 2% in HBV infections, but 10% or more in post-transfusion hepatitis, since the infecting dose is high in the latter.

Chronic hepatitis: This is defined as continuing inflammation of the liver persisting for more than six months. HBV is responsible for chronic hepatitis in 30-50%. Chronic hepatitis may take the form of chronic persistent hepatitis which is benign and self-limiting or chronic active hepatitis which is more sinister and often ends up in hepatic failure or cirrhosis.

Cirrhosis: HBV and HCV can progress to cirrhosis directly or passing through a stage of chronic active hepatitis. HCV relentlessly progresses to chronic liver failure and it is a frequent cause for hepatic transplantation. Median time from infection to cirrhosis is $\pm$ 30 years.

Hepatocellular carcinoma: Both HBV and HCV are oncogenic. Persistence of the virus in the system for 25 years or more predisposes to carcinoma. The risk of developing hepatocellular carcinoma is high in HBV carriers. The incidence of cancer in a community correlates directly with the HBV carrier rate. In areas where HBV carrier rate is very high (15%), the mean age for carcinoma is 25 years, since a good number of subjects get infected perinatally. In areas where the HBV carrier rate is low (1% or less), the mean age for cancer is 50 years or more, since the main source of infection is parenteral or sexual route. Malignancy may follow hepatitis directly or through a phase of cirrhosis. HCV is also carcinogenic.

Post-hepatitis syndrome: Sometimes symptoms of illhealth persist for many months after apparent recovery. The liver may remain slightly enlarged with evidence of mild or moderate dysfunction. Such persons generally show anxiety and loss of morale which aggravate the disability. If followed up, many recover. Only reassurance is needed.

Extrahepatic manifestations: Patients with HBV or HCV infection have circulating immune complexes, which lead to the development of serum sickness-like picture early in the disease. These are more prominent in the case of HCV.

Aplastic anemia: Aplastic anemia may follow HAV and HCV infection rarely. This is an immune mediated process.

Differential diagnosis: Drug-induced hepatitis, intra-hepatic cholestasis due to other causes and cholangitis present with jaundice, and these have to be differentiated.

Though hepatic amebiasis is not generally associated with jaundice, in a few cases it may create problems when mild or moderate jaundice occurs. Hepatic amebiasis presents with tender hepatomegaly, moderate leukocytosis, no impairment of hepatocellular function and recovery with anti-amebic drugs. Outbreaks of liver damage resulting from toxic products (e.g., veno-occlusive disease and aflatoxicosis) may be initially mistaken for viral hepatitis. Falciparum malaria should be excluded in all cases. Leptospirosis is a common cause for acute hepatitis at present.

Differential Diagnosis of Viral Hepatitis

Drug induced hepatitis	Rise of ALT is only moderate – compared to the rise in bilirubin
Alcoholic hepatitis	
Falciparum malaria	This should be considered in all cases and excluded by repeated examination of blood smear.
Gallstone disease with acute biliary obstruction	The transaminases may rise abruptly to high levels and fall soon. Serum bilirubin and alkaline phosphatase may rise later. Ultrasonography is most often diagnostic.
Acute anoxic damage to liver	This occurs in passive venous congestion occurring abruptly. This may lead to abrupt rise of SGPT to very high levels even 10000 IU/L, but unlike as in viral hepatitis where LDH level is only moderately increased, here LDH is also very much raised.
Leptospirosis	This presents with acute hepatitis and jaundice, proteinuria, hemorrhagic manifestations and neutrophil leucocytosis. Leptospira antibodies are demonstrable.

PROGNOSIS

Virus A hepatitis is a benign disorder which recovers uneventfully in most of the cases with mortality below 2%. In children the disease runs a milder course whereas in the elderly patients complications occur. Fulminant hepatitis carries a grave prognosis. During pregnancy viral hepatitis carries a higher risk of mortality and morbidity, especially in the malnourished subjects. The prognosis of HBV is more serious, mortality and morbidity being higher. Though the vast majority recover, 1-2% go on to chronic hepatitis and carcinoma. In 5-10% of cases the carrier state persists and such people can be infective to others.

HCV follows the same long-term behaviour as HBV. Unlike HBV which can exist in a carrier state with no lesion in the liver, HCV tends to produce chronic lesions in the liver in most cases.

HDV aggravates the clinical picture of HBV and leads to greater incidence of acute hepatic failure. HDV gets eradicated when HBV disappears.

HEV is more benign, except when it occurs in pregnant women in whom the mortality may reach up to 40%.

MANAGEMENT

Bed rest: All patients with acute viral hepatitis should be put to bed since this helps in speeding up recovery and avoiding complications. Heavy physical exertion is better avoided for a period of six months.

Diet: It is customary to recommend a low fat diet in the early stage of viral hepatitis so as to reduce nausea and abdominal discomfort. A normal diet can be resumed as the appetite returns.

Specific therapy: Drugs which are effective against HBV include ribavirin, lamivudine, adefovir, tenofovir, entecovir and interferon alfa (IFN α).

Ribavirin is an antiviral antibiotic given in a dose of 1000-1200 mg/ day oral for long periods. It is effective against HBV.

Lamivudine (Zeffix Glaxo SmithKline) It is a nucleoside analogue which inhibits DNA chain synthesis. The dose is 100 mg to 300 mg oral/daily. The drug is effective against HBV. It is also effective against HIV. Resistance to lamivudine therapy may develop and this is a major disadvantage. Main adverse side effects include anemia and teratogenic potential.

Adefovir dipovaxil (Hepsera-Gilead): This is an inhibitor of reverse transcriptase, effective against HBV. The dose is 10 mg/ day. It is indicated when the virus develops resistance against lamivudine. Doses above 30 mg/day may lead to nephrotoxicity.

Tenofovir (Viread-Gilead): This is also an analogue of adefovir and is a reverse transcriptase inhibitor. The dose is up to 300 mg per day oral. In cases resistant to adefovir, tenofovir may still be effective.

Entecovir is a newer analogue where is reported to be safe and effective.

The viruses may become resistant to all these drugs. The exact duration of therapy has not been conclusively determined. In those with favorable response the treatment has to be continued for several years (4 or more).

Indigenous drugs have been introduced from time to time. Though many of them have not undergone rigorous

clinical trials, some of them especially extracts of *Phyllanthus niruri* have shown benefit and seroconversion in a small proportion of cases.

Interferon Alpha (IFN- α)

This is used for hepatitis B, hepatitis C and also hepatitis D infections. This treatment is effective.

Interferon therapy is started when there is no further chance of natural cure and if the abnormal liver functions and liver biopsy findings persist after six months of clinical remission.

Combination of ribavirin 1000 mg oral bd and interferon 2-3 million units IM daily gives better results than either drug given alone. With higher doses of interferon the cure rate may go up to 60%.

Side effects of interferon include malaise, fever, shivering and 'flu' like symptoms within a few hours of injection. With successive injections the side effects came down. These side effects can be controlled by paracetamol 500 mg given orally. Other side effects include anorexia, hair loss, depression weight loss, marrow suppression, seizures and susceptibility to bacterial infection. Beneficial effects are monitored by the level of transaminases and clinical improvement. Majority of the cases that improve do so within 2 months. Maintenance of normal transaminase levels for six months or more after cessation of therapy indicates cure.

- Cure rates in HBV on interferon are 25-40%
- In HCV 6-12 months therapy gives cure rates of up to 40%.
- In HDV the remission rate is up to 25%.

Earlier the treatment is started, better is the response. Absence of cirrhosis, absence of high levels of hepatic iron in biopsy before therapy and HCV genotypes 2 and 3 indicate favourable prognosis.

Pegylated interferon (interferon attached to polyethylene glycol) which has longer duration of action gives better cure rates with less of side effect. The drug is more expensive.

Indications for Specific Therapy in HBV Infections

1. Presence of HBeAg with raised transaminase
2. HBe negative, but HBV DNA+, with raised transaminase
3. and HBe + cirrhosis

Treatment is by suitable combination of ribavirin, lamivudine, adefovir and interferon α . Dose of IFN for hepatitis B is 2-5 million units daily or 10 million units three times a week for 16 weeks or longer. The response to IFN varies with the type of virus. In HBV 30-40% respond with disappearance of hepatitis B antigen and HBV DNA from serum. There is an initial transient

exacerbation of hepatitis, followed by eventual recovery. The serum transaminases return to normal and HBsAg is also cleared gradually in 60% of cases or more. Recurrence is unusual. Alpha interferon is available as Roferon and Viraferon.

Duration of therapy should be from 1 year or more. Up to 30% develop resistance to the drugs and alternate drugs may be required. On stopping therapy HBV DNA may reappear. When HBV coexists with HIV, the dose of lamivudine has to be increased to 300 mg / day. It is likely that prolonged lamivudine therapy delays the onset of cirrhosis and carcinoma.

Results of therapy: Seroconversion rate is up to 32%, disappearance of HBsAg in < 1%, and normalization of transaminases in 41-72%. Histological improvement occurs in up to 50%.

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Treatment of HCV

Acute HCV infection: IFN α 2b, 5 million units/day IM injection for 4 weeks and thereafter 3 times a week for 20 weeks. In chronic hepatitis C the pattern is different. Hepatitis C is more susceptible to interferon and smaller doses (3 million units given thrice a week for 6 months) are sufficient. Patients without cirrhosis do better than those with cirrhosis. In 50% of cases the transaminases fall to normal level and HCV RNA disappears from serum by the end of therapy. Relapses are more common and only 20-25% get permanent cure.

Chronic hepatitis C standard treatment Peginterferon + Ribavirin. Two formulations of peginterferon are available to treat HCV: The recommended dose for peginterferon alpha-2a is 180 μ g per week and that of peginterferon alpha 2b is 1.5 μ g/kg bw weekly. Ribavirin is also given in daily doses of 1000 mg oral for those <75 kg bw, and 1200 mg for those >75 kg bw. Duration of treatment for HCV genotype 1 is 48 weeks. For genotypes 2 and 3 the duration of treatment is only for 24 weeks with a dose of ribavirin of only 800 mg daily. For genotype 4, 5 and 6, the regimen for genotype 1 is given. Cost of treatment for 48 weeks is \$ 30-40,000. Persons with HCV above the age of 18 years should be treated if HCV-RNA is detectable in serum and evidence of chronic hepatitis such as elevation of SGPT and necroinflammatory changes are present in liver biopsy.

Follow-up: Prolonged follow-up is necessary in cases which have developed complications.

PROPHYLAXIS

HAV and HEV infections can be prevented by boiling drinking water for 10 min during the epidemics. General precautions to prevent fecal-oral spread should be instituted. These include personal hygiene, disposal of excreta and control of flies.

Passive immunization: Immune serum globulin (ISG or pooled human gammaglobulin) prevents or modifies virus A infection. The dose is 0.02 to 0.12 mL/kg given intramuscularly within 14 days of exposure. Passive immunisation is indicated in contacts of HAV hepatitis, pregnant women at risk, travellers to endemic areas and those who have received probably infected blood. The protection lasts for 4- to 5 months, therefore, the dose has to be repeated at 5 month intervals. Sexual and familial contacts of cases of HAV hepatitis during the incubation period should be given gamma globulin.

Active Immunization

Hepatitis A be prevented by vaccination. The vaccine is effective in 94-100% of the vaccinees. Formalized inactivated HAV virus vaccine is available.

Dose 2-18 years of age— 2 doses of 0.5mL at intervals 6-18 months.

Above 18 years of age— 2 doses of 1 mL. 6-18 months apart.

HAV vaccine is indicated for children in endemic areas, high risk groups such as hospital staff and travellers into endemic areas. Immunity against HAV lasts for several years (> 6). Further prolonged follow up is needed to assess the exact period of immunity. The vaccines costs about Rs.700/ dose adverse effects include local pain and mild general symptoms.

Combined HBV and HAV vaccines (TWINRIX) is available. Schedule is the same as for HBV (i.e.) 1mL each at 0, 1 and 6 months. The immunity agent HBV is strong for 10 years after which it may wane.

At present vaccines against HEV are not commercially available.

Hepatitis B: Avoidance of professional blood donors, avoidance of pooled blood products and screening of all blood donors for HBV and HCV help to minimize the risk of transmission. Boiling all equipment for ten minutes or autoclaving will destroy the virus. Those who have had jaundice during the past six months and those who are known to have caused post-transfusion hepatitis should be rejected as blood donors. Use of disposable needles and syringes for injections helps to safeguard against hepatitis.

Passive immunization: Passive immunization is required for those who have no demonstrable antibody against HBsAg. Hepatitis B immune globulin (HBIG) contains a high titer of anti-HBs and affords passive protection for three months if given within two days of exposure. The initial dose is 0.05 to 0.07 mL/kg body weight intramuscularly. A second dose is given 25 to 30 days later. The immunity lasts for a period of six months.

Indications for HBIG

1. Needle prick injury.
2. Spouses and sexual partners of acute HBV hepatitis patients.

- 3. Accidental transfusion of HBsAg +ve blood or blood product.
- 4. Mucosal contact with HBsAg +ve blood or other infective material in laboratory workers.
- 5. Babies born to HBsAg +ve mothers.

Babies born to mothers who develop hepatitis B during the third trimester or who are positive for HBsAg at the time of delivery should be given 5 mL HBIG on the day of birth and then every five weeks for six months till the baby is actively immunized. HBIG is available in India, but the cost is high. Immunization against HBV also protects against HDV.

Active Immunization

Effective vaccines are available widely for immunization. Commercial vaccines are prepared from two sources mainly.

- 1. Vaccine prepared by HBsAg of carriers— This plasma vaccine is cheaper and still used widely in many countries (Heptavac). Cost/dose around Rs. 50. Side effects include local soreness and mild febrile reactions.
- 2. Vaccine produced by recombinant DNA technology in yeast. This vaccine is more expensive costing about Rs. 400/- per mL. Each mL contains 20 mg of the material.

Vaccination is given to children after the first year of life by which time the maternal antibodies would have disappeared.

Dose children

2-18 years 0.5 ml (720 ELISA units) at 0, 6 and 12 months by IM injection

Adults

above 18 years 1 ml (1440 ELISA units) at 0, 6 and 12 months.
Antibodies start appearing by 3 weeks after vaccination. Immunity lasts for 10 years. The vaccine should not be frozen.

Side effects are few and it is one of the safe vaccines.

Indications for Vaccination

- 1. High risk groups—medical students, medical and paramedical personnel.
Those receiving hemodialysis, peritoneal dialysis, repeated doses of blood and blood products, babies born to HBsAg +ve mothers, spouses and sexual contacts of HBsAg +ve subjects.
- 2. Elective—Since the best method to reduce carrier state is to prevent the spread of infection, vaccination is indicated to all persons (irrespective of the age at onset of vaccinating schedule), if facilities permit.

In many countries, hepatitis vaccine has been included in the schedule for vaccination of infants, along with the DPT, polio and measles vaccines.

Schedule for vaccination

	1st dose	2nd dose after one month	3rd dose after six months
Adults	1 mL	1 mL	1 mL
Infants and newborns	0.5 mL	0.5 mL	0.5 mL
Booster at 5 years			

For infants of HBsAg +ve mothers HBIG and vaccine are given within 12 hours of birth and thereafter at 1, and 6 months. Protective titer of antibodies are not impaired by concurrent administration of HBIG and vaccine. The protective antibody level is 10 µIU/mL.

Immunity starts in about 1 month of first dose, and is strong by the third month. By six months more than 90% are immune. When the protection is desired early, accelerated course of vaccination can be given. This consists of 3 doses given at 1 month intervals and a booster at 12 months. Immunogenicity is more if IM injections are given over the deltoid region than over the gluteal region and therefore the former site should be chosen.

Intradermal injection of 0.1 ml of vaccine is also effective, but the immunization rates are lower.

Procedure to be followed if health care personnel get needle stick injuries with HBsAg positive blood contamination.: - Passive, immunization should be given with 3 mL HBIG (1 mL = 200 units) as early as possible and active immunization should be started simultaneously. Extensive vaccine coverage over the previous three decades have significantly reduced the incidence of hepatic cirrhosis and carcinoma in young adults in several countries.

Vaccine Against Hepatitis E Virus

A recombinant anti HEV vaccine has been tried in Nepal. 3 doses were given IM at 0, 1 and 6 months. Compared to placebo it gave 95.5% protection. Further trials are in progress.

Ref: Sreshta MP, et al. N Engl J Med 2007;356:895-903.

Points to remember

- 1. Hepatitis viruses belong to six different families
- 2. Infection is very common
- 3. Viruses A and E are feco-orally transmitted
- 4. Virus B, C and D are transmitted by parenteral inoculation
- 5. Viruses B and C lead to cirrhosis and carcinoma of the liver
- 6. Effective preventive measures are available for HAV and HBV.

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Enteroviruses

K.V. Krishna Das

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These are viruses which are found in the alimentary tract of man. These include poliomyelitis, Coxsackie, echo and several other viruses. They are isolated from the feces of healthy and sick individuals. Most of them are host specific and antigenically distinct.

Poliomyelitis*Syn: Heine Medin Disease, Infantile paralysis*

Poliomyelitis is an acute contagious disease producing a wide clinical spectrum ranging from a non-paralytic illness in which the patient develops symptoms and signs of meningeal involvement without paralysis to a severe paralytic form in which flaccid paralysis results from affliction of spinal motor neurons and brainstem nuclei. Poliomyelitis viruses belong to the group of *picorna viruses*. Three types are pathogenic—types 1, 2 and 3. Type 1 is most common and is responsible for the majority of paralytic cases. Types 1, 2 and 3 do not show cross-immunity.

Epidemiology

The disease is worldwide in distribution, spread by the feco-oral route. The virus is eliminated in feces by cases and carriers. The disease may occur sporadically or in outbreaks. Majority of cases of infection are inapparent with only transient nonspecific symptoms and a rise in antibody levels. Classic paralytic polio develops only rarely. Poliomyelitis used to be common in India with an incidence of 20-30/100,000 of the population. About 90% of children aged 5 years and above showed the presence

of neutralizing antibodies to all the three types of polio viruses acquired naturally, during the 1980s. Worldwide efforts to contain poliomyelitis started in 1988 with the aim of eradicating poliomyelitis from the world. Only humans act as reservoir of the virus and therefore it may lend itself to eradication by eliminating the human reservoir by vaccination coverage. By intensive and extensive mass vaccination programmes conducted nation wide, the incidence of poliomyelitis has been considerably reduced, though India is still not polio-free. With the decrease in incidence of paralytic poliomyelitis the relative frequency of non-polio paralytic lesions have increased.

Pathogenesis and Pathology

The virus enters the system by ingestion. It proliferates in the cervical and mesenteric lymph nodes and Peyer's patches. At this stage the virus may be present in the oropharyngeal secretions and feces. The next stage is one of viremia. The virulence of the virus and immune status of the host determine the localization of the virus to the central nervous system. Even a genetic predisposition to paralytic polio has been postulated. Physical exhaustion, intramuscular injections, tonsillectomy and local injury have all been known to be associated with paralysis localized to the affected part.

In the paralytic cases, the anterior horn cells of the spinal cord and the medullary nuclei are, swollen and congested. As the condition proceeds chromatolysis and pericellular infiltration occurs. The neurons are totally destroyed. Occasionally other parts of the CNS such as roof of the fourth ventricle and vermis, midbrain, substantia nigra, thalamus, globus pallidus and hypothalamus may be involved. In the early stages, the CSF shows increase in cells, mainly polymorphs, but this gives way to lymphocytic increase with the passage of time. Protein level may be moderately increased (up to 150 mg/dL) and the sugar level is normal.

CLINICAL FEATURES

The incubation period is 7-14 days. The disease manifests a bimodal pattern, the initial features are due to viremia

and the second one is due to neurological damage. Initial symptoms are nonspecific such as fever, headache, muscle pain and diarrhea. The second phase, which sets in after a period of three to four days, is characterized by paralysis. In many the infection may be subclinical.

Nonparalytic polio: Features of meningitis develop in nonparalytic polio. These include fever, headache, neck rigidity and muscle pains. Physical examination may reveal signs of meningeal irritation. The condition subsides without further events within a week.

Paralytic polio: In paralytic polio, paralysis may involve the spinal group of muscles, bulbar muscles or a combination of both.

Spinal form: The initial manifestations in this form are followed by diffuse muscle twitching and cramps. The muscles may be tender. Transient fasciculations may be noted. Paralysis of muscles sets in rapidly by the third or fourth day of illness. The spectrum ranges from mild weakness of a limb or a part thereof to extensive flaccid quadriplegia. Paralysis usually takes place within hours in the majority of cases, rarely it may take four to five days or more. There seems to be a predilection for the cervical and lumbar segments of the spinal cord. The tendon jerks are abolished. Objective sensory changes do not occur. The paralysis is asymmetrical, maximal in the beginning and tends to recover with time. Total destruction of neurons leaves behind complete paralysis, partially affected groups recover to varying degrees. The final picture is one of different combinations of muscle paralysis. Often part of a muscle is affected, leaving the remaining part unaffected. Ventilatory insufficiency may develop, if the diaphragm and intercostals are paralyzed. Respiratory failure manifests as restlessness and tachypnea, with shallow irregular respiration.

Bulbar form: Affection of the lower cranial nerves occurs early in this form. It may precede or follow the spinal involvement. Dysphagia, dysarthria and dysphonia occur commonly. Facial palsy may develop less commonly.

Involvement of the nuclei of the medullary reticular formation results in dysfunction of the vital areas such as the respiratory and vasomotor centers. These manifest as irregularity of respiration with apnoeic spells, vasomotor collapse, transient hypertension, and acute pulmonary edema.

Polioencephalitis: This form is unusual and is characterized by alteration in the level of consciousness, convulsions, signs of brainstem involvement and varying combinations of spastic or flaccid paralysis. This condition may mimic other forms of encephalitis.

Diagnosis: Poliomyelitis should be diagnosed clinically in any unimmunized child who develops an initial febrile illness and proceeds to acute paralysis within a few days. The clinical features and the CSF findings help to make a bedside diagnosis in almost all cases. Rarely Coxsackie

and Echo viruses are also capable of producing paralytic disease. There are reports of increasing incidence of Japanese encephalitis virus causing polio like presentation with asymmetric flaccid paralysis of limbs, meningism and lymphocyte pleocytosis in the CSF.

Laboratory Investigations

The virus can be grown in tissue culture from specimens such as feces, rectal swab and CSF. PCR studies help to identify the virus and distinguish it from other wild polio viruses. CSF shows moderate lymphocytic pleocytosis (100-200 cells/cmm) and mild elevation of proteins (40-50 mg/dL). These changes occur in several other conditions and therefore may not help in specific diagnosis. Serological diagnosis is established by demonstrating rising titers of neutralizing and complement fixing antibodies in the serum.

Differential Diagnosis

Nonparalytic poliomyelitis has to be differentiated from other conditions causing aseptic meningitis. *Acute motor polyneuropathy* occurring in nutritional and toxic neuropathies, viral encephalitis and Guillain-Barré syndrome may cause difficulty in diagnosis. In *Guillain-Barré syndrome* there is considerable rise in CSF proteins without rise in cells (albuminocytological dissociation), whereas in polio the cellular response occurring before the rise in proteins is marked. Nerve conduction studies also help in diagnosis. Slowing of the velocity of nerve conduction in the peripheral nerves and nerve roots is suggestive of Guillain-Barré syndrome. *Acute intermittent porphyria* may present rarely with motor paralysis. Other features of the disease such as psychiatric disturbances, abdominal pain and hypertension may be evident. Demonstration of excess of porphobilinogen in the urine supports the diagnosis. Sometimes painful conditions near the joints result in restriction of movement of the part. Such *pseudoparalysis* may occur in osteomyelitis, periosteitis, arthritis, hemophilia, scurvy with subperiosteal bleeding, syphilitic epiphysitis, etc. These have to be carefully looked for and excluded by local examination. Rarely hysterical paralysis may be mistaken for poliomyelitis. This has to be borne in mind when other features of hysteria are suggestive.

Prognosis

In the spinal form of paralytic poliomyelitis in children, mortality is 2-5%. Morbidity is variable. In adults mortality may go up to 15-30%, reaching 75% in bulbar polio. Death is due to respiratory paralysis, autonomic disturbances and encephalitis syndrome.

Treatment

Complete bed rest, analgesics and local heat to sore muscles give symptomatic relief. Since there is no specific

treatment, supportive measures are all important. The tendency to tire out muscles which are in a state of partial paresis should be avoided. The respiratory rate, deglutition and blood pressure should be closely monitored to detect complications early. In cases with bulbar polio, feeding by nasogastric tube and parenteral administration of nutrients and fluids may be required. Cases showing signs of respiratory embarrassment should be nursed in a respiratory intensive care unit. When the vital capacity drops to 25-30% of normal, endotracheal intubation and artificial respiration are called for. Normal vital capacity (VC) for adults = $25 \times \text{height in cm}$; VC for children is $200 \times \text{age in years}$. If ventilatory failure tends to persist, tracheostomy is indicated.

Once the acute phase is over, the muscle strength returns to varying degrees. This improvement is brought about by the recovery of partially damaged neurons, compensatory hypertrophy of the remaining motor units and sprouting of the peripheral nerve endings. In most cases considerable improvement in function is evident in 3-4 months. Further improvement is facilitated by active physiotherapy which is intended to prevent wasting and contractures and stimulate and restore function in partially paralysed muscles.

Deformities of the axial skeleton develop in severely paralysed patients. The affected limb fails to grow whereas the normal one undergoes compensatory hypertrophy. Contractures may result in further loss of function of the limbs. Planned orthopedic surgery and rehabilitation help to relieve functional and cosmetic disability in such cases.

Post-polio syndrome (PPS): This is progressive muscular atrophy and muscle weakness occurring several years after apparent recovery from poliomyelitis with residual paralysis. The distinctive features include weakness, pain, fasciculations and atrophy of muscles. Muscles supplied by bulbar nuclei, and diaphragm may be affected. Sleep apnea may develop. The exact pathogenesis is not clear. The severity of PPS before some relation to the severity of the original attack of polio.

The possibilities include:

1. Progressive attrition of surviving motor neurons and eventual loss of the axonal terminals, and
2. Following paralytic polio some of the surviving neurones sprout new endings in an attempt to restore muscle function. This may account of the partial recovery of strength for several years following the acute attack. It is likely the metabolic function of these neurones deteriorate and this leads to PPS.

The CSF shows elevation of IgM and interleukin-2 which point to an immunological basis for this syndrome.

PREVENTION

By and large poliomyelitis is a preventable disease. Prophylactic vaccination has significantly reduced the

occurrence of polio epidemics. Two types of vaccines are available-live vaccine (Sabin) which is given orally and the killed vaccine (Salk) which is given subcutaneously. The live vaccine is more widely used. The vaccines contain all the three viruses. The trivalent vaccine is given in three doses in the second, fourth and sixth months of age. The immediate response is the formation of IgM antibodies, to be followed later by the appearance of IgG antibodies in 90-99% of cases. In addition, the live attenuated vaccine also stimulates the formation of local IgA which gives immunity in the gut also. Booster doses are given at the age of 1½ and 5 years. Clinical trials conducted in several parts of India have suggested that the standard course of oral vaccination gives protective levels of antibody only in 60-70% cases. Therefore, five doses are recommended at monthly intervals (2,3,4,5 and 6 months) for better protective levels.

The vaccines are generally safe. Oral vaccine has produced limited outbreaks of minor paralytic disease, but with the present vaccines this risk is very low. While immunising children in closed community like a slum or a hostel, it is advisable to cover all the eligible children (up to the age of ten years if they have not been previously vaccinated). The killed vaccine may produce trivial adverse effects like pain at the site of injection and fever.

Eradication of poliomyelitis can be achieved by full coverage of the population by vaccination, provision of protected water supply and general improvement in hygiene. Continued surveillance is absolutely essential to prevent outbreaks. In several countries occurrence of fresh cases has been arrested. India has not achieved this goal yet.

As part of a strategy to eradicate the major infectious diseases of childhood, especially poliomyelitis, the Indian Medical Association (IMA) has recommended the following regime for immunization,

Contact	Age of child	Vaccine	Other care
1	At birth	BCG, OPV	
2	6 weeks	DPT, OPV	
3	10 weeks	DPT, OPV	
4	14 weeks	DPT, OPV	
5	9 months	Measles	Vit. A
6	16 months (Booster)	DPT, OPV	Vit. A

At present Indian Medical Association (IMA) is the main agency working with governmental institutions in giving effect to the pulse polio programmes.

Echo Viruses

Syn: Enteric cytopathogenic human orphan viruses

These are RNA viruses ranging in size from 20-30 nm which produce a spectrum of diseases ranging from mild upper respiratory infection, fever with rash, aseptic

meningitis to acute hemorrhagic conjunctivitis. Over 30 serotypes have been identified by using virus neutralization tests.

Pathogenesis

The virus gets in by ingestion and the mode of spread is feco-oral. After an initial period of viral multiplication in the epithelium of the intestines and respiratory tract, they enter the bloodstream to produce viremia. The organisms reach the various target organs from the bloodstream.

Clinical Features

The incubation period is generally 2-5 days but for hemorrhagic conjunctivitis it is shorter (12-72 hours).

The clinical manifestations include nonspecific fever, upper respiratory tract infections, exanthems, diarrheas, pneumonia, myopericarditis and serious neurological involvement.

Aseptic Meningitis

Aseptic meningitis may occur as a result of infection by several strains of echo viruses. Signs of meningeal irritation or rise in intracranial tension may be evident. The acute phase may last for 4-7 days.

The CSF shows lymphocytic pleocytosis usually less than 500/cmm. Mixed pleocytosis may occur in some cases. Complete recovery is the rule, but rarely complications such as transverse myelitis, bulbar paralysis, Guillain-Barré syndrome, cerebellar lesions and coma may develop.

Treatment

There is no specific treatment and, therefore, treatment is symptomatic and supportive. Prophylactic measures include improvement of environmental sanitation, provision of protected water supply and elimination of flies. Vaccines are not available for general use.

Acute Hemorrhagic Conjunctivitis (AHC)

This disease occurs in pandemics from time to time (1971, 1981). Most of the cases are caused by the *enterovirus EV 70*. All age groups are affected, children being more. The age group of 21-40 are more prone to develop neurologic complications. Infection is acquired by direct spread to the eyes from contaminated fingers, or by fomites. Incubation period is 12-72 hours. Initial symptoms are bilateral conjunctivitis with irritation of the eyes and watery discharge. The conjunctiva may show blotchy hemorrhage. In the vast majority of cases the symptoms subside without other local complications within 7-10 days. Secondary bacterial infection and keratitis may develop. The virus can be isolated from the

conjunctival secretions. In a small proportion constitutional symptoms such as fever, malaise and limb pains may occur.

Neurological complications may develop in a few, usually within 2-3 weeks (even upto four months). Adult males are affected more. These may take one of three forms—spinal, cranial or combined.

Spinal form: Asymmetric flaccid paralysis of the proximal muscles of the lower limbs, associated with backache and followed by muscular wasting.

Cranial form: Isolated or combined cranial nerve palsies.

Combined form: A variable combination of both. Sensory symptoms are absent or minimal. Examination of the cerebrospinal fluid (CSF) during the early stages may reveal mild lymphocytosis and moderate rise in proteins. Neutralizing antibodies against EV70 can be demonstrated in the majority of cases, in the serum as well as CSF. Treatment is symptomatic.

Coxsackie Virus Infections

Coxsackie viruses are picorna viruses which can be grouped into A and B. They were first isolated from the village of Coxsackie in New York by Dalldorf in 1948 and the name is derived therefrom. About 30 immunological types have been isolated. Many strains are commensals in the alimentary and respiratory tract of man. Spread is by the feco-oral route and small outbreaks occur especially in summer. The causative role of these viruses in any specific illness can be established only by isolating it from specific lesions in the affected organs, or tissue fluids.

Pathogenicity

Several lesions are produced by these viruses group A and B. These include (1) neurological lesions, (2) respiratory disorders, (3) carditis, (4) hand-foot and mouth disease and others. The incubation period is 2-14 days.

CLINICAL FEATURES

Neurological lesions: The clinical syndromes include polio-like paralysis, meningoencephalitis and aseptic meningitis. The pathological lesions are:

- Neuronophagia of the anterior horn cells of the spinal cord and perivascular infiltration, by lymphocytes,
- Meningoencephalitis, and
- Scattered foci of degeneration in the spinal cord, cerebral hemispheres, pons and cerebellum.

Respiratory lesions: Pleura is most characteristically involved. The syndrome of pleurodynia (*devil's grip*, *Bornholm's disease*, *epidemic myalgia*) is caused by Coxsackie B group viruses.

Severe pain develops in the chest and upper abdomen, after a prodromal febrile illness. Breathing becomes painful, short, shallow and rapid. Physical examination may reveal

pleural rub, pleural effusion, pneumonia, myocarditis, pericarditis, hepatitis or orchitis. The acute phase subsides in 2-3 days but mild fever and pain may persist for a longer period. Pleurodynia has to be distinguished from acute myocardial infarction, other forms of pleurisy and surgical abdominal emergencies. Symptomatic treatment with rest and analgesics gives relief.

Cardiovascular lesions: The heart is affected by both groups of Coxsackie viruses, but group B is more common to produce acute myocarditis and pericarditis. Infection acquired congenitally or neonatally tends to be serious and rapidly fatal. This may be associated with encephalitis or adrenal necrosis. Pericarditis is more common in older children and adults. Myocarditis may lead to cardiac failure, arrhythmias or the late development of chronic cardiomyopathy and calcific or constrictive pericarditis. Electrocardiographic changes may occur. Congenital heart disease is associated with Coxsackie B types 3 and 4 infection acquired *in utero*.

Hand-Foot-and-Mouth Disease

Infections caused by Coxsackie viruses types A-4, 5, 7, 9, 10 and 16 give rise to a febrile illness followed by superficial vesicular eruptions inside the mouth, fingers, palms and soles. Occasionally small outbreaks may occur. The whole course lasts for 4-8 days after which the vesicles develop into shallow ulcers which heal completely without leaving behind any scar.

Diagnosis

Hand-foot-and-mouth disease may be mistaken for chickenpox, aphthous stomatitis or herpangina. In chickenpox the vesicles are more widely distributed, multiple crops occur and pustulation and scab formation are seen. These are absent in hand-foot-and-mouth disease. The virus can be isolated from the vesicle fluid. Neutralizing and complement fixing antibodies are also demonstrable. Treatment is essentially symptomatic.

Other Manifestations

Coxsackie viruses have been implicated in the production of herpangina (painful vesicles in the throat and pharynx), lymphonodular pharyngitis, hepatitis, exanthematous fevers and pancreatitis.

Laboratory Diagnosis

It is aimed at isolation of the virus and demonstration of rising titers of antibodies.

Treatment

There is no specific therapy. Majority of the cases recover completely in one to six weeks. Absolute bed rest and symptomatic treatment should be continued till the ECG becomes normal.

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Adenovirus Infections

K.V. Krishna Das

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Adenoviruses are a group of DNA viruses which cause a range of febrile disorders characterized by inflammation

of the respiratory tract and conjunctiva and accompanied by submucous and regional lymphadenopathy. The name is derived from the fact that these viruses were first isolated from adenoid tissue removed surgically.

The virus is 60-90 nm in size. Several serotypes are known. Adenoviruses are implicated in the production of acute respiratory disease, intestinal infections and mesenteric adenitis. Adenovirus is a common cause of respiratory disease especially in children below 15 years

of age. The disease spreads by droplet infection. Oronasal secretions of infected persons contain about 10^6 - 10^7 virus particles/mL. Even as low as 5 viral particles can result in infection and therefore the infection spreads fast. The incubation period varies between 3 and 14 days.

Clinical Features

Several clinical disorders are caused by these viruses.

1. **Acute febrile respiratory illness** occurs more frequently in children. Paroxysms of cough may occur. X-ray shows patchy lobular pneumonia. Encephalitis may develop as a complication.
2. **Acute pharyngoconjunctival fever** produces the classical triad of fever, pharyngitis and conjunctivitis. The disease subsides in 1-2 weeks. Unilateral or bilateral simple conjunctivitis may develop in some.

3. **Epidemic keratoconjunctivitis** may occur in outbreaks, affecting particularly shipyard workers and in harbour personnel. The onset is sudden with unilateral edema, conjunctivitis, superficial corneal opacities and lymphadenopathy. Later the other eye is also involved. The course is for 3-4 weeks. The majority recover completely, though in a small proportion blindness may result from corneal lesions.

Diagnosis

Specific diagnosis is established by isolation of the virus or demonstration of viral DNA by PCR.

Treatment

It is symptomatic and supportive. Severe pneumonia in infants and epidemic keratoconjunctivitis require special management.

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Arena Virus Infections and Hemorrhagic Fevers

K.V. Krishna Das

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General Considerations

Since 1930 several viruses especially arena viruses are known to produce hemorrhagic manifestations, though other groups of viruses can also cause the same. The hemorrhagic fevers can be grouped under three headings depending upon the virus and the vector. Localized or generalized hemorrhage may occur as alarming symptoms in infections by dengue, yellow fever, chikungunya, Kyasanur forest disease and arena virus infections.

1. **Mosquito-borne hemorrhagic fevers** e.g. Dengue types 1, 2, 3 and 4, Chikungunya, yellow fever virus.

2. **Zoonotic viruses which may be transmitted to man**, e.g. Korean hemorrhagic fever, Argentinian hemorrhagic fever and Lassa fever (Lassa virus).
3. **Tick-borne hemorrhagic fevers**, e.g. Kyasanur forest disease. Omsk hemorrhagic fever and Crimean congo hemorrhagic fever group. The vectors in some hemorrhagic fevers have not been identified yet.

Newer and newer viruses capable of producing this syndrome are being added to the list even now. Small outbreaks of hemorrhagic fevers caused by dengue and chikungunya viruses have occurred in several parts of India, particularly W. Bengal.

Hemorrhagic fevers of South Asia: Viral hemorrhagic fevers occurring in Philippines, Malaysia, Vietnam and eastern parts of India are collectively referred to as hemorrhagic fevers of south east Asia." These are all transmitted by *Aedes aegypti* mosquitoes. All types of dengue viruses (especially type 2) and chikungunya virus are responsible for most of the cases.

Diseases Caused by Infections

Arena viruses are RNA viruses belonging to three families. They may be round, oval or pleomorphic, ranging in size from 110 to 130 nm. Under the electron microscope they resemble grains of sand and hence the name arena viruses (Latin-arenosus means sandy)

They all occur as natural inhabitants in rodents.

Except Machupo virus the others exist without producing diseases in them. The infection is transmitted from parent to offspring in utero and thus a reservoir of infection is maintained. Man may get the infection directly through cuts and wounds. Lymphocytic choriomeningitis, Lassa fever and viruses causing hemorrhagic fevers come under this group.

Lymphocytic Choriomeningitis

LCM virus (LCMV) was one of the earliest viruses to be isolated in the mid 1930s. It belongs to the family, arenaviridae which contains, about 20 known viruses affecting different rodents which shed the virus without themselves suffering from disease.

LCMV has assumed importance with the infection occurring more commonly in transplant recipients. Most of the cases are subclinical with < 1% developing meningitis and with mortality < 1% LCMV infection may be transmitted by donors who themselves do not show signs of overt disease.

Incubation is one week. Disease starts with prodrome and fever. Meningitis occurs by about 15-20 days. CSF shows moderate lymphocytosis, up to 700/cmm. LCM occurring in transplant recipients is generally obscure and fatal if, on detected.

Another pattern of LCMV infection is that of a fatal hemorrhagic fever typical of that of Lassa fever which is also an arena virus.

Ribavirin is effective against the virus. LCMV infection occurring in pregnant women may lead to hydrocephalus, mental retardation and chorioretinitis in the newborns.

Lassa Fever

This occurs mainly in Africa. Majority of infections are subclinical. Symptomatic cases may present with chest pain, sore throat, cough, abdominal pain, vomiting, diarrhea, facial puffiness, myocarditis and conjunctivitis. Minor hemorrhagic manifestations may develop due to increase in capillary leak. Nerve deafness may occur as a complication.

Treatment is symptomatic. Ribavirin given orally in dose of 1000-1200 mg/day may be beneficial.

South American Hemorrhagic Fevers

Important in this group are *Argentine and Bolivian hemorrhagic fevers* and *Venezuelan hemorrhagic fever*. The general symptoms include fever, malaise, myalgia, hypotension, petechiae, capillary leak syndrome and neurological complications including convulsions and coma.

Serological tests may show antibody by ELISA. Virus can be isolated from blood and other tissues by cell-culture. Mortality ranges from 10-20%. Mainstay of treatment is intensive care with correction of fluid and electrolytes and symptomatic management of hemorrhagic manifestations. Vaccines against Argentine hemorrhagic fever and Lassa fever are under trial in endemic areas.

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Rabies

K.V. Krishna Das, K. Sreekanthan, Aswini Kumar

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General Considerations

Syn: Hydrophobia, Lyssa

Definition

Rabies is an acute viral disease, primarily of animals, clinically characterized by rapidly progressive and fatal encephalitis, acquired by man through the bites or licks of infected animals.

Etiology

The etiological agent is an RNA virus belonging to the group of rhabdo viruses. The rhabdoviridae consists of five genera each of which has several species. Rabies virus is a species of (sero type1) of the genus Lyssa virus of the family rhabdoviridae. It is a rod shaped virus approximately 180 by 75 nm. When isolated first from animals, it was called “*street virus*”. This has a long incubation period and the virus multiplies in the salivary glands and the central nervous system. By repeated intracerebral passage in laboratory animals, it adapts to them. At this stage it is called “*fixed virus*”. It has a uniformly shortened incubation period (4 to 6 days) and it loses its ability to multiply in the salivary glands. It has reduced pathogenicity and is used in vaccine production. Rabies virus is rapidly inactivated by heat. At 56° C, the virus dies in less than a minute, whereas at 37°C, it survives for several hours under moist environment. The virus is also inactivated by ultraviolet light, detergents and soap solution, ethanol, iodine and quaternary ammonium compounds.

Distribution and Incidence

Rabies is enzootic worldwide except in a few countries. Rabies is widely prevalent in India, but human rabies is generally underreported. *In India, 30,000 deaths were reported to the WHO in 1998.* Other countries reporting high incidence of human rabies are Bangladesh, Nepal, Sri Lanka, Pakistan, Vietnam, Philippines, Indonesia, Mexico and Ethiopia.

All warm-blooded animals are susceptible to rabies. Dogs are most important in transmitting the disease to man. Among mammals, different animals differ in their susceptibility to infection. Very highly susceptible animals include wolves, foxes, jackals, kangaroo rats and cotton rats. Highly susceptible animals include hamsters, skunks, raccoons, domestic cats, rabbits, bats and cattle. Dogs and primates are moderately susceptible. Opossums have low susceptibility. ***Dogs and other animals may or may not succumb to the infection.***

Transmission and Epidemiology

Virus enters through cuts or wounds caused by bites, scratches or licks of rabid animals, which contain virus

in their saliva. Rare modes of transmission include inhalation of virus aerosols. When dogs bark the saliva may be sprayed to a distance of up to 2 meters. Inhalations of aerosols created in caves inhabited by vampire bats, which suck blood from animals and man, have also resulted in rabies. Laboratory accidents of rabies following inhaled aerosols of fixed virus also been reported. Less commonly injury from cats, jackals, mongoose, wolves and other canines may transmit the disease. Rabies following accidental injection of vaccines containing live rabies virus are also reported.

Human-to-Human Transmission

Man to man transmission from contact with human saliva is extremely rare, though theoretically possible. Transmission has occurred through grafting of infected corneas and organ transplantation.

Pathogenesis

After entering a susceptible host, the rabies surface glycoprotein attaches to a cell and enters it by endocytosis. The surface envelope of the virus fuses with the vesicle membrane and the ribonucleoprotein enters the cytoplasm. Local replication may occur in striated muscle near the site of the bite, but there may also be direct invasion of nerve cells. Postsynaptic nicotinic acetylcholine receptors at neuromuscular junctions are important binding sites. Once inside the peripheral nerves, the virus is carried in the flow of axoplasm at the rate of about 3mm/hr to the dorsal root ganglia where replication occurs. This may give rise to prodromal paresthesia at the site of the bite. In the central nervous system, there is massive replication with viral budding from intracellular membranes of neurons and trans-synaptic transmission of virus from cell to cell. Passive centrifugal spread of virus from the CNS in the axoplasm of many efferent nerves including those of the autonomic nervous system occurs. By this route the virus spreads to the salivary glands and to lachrymal glands and several other tissues.

Pathology

The white and the grey matter of the cerebrum show severe congestion. Perivascular and perineuronal infiltration with mononuclear cells occur. Intracytoplasmic inclusion bodies (Negri bodies) are formed and these are demonstrable in 80% of the cases. Negri bodies are seen in large numbers in the hippocampal gyrus, Purkinje cells of the cerebellum, and the pyramidal cells. They are also seen in the basal ganglia and the cranial nerve nuclei and spinal cord. While their presence is diagnostic of rabies, their absence does not exclude the diagnosis. Extra neural changes include focal degeneration of salivary and lachrymal glands, pancreas, adrenal medulla and lymph

nodes. Interstitial myocarditis with round cell infiltration may occur.

Immune Responses

The immune response to natural rabies infection is insufficient to prevent rabies. Rabies can produce immunosuppression and only a minority of unvaccinated patients develops a measurable antibody response. Patients developing a cellular immune response tend to have the furious form rather than the paralytic form and die faster than those who do not mount such a response. The virus may persist in macrophages and may later emerge to produce disease. This may explain some cases with very long incubation periods.

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CLINICAL FEATURES AND COMPLICATIONS

In Animals: In dogs the incubation period is usually between 2 weeks and 4 months (extreme range, 5 days to 14 months). The illness may start with 2 to 3 days of prodromal symptoms. e.g.: A change in behavior, fever and intense irritation. Dogs with the less common but more familiar, furious form of the disease become aggressive wander away from home and may develop convulsion, dysphagia, pharyngeal paralysis causing an altered bark, and hyper salivation. Those with paralytic or “dumb” rabies hide themselves and develop paralysis of the jaw, neck and hind limbs. Dysphagia and drooling of saliva may raise the suspicion of a foreign body stuck in the throat. Virus may be excreted in the saliva for 2 or 3 days before there are signs of rabies and the animal usually dies within the next 7 days. A small proportion of infected animals recover and may continue to excrete virus for long periods. Horses and cats usually exhibit furious symptoms whereas paralytic disease is the rule in foxes and bovines. Hydrophobia is not seen in animals but inability to drink is a common symptom of rabies.

Clinical Features

The incubation period is usually between 20 and 90 days (extreme range, 4 days to >19 years). Relatively short incubation periods are observed after facial and severe multiple bites. Bites from stray wild animals are more risky and dangerous. The disease manifests with prodromal symptoms like excitement, fever, malaise, anorexia, nausea and headache and nonspecific upper respiratory tract symptoms. Attention to the site of bite may be drawn by the tingling pain and paresthesia especially itching, which develops before the appearance of spasms. Psychotic behaviour with irrational and violent spells with intervening periods of calm may develop.

Neurological involvement may present as (1) the spastic (furious) form and (2) the paralytic form. In the former the lesions are more marked in the brain stem,

cranial nerves, limbic system and higher centres. In the paralytic form the lesions are mostly in the medulla, spinal cord and the spinal nerves.

The spastic form sets in at various intervals (hours to a day or so) after the prodromal symptoms. Sensory stimuli, which may be tactile, auditory or photic, provoke painful spasms. These are most marked and characteristic in the oropharynx. Swallowing liquid and later on a spray of water, its sight or even thought of it produces painful oropharyngeal spasms with respiratory distress. This symptom is called **hydrophobia**. Though not pathognomonic, this is almost confirmatory of the diagnosis. Aerophobic spasms caused by a draught of air on the face or switching on the fan are also diagnostic. The whole course extends to less than 5 days in almost all cases. The patient becomes comatose and death is due to respiratory paralysis resulting from bulbar involvement.

Paralytic form – This is characterized by ascending paralysis. It may start as monoplegia or paraplegia. Spasms are not prominent. Paralytic form is known to occur more often after vampire bat bites. Hydrophobia is rare. Patients may survive for a month even without intensive care. In India, the primary paralytic form occurs only in less than 20% of cases.

Complications: Neurologic, cardiac and pulmonary complications may develop.

- a. **Neurological:** Cerebral edema, generalized convulsions, polyneuropathy, severe autonomic dysfunction and inappropriate secretion of anti-diuretic hormone.
- b. **Cardiac:** Tachy- or brady-arrhythmias, hypotension, myocarditis with congestive cardiac failure.
- c. **Pulmonary:** Hyperventilation, respiratory alkalosis, hypoxia, aspiration pneumonia, pneumothorax, pulmonary edema, respiratory failure and respiratory arrest.
- d. **GIT:** Hematemesis due to ulceration or tears in the mucosa of the upper gastrointestinal tract.

Diagnosis

Development of mental excitement, hydrophobia and spasm or paralysis in persons who have sustained bites or licks from any warm-blooded animal within 6 months should suggest the possibility of rabies. A bite by an unusually excitable or partially paralyzed mammal indicates high risk of exposure to rabies. However in up to 16% of cases no history of exposure can be elicited. In the initial stages the diagnosis of rabies may be difficult.

Differential Diagnosis

Rabies has to be differentiated from encephalitis and other neurological disorders leading to paralysis. Paralytic rabies may be mistaken for adverse reaction to vaccination in

persons receiving anti-rabies vaccination. The spasms of tetanus may resemble hydrophobia especially if they involve the pharyngeal muscles (hydrophobic tetanus). Psychiatric conditions, such as maniac excitement and hysteria and drug reactions such as akathisia have to be differentiated at times. Hysterical subjects adopt hydrophobic manifestations, but absence of aerophobia excludes this condition.

Laboratory Diagnosis

In practice, diagnosis of rabies is primarily clinical. Where laboratory facilities exist tests are available for confirmation of diagnosis. The virus can be isolated in saliva or CSF for the initial 2 weeks of the illness, but this takes about 3 weeks and hence is not a practicable method for day-to-day use.

Neutralizing antibodies against rabies virus can be demonstrated after the initial 10 days of onset. Levels of antibody are much higher in CSF, compared to serum. Vaccinated individuals develop antibodies by 8 days after vaccination, but the titers are much higher in the patients who develop clinical rabies.

Antigen Detection

Rapid rabies diagnosis by PCR tests on saliva –CSF and skin biopsy are available in a few reference laboratories. A *direct immunofluorescent antibody* (IFA) test also rapidly identifies antigen in frozen sections of the skin biopsies taken from a hairy area, usually nape of the neck. Rabies- specific immunofluorescence appears in nerve twigs around the base of hair follicles. This test is 60-100% sensitive. False positives have not been reported.

Prognosis

In the ordinary settings rabies is invariably fatal. This underscores the need for preventing the development of rabies in persons exposed to the risk either by animal bites or by occupation. Recent reports of stray survivors by intensive and continuous prolonged life support measures are available.

Treatment

Once the disease is manifested treatment is only symptomatic. There is no specific treatment. Treatment aims at controlling spasms with muscle relaxants, maintenance of hydration by intravenous fluids, and assistance to ventilation. Those who attend on the patients should use gloves, masks, and protective goggles. Though the virus eliminated in human saliva is not very virulent, as a matter of abundant caution, attendants who have been inadvertently exposed to very close contact with rabies

may be advised to take a course of prophylactic inoculation.

Prophylaxis

Local treatment of bites, scratches, and licks: Thorough cleaning of the wound by washing with soap and water repeatedly and then by 40-70% alcohol or 0.1% quaternary ammonium compounds (*Cetavlon*) eliminates the virus present superficially. Bite wounds should not be sutured straight away. In severe bites local injection of antirabies serum or hyperimmune globulin helps in reducing the risk further.

Assessment of the risk: Animals incubating the disease may be apparently normal for five days before becoming symptomatic. Once they develop the disease, majority of them die within 5 days. Therefore, the animal should be observed for 10 days, to decide on the need for vaccination. If the animal is obviously rabid or it is not traceable vaccination is started straightaway without any delay. If the risk is only class I or II, vaccination can be undertaken after observing the animal. In class III risk, vaccination is started, but if the animal is normal, it can be stopped. A rabid dog shows features like recent change in behaviour, aggressiveness, characteristic howl, tendency to bite objects indiscriminately, ataxia, paralysis and excessive salivation. Paralysis of bulbar muscles may be mistaken for impaction of foreign bodies in the throat.

Post-exposure prophylaxis: The risk of developing infection can be estimated from the nature of initial injury.

Active immunization: This is achieved by antirabies vaccination (ARV). Vaccination affords considerable degree of protection, though this is not absolute. Immunity is established after 10-14 days of starting the course and it lasts up to 1 year. Antirabies vaccine was originally introduced by Louis Pasteur in 1885. *All the vaccines used for anti-rabies prophylaxis are killed vaccines.* The original vaccines were nerve tissue vaccines in which the fixed virus grown in the nervous tissue of sheep was killed by phenol or beta propiolactone. The course of injections used to be long, injections were painful and about 6 to 10% of patients used to get minor or moderate complications. A smaller number used to get serious neuro-paralytic and encephalitic complications. These vaccines are practically never given now due to this risk and the availability of safer and more effective cell culture vaccines.

Avian embryo vaccines: These are produced in chick (Flury) or duck embryos. Though allergic reactions may occur, neuroparalytic accidents are much less common with this vaccine. The vaccines are used mainly for active immunization of dogs and other pets.

TABLE 59.1

Classification of risk

Class I (Light risk)

1. Licks except on face and fingers.
2. Licks on intact mucous membranes.
3. Light bites and scratches over parts of the body except head, neck, face and fingers.
4. Consumption of unboiled milk or handling raw flesh of rabid animal.

Class II (Moderate risk)

1. Licks on fresh wounds and cuts and abrasions on fingers.
2. Scratches on fingers.

Class III (Great risk)

1. Licks on fresh cuts, scratches and bites on head, neck or face.
2. Bites on fingers and all lacerated wounds.
3. Jackal and wolf bites.
4. Any class II patient who has not received ARV within 2 weeks.

Cell Culture Vaccines

The available popular vaccines are

1. Monkey kidney cell vaccine marketed as Vero-rab
2. Purified chick embryo cell vaccine marketed as Rabipur
3. Human diploid cell vaccine (HDCV). The human cell derived vaccine costs about Rs. 750/dose whereas the other two cost about Rs. 250.

All are equally antigenic. Dose of monkey kidney cell vaccine is 0.5 mL, that of human diploid cell vaccine (HDCV) is 1 mL each time. All these vaccines are safe, painless and free from permanent neuroparalytic accidents. At present all these vaccines are imported. Immunity starts by the seventh day after the first dose. It lasts for 3 years.

Five injections of the vaccine on day 0, 3, 7, 14 and 28 given intramuscularly give rise to sufficient protection. A booster dose of 1 mL is given on day 90, if antibody level is not adequate. Injections over the deltoid are more immunogenic than gluteal injections (Table 59.1).

The course of cell culture vaccine is the same for all classes of bites, and the classification of the risk is only

to decide the need and timing of vaccination. Being a killed vaccine there is no contraindication for antirabic vaccination during pregnancy.

Passive immunization: If the risk is class III or even II, passive immunization should be given as early as possible, since active immunization will not be completed within the incubation period. Antirabic serum prepared in humans (*human rabies immunoglobulin HRIG*) should be given in a dose of 20 units/kg IM at a site away from the vaccine dose. If there is a lacerated wound, 50% of the dose should be infiltrated around it and the remainder should be given intramuscularly. The half-life of HRIG is for 21 days and this is probably the duration of passive immunity.

Antirabic serum (ARS) produced in horses is also used in a dose 40 u/kg bw IM. If horse serum is used the risk of anaphylaxis is higher. The equine antiserum is much cheaper than the human immunoglobulin. Both are effective. When the former is used, prior skin testing should be done to avoid anaphylactic reactions.

Pre-exposure immunization: Personnel who have occupational risk of rabies, e.g., veterinary surgeons, and kennel trainers can be actively immunized with HDCV. When an immunized person is exposed to the risk of rabies, he should receive booster doses of the vaccine.

Three doses of cell culture vaccines given as IM injections on day 0, 7, 21 or 28 give adequate antibody levels for up to 2 years. If facilities permit, antibody levels should be estimated and if the titer is inadequate a booster dose of 1 mL should be given. It is better to administer booster doses only when indicated, since over-immunization can be associated with serum sickness-like reaction in up to 6% of cases.

An alternate method is to give HDCV in a dose of 0.1 mL intradermally on days 1, 7, 21 or 28. Protection starts after four weeks. The intradermal route is inadequate for post-exposure prophylaxis. In persons who have received pre-exposure prophylaxis, if risk of infection occurs two booster doses of the vaccine should be given on days 0 and 3. Local washing of the wound and wound toilet are absolutely necessary to reduce the risk.

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General Considerations

Arthropod borne (ARBO) viruses are a group of viruses with complex transmission cycles involving arthropods. These viruses have diverse physical and chemical properties and are classified into several virus families.

The arboviruses are transmitted by blood sucking arthropods from one vertebrate host to another. The vector acquires a lifelong infection through the ingestion of blood from a viremic vertebrate. The viruses multiply in the tissues of the vector without evidence of disease or damage. Some arboviruses are maintained in nature by transovarian transmission in the vector. The main pathogenic arboviruses includes members of the flavivirus, togavirus and bunyavirus families.

The major arbovirus diseases world wide are, dengue fever, yellow fever, sandfly fever, Kyasanur Forest Disease, chikungunya fever, West Nile fever and various forms of encephalitis like Japanese encephalitis, St.Louis encephalitis, Western equine encephalitis, Eastern equine

encephalitis, Russian spring-summer encephalitis and others.

The diseases with public health importance in India are dengue fever, chikungunya fever, sandfly fever, West Nile fever, Kyasanur Forest Disease, yellow fever and Japanese encephalitis.

Dengue Fever (DF)**Syn. Break bone fever, Dandy fever**

Dengue is an acute febrile illness, characterized by high fever, severe pain of bones and joints, lymphadenopathy and a characteristic rash.

History

Benjamin Rush in Philadelphia first described the clinical syndrome in 1789. Viral etiology and mode of transmission by mosquitoes were established in early 20th century. DF is found mostly during and shortly after the rainy season in tropical and subtropical areas of India Africa, Southeast Asia, China, Middle East, Carribean islands and Central and South America. In 1954 dengue became epidemic in many areas of tropical Asia. Large outbreaks of DF have occurred in many areas of India after 2000 and in Kerala particularly during July –August 2003. At present sporadic cases occur all over the country.

Etiology

Dengue is caused by four distinct serotypes of dengue viruses (Type DEN-1 to DEN 4) within the *flavivirus* genus of the family *Flaviviridae*. Dengue viruses are small 40-50 nm spherical particles composed of a lipoprotein envelope and nucleocapsid of single strand RNA genome. The major envelope glycoprotein E which is exposed on the virion surface contains type-specific and group specific antigens. There are genetic variations within serotypes. Some genetic variants within each serotype appear to be more virulent or have more epidemic potential. After primary infection each serotype provides specific lifetime immunity and short term cross-immunity.



Fig. 60.1: Aedes mosquito vector

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Transmission

Man is the usual reservoir of infection. The main vectors are *Aedes aegypti*, *Aedes albopictus* and to a lesser extent *Aedes polynesiensis*. These are fresh water breeders existing in domestic surroundings and which bite frequently several persons during all times of the day. The bites may be painless and they do not fly long distances. The extrinsic incubation period in the mosquito is 8-14 days by which time the mosquito becomes infective and it remains so for the rest of its life (15-65 days). There is transovarian transmission of the dengue virus with the *A. albopictus* mosquito (Fig. 60.1).

Pathogenesis and Pathology

First attack of dengue: After the bite of an infected mosquito, the virus replicates in regional lymph nodes and is disseminated via the lymphatics and the blood to other tissues. Replication in the reticuloendothelial system and skin produces viremia, which begins 3-7 days after infection. Viremia is present for the first 3 days early in the illness. After the clearance of the viremia the virus persists in the infected mononuclear cells. In the majority of dengue infections the disease is self-limited.

Subsequent attacks of dengue: Though immunity in dengue is solid for the particular serotype, there is no cross immunity between the different species. Therefore re-infection with different serotypes can occur. The speed and extent of viral spread is much higher in subsequent infections by different serotypes of dengue viruses compared to the first attack. In this group, some develop severe complications such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). Infection by DEN-2 following DEN-1 infection is likely to be more serious in this regard.

The hallmarks of DHF-DSS are increase in the permeability and fragility of the capillaries and abnormalities

of hemostasis. Ninety percent of cases of DHF-DSS occur during subsequent infections. Less commonly, infants born to mothers who transmit dengue antibodies transplacentally and are sensitized to the dengue virus may develop DHF-DSS in the first attack itself.

The immune status of the host plays an important role in determining the course of dengue infection and subsequent complications. The presence of non-neutralizing antibodies to a heterologous dengue virus may form virus-antibody complexes and facilitate the entry of dengue virus into the mononuclear cells and viral multiplication (antibody-dependent enhancement). The increased numbers of infected cells (monocytes and lymphocytes) with the release of cytokines like $\text{TNF-}\alpha$ and complement activation leads to endothelial swelling of small blood vessels, peri-vascular edema and mononuclear cell infiltration. The pathologic changes in complicated cases and DHF include arrest of megakaryocyte multiplication in the bone marrow and thrombocytopenia. Hemorrhages occur due to thrombocytopenia, platelet dysfunction and coagulopathy. There is also generalized abnormality of the vascular endothelium resulting in extensive leakage of fluid from the intravascular compartment.

In DHF there is widespread dissemination of the virus into several organs including liver, spleen, heart, bone marrow and rarely the brain. Liver shows focal midzonal necrosis, fatty changes and hyaline necrosis of hepatocytes.

CLINICAL FEATURES

Dengue fever is an acute febrile disease with headache, musculoskeletal pain, and rash, but the severity of illness and clinical manifestations vary with age. All age groups are affected.

Dengue can present in the following clinical syndromes.

1. Undifferentiated fever, particularly in children
2. Classic dengue fever
3. Dengue hemorrhagic fever and
4. Dengue shock syndrome.

Undifferentiated fever: Infection is asymptomatic in 80% of infants and children. In the ordinary case the illness presents as fever, malaise or irritability, pharyngeal injection, upper respiratory symptoms and rash. This resembles other common childhood infections.

Classic dengue fever: This is most common in adults and older children. The incubation period is 3-8 days. It starts abruptly with fever, headache, pain in the muscle, bone and joints, retro-orbital region and lumbosacral ache. A transient generalized macular rash may be present during the first 24 to 48 hours. Generalized myalgia increase in severity. Other symptoms such as anorexia, nausea,

vomiting, marked lassitude, cutaneous hyperaesthesia and dysgeusia appear on the second to the fourth day. Orbital pain may develop and movements of the eyeball may be painful. The temperature rises up to 40-41.5°C with relative bradycardia. Conjunctival congestion is common. Posterior cervical, epitrochlear and inguinal lymph nodes are enlarged, but non-tender.

The fever usually subsides after three days. A second bout of fever may occur after two days. This is milder than the first and lasting for 2-3 days (saddle back pattern). The second episode of fever comes down by lysis.

A maculo-papular rash occurs with the second bout of fever on the trunk, limbs and face. It disappears as the temperature falls. Mild hemorrhagic phenomena such as petechial hemorrhages, ecchymoses at injection sites, epistaxis and menorrhagia may occur during the course of the illness, even in uncomplicated cases.

DENGUE HEMORRHAGIC FEVER

This syndrome, characterized by increased capillary permeability and hemostatic derangements, occur more frequently in children. Based on the severity, cases of DHF can be categorized into four grades (WHO guidelines).

Grading Severity of Dengue Hemorrhagic Fever (DHF)

DHF is classified into four grades of severity, where grades III and IV are considered to be DSS. The presence of thrombocytopenia with concurrent hemoconcentration differentiates grades I and II DHF from DF.

Grade I: Fever accompanied by non-specific constitutional symptoms; the only haemorrhagic manifestation is a positive tourniquet test and/or easy bruising.

Grade II: Spontaneous bleeding, in addition to the manifestations of Grade I patients, usually in the forms of skin or other hemorrhages.

Grade III: Circulatory failure manifested by a rapid, weak pulse and narrowing of pulse pressure or hypotension, with the presence of cold, clammy skin and restlessness.

Grade IV: Profound shock with undetectable blood pressure or pulse

The minimum diagnostic criteria for DHF are a positive tourniquet test or spontaneous hemorrhages from multiple sites, thrombocytopenia ($<100,000$ /cmm), and evidence of plasma leakage as shown by increase in hematocrit by 20% or more from baseline, ascites or pleural effusion.

Early in the illness these children are clinically identical to those with classical dengue. But around the time of defervescence, a second phase of illness develops. This is characterized by petechiae, ecchymoses, epistaxis

and other spontaneous hemorrhages including gastrointestinal hemorrhage and menorrhagia. Variable ascites, or pleural effusion more common on the right side may develop. Liver may be enlarged and tender.

DENGUE SHOCK SYNDROME (DSS)

Dengue shock syndrome is the most serious complication of dengue hemorrhagic fever, seen widely in Asia and South America. It is seen in all hospitals in India, though infrequently. Some patients manifest signs of restlessness, abdominal pain and shock with cold and clammy extremities, diaphoresis, circum-oral cyanosis, irritability, or change in mental status. Hypotension with narrowing of pulse pressure below 20 mm Hg, severe shock and rapid deterioration, typically occurs on the second to fifth day of illness. Untreated, 50% of such patients may die. Patients with less severe illness or those successfully treated recover rapidly after a 1-2 day period of acute illness.

Other manifestations: Less commonly dengue may present with encephalopathy, intracranial bleed, renal failure, fulminant hepatitis and acute respiratory distress syndrome.

Course and Prognosis

Diagnosis

Dengue should be suspected when fever with severe body pain and rash occurs. In the initial stage it should be differentiated from Influenza, leptospirosis, malaria, and typhoid fever. In endemic areas sand fly fever and chikungunya have to be kept in mind.

Investigations

Usually there is leukopenia, mainly neutropenia and mild thrombocytopenia. Severe thrombocytopenia may occur in DHF. S. bilirubin is usually normal unless there is hepatic involvement. Serum transaminases show mild elevation even in uncomplicated cases.

Blood urea and creatinine are elevated in complicated cases. X-ray chest may show pleural effusion. Ultrasonogram of abdomen may reveal serous effusions.

Virological Diagnosis

Virus isolation is by cell cultures, done with blood culture within the first week of illness in specialized laboratories for special purposes. Viral RNA can be identified by is done by reverse transcriptase PCR (RT-PCR).

Serology

Virus can be isolated by blood culture within the first week. Complement fixation and neutralizing antibody titers can be demonstrated in paired sera drawn at intervals of 7 to 14 days.

Diseases Caused by Infections

The IgM Antibody capture ELISA has improved the serodiagnosis of dengue. By the end of first week IgM antibodies are detectable. They rise rapidly and by 2-3 months they become undetectable. A very high rise of IgG antibodies early in the disease indicates a second dengue infection. IgM antibodies are relatively specific for dengue without cross-reaction with other heterologous flaviviruses, but IgM antibodies do not distinguish individual dengue serotypes.

TREATMENT

Vast majority of patients can be managed as outpatients with paracetamol for fever, anti-emetics, oral fluids, reassurance and rest. Indications for inpatient treatment are fever above 40.5°C, prostration, severe vomiting requiring IV fluids and other complications.

Treatment of Complicated DF, DHF and DSS

The treatment is mainly supportive. Patient has to be treated in an intensive care facility with proper monitoring of vital parameters, attention to nutrition and fluid and electrolyte balance. The blood pressure, hematocrit, platelet count, bleeding manifestations, urinary output and level of consciousness should be monitored systematically to identify complications.

Hypotension, signs of increased capillary fragility and toxemia are indications for IV fluids. Normal saline, 5% dextrose saline, Ringer lactate, colloid plasma expanders and plasma have to be given with proper monitoring to maintain the blood pressure and vital functions. It is important to correct fluid and electrolyte balance early in the disease in order to prevent irreversible changes.

Indications for Blood Components/ Blood Transfusion

Platelet counts <25000/cmm with bleeding is an indication for platelet rich plasma or platelet concentrates.

In massive bleeding give blood transfusion.

IV fluid therapy should be properly monitored and stopped at the appropriate time so as to avoid fluid overload.

There is no specific antiviral therapy. Secondary bacterial infections and concurrent infections like malaria should be looked for and treated appropriately.

Prevention

General measures include anti-mosquito operations and personal protection using nets or mosquito repellants. Live attenuated vaccines against all 4 serotypes are currently under development.

Points to remember

1. Dengue, which was considered to be a mild infection is emerging as a serious problem
2. Four distinct viruses can cause the disease. No cross protection is present. But may produce DHF and DSS in subsequent attacks.
3. Main cause of death: DHF and DSS –increased capillary permeability
4. Early fluid replacement and supportive measures save life.

Sandfly Fever

Syn: Phlebotomus fever, Papatasii fever, 3 days fever.

It is a short, self-limited, undifferentiated febrile illness caused by sandfly-borne viruses.

Etiology

The disease is caused by members of phlebovirus subgroup of the family Bunyaviridae.

The disease is present in India mainly northern states and Himalayan areas. It is prevalent in other tropical countries, Middle East and Mediterranean countries.

It is transmitted by the sandfly *Phlebotomus papatasii*. Female phlebotomus sucks blood. It becomes infective 6-7 days after an infective feed and remains infective for the rest of its life. Sand fly fever viruses are trans-ovarially transmitted in their vector species. In the tropical environment sand flies are active throughout the year. In temperate climates they are seen only in summer. They are small (2-3 mm) and readily pass through bed nets and screens. They are nocturnal biters.

Clinical Features

Incubation period is 2-6 days. The illness starts abruptly with fever and rigor. The temperature rises rapidly to 40°C with headache, malaise, retro-orbital pain, photophobia, myalgia, nausea and vomiting. The absence of rash, lymphadenopathy, and respiratory symptoms may help in differentiating the illness from other viral syndromes. The acute febrile illness lasts approximately 3 days. This may be followed by a period of weakness, fatigue and depression lasting 1-2 weeks. Aseptic meningitis can occur in 12% of cases. There is associated neck rigidity, changes in mental status and sometimes convulsions. There is CSF pleocytosis with predominant mononuclear cells. The disease resolves without sequel.

Diagnosis

The diagnosis is mainly clinical. There is leucopenia. The diagnosis is established by culture of the virus, PCR test or serological assays. The most commonly used test is IgM capture ELISA. This is to be done 4-5 days after onset of

symptoms. It gives only a probable diagnosis. By 7-10 days IgG antibodies develop in the majority.

Prognosis and Treatment

The disease is self-limiting, benign and non-fatal. Treatment is symptomatic with analgesics and supportive measures. Prevention and control.

No vaccine has been developed. Spraying residual insecticides can control sand flies. Personal protection is achieved by using insect repellants. A new strategy tried in Vietnam against *Aedes aegypti* is to grow predator copepods in domestic water collecting vessels and tanks.

Yellow Fever

Yellow fever is an acute mosquito-borne infection of varying severity characterized by the triad of hepatitis, hemorrhagic diathesis and proteinuria.

Etiology

The causative virus is an arbo virus belonging to the genus *Flavivirus*, in the family *Flaviviridae*.

Distribution and Incidence

Yellow fever is prevalent in many parts of Africa, tropical parts of South America and Panama. The disease has not been reported in India. The presence of the efficient vector *Aedes aegypti* mosquitoes and the non-immune population pose a threat of the disease spreading in India, if the virus is introduced. Hence, this disease is of importance to India.

Yellow fever is notifiable under the International Health Regulations.

Transmission and Epidemiology

Epidemic (urban) yellow fever is transmitted from human to human by *Aedes aegypti* mosquitoes. Infected monkeys and the vector mosquitoes maintain the reservoir of infection in the jungle. These act as a source of infection when the humans intrude into endemic areas.

Pathology and Pathogenesis

The incubation period after an infectious mosquito bite is 3 to 6 days.

Liver and kidneys show maximal lesions but hemorrhage may occur in all organs. Hepatic changes include widespread necrosis, and degeneration of liver cells. Renal changes include acute tubular necrosis and subcapsular hemorrhages.

Bleeding diathesis is due to depletion of hepatic clotting factors, intravascular coagulation, and platelet

abnormalities. Direct damage to the myocardium, kidneys and other organs and the effects of vasoactive cytokines, lead to fatal complications such as multi-organ failure and shock.

CLINICAL FEATURES

In the majority of cases the disease is a self limited with fever and myalgia. 25 to 50% of cases may develop the full syndrome with complications such as hemorrhages, jaundice, renal involvement and shock.

The first stage (i.e. period of infection) is due to the direct effect of the virus. It starts abruptly with fever, headache and myalgia. In severe illness there is, nausea vomiting, abdominal pain and distressing pain in the back, and limbs. There is relative bradycardia. This stage lasts about 3 days and by 4th day the temperature comes down and **the second stage** (period of remission) starts. Many cases recover without going to the third stage. Some progress to **the third stage** (period of intoxication). It starts after a day or a few days, with resumption of high fever, body pains, nausea, vomiting, abdominal pain and changes in the level of consciousness. Bradycardia, jaundice, wide spread hemorrhages and renal failure may supervene. Death is due to hepatic or renal failure and shock.

Diagnosis

In endemic areas, fever, leukopenia and proteinuria with or without jaundice should suggest the possibility of yellow fever. Specific diagnosis is established by the isolation of the virus from the blood in the first few days of fever or demonstration of rising titer of antibodies in serum.

Treatment

There is no specific antiviral treatment. Symptomatic and supportive measures should be instituted. Hepatic and renal failure have to be anticipated and managed accordingly.

Prevention

Vaccination using live attenuated vaccine (17D strain) is very effective. Vaccination gives immunity starting from ten days and full protection for 10 years. Though side effects are generally negligible, children below 9 months may develop encephalitis. Pregnancy is not a contraindication for vaccination.

India and many other countries insist on yellow fever vaccination for persons entering the country or remaining during transit, if they come from endemic areas. Persons travelling to endemic areas have to take vaccination. Yellow fever vaccination is available at recognized centers in India.

Kyasanur Forest Disease (KFD)

Kyasanur forest disease (KFD) is an acute febrile illness caused by a *group B arbovirus*, clinically characterized by sudden onset of fever with rigor, severe body pains, headache, meningism, delirium, mental confusion and dehydration. The original description was from Shimoga district of Karnataka State in South India in 1956.

The disease was prevalent among people living in the villages around the forest area. The infection developed in persons who had gone into the forest (usually to fetch wood) and who had come into contact with dead monkeys. The ticks *Hemaphysalis spinigera* and *Ixodes* act as vectors to transmit the disease from animals to man. Monkeys (black faced langur and macaques), shrews and rats are known to harbor the virus. Man gets infection by the bite of the nymph of *H. spinigera*. Infected ticks carry the virus for long periods. Personnel working in laboratories handling the virus or investigators working in the affected areas are susceptible to infection. In addition to vector transmission, infection can also be spread by inhalation of infected material.

Clinical Features

After the incubation period lasting for 2 to 7 days, sudden fever sets in with chills and rigor. Fever is associated with headache and severe myalgia in the nape of the neck, back and calf. These may be mistaken for dengue fever. Abdominal pain, diarrhea and vomiting may occur between the third and the seventh day. Uncommonly, bleeding tendencies such as epistaxis, bleeding gums and melena may develop around third day. Lymphadenopathy of the neck and axilla, and conjunctival injection may also be seen. Bradycardia and hypotension may develop. Hepatosplenomegaly may occur in some cases. Alteration in mental state, neck rigidity, giddiness, tremors, listlessness and dyspnea have all been reported.

In uncomplicated cases, the fever lasts for about 10 to 12 days and temperature comes down. A second febrile phase may follow 2 to 12 days after the temperature has touched normal and this may continue so for 9 to 21 days. The mortality rate is around 5%. Death is usually caused by pulmonary edema.

Laboratory Diagnosis

Leukocyte count is low (about 3000/cmm). The virus can be isolated from blood during the course of the fever. Paired sera show rise in antibody titers. During the second febrile phase CSF may show features of aseptic meningitis.

Treatment

In the absence of specific treatment only supportive therapy is to be given.

Prevention

Anti-tick measures have to be instituted during jungle clearing operations. Persons at risk should use protective clothing and insect repellants. Though a vaccine was developed against KFD, it was not found to be very effective.

Chikungunya

Chikungunya (CHIK) fever is an acute infective disease, characterized by symmetric polyarthropathy, fever, rash, and rarely, generalized hemorrhages and CNS symptoms. The disease derives its name from the sudden onset of severe joint pain, which cripples the victim. The disease was first described in 1955 following an outbreak in Africa in 1952.

Etiology

CHIK virus is an *alphavirus* in the Semliki Forest complex (Togaviridae) and most closely related to *o'nyong nyong* (ONN) virus.

Distribution and Incidence

CHIK is widely distributed in Africa, the middle east, and Asia. The disease has now become endemic in several parts of India. Epidemics have been reported from southern and eastern parts of India including Tamil Nadu and Kerala. In 1964 an epidemic occurred in Tamil Nadu and surveys showed 38% of the population had antiviral antibodies. It is possible that sporadic or small outbreaks may occur from time to time. A localized outbreak is reported from Tamil Nadu during June-July 2006. Thiruvengadam et al studied epidemic of chikungunya which occurred in the Madras Metropolitan area in 1964. The virus was isolated and rise in antibody titer was confirmed at the ICMR Virus Research Laboratory Pune in a third of the patients studied.

In recent years as extensive epidemic affected several African and Asian countries, affecting millions of people. It is possible that the original virus has undergone genetic mutation.

Charrel RN, et al. N Eng J Med 2007;356:767-71.

Transmission and Epidemiology

In India *Aedes aegypti* mosquito is the main vector. *Aedes albopictus* is also implicated. In Africa there is a sylvian cycle involving forest mosquitoes, humans and possibly other mammals. In Asia, sylvatic viral reservoirs have not been defined.

CLINICAL FEATURES

The incubation period varies from 2-10 days, usually 3-7 days. The onset is sudden with abrupt fever (above

40°C), chills and rigor, headache, body pains and joint pains. There may be mild conjunctivitis, pharyngitis and erythematous rash over the body and face. The joints may be so inflamed that normal activities, standing and walking become painful. Arthropathy is symmetric, affecting the extremities and less often the shoulders and hips. Definite joint effusion is seen in 10% of cases. Small joints of the hands and feet and major joints of the lower limbs are affected most. Pain may be excruciating, crippling the patient quite out of proportion to the general disability. Fever and joint pains persist for up to six days after which they subside. Residual arthropathy lasting for months may occur in up to 30% of adults; especially in elderly patients. Morning stiffness and pain may persist for even a few months. Pre-existing joint problems and neurological disorders considerably worsen the disability and delay recovery. Joint pains are milder and may be even entirely absent in children. A faint maculopapular rash may appear concurrently with defervescence. Complications such as hyperpyrexia, hemorrhagic manifestations, encephalitis, polyneuropathy of the Guillain-Barré type and ECG changes suggestive of myocarditis were recorded in the Madras outbreak. Hyperpyrexia caused death in one patient. Among asymptomatic subjects 38.4% showed hemagglutination (HI) antibodies to chikungunya virus, confirming the presence of the virus in the community.

Ref: Thiruvengadam et al, Clinical and Pathological Studies on Chikungunya fever in Madras city Ind J Med Res 1965; 53 729-43 quoted by JAPI 2006 54, 898.

Hemorrhagic manifestations occur occasionally. CNS manifestations like meningism, convulsions and acute polyneuropathy has been reported in a minority of patients, especially children and infants.

Course and Prognosis

The disease may run a benign course with slow recovery even if untreated. Arthropathy may persist for varying periods and can be disabling. The acute illness in children and infants and elderly persons can be fatal. The primary role of uncomplicated chikungunya as a cause of death is not established. It produces considerable morbidity and impairment of the quality of life for prolonged periods.

Diagnosis

Routine laboratory investigations are not specific. The ESR may be elevated to 20-50 mm/hr and CRP may also be elevated. Isolating the virus or identifying genomic products by PCR in acute phase blood specimens can confirm the diagnosis. Serologically specific IgM or other antibodies can be demonstrated by IgM capture ELISA test. This test will distinguish the condition from dengue which is also transmitted by the same vector. During the prevailing epidemic in south Kerala a few cases of co-infection by chikungunya and dengue have been observed.

Treatment

Rest and symptomatic treatment with non-steroidal anti-inflammatory drugs give relief. Prolonged arthropathy demands symptomatic treatment. Chloroquine given in a dose of 250 mg od or bd has been reported to be useful. In any case results are not impressive.

Prevention and Control

An experimental live attenuated vaccine has been shown to produce high levels of neutralizing antibody in human volunteers but efficacy has not been tested. Anti-mosquito measures and personal protection with mosquito repellents will reduce the spread.

Japanese Encephalitis (JE)

Japanese encephalitis (JE), a severe mosquito-borne infection of the CNS, is a leading cause of childhood encephalitis in Asia.

GENERAL CONSIDERATIONS

Etiology and History

The causative *flavivirus* is related antigenically to *West Nile virus*. The virus was first isolated from human brain of an epidemic case in Japan in 1924 and its transmission by mosquito was proved in 1936. It is an RNA virus. This disease has been reported from several countries in both tropical and temperate zones.

Distribution and Incidence

The disease is widespread in India and south-east Asian countries. Surveys done by National Institute of Virology, Pune, suggest that the flaviviruses are widely distributed in India. Neutralizing antibodies to JE virus were demonstrated in all regions, which had epidemics. In north and north-east India, the disease occurs more during the summer monsoon, whereas the maximum incidence in the south is from September to January. Epidemics occur in several parts of India from time to time. About 30,000 cases occur annually. The outbreaks coincide with the density of mosquito population.

Transmission and Epidemiology

The virus exists in reservoir hosts and man is affected from them. Pigs, birds such as pond herons, cattle-egrets, bats, buffaloes, and cattle harbour the virus. In India, pigs constitute the major reservoir in which the virus multiplies. Migration of birds accounts for the regional spread of infection. Though the virus is seen in several animals, it is pathogenic only to man and a few other mammals like horses. Poverty, unsatisfactory dwelling conditions and co-existence with cattle, birds and pigs facilitate transmission.

The vector Culicine mosquitoes act as the main vectors. Important among them are *Culex tritaeniorhynchus*, *C. pseudovishnui* and *C. vishnui*. *Anopheles barbirostris* can also transmit this virus.

The natural transmission cycle of the virus is birds → mosquito → bird and pig → mosquito → pig. Human infection occurs only when the mosquito population increases and man – mosquito contact is established. Risk for infection is highest in rural locations where rice fields, pigs and humans coexist.

In the vast majority, the infection remains subclinical. The ratio of overt to inapparent infection varies from 1:300 to 1:1000. Children below 15 years suffer more. The peak incidence is between 2 to 10 years and males suffer more.

6

Pathogenesis and Pathology

After an infective bite by the mosquito, the virus propagates locally and in the regional lymph nodes. Viremia leads to affection of several organs mainly the brain unless the infection is modulated by prompt immune response. Neuroinvasion probably occurs as the virus grows through vascular endothelial cells to the parenchymal side. The virus enters the neurons and leads to widespread degenerative and necrotic changes. Most marked lesions occur in the cerebral cortex, thalamic nuclei, corpus striatum, and brainstem with relative sparing of the white matter. Cerebellar cortex and spinal motor neurons may also be affected, but the affection is less marked. There is occlusion of the smaller arterioles leading to extensive focal ischemia and necrosis. Perivascular hemorrhages and mononuclear infiltration are seen.

CLINICAL FEATURES

The incubation period ranges from 5-15 days. Three stages are recognizable- prodrome, acute encephalitis and convalescence.

Prodromal stage: The onset may be gradual (4-5 days) or acute (12-24 hrs) or abrupt (1-6 hrs). The disease starts as fever with chills, headache, meningism, convulsions, psychotic behaviour and coma. Majority of cases recover in 4-5 days and clinical diagnosis can be made initially, only during epidemics.

Acute encephalitic stage: The fever persists at 40-41° C, the pulse is rapid and neurological manifestations predominate. Symptoms such as convulsions (70%), altered sensorium (90%), focal neurological deficits, signs of meningeal irritation (30%) and coma supervene. Supranuclear ocular palsies are common. Cranial nerve palsies and papilledema are uncommon. These features help to identify JE from tuberculous meningitis. Rapid onset of paralysis such as hemiplegia or monoplegia is

characteristic. Plantar responses are bilaterally extensor. Other manifestations of brain involvement include cerebellar signs, extrapyramidal signs and dystonic postures. The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) occurs in about 30% of cases reported from Kerala.

Convalescence: Neurological function is regained gradually over several weeks, most of them by 6-12 weeks. For the rest further recovery occurs after discharge over intervals of months to years.

Laboratory Findings and Diagnosis

Leukocytosis may be present and liver enzymes may be mildly elevated. CSF shows lymphocytic pleocytosis. The cell count varies from 10-1000 cells/cmm, with an average of 100-200 cells. CSF protein may be raised to 50-250 mg/dL; sugar is usually normal. EEG abnormalities are present in the acute phase. These include a pattern of diffuse delta wave activity and rarely, spike and wave discharges. EEG findings are not helpful in predicting the outcome. ECG may show nonspecific ST-T changes indicating myocarditis.

MRI reveals diffuse white matter edema and abnormal signals mainly in the thalamus, often with evidence of hemorrhage in the basal ganglia, cerebellum, midbrain, pons and spinal cord. The clinical diagnosis is easy during epidemics. Since this disease often occurs sporadically, JE should always be considered in cases of encephalitis.

Laboratory diagnosis in most cases depends principally on the serologic testing of the serum and also CSF by antibody capture enzyme linked immunosorbent assay (ELISA).

IgM and IgG antibodies can also be detected by indirect immunofluorescence assay. The assay is more than 95% sensitive when serum specimens are tested 7 to 10 days after the onset.

Hemagglutination inhibition (HI) or complement fixing antibodies can be demonstrated in paired sera and these give evidence of infection in retrospect. Neutralizing antibody titer of 80 in the serum is suggestive. Fourfold rise in titer is confirmatory. CSF neutralizing antibody titer of 10 is confirmatory.

The virus can be isolated from blood only during the first few days of illness, usually preceding the onset of neurologic symptoms. Isolation of the virus from the CSF indicates the absence of protective antibodies and therefore, poor prognosis.

Differential Diagnosis

Features of JE have to be distinguished from various types of meningitis and encephalitis, cerebral malaria, toxic encephalopathies, cerebral tumours and Reye's syndrome.

Prognosis

Complete recovery occurs in one-third of cases, neurological sequelae occur in another one-third and

mortality in the rest. In India mortality rate is 25-45%. Death is usually due to neuronal damage, cerebral edema, pulmonary edema or intercurrent complications like infections from stasis ulcers, urinary tract infection, pneumonia, and bacteremia. Prognosis has to be guarded since it is not always possible to predict the outcome from the clinical features. Neurologic sequelae such as intellectual impairment, motor deficits, extra-pyramidal features and cerebellar disturbances are common. Polio like flaccid paralysis may occur rarely. Parkinsonism is uncommon and this stands in contrast to encephalitis lethargica. The first attack of JE produces immunity, but second attacks do occur since immunity is not lifelong. JE occurring in the first or second trimester of pregnancy may lead to fetal infection and fetal death. Cases acquired in the third trimester have not been reported to interrupt pregnancy.

TREATMENT AND PREVENTION

Treatment

There is no specific treatment. Supportive treatment includes the correction of fluid and electrolyte abnormalities, measures to control cerebral edema, anticonvulsants and maintenance of nutrition. Use of human immunoglobulin in a dose of 150-200 mg/kg bw early in the disease has been claimed to reduce the severity and mortality of the disease. There are preliminary data on the possible effectiveness of alpha-interferon for treatment of JE. Further studies are required to confirm the effect.

PREVENTION

Killed vaccine using Nakayama Yoken strain of the virus is available for prophylaxis. Indian vaccine is available,

originally prepared from Nakayama JE virus at Central Research Institute, Kasauli, HP. It is a formalin-inactivated vaccine. It is supplied as freeze dried vaccine, which has to be stored below 10°C. The reconstituted vaccine should be used within eight hours if kept cold. It should not be frozen. The recommended schedule for adults in JE endemic areas is two doses of 1 mL each given SC at an interval of 1-2 weeks. Protection starts one month after second dose. A booster dose should be given after one month but within one year. One more booster should be given after three years for full protection. In non-endemic areas repeated booster doses should be given every three years.

For children below three years the dose of vaccine is 0.5 mL, other conditions remaining the same. The vaccine is immunogenic, and safe with only rare side effects.

A live attenuated cell culture derived vaccine (SA14 14-2 strain) has been used safely and with high effectiveness in China.

Note: Zydus Biogen manufactures this vaccine in India.

Anti-mosquito measures help to limit the spread. Travellers to endemic areas should protect themselves against mosquito bite.

Points to remember

- 1. Japanese encephalitis is endemic in several parts of India occurring sporadically and as small outbreaks.
- 2. Co-existence of birds, cattle and humans and proliferation of culex mosquitoes provide the ideal environment.
- 3. Once the disease occurs, treatment is only symptomatic.
- 4. Effective vaccination is available for producing solid immunity.

Other Viral Infections

Epstein Barr Virus, Cytomegalovirus, Parvovirus, Hantavirus, Marburg/Ebola Virus, Chandipura Virus

K.V. Krishna Das

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Epstein Barr Virus

INFECTIOUS MONONUCLEOSIS

Introduction

This is worldwide in distribution, occurring in young individuals more frequently and caused by *Epstein-Barr virus (EBV)*. EB virus has been associated with several diseases both benign and malignant. These include infectious mononucleosis, Burkitt's lymphoma, hairy cell leukoplakia of the tongue, seen in relation to AIDS, nasopharyngeal carcinoma prevalent in China and post-organ transplantation lymphomas.

EBV is a member of the herpes virus family. It infects B-lymphocytes. MHC class II molecules act as cofactors for infection. The virus infects epithelial cells primarily and replicates in them, leading to lysis of the cells. In EB virus induced pharyngitis, the saliva contains infective virus. Other sites of invasion are the cervical epithelium and B-lymphocytes. Immunosuppressant therapy predisposes to, and augments the development of EB virus induced lymphoproliferative syndromes. One of the modes of spread of infection is through saliva and kissing is attributed to play a role.

Pathogenesis

Only B lymphocytes have receptors for EB virus, and therefore, EB virus attacks B lymphocytes initially. These cells begin to proliferate and are altered antigenically. Though T lymphocytes are not affected by EB virus they also proliferate enormously. Around 90% of the atypical lymphocytes which are characteristic of the disease have T lymphocyte markers, whereas only 10% have B lymphocyte markers. The T cells destroy EB virus infected B cells resulting in the liberation of antigenic materials which stimulate the formation of autoantibodies. The antigenic stimulus to heterophilic antibody is not known. Both cellular and humoral responses occur, the former is more effective in conferring immunity. The virus develops strategies to elude the immune system and the infection tends to persist.

Clinical picture resembling infectious mononucleosis can be evoked by *Toxoplasma gondii* and *cytomegalovirus*, but in these the antibody responses are not seen.

CLINICAL FEATURES

The incubation period may range from 1 to 10 weeks, usually 2 weeks. The clinical spectrum may vary from that of a mild benign illness to that of a more severe and prolonged one. In children the infection is less severe whereas in adolescents and adults it produces the syndrome of infectious mononucleosis. The onset is

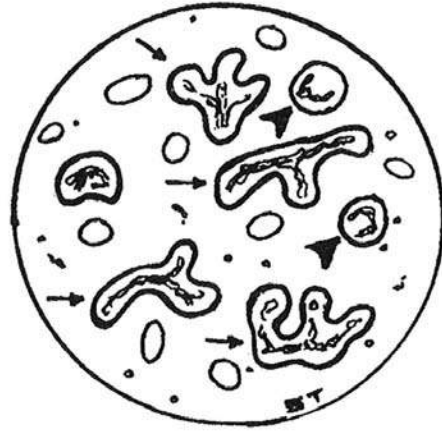


Fig. 61.1: Blood film atypical lymphocytes—line drawing. Arrows-note the amoeboid shapes. Arrow heads—neutrophils

usually insidious with general malaise, headache, diffuse myalgia, variable grades of fever, and other constitutional symptoms. A petechial rash occurring at the junction of the soft and hard palate associated with sore throat may herald the onset. The sore throat may persist for days and this may be mistaken for follicular tonsillitis. The posterior cervical lymph nodes enlarge initially, later generalized lymphadenopathy may occur. Spleen is moderately enlarged to 2 to 3 cm below the costal margin, it is soft and non-tender. If gross splenomegaly occurs, the organ tends to rupture even with slight trauma. Rarely jaundice and neurological manifestations may develop.

Blood: Initially there is leukopenia due to decrease in neutrophils, but this is followed by leukocytosis in which the leukocyte count may go upto 15-20,000/cmm. The characteristic finding is the presence of atypical lymphocytes which may form 60-80% of the total. The nuclei of the atypical lymphocytes do not have a regular shape but may be kidney shaped, oval, lobulated, or polymorphic. Nucleoli are not seen. The cytoplasm is non-granular, foamy, vacuolated, and appears amoeboid. The rest of the cells are mononuclear cells. In uncomplicated cases platelet count is normal (Figs 61.1 and 61.2).

Complications may occur. These include hemolytic anemia, thrombocytopenia, aplastic anemia, myocarditis, hepatitis, genital ulcers, splenic rupture and Guillain-Barré syndrome. Some cases go into chronicity.

Diagnosis

Clinically the disease should be suspected when small outbreaks occur in closed communities like hostels and dormitories, or when there is close personal contact with cases. The presence of oral lesions, posterior cervical lymphadenopathy, splenomegaly, and erythematous rashes

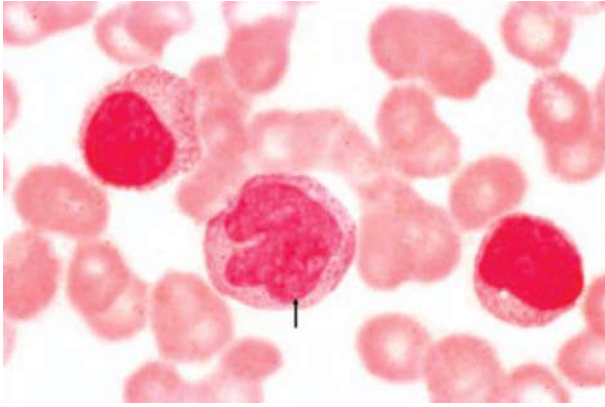


Fig. 61.2: Infectious mononucleosis—blood film arrow points to atypical lymphocyte

are suggestive. Diagnosis should be strongly suspected if the proportion of atypical lymphocytes exceeds 50%.

Presence of heterophile antibodies demonstrable by the *Paul-Bunnell test* (*sheep-cell agglutination*) strongly suggests the diagnosis of infectious mononucleosis. The titre of antibodies increases with the passage of time. They are detectable for 4 to 6 weeks. Since similar antibodies develop in serum sickness as well, differential absorption techniques are employed to differentiate infectious mononucleosis antibodies from those due to serum sickness.

Recently a rapid slide test called *monotest* has become available for quick diagnosis. Specific antibody to EB virus can be demonstrated by immunofluorescence, complement fixation, and gel diffusion wherever facilities exist.

Chronic active EBV infection is diagnosed by the following features:

1. Severe illness more than six months duration.
2. Histological evidence of organ involvement such as pneumonitis, hepatitis, bone marrow hypoplasia and uveitis and
3. Demonstration of EBV antigens or EBV DNA in tissues.

The differential diagnosis includes rubella, measles, viral hepatitis, secondary syphilis, follicular tonsillitis, diphtheria, and herpetic pharyngitis. The prolonged fever and constitutional symptoms may suggest enteric fever, influenza, or even acute rheumatic fever. The cases which present with neurological manifestations may have to be distinguished from encephalitis or lymphocytic choriomeningitis. Other hematological disorders like acute leukemia and lymphoma have to be distinguished by suitable tests.

Treatment

There is no specific therapy and symptomatic measures are indicated. Acyclovir arrests viral growth, but does not effectively allay the clinical course. This drug is quite

effective in oral hairy leukoplakia. It is seen that ampicillin aggravates the lymphadenopathy, skin rash, and laryngeal edema in many cases and hence this drug should not be employed. Other antibiotics are indicated if there is evidence of secondary infection.

In severe cases acyclovir and corticosteroids may help, especially when there is respiratory distress. In the vast majority recovery is usually complete in 3-4 weeks without any sequelae. Recent epidemiological evidence suggest that in some cases, due to continued antigenic stimulation, a lymphomatous process may be triggered off. Attempts to produce a vaccine are going on.

Cytomegalovirus Infection (CMV)

This virus which belongs to the family herpesviridae commonly affects humans and 40-90% of adults may show antibodies to the virus. The virus is shed in saliva and urine and from the genital tract. Infection is acquired by contact with saliva or urine or by sexual contact. Uncomplicated CMV infection in immunocompetent subjects may be asymptomatic in the vast majority. Clinical illness resembles infectious mononucleosis caused by Epstein Barr virus (EBV), with rash, Hepatitis, retinitis and neuropathy resembling Guillain-Barré syndrome may occur rarely.

In immunocompromised states the virus produces more severe illness leading to retinitis, pneumonitis, enteritis and generalized infection. It may occur as a co-infection in AIDS when the CD4 counts falls below 50/cmm. Patients receiving immunosuppressive therapy after organ transplantations may get CMV super-infection. Pregnant women who develop CMV infection may transmit the same to the fetus in up to 40%. Congenital infection may lead to hepatosplenomegaly, purpura, encephalitis, deafness and mental retardation in a small proportion.

Treatment

The drug of choice is **ganciclovir** 5 mg/kg bw given IV infusion given slowly over 1 hour b.d for 2 to 3 weeks. Maintenance dose is 5 mg/kg/day for long periods. An alternate drug is **foscarnet** given I V in a dose of 90 mg/kg b. d for 14 to 21 days. Intravenous administration of hyperimmune anti-CMV globulin given during pregnancy protects the fetus. An oral preparation of ganciclovir is available for prophylaxis in immunocompromised person.

Parvovirus Infections

Parvoviridae is a large family containing several members pathogenic to vertebrates. Of particular importance is parvovirus B19 belonging to the genus erythrovirus, and it propagates best in erythroid progenitor cells. Spread is

by respiratory droplets and through transfusion of blood and blood products. The virus does not have a lipid envelope and therefore it is resistant to heat-inactivation and solvent detergents. Infection is very common and more than 50% of people acquire antibodies to the virus by 15 years of age. The natural host for parvovirus B₁₉ (PV B₁₉) is the human erythroid precursor cells which contain globoside, which is a neutral glycolipid which acts as a cellular receptor (also known as group P antigen) on the RBC. Antibodies develop against the virus. These help to limit and eliminate the infection. Failure to produce antibodies results in persistence of the infection. Most of PB B₁₉ infections go without consequence. Active infection can lead to significant pathology especially in those with impaired red cell production, accelerated destruction or immunosuppression. PV B₁₉ directly infects erythroid progenitor cells leading to their lysis. The impaired erythropoiesis lasts for 7-10 days, with a drop of hemoglobin of up to 2g/dL in otherwise normal people. Markers of infection include B₁₉ IgM and/or B₁₉ DNA.

Clinical Features

Several syndromes are caused by parvovirus B₁₉.

1. *Fifth disease in children*: This manifests as fever with rash on the cheek-called erythema infectiosum. This rash is due to the deposition of immune complexes in the skin. The rash may tend to recur.
2. *Arthralgia and even arthritis* in older age groups
3. *Pure red cell aplasia*: This may lead to insidious onset of anemia in otherwise normal people. Generally the infection is short lived and spontaneous recovery is the rule. In hemolytic anemias where erythrocyte life span is reduced such as sickle cell disease, hereditary spherocytosis, thalassemias, congenital aplastic anemias and even iron-deficiency anemia, the virus causes aplastic crises.
4. *Persistence of parvovirus infection*: This leads to severe pure red cell aplasia of prolonged duration.
5. In pregnant women the virus may infect the fetus and produce fetal loss, or hydrops fetalis. 20% of non-immune-mediated hydrops fetalis is due to parvovirus infection.

Diagnosis can be established by demonstrating the antibodies.

Treatment: is symptomatic.

Hantavirus Infections

Hanta virus is a natural inhabitant of rodents and the virus is shed in their urine, feces and saliva. This virus affects the vascular endothelium and causes two major syndromes:

1. Hemorrhagic fever with renal syndrome (HFRS) and
2. Hantavirus cardiopulmonary syndrome (HCPS)

Antibodies to these virus has been reported in 15% of febrile patients in Vellore. S. India (Chandy S et al. Indian J Med Res 2005;122:211-5). Infection is by aerosol inhalation of infective material. Incubation period is about 3 weeks.

The virus affecting the endothelium leads to immune response against viral antigens expressed on the endothelial cells of the heart, lungs, kidney and lymphoid organs. The immune reactions are mediated by T-lymphocytes and macrophages. TNF- α and IL-1 beta increase capillary permeability. Nitric oxide released by TNF leads to vasodilation and shock.

HFRS: Nonspecific constitutional symptoms occur followed by hemorrhagic manifestations along with renal lesions.

Shock, oliguria and DIC follow. Survivors enter a diuretic phase by day 10-14. Thrombocytopenia, leukocytosis with shift to the left, increase in the number of circulating immunoblasts (up to 10% of circulating lymphocytes) and increase in serum levels of LDH should suggest the diagnosis. Specific tests include the demonstration of IgM and IgG antibodies by ELISA.

HCPS: Constitutional symptoms lasting for 3-7 days are followed by hypotension and shock. Pulmonary edema, cardiac arrhythmias and cardiac arrest may occur. Renal lesions may develop leading to oliguria lasting for 3-8 days, and later followed by polyuria.

Treatment is supportive with I V fluids, ionotropes, mechanical ventilation and blood products. Ribavirin has been used in usual doses- with variable results.

Marburg Virus and Ebola Virus

Marburg virus and Ebola virus are filoviruses which cause a severe, and often fatal hemorrhagic disease. In 2004-2005 an outbreak occurred in Angola with a case fatality of about 90%. Authentic reports on their presence in India are not available. Studies are going on with live attenuated recombinant vesicular stomatitis virus (rvsv) expressing the glycoprotein of Marburg virus and vaccination with this vector completely protected non human primates against experimental infection. The use of such vaccines for post exposure and pre-exposure prophylaxis in experimental animals shows promising results.

Chandipura Virus Encephalitis

This is a rapidly developing encephalitis which has affected parts of India from time to time. The virus belongs to the genus vesiculovirus and family Rhabdoviridae. An outbreak was documented in Jamshedpur in 1954. The virus was originally discovered in 1965 at the National Institute of Virology, Pune. A recent outbreak was described in 2003 in Andhra Pradesh and adjoining

areas of Maharashtra. In 1980 the virus was isolated from a case in Madhya Pradesh. It has also been reported from Senegal and Nigeria. Vectors are most probably female sandflies- *phlebotomus* spp.

The onset is with sudden fever, rigor, drowsiness leading to unconsciousness and death in 6-48 hours. The age group ranged from 2.5 to 15 years. The case fatality was 52.3%.

Ref: (Rao BL, et al. The Lancet 2004;364:869-74).

62

Systemic Fungal Infections

6

K.V. Krishna Das

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General Considerations

Fungi are present in abundance in the soil as saprophytes and they generally invade immunologically compromised hosts. In the human body they are present as commensals abundantly in the mucosal regions, skin and alimentary tract. The normal flora keep the fungi under check. With the widespread use of antibacterial drugs and immunosuppressive therapy fungal infections have assumed greater importance. Advances in surgery, organ transplantation, widespread use of prosthetic materials inside tissues, extensive use of broad-spectrum antibacterial agents and long-term use of immunosuppressant drugs have paved the way for the emergence of life-threatening fungal infections. Prophylaxis against such infections and vigorous curative therapy have to be undertaken to achieve the desired benefits in such patients.

Fungi may be unicellular such as *Cryptococcus* or multicellular such as *dermatophytes* and they show varying degrees of differentiation. Hyphae are elongated tubular structures formed by the cells. Hyphae may be

septate or nonseptate. A tangled mass of hyphae is called mycelium.

Pathogenic fungi may be classified into four groups morphologically.

1. **Yeasts:** These are unicellular fungi, spherical or ellipsoidal in shape, which reproduce by simple budding, e.g., *Cryptococcus neoformans*.
2. **Yeast-like fungi:** These show spherical and hyphal forms, e.g., *Candida albicans*.
3. **Moulds:** These are filamentous fungi which are capable of spore formation, e.g., *dermatophytes*.
4. **Dimorphic fungi:** These may grow as yeasts in tissues and moulds in the soil. Most of the systemic mycoses are due to such organisms.

Another basis for classification takes into account sexual spore formation. According to this classification, fungi may be divided into phycomycetes, ascomycetes, basidiomycetes and fungi imperfecti. Most of the human fungal pathogens belong to the class of fungi imperfecti.

Diagnosis of fungal diseases is established by demonstration of the organism in tissue specimens, body fluids or discharges. Fungi can be easily cultured in prepared media such as Sabouraud's glucose agar at pH 5.4.

Fungal lesions occurring in man can be broadly classified into superficial and deep mycoses. Superficial mycoses are more common and include the various types affecting the skin, nails, hair and mucous membranes. They are more common in those parts which are prone to be moist, such as intertriginous areas of skin, e.g., groin, gluteal folds, and webs of fingers. They occur in individuals who are otherwise healthy.

Primary systemic fungal infections are caused by organisms that are mostly soil saprophytes and the infection is accidental. Immunocompromised individuals run the risk of opportunistic infections by fungi that are usually avirulent such as mucor, cryptococcus, candida and aspergillus, but which become invasive when body resistance goes down.

A range of antifungal drugs are available at present for topical and systemic use. Early detection of fungal infection and appropriate therapy are essential for successful result.

Candidiasis

Candida albicans is a common inhabitant of the oropharyngeal, genital and intestinal cavities of man. Candidiasis is infection by *Candida albicans*. In most of the cases it remains as a local infection affecting the skin or mucous membranes of the mouth or genitalia. In the mouth it presents as oral thrush which is seen at the extremes of ages, those on antibiotic therapy or in immunosuppressed individuals. In the genitalia it usually presents as vulvovaginitis in diabetic women who are not well-controlled. Cutaneous candidiasis usually affects the intertriginous areas.

Systemic candidiasis occurs in immunocompromised individuals and in drug addicts who share needles. The fungus becomes invasive and spreads through the blood stream to produce several lesions.

1. Localized lesions: Urinary tract, liver, heart valves, meninges and peritoneal cavity.
2. Widely disseminated: Associated with septicemia (candidemia).

In disseminated candidiasis also the main targets of attack are the kidneys, brain, liver, gastrointestinal tract, eye (endophthalmitis) and heart valves.

Extensive, recurrent and persistent oropharyngeal and esophageal candidiasis is a common AIDS associated infection.

Diagnosis

The organism can be demonstrated microscopically by examining samples from local lesion. In tissues, PAS staining or methenamine silver staining reveals the organism.

The fungus can be grown in Sabouraud's medium. Antibodies to *Candida* can be detected by ELISA or immunodiffusion. The candidal antigen can be demonstrated by ELISA or radioimmunoassay.

Treatment

Amphotericin B, fluconazole, ketoconazole and itraconazole are all effective in appropriate dosage to control the systemic infection. Local surgical therapy should be aimed at removal of the source of infection.

Dose: Amphotericin B up to 50 mg/day IV for 1-2 weeks and more.

Fluconazole 400 mg/day.

Ketoconazole 400 mg/day for several weeks.

Itraconazole 200-400 mg/day (Table 62.1).

Itraconazole and fluconazole are less adreno-suppressive compared to ketoconazole. Superficial skin and mucous membrane lesions respond well to nystatin ointment or nystatin mouth washes. Fluconazole given orally is very effective to cure vaginal candidiasis.

Aspergillosis

The species of aspergillus pathogenic to man are *A. fumigatus*, *A. niger*, *A. flavus*, *A. terreus* and *A. nidulans*. Of these *A. fumigatus* is most common. Infection occurs when general resistance is lowered or local disease favours superinfection. Aspergillus is very widespread in nature and their spores are found in dust. Both superficial and systemic lesions may develop. The commonest superficial lesion is otomycosis. Systemic infection may be pulmonary or disseminated. Major portal of entry is the respiratory tract.

Pulmonary form: Allergic alveolitis may develop due to inhalation of fungal spores in sensitized individuals. *Aspergillus* may grow in the bronchi to produce bronchopulmonary disease. The hyphae may obstruct the lumen. Healed tuberculous cavities or other types of cavities may be the seat of colonization by the fungus. The mycelia grow to form a tangled fungal ball which is recognizable in X-rays (aspergilloma) (Fig. 62.1). It may remain asymptomatic or may cause massive hemoptysis. Invasive aspergillosis occurring in immunosuppressed individuals leads to widespread pulmonary necrosis with marked systemic symptoms.

TABLE 62.1

Comparative data of the three azole antifungal drugs

	Water solubility	Bioavailability	Urinary excretion	Half-life (hours)	Level in CSF/ Serum %
Fluconazole	Good	85%	64%	22	60
Ketoconazole	Poor	75%	2%	8.1	10
Itraconazole	Poor	99.8%	1%	17	10



Fig. 62.1: Skiagram aspergilloma in cavity, left lung and upper zone

Other sites of lesion are the central nervous system and naso-orbital cavities. Diagnosis can be made by histological demonstration of the fungus and isolation of the organism from the exudates. Since *Aspergillus* is a common contaminant in respiratory secretions, mere isolation does not prove its pathogenic role. Precipitating antibodies can be demonstrated by gel diffusion test and this test is of great value in diagnosis.

Treatment

Amphotericin B in a dose of 1 mg/kg/day is effective in systemic aspergilloma. Amphotericin B and 5-fluocytosine are effective in CNS disease. The underlying predisposing factor should be attended to. Cavities containing aspergilloma producing intractable hemoptysis have to be removed surgically. Other drugs like clotrimazole which are also effective *in vitro* are being evaluated. Other drugs effective against aspergillus include oral fluconazole itraconazole, voriconazole and posaconazole. Posaconazole can be given prophylactically against aspergillus and other fungal infections in neutrophilic patients. The dose is 200 mg tds oral. Caspofungin a new anti-fungal drug effective against aspergillus and other yeast species.

Histoplasmosis

Syn: Darling's disease, cave disease

Etiology

This infection is worldwide in distribution but maximum number of cases have been reported from the West, especially the USA. Limited studies show that the infection is present in India. *Histoplasma capsulatum* is



Fig. 62.2: X-ray chest histoplasmosis—
Lesion resembling tuberculosis

seen in soil enriched by the droppings of birds especially fowls. When the spores are inhaled yeast-like forms develop in tissues. It grows as a mould in its natural habitat and *in vitro*.

Pathology

The lesions are granulomas produced in several organs. Reticuloendothelial organs, lungs, adrenals, brain and other tissues may be affected. Lesions may resemble tuberculosis. Healing occurs with calcification. Cerebral lesions can be mistaken for those of cerebral thrombosis or hemorrhage.

Clinical Features

The majority of cases are asymptomatic. Pulmonary lesions may resemble different types of tuberculosis (Fig. 62.2). Common manifestations include fever, cough, hilar adenopathy, pneumonitis, apical infiltrates, fibrocavitary lesions and subpleural solitary pulmonary nodules. Scattered miliary calcification may develop in disseminated histoplasmosis (Fig. 62.3). Other manifestations include mediastinal syndrome, uveitis and adrenal insufficiency.

Disseminated Histoplasmosis

Fatal disseminated histoplasmosis may develop in persons who harbour the infection, and who receive corticosteroid therapy. Lesions occur in the liver, spleen, bone marrow, lymph nodes and adrenals. Clinical features include fever,



Fig. 62.3: X-ray chest histoplasmosis—Miliary calcification

hepatosplenomegaly, generalized lymphadenopathy and mucocutaneous ulceration.

Diagnosis

X-ray chest shows the pulmonary lesions. Delayed hypersensitivity test using histoplasmin is helpful in diagnosing past infection. The test shows cross-sensitivity with other fungi. It is more useful for epidemiological studies to determine the prevalence of histoplasmosis in the community. Its use in the diagnosis of individual cases is limited. Complement fixing antibodies are detectable in the serum and these, being more specific, are useful in diagnosis. Diagnosis can be confirmed by demonstrating the fungus in tissue biopsies or other suitable material.

Prognosis

Histoplasmosis is generally benign. In immunosuppressed individuals complications are more.

Treatment

Specific treatment is not indicated in asymptomatic cases. In disseminated disease and in chronic pulmonary lesions, intravenous amphotericin B given for 10-12 weeks is curative.

The dose is 0.5 to 0.6 mg/kg bw daily or 1.0-1.2 mg/kg bw on alternate days. Immunocompromised subjects should receive amphotericin as the drug of choice.

Ketoconazole 400 mg daily for 6 months is a less toxic alternative. This drug may produce transient adrenocortical insufficiency.

Persistent cavities and mediastinal fibrosis may demand surgical removal.

Cryptococcosis

Syn: Torulosis, European Blastomycosis, Busse-Bushke's disease

Infection by *Cryptococcus neoformans* leads to a clinical picture of subacute or chronic meningoencephalitis commonly. Sometimes the infection becomes generalized and lungs, skin, bones and viscera may be involved. The fungus is present in nature especially in soil contaminated by the droppings of birds like fowls and pigeons.

Etiology

Cryptococcus neoformans is a yeast like fungus, distributed all over the world. In tissues it remains encapsulated in a polysaccharide capsule. Infection in the majority of cases is subclinical, but generalized disease occurs in immunologically deficient subjects. It is a common opportunistic infection in AIDS.

Pathogenesis and Pathology

It is probable that the fungus reaches the lungs by inhalation. The pulmonary lesions tend to heal spontaneously without becoming symptomatic. Histologically, the lesions range from mild inflammatory reaction to definite granulomas. Intracranial infection leads to basal meningitis. The organism reaches the meninges by the bloodstream.

Clinical Features

The pulmonary involvement may be subclinical. It may be detected during routine investigation or accidentally, as inflammatory or tumour-like lesions. Often these lesions are mistaken for tuberculosis. Meningoencephalitis closely resembles tuberculous meningitis. Papilledema and cranial nerve palsies occur in some cases. The course is prolonged with remissions and exacerbations.

Papular or suppurative lesions occur in the skin in 10% cases. These ulcerate and discharge hairy material containing the fungus. Other viscera such as liver, pericardium and endocardium may be affected.

Diagnosis

Diagnosis is confirmed by finding the encapsulated fungus in the sputum, urine, tissues and cerebrospinal fluid. The fungus can be cultured and identified. *The encapsulated organism can be demonstrated in the CSF by microscopic examination after mixing with a drop of India ink.* Serological tests like complement fixation and latex agglutination are available, but being non-specific, they are not of great help. Cryptococcal antigen can be detected in CSF or blood by enzyme immunoassay.

Treatment

Cryptococcosis of the CNS is treated with fluocytosine, given 150 mg daily orally in four divided doses or intravenous amphotericin B. Amphotericin B is started in a daily intravenous dose of 10 mg in a drip as the initial dose and it is increased to 50 mg/day to reach a total dose of 2 g or more. Mild toxic effects include nausea, vomiting, chills, fever, headache and malaise. The drug is nephrotoxic and increase in blood urea is a contraindication for further therapy. Fluconazole 400 mg/day can be given IV daily for 14 days or more.

Combination of amphotericin B 0.7 mg/kg bw and fluconazole 200-400 mg I V daily along with other drugs results in earlier resolution of both meningitis and pneumonia. In cases where cryptococcosis complicates AIDS treatment has to be continued till the CD4⁺ count rises about 200/cmm with ART.

Rhinosporidiosis

It is a chronic localized proliferative lesion caused by *Rhinosporidium seeberi* which affects the mucous membranes of the nose, larynx, eyes, ears, mouth, genitalia, rectum and skin.

Etiology

The etiological agent which is most probably a fungus was included under the class phycmycetes. The source of infection is stagnant water or aquatic life. The disease is endemic in Sri Lanka and India, but only rarely seen in other parts of world. Mode of infection is not clearly known.

Pathology

Typical lesions are soft, nodular, and polypoid with greyish-white areas over the surface. Chronic inflammatory cell infiltration may be demonstrable. Histology shows a large number of fungal spherules containing endospores, embedded in a stroma of vascular connective tissue.

Clinical Features

The incubation period is not clearly known. The patients often seek medical help only when polypoidal masses have developed. The symptoms depend on the site of affection. Nasal cavity is affected most commonly (Fig. 62.4). Symptoms include local pruritus, presence of mass, nasal block and epistaxis. The polyps are soft, pink, friable, and easily bleeding on touch. Their sizes vary and they show small yellowish dots on the surface. Cutaneous lesions resemble warts and are initially painless but become painful later.

Diagnosis can be made clinically in endemic areas. Nasal discharge may show free spores demonstrable microscopically. Histology is confirmatory.

Treatment consists of surgical removal.

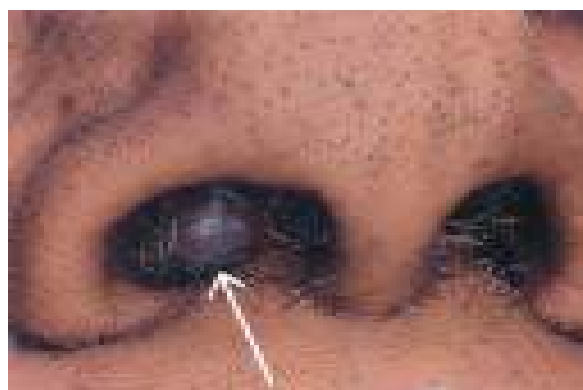


Fig. 62.4: Rhinosporidiosis—
Note the polypoid lesions - arrow

Pneumocystis Jirovicii Infection

This organism, previously known as *Pneumocystis carinii* is considered to be more similar to fungi, though for several decades it was included among the protozoa. The parasite that is specific to man has been re-designated as *Pneumocystis jirovicii*. It is a pathogen of low virulence. It measures 1-8 μ and is round or elongated. It is seen widely in nature in man and several animals. It is not very clear how *P jirovicii* is transmitted. It may spread from the environment or from person to person. In those with suppression of immunological function it becomes invasive and causes pneumonia. This parasite has unique tropism for the lungs where it remains as an alveolar pathogen without invading deeper tissues. Tissue reaction to infection leads to inflammation and diffuse alveolar damage. Immunity is CD4 T cell mediated.

Pneumocystis jirovicii infection complicates hematological malignancies, immunosuppressant therapy and organ transplantation.

Homosexual men and subjects with acquired immunodeficiency syndrome (AIDS) show predilection. In children, pneumocystosis may supervene on congenital immunodeficiency states and protein-calorie malnutrition.

Immunodeficiency also predisposes to infection by *cytomegalovirus*, *candida* and *mycobacteria* which may coexist with pneumocystosis. In many patients with AIDS, the presentation is pneumocystis pneumonia. Infection is heralded by fever, nonproductive cough and progressive dyspnea. The condition generally deteriorates within weeks to months. Physical examination may show nil, or only minimal signs. X-ray shows infiltration, going on to extensive consolidation. Less commonly other organs such as lymph nodes, spleen, liver, bone, bone marrow, meninges, pancreas and endocrine glands may show lesions (See also Chapter 48 AIDS).

Diagnosis

Pneumocystis pneumonia should be suspected when fever and respiratory symptoms occur in immunosuppressed

individuals. Chest skiagram shows diffuse interstitial infiltrates. The organisms can be demonstrated in bronchial aspirates or lung biopsy specimens taken at bronchoscopy or by needle biospy. Though positive results confirm the diagnosis, negative results do not exclude the condition.

Treatment

Cotrimoxazole in doses up to 6 to 7 g/day in divided doses for 2 weeks is beneficial. Pentamidine isothionate given intramuscularly in a dose of 2-4 mg/kg body weight daily for 10-14 days is also effective as a curative drug. If the drug is started early, results are good. Improvement starts in 5-7 days. Other drugs which are also beneficial include dapsone and pyrimethamine.

If the results are not good with the specific drugs alone addition of prednisolone in a dose of 1 mg/kg bw brings about rapid relief. This has to be tapered off with improvement. The underlying condition should also receive attention.

Prophylaxis against pneumocystis pneumonia should be instituted in patients infected with HIV when the CD4 lymphocyte count falls below 200/cmm. Cotrimoxazole is very effective in preventing infection, if given in a dose of one double strength tablet daily for prolonged periods.

TABLE 62.2

Other fungal infections		
Disease	Organism	Geographical distribution
Coccidioidomycosis	Coccidioidis immitis	Worldwide
Paracoccidioidomycosis	Paracoccidioides brasiliensis	South America
Blastomycosis	Blastomyces dermatidis	Worldwide
Sporotrichosis	Sporothrix schenkii	Worldwide
Chromoblastomycosis and mycetoma	Genera Fonsecaea and Cladosporium	Tropics
Zygomycosis	Absidia, Mucor, Rhizopus	Worldwide

Other Fungal Infections

With the advent of numerous antimicrobial drugs and immunosuppressant drugs, the number of immunocompromised subjects has increased. The epidemic of HIV has rendered many patients immunosuppressed. Due to all these factors the number and variety of fungal infection have also increased. Some of the less common fungal infections are given in Table 62.2.

63

Actinomyces and Nocardia

K.V. Krishna Das

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These are gram-positive bacteria with branching filaments sometimes forming a mycelium. These are included under the order Actinomycetales. Mostly they are soil saprophytes. Two genera—Actinomyces and Nocardia are pathogenic to man.

Actinomycosis

Syn: Ray-fungus disease

Actinomycosis is a chronic, slow-growing, progressive, granulomatous lesion caused by *Actinomyces israeli*. Actinomycetes are bacteria. They form mycelia like fungi. They are susceptible to antibiotics and in this regard behave more akin to bacteria. They are gram-positive. The two genera of medical importance are *Actinomyces* and *Nocardia*. *Actinomyces* are anaerobic or microaerophilic whereas *Nocardia* are aerobic. *Actinomyces israeli* is

present in the mouth as a commensal and tissue invasion occurs due to minor trauma.

Pathology

The lesions are granulomas with added suppuration. The pus shows microcolonies of the organisms as yellowish granules (sulphur granules). These granules become more distinct when the pus is shaken vigorously with water.

CLINICAL FEATURES

The disease presents as the cervicofacial form, thoracic form, abdominal form and bony lesions. Symptoms depend on the anatomic location.

1. **Cervicofacial form:** 40-60% of the total. This form starts as painless, slow growing lump near the jaw or a painful lesion resembling an abscess. The lesion progresses to involve deeper tissues and bone and sinuses develop. Trismus may occur. Lymph nodes are generally spared. Systemic symptoms are few or absent. The lesion progresses slowly to destroy all tissues and discharge the characteristic pus. Presence of extensive destructive lesions in the presence of minimal general symptoms should suggest the possibility of actinomycosis.
2. **Thoracic form:** This form results from aspiration of the organism from the mouth. Manifestations include pulmonary infiltration and cavitation, pleurisy, empyema and pericarditis. Pulmonary lesions may be unilateral or bilateral and may closely resemble tuberculosis. The lesion may spread to the pleura and chest wall leading to periostitis of the ribs and formation of discharging sinuses.
3. **Abdominal form:** This form results from ingestion of the organisms. Lesions occur in the cecum and appendix. The disease may present as acute appendicitis or a slow growing lump in the right iliac fossa. This may resemble ileocaecal tuberculosis, Crohn's disease or malignancy. The lesion may become adherent to the anterior abdominal wall and form sinuses. Rarely the liver and genitals may be involved.
4. **Bone:** The bony lesions include osteomyelitis of the mandible, ribs and lumbar vertebrae.

Diagnosis

Strong clinical suspicion is necessary to make the diagnosis. Microscopy of the discharges reveals the mycelia. Histopathological examination confirms the diagnosis. The organism can be grown in culture anaerobically.

Prognosis

Early diagnosis and proper treatment result in resolution of the lesions.

Treatment

Penicillin is the drug of choice giving cure rates over 80% in 6-8 weeks. Tetracycline and stilbamidine have to be given when penicillin is contraindicated. Erythromycin, fusidic acid, lincomycin and rifampicin are all effective. Surgery may be necessary in advanced cases if drug treatment fails.

MYCETOMA

Syn: Madura foot, Maduramycosis

Definition

This is a chronic granulomatous inflammation caused by several species of nocardia, actinomycetes and fungi. *Nocardia* are normally present in soil and infection may be exogenous.

The classic lesions are Madura foot and other mycetomas. The organisms causing Madura foot are *Nocardia madurae*, *N. asteroides* and *N. brasiliensis*. In addition to nocardia actinomycetes and fungi can also lead to mycetoma.

The lesion starts in the subcutaneous tissues and later on involves deeper structures, including the bones, to form sinuses leading to the eventual destruction of the part. *This condition was described in Madurai in 1842 by Gill.* This disease is confined to the tropics and is particularly endemic in India, Africa and South America. Most of the cases in India have been reported from Tamil Nadu, Andhra Pradesh and Maharashtra.

Pathogenesis and Pathology

The organisms enter through abrasions on the skin. The lesions are manifest after a long incubation period. A granuloma develops. The organisms are seen to lie in abscesses, surrounded by a zone of chronic inflammatory cells. The organism can be easily identified on microscopic examination. The inflammation spreads along fascial planes by contiguity. Nerves and tendons are highly resistant to invasion. Regional lymph nodes are not generally affected.

Clinical Features

A small painless firm subcutaneous tumour develops in both the nocardial and actinomycotic types. The lesions slowly progress to destroy the part. Sinuses develop which discharge pus containing the organisms. The progress of an actinomycotic granuloma is more rapid than that of a nocardial lesion.

The most common site is the dorsum of the foot, but other regions like the hands, buttocks, back, scalp and orbits may be affected. Systemic symptoms do not occur.

Radiological Features

Bone destruction and endosteal or periosteal new bone formation may be demonstrable in localized areas or more diffusely.

Progressive painless destructive lesions of the extremities occurring in endemic areas should raise the possibility of mycetoma. The differential diagnosis includes chronic osteomyelitis, tuberculosis, syphilis, elephantiasis and neoplasms. Histology of the lesion and isolation of the organism from the lesion help to establish the diagnosis. Antibodies to the organism can be demonstrated by agar-gel precipitation tests.

Treatment

Drug treatment is effective for actinomycotic lesions, but not so readily for nocardial lesions. Actinomycetomas respond well to prolonged treatment (6-12 months) with dapsone (200 mg/day), sulfisoxazole, streptomycin, sulphamethoxypyridazine, cotrimoxazole, nalidixic acid or rifampicin. Therapy of choice for nocardia is sulphonamide with or without trimethoprim.

Surgery

In addition to drug therapy, surgery may be needed to excise early lesions or to amputate grossly damaged limbs. The lesion may recur after surgery. Mycetomas can be prevented by hygienic habits and regular use of footwear.

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Disease Caused by Protozoa

Malaria, Leishmaniasis, Trypanosomiasis

V.P. Gopinathan, K.V. Krishna Das

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Protozoal Diseases

General Considerations

Protozoa are unicellular organisms containing cytoplasm, nuclei and other organelles. Based on the mode of locomotion, protozoa have been classified into flagellates, ciliates, amebae and sporozoa. Even though differences occur between the different classes, basic similarities exist. The cytoplasm is divided into an outer ectoplasm and inner endoplasm. Both layers contain several organelles, the ectoplasm performs the functions of protection, locomotion, respiration, nutrition and excretion.

The nucleus is made up of fine delicate filaments studded with masses of chromatin granules and is enclosed by the nuclear membrane. The karyosome lies in the center of the nucleus. It may be minute or large and conspicuous. Under adverse conditions, free-living protozoa change from the vegetative to the cystic form by encasing themselves in a tough membranous wall.

Protozoa are found extensively in the environment. Many, such as *Entameba coli* and *Trichomonas hominis* are free living commensals, while others become invasive and pathogenic when circumstances are favourable, e.g.,

Entameba histolytica, and *Giardia lamblia*. Some are obligate parasites of man or other vertebrate hosts, e.g., malarial parasites, trypanosomes and leishmania. These have a developmental cycle in arthropod vectors. Distribution of the vector determines the endemicity to particular geographical regions. Rise in vector population leads to outbreaks of epidemics from time to time. Since tropical climate offers the ideal situation for the breeding and proliferation of the vector arthropods, such vector-borne diseases are most prevalent in the tropical belt. High density of population, low socioeconomic conditions and poor hygienic environment favour the persistence and spread of many of the diseases – both faeco-orally transmitted and vector-transmitted.

Malaria

Definition

This is a febrile illness caused by the hemoprotozoa of the genus *Plasmodium*. It is characterized by periodic fever, splenomegaly, hemolytic anemia, and a recurrent and chronic course. The plasmodia affecting man are *P. vivax*, *P. falciparum*, *P. ovale*, and *P. malariae* and they produce benign tertian, malignant tertian, ovale tertian and quartan malaria respectively. The falciparum variety, is the most serious form, with high morbidity and considerable mortality, especially so in children and in travellers who visit endemic area. Malaria also may run a chronic course with variable morbidity and uncommonly, mortality. The disease is transmitted from man to man by the infective bites of female anopheles mosquitoes. Several vertebrate animals, birds and other members of the animal kingdom have malaria caused by parasites exclusive to them.

EPIDEMIOLOGY

Malaria is endemic in all tropical countries like India, Bangladesh, Sri Lanka, Myanmar, Middle East, Far East, several parts of Africa and tropical America. Present facilities for quick travel and migration of population have helped to introduce this disease in all countries. The disease is rare in stations above an altitude of 1500 m or where the ambient temperature is low. Presence of susceptible population, vector mosquitoes, and availability of reservoir hosts determine the endemicity.

Vivax malaria is more widespread generally, but in some parts falciparum is more common. Malaria, occurs in 90 countries of the world. 500 million cases occur annually with 2.7 million deaths. At present along with *M. tuberculosis* and measles, malaria has the distinction of being one among the three pathogens causing the maximum human morbidity and mortality especially in the developing countries. For India it is a major medical problem (Fig. 64.1).

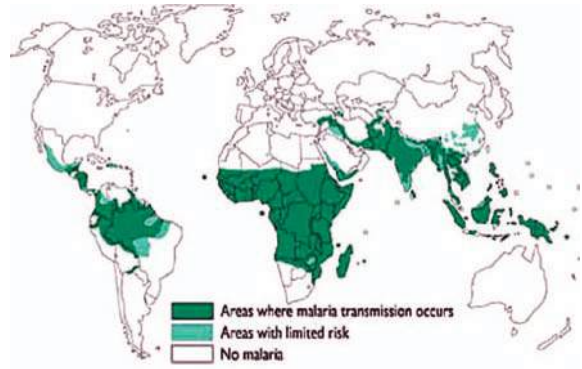


Fig. 64.1: Epidemiology of malaria

After successful attempts at reducing the incidence and prevalence of malaria in India, due to several factors the disease re-emerged and by 1976 the annual incidence went up to 6-7 million. With preventive strategies to control the epidemic, incidence of the disease is stable around 2 million annually at present.

World Bank assisted enhanced Malaria Control Project is in operation in high risk districts. Resurgence and persistence of malaria are due to insecticide resistance of the vector, drug resistance of the parasite, slack organizational structure and financial constraints. There is relative and absolute increase in *Plasmodium falciparum* cases which are multi-drug resistant. This poses difficulty in treatment and control and also causes heavy economic burden to India and all developing countries. The term **airport malaria** denotes the spread of malaria to people living near airports. Spread of malaria to persons traveling in aircraft caused by mosquitoes lurking in the aeroplane is called **commuter malaria**.

The vectors are female anophelene mosquitoes. The main anophelene mosquito vectors in India are *Anopheles culicifacies*, *A. stephensi*, *A. fluviatilis*, *A. minimus*, *A. dirus* and *A. sundaicus*. Ronald Ross, an English doctor belonging to the Indian Medical Service demonstrated the transmission of malarial parasite by anophelene mosquitoes, while working in Hyderabad, Andhra State. He was awarded the Nobel Prize for his discovery.

Depending on their individual preferences, these thrive in stagnant and/or running fresh water or brackish water.

Terms used in Malariology

The prevalence of malaria in a community is estimated by the **spleen rate**, **parasite rate**, **infant parasite rate** and other indices (Table 64.1). *Spleen rate* represents the percentage of children aged 2-9 years showing palpable spleens. *Parasite rate* represents the percentage of positive cases of malaria detected by the examination of thick or

TABLE 64.1

Classification of endemicity		
Endemicity	Spleen rate	Parasite rate
Hypoendemic	0-10%	0-10% in children aged 2-9 years
Mesoendemic	11-50%	11-50% in children aged 2-9 years
Hyperendemic	over 50%	over 50% in children aged 2-9 years
Holoendemic	over 75%	over 75% in infants

thin blood films in a community. *Infant parasite rate* is the percentage of positives among children aged 0-11 months. This is closely related to the incidence of malaria and active transmission.

In hyper- and holoendemic areas, the local inhabitants develop immunity due to repeated encounter with the parasite. Such persons do not develop clinical disease even though parasites are demonstrable in blood. This phenomenon is called **premunity**. Children and newcomers suffer heavily. In hypo- and mesoendemic areas, the local inhabitants do not acquire strong immunity and, therefore, both local inhabitants and newcomers suffer. Single attacks of malaria do not give immunity since the parasite especially *P. falciparum*, undergoes rapid antigenic variations. Repeated attacks produce variable degrees of immunity which includes both the humoral and cellular types. Hyperimmune individuals, in hyper- and holo endemic areas remain asymptomatic even while harbouring the parasites. This immunity may wear off over a period of time, if they leave the endemic areas.

LIFE CYCLE OF THE PARASITE

There are two stages-sexual cycle (**sporogony**) in the mosquito which is the definitive host and the asexual cycle (**schizogony**) in man who is the intermediate host. In the human, schizogony leads to the development of the vegetative forms such as merozoites, trophozoites and schizonts which all can divide and multiply further and invade more erythrocytes. A proportion of the parasites develop into sexual forms which are the male and female gametocytes. These are incapable of further division and development in the humans, they develop further only if taken up by the mosquito. Gametocytes remain viable in circulation for 2-3 weeks. They die if not ingested by the mosquito. Female gametocytes outnumber the male gametocytes.

Mosquito Cycle (Sporogony)

Sporogony (Sexual Cycle)

When the female anophelene mosquitoes take blood from infected persons, gametocytes are also ingested. Only

gametocytes develop further. In the mosquito's stomach the gametocytes are released from the erythrocytes and they transform into gametes which develop further. The asexual forms of the parasite die. The male gametocyte exflagellates into 6-8 flagella and each flagellum fertilizes a female gamete. A zygote is formed which develops into ookinete and oocyst in the stomach wall. About 10,000 sporozoites develop within each oocyst. A mosquito may harbour a few to more than a hundred oocysts at a time. The time taken for the sporozoites to develop depends on the environmental temperature and humidity, higher temperatures favouring quicker maturation. The oocysts rupture releasing the sporozoites into several tissues. Many reach the salivary glands and remain in the saliva ready to be injected into the next victim during the blood meal. Once infected, the mosquito remains infective for its life span of about a month. Since *P. vivax* can develop even at lower temperatures compared to the other species of parasites, the former has a more widespread distribution over the globe.

Human Cycle—Schizogony

Schizogony (asexual cycle): This occurs in man and it consists of the exo-erythrocytic and erythrocytic cycles.

Primary Exoerythrocytic Cycle (Pre-erythrocytic Cycle)

This is the phase in which the parasite adapts to the new host; and this takes place in the liver. After inoculation by the mosquito, the sporozoites circulate in blood and within hours they enter the hepatocytes to develop and multiply within them. Each sporozoite can produce several thousands of merozoites within a few days. Merozoites come out of the liver cells after about a week and invade erythrocytes to initiate the erythrocytic cycle.

Entry of sporozoites into liver cells and attachment of merozoites to surface of erythrocytes are all processes mediated by specific receptors. The interval required for the sporozoites to develop in the liver cells and merozoites to appear in erythrocytes is called the *pre-patent period*. Sporozoites do not cause any permanent damage to the liver cells.

All the sporozoites do not complete their development and emerge out of the liver cells at the same time. In the case of *P. vivax* *P. malariae* and *P. ovale* many of the sporozoites can remain dormant in the liver cells for periods extending up to several months or years and get released into the circulation to start their erythrocytic phase. These dormant sporozoites are called *hypnozoites*. They lead to late relapses in case of *P. vivax* and *ovale*. It is now the consensus that *P. falciparum* and *P. malariae* do not have the hypnozoite stage. In them the relapses are caused by merozoites lurking in erythrocytic cycle, depending on the immune status of the individual.

Erythrocytic Cycle

The merozoite develops in the erythrocyte utilizing its hemoglobin for metabolism. The parasite makes a vacuole within the red cell for it to grow. It absorbs nutrients voraciously. It grows into a ring form and later becomes the *trophozoite* which shows ameboid movement.

Within 48-72 hours the trophozoite reaches full growth and divides by binary fission to form a *schizont*, which contains several *merozoites*. The parasite utilizes glucose and oxygen for its metabolism while developing in the erythrocyte. Hemoglobin is converted into its metabolic end product hemozoin, which is ingested by macrophages. This appears as malarial pigment in the parasites, when stained appropriately. Accumulation of malarial pigment occurs in the reticuloendothelial organs such as the spleen, liver and bone marrow. The spleen and liver enlarge progressively.

Several abnormalities of erythrocytes inhibit the development of the parasite in them and render natural immunity. *P. falciparum* fails to thrive in erythrocytes having glucose-6-phosphate dehydrogenase (G-6-PD) deficiency and sickle cell hemoglobin. Heterozygous sickle cell trait, alpha and beta thalassemias, female heterozygous G-6-PD deficiency and hereditary ovalocytosis give partial protection against *P. falciparum* infection. Duffy negative blood group individuals show resistance to the development of *P. vivax* in the erythrocytes. This advantage offered by inherited abnormalities in hemoglobin is attributed to be a reason for the widespread prevalence of hemoglobinopathies in many tropical countries.

After full development, the erythrocyte is ruptured and the contents-merozoites, metabolites and toxic products are liberated into circulation and this gives rise to the febrile paroxysm. The periodicity of the febrile paroxysms generally correlates with the liberation of the merozoites at the end of the erythrocyte cycle. It may be tertian (occurring once in 3 days), quartan (occurring once in 4 days), or sub tertian or quotidian (occurring daily).

The average number of merozoites and time taken for schizogony vary with each species (Table 64.2).

P. falciparum can multiply much faster than the other species and also reach dangerous parasitemic levels, on account of the larger number of merozoites and shorter period for maturation.

TABLE 64.2		
Number of merozoites and time for their development		
	No. of merozoites	Time for schizogony
<i>P. vivax</i>	8-16	48 hours
<i>P. falciparum</i>	12-24	48 hours or less
<i>P. ovale</i>	8-12	48 hours
<i>P. malariae</i>	6-12	72 hours

The erythrocyte ruptures liberating the merozoites into the plasma. Many of them are destroyed, but others attach to fresh erythrocytes and successively repeat the cycle of multiplication. The number of parasites progressively increases. When the parasite level reaches a threshold, clinical symptoms set in. In a primary infection, after a few erythrocytic cycles lasting for 2-3 weeks, some of the merozoites develop into the male and female gametocytes, which are the sexual forms destined to continue sporogony in the mosquito. They continue further development only if ingested by the vectors. If not, they die within 2-3 weeks (upto 8 weeks for *P. falciparum*) and are disposed off by macrophages. The erythrocytic merozoites infect only further erythrocytes and do not re-enter liver cells.

PATHOPHYSIOLOGY

The pathogenesis of malaria is complex, multifactorial and only partly understood. Most of the studies have been done on malaria in general and on the development of complications associated with *P. falciparum*(Pf). The factors contributing to pathogenesis include direct invasion of erythrocytes leading to hemolysis, affection of vascular endothelium, immunological phenomena and toxemia affecting one or more organ systems.

During schizogony *P. falciparum* (Pf) leads to adhesion of parasitized erythrocytes to endothelium, and to themselves (cyto-adherence) and endovascular sequestration leading to rosette formation, vascular occlusion, release of cytokines and vasomediators and, organ dysfunction. This is the basic pathology in complicated forms of Pf malaria. The clinical features may not directly correlate with the immunopathological alterations, since host immunity and antigenic make up of the parasite also play their roles. Pf erythrocyte membrane protein (PfEMP-1) antigen forming knobs on the surface of red cells are responsible for cyto-adherence. They bind to the vascular endothelium. Platelets and leukocytes adhere and this slows the circulation and initiate the coagulation cascade. In cerebral malaria this is the major event that occurs. In pregnant women, placental syncytiotrophoblast is a particularly vulnerable site for these changes.

Parasites can be demonstrated in variable numbers in the erythrocytes and tissues such as bone marrow, liver and spleen depending on the severity of infection. Fever develops when the parasite number reaches the threshold minimum and this is achieved by successive schizogony after the pre-erythrocytic phase. In *P. vivax*, all stages of the developing parasites are seen in peripheral blood. On the other hand only the ring forms and gametocytes of Pf are seen in peripheral blood except in severe infection. The growing stages of Pf adhere to the small blood vessels of vital organs and, therefore, in uncomplicated malaria the peripheral blood does not contain all the stages. The alteration in physical state of the erythrocyte leads to

stickiness of the red cells and their sludging in the microcirculation. Such erythrocytes, along with a large number of phagocyte cells, occlude the small blood vessels. Falciparum malaria causes significant mortality; the others do so only less commonly.

The virulence of *Pf* depends mainly on its capacity to induce erythrocytes to adhere to vascular endothelium and disrupt the blood flow. The changes in the parasitized erythrocytes include the following:

1. Visible change in shape
2. Reduced deformability leading to inability to negotiate the microcirculation
3. Formation of electron-dense protrusions (knobs)-consisting of Plasmodium falciparum erythrocyte membrane protein PfEMP-1
4. Expression of new sugar moieties on the surface
5. Presence of new metabolic channels.
6. Appearance of new parasite- specific antigens on the red cell membrane.
7. Reorganization of the normal components of RBC, expressed as surface antigens.

Cerebral Malaria

Of all pernicious forms, involvement of the central nervous system (CNS) is the most important life-threatening event that should be recognized early. Vivax malaria causes central and peripheral neuronal alterations only very rarely, whereas for *Pf* neuronal involvement is much more common so as to make the term “cerebral malaria” is almost synonymous with *Plasmodium falciparum* lesion. The two major pathological processes in cerebral malaria are:

1. Sequestration of parasitized erythrocytes and
2. Metabolic changes including hypoglycemia and acidosis.

In adults the former mechanism predominates, whereas in children the picture is a combination. There is increased expression of vascular and intercellular adhesion molecules and rise in tumour necrosis factor (TNF), interleukin-1, soluble thrombomodulin (sTM) and lymphotoxin. The clinical spectrum is related to the extent, site and duration of involvement.

Changes in Liver

Malarial hepatitis leads to predominantly conjugated hyperbilirubinemia, raised hepatic enzymes-(transaminases and lactic dehydrogenase) along with histopathological evidence of centrilobular hepatocellular necrosis, Kupffer's cell hyperplasia, malarial pigment deposition and hepatocyte congestion. Hemolysis which occurs as a consequence of rupture of red cells increases the hyperbilirubinemia. Fulminant hepatic necrosis, and hemolytic anemia can be fatal, unless recognized and managed early.

Blood

Anemia is a common complication of moderate and severe forms of malaria, both acute and chronic. Anemia is caused by;

1. direct destruction of erythrocytes by the parasites
2. immune-mediated hemolysis
3. partial suppression of bone marrow function caused by toxins and cytokines and
4. in some cases adverse effects of drugs. Anemia is worsened by co-existing nutritional deficiencies, parasitic diseases and sources of blood loss.

Co-infection with human immunodeficiency virus (HIV) and malaria increases the severity of both diseases.

Other organs: (Kidneys, lungs, peripheral nerves)

Abnormalities in parasitized erythrocytes result in changes in the microcirculation. In addition abnormal immune processes develop leading to changes in renal glomeruli and tubules, pulmonary alveoli and interstitium, intestines and other tissues. Both IgM and IgG antibodies are formed and these may persist for long periods. They do not confer absolute protection. Acute nephritic syndrome, nephrotic syndrome, hemolytic anemia, particularly **black water fever** and polyneuropathy are all mainly immune mediated. Nephrotic syndrome is more common in *P. malariae* infection. Depression of monocyte- macrophage phagocytic function predisposes to secondary bacterial infections.

Autopsy Changes

Enlargement of spleen and liver, bile staining of tissues and fibrosis due to deposition of malarial pigment and parenchymal and vascular changes in the brain and other organs constitute the main findings.

CLINICAL FEATURES

General Considerations

The immune status of the individual determines the clinical picture. The immunity is both humoral and cell-mediated. The classic picture develops in non-immunes. Manifestations are milder in semi-immunes. Maternal antibodies are passively transferred to the fetus and these persist for the first few months of life after which the infant becomes susceptible. Antibodies passed in mother's milk may have a mild protective role. In general, the normal placenta acts as an effective barrier against congenital transmission, though such transmission may occur in non-immunes.

Co-infection of HIV with *Pf.* malaria leads to greater viral load, possibly higher infectivity, and more rapid disease progress.

Vivax Malaria (Benign Tertian Malaria)

The incubation period in this infection ranges from 10 to 15 days which may be prolonged in subjects taking

antimalarial prophylaxis irregularly. The disease manifests with fever, headache, vague discomfort, aches and pains, nausea and vomiting, all of which may resemble other febrile illnesses. The pattern of fever does not show periodicity in the early phase of the illness.

After a week or two of the primary attack, periodicity gets established. The paroxysms occur in three stages-*cold stage, hot stage and sweating stage*. These stages are very characteristic of malaria.

The cold stage starts with the feeling of chills and rigor. The temperature shoots up to 40 °C or more, and the pulse is rapid. The skin is pale and cold.

The hot stage sets in 30-60 min. later with flushing of the skin, bounding pulse, severe headache and restlessness. Hyperpyrexia may occur in non-immunes. Herpes labialis is common. Sweating starts after 2 to 6 hours and this becomes profuse. Temperature rapidly comes down to normal, the pulse becomes slow and the patient goes to sleep, fully exhausted and dehydrated, to wake up fresh. These paroxysms repeat at an interval of 48 hours. This is the tertian periodicity-i.e. fever once in 3 days. The temperature is normal and the patient feels well in between the attacks. These paroxysms recur for about three months after which they subside even without treatment. Late relapses may occur even 2-3 years after leaving the endemic area. Liver and spleen become palpably enlarged after two weeks of illness. Vivax malaria is not usually fatal. The relapse may resemble the primary attack except for the fact that the typical periodicity is evident from the beginning.

Ovale tertian malaria is similar to vivax malaria, but the paroxysms may be milder.

FALCIPARUM MALARIA: (Malignant tertian malaria)

The incubation period ranges between 10-14 days. Prodromal symptoms like bodyache, headache, and vomiting may be more severe than those of vivax malaria. The disease starts either acutely or insidiously in the classical form with the three stages, or atypically. Unlike as in vivax malaria, the patient may not feel well in between the febrile paroxysms. The periodicity may be either quotidian (daily) or subtertian (less than 48 h). In some cases, the fever may be remittent or continuous when two groups of parasites develop simultaneously and sporulate on alternate days. The initial symptoms may be deceptively mild and fatal complications may set in unexpectedly at any time. When mixed infections with different species occur, symptoms due to *P. falciparum* predominate.

Rapid hemolysis may give rise to normocytic anemia. In severe cases hemoglobinuria may develop. In the majority of cases only ring forms and gametocytes are present in peripheral blood. Leukopenia, especially

neutropenia, is common. Pregnancy may result in abortion or premature labour.

Complications

Falciparum malaria is dreaded on account of the development of pernicious complications. Pernicious complications should be anticipated (1) when more than 5% of erythrocyte are parasitized (2) more than one parasite is seen in the same RBC and (3) the growing forms of the parasite are seen within erythrocytes in peripheral blood.

The pernicious complications of malaria include *cerebral malaria, malarial hyperpyrexia, gastrointestinal and hepatic forms, renal failure, algid malaria and black water fever*.

The WHO (1990) has stated that the occurrence of any one of the following clinical presentations would qualify for the term '**severe falciparum malaria**'.

1. Cerebral malaria
2. Severe anemia PCV < 15% or Hb < 5g/dL in the presence of parasitemia > 10000/uL
3. Renal failure-urine output < 480 mL/24 hours in adults or 12 mL/kg/24 hours in children and serum creatinine > 3 mg/dL
4. Pulmonary edema or respiratory distress syndrome
5. Hypoglycemia- whole blood glucose < 40 mg/dL
6. Shock –systolic BP < 50 mm Hg in children or < 70 mm Hg in adults
7. Spontaneous hemorrhage
8. Repeated generalized seizures
9. Acidosis-This is a marker of severe malaria
10. Hemoglobinuria

CEREBRAL MALARIA

Involvement of the central nervous system is the most severe presentation of falciparum malaria. This is invariably fatal if untreated. If recognized and treated early the mortality may still be upto 10%. Delay in treatment worsens the prognosis for mortality and morbidity. Clinical presentation depends on the site of maximal affection.

Predominant Features in Cerebral Malaria	
Site of Maximum Lesions	Clinical Presentation
1. Frontal Lobe	Organic brain syndrome
2. Cerebellum	Cerebellar disturbances
3. Pyramidal and /or extrapyramidal system	UMN lesions, or extra-pyramidal lesions
4. Cerebral blood vessels	Strokes
5. Brainstem	Brainstem syndromes
6. Spinal cord	Paraplegia, monoplegias
7. Spinal roots, peripheral nerves	Guillain-Barré syndrome, peripheral neuropathy
8. Meninges, subarachnoid bleed	Meningial syndrome

Onset may be sudden or subacute with changes in higher function, signs of meningitis or seizures. Affected patients may, all on a sudden, throw seizures followed by persistent coma. Subarachnoid bleed, retinal and intracerebral bleed, vasculopathy, or disseminated intravascular coagulation (DIC) are other forms of presentation. Presence of neck stiffness raised intracranial tension and cerebrospinal fluid alterations such as increase in protein, and lymphocytosis are common. Presence of features such as urticaria and disseminated intravascular coagulation (DIC) may suggest a clinical diagnosis of bacterial or other forms of meningo-encephalitis.

Neurological sequelae may develop in up to 10% of cases. These include hemiplegia, cranial nerve palsies, paraplegia, aphasia, extrapyramidal features, cerebellar dysfunction, peripheral neuritis, amyotrophic lateral sclerosis- like picture and psychoses.

Even though those complications accompany or follow the clinical picture of cerebral malaria in most cases, occasionally post malarial neurological complications may develop after full clinical recovery and parasite clearance. These include convulsions, cerebellar ataxia, tumour-like syndromes and psychoses. Retinal lesions include hemorrhage, pallor of optic disc, retinal vessel changes, papilledema, and cotton-wool patches. Retinal lesions may be associated with higher mortality. With clinical recovery, the retinal lesions also resolve and prognosis for vision is good. At times retinal lesions occur without clinical cerebral malaria.

Malarial hyperpyrexia: Hyperpyrexia (temperature 41°- 43°C) may develop and this may be mistaken for heat stroke.

Gastrointestinal Form

This manifests with severe nausea, vomiting, epigastric tenderness, hematemesis and diarrhea. In some cases, the stools are watery as in cholera, in others it is bloodstained as in dysentery. Some patients develop severe jaundice, hepatomegaly and a picture clinically resembling fulminant hepatic failure. This used to be known as *bilious remittent fever*. Death may occur due to dehydration, shock, acute renal failure or hepatic failure.

Renal Form

Clinically this may resemble acute glomerulonephritis or tubular necrosis, with all their associated consequences. Black water fever results from acute tubular necrosis.

Pulmonary Complications

These may develop uncommonly. When present they worsen the prognosis. These include non-cardiogenic pulmonary edema, aspiration pneumonia and respiratory

distress. These necessitate treatment on their own merits. Idiopathic pulmonary edema may occur without warning, sometimes during apparent recovery. If this is missed mortality may reach 50%.

Hypoglycemia

This occurs not infrequently and is missed unless particularly looked for. It may be spontaneous, occurring as part of the infection or hepatic involvement. Drugs like quinine also lead to hypoglycemia as an adverse effect. Non-recognition of hypoglycemia may increase mortality.

BLACK WATER FEVER (BWF)

This condition is only rarely reported at present. This is immune mediated intravascular hemolysis occurring in persons suffering from chronic *Pf* malaria. Intermittent and inadequate drug therapy with quinine or other suppressant drugs may trigger the hemolysis. Onset of hemolysis is sudden associated with, fever, rigor, rapidly developing anemia, jaundice and hemoglobinuria. In severe cases shock and acidosis supervene.

Urine contains hemoglobin and this accounts for the dark colour of urine which is indicated by the term *black water fever*. If untreated, many of them may die of renal and hepatic failure, severe anemia and secondary infection.

Malaria in Children

Manifestations of *Pf* malaria may differ in children (Table 64.3).

In non-immunes *P. falciparum* malaria carries a higher mortality than in partially immunes. Children are the more frequent victims. In them the poor prognostic factors are:

- 1. age below 3 years
- 2. deep coma
- 3. witnessed convulsions
- 4. absence of cortical reflexes
- 5. organ dysfunction—renal failure or pulmonary edema
- 6. retinal hemorrhage, and

TABLE 64.3

<i>Pf</i> malaria in children and adults		
Clinical feature	Children	Adults
Cough	Uncommon	Common
Convulsions	Common	Rare
Neurological sequelae	Common	Rare
Jaundice	Rare	Common
Pretreatment hypoglycemia	Common	Uncommon
Pulmonary edema	Rare	More frequent
Renal failure	Rare	More frequent

7. laboratory features such as signs of hyper infection, blood glucose below 40 mg/dL and blood urea nitrogen above 60 mg/dL.

Malaria in Pregnancy

Maternal death, abortion, still-birth and premature delivery are all common, so also low-birth weight babies. Both hypoglycemia and pulmonary edema are more frequent. Placenta is the site of preferential sequestration and development of malarial parasites. Congenital malaria in the newborn is a rare sequel. Early intensive treatment is mandatory for maternal and fetal recovery.

Atypical Features

In endemic areas, rarely atypical presentation may be encountered. These include

- 1. Mild non-characteristic fevers,
- 2. Chronic refractory anemia,
- 3. Presistant jaundice,
- 4. Neuro-psychiatric syndromes and
- 5. *Tropical splenomegaly syndrome*.

In meso-or hyper endemic areas, spleen may assume large sizes and such patients may manifest with pancytopenia or depression of one of the formed elements of blood. Thrombocytopenia may lead to hemorrhages, subcutaneous or visceral.

Course

Majority of cases vivax malaria recover without sequelae after suffering from the disease for varying periods which may extend for years, even if untreated. Due to the persistence of the exoerythrocytic cycle, *P. vivax* and *P.*

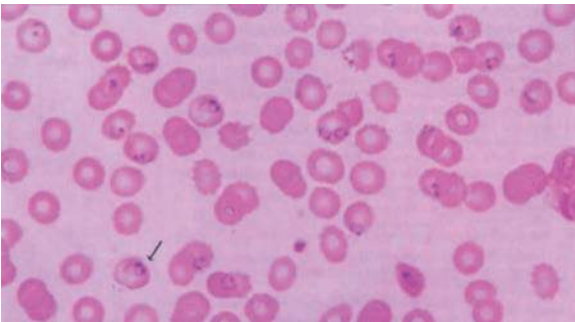


Fig. 64.2: PB slide Plasmodium falciparum malaria. Arrow points to parasite in RBC

ovale may give rise to relapses for prolonged periods. The longest relapses occur for *P. malariae*, caused by parasites lurking in the erythrocytes. In endemic areas re-infection has to be distinguished from relapses. Plasmodium falciparum is associated with higher mortality, variable clinical picture, unexpected deterioration and serious pernicious complications. Those who recover do so within a year if re-infection is avoided. In all cases the patients remain infective to others as long as they harbour the parasites.

DIAGNOSIS

Malaria should be considered in the differential diagnosis of fever in all tropical countries. Fever may be associated with severe headache, splenomegaly and or anemia. Examination of stained blood film is mandatory for diagnosis. Demonstration of the parasites in the peripheral blood confirms the diagnosis of infection. Examination of a properly stained blood film reveals parasites in most of the cases. Leishman’s, Wright’s, or Giemsa’s staining is usually done (Fig. 64.2 and Table 64.4). Thick smear

Morphological features of the different species of plasmodium				
	<i>P. vivax</i>	<i>P. falciparum</i>	<i>P. malariae</i>	<i>P. ovale</i>
Size of parasitized erythrocyte	Larger	Not larger	Normal size	Variable, the erythrocyte is often oval
Common stages present in peripheral blood	All stages gametocytes	Only rings and	All stages	All stages
Pigmentary change in erythrocyte	Schuffner’s dots seen in the erythrocyte outside the parasite	Maurer’s clefts	Nil	Schuffner’s dots
Number of merozoites in the schizont	8-16	12-24	6-12	8-12
Morphology of the rings	Thick and large	Fine rings-marginal forms (applique)*	Large coarse ring	Large ring
Multiple infection in erythrocyte	Nil	Present	Nil	Nil
Number of chromatin in the rings	One	One or two	One	One
Gametocyte	Oval or circular	Crescentic	Oval or circular	Oval or circular
* Applique forms of <i>P. falciparum</i> are the ring stages of the parasite attached along the margin of the erythrocyte.				

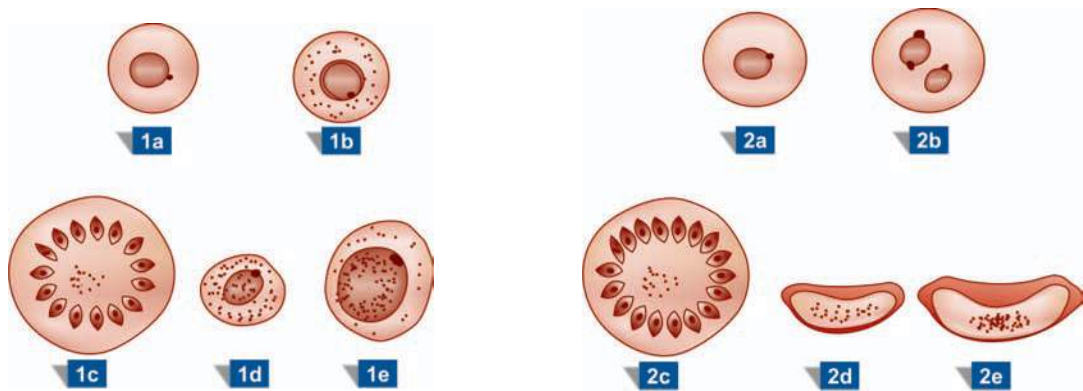


Fig. 64.3: (1) *P. vivax* and (2) *P. falciparum*. a. Ring form, b. Trophozoite, c. Schizont with merozoites, (rosette), d and e. Male female gametocytes (Diagrammatic)

examination may be required if parasites are scanty. Identification of morphological details is done in the thin blood smear. Prior administration of anti-malarial drugs reduces the number of circulating parasites within hours if they are sensitive and therefore they may not be readily visible in peripheral blood smears. Hence blood smear should be taken for microscopy before starting drug therapy. In any case therapy should not be delayed for want of definite diagnosis if the clinical suspicion is strong. Presence of only gametocytes indicates chronic infection without active malaria (Fig. 64.3).

Other Diagnostic Methods

Though properly stained smear microscopy remains the gold standard for the diagnosis of malaria, alternate rapid tests are becoming increasingly available. These include Para sight F test (Becton Dickinson, France) based on the detection of the HRP-2 antigen secreted by Pf and a test that detects parasite specific lactic dehydrogenase (PLDH). Use of fluorochrome stains and quantitative buffy coat (QBC) analysis gives higher positive rates. These tests are also reliable if properly done. Their availability is less and costs are higher.

Serological tests for malarial antibodies do not have value in the initial diagnosis and often do not differentiate between past and current infection. They may however, be valuable for community studies.

Differential Diagnosis

This includes all febrile conditions, other causes of jaundice, anemia splenomegaly, neurological syndromes, acute liver syndromes, and nephritis, in endemic areas and travelers who have visited endemic areas.

Drug Resistance

Prior to 1959 all species of parasites were susceptible to chloroquine which was the most widely used drug for all forms of malaria both uncomplicated and complicated forms. Resistance to chloroquine was demonstrated in *P. falciparum* in 1959 in Venezuela followed by observation in India and south east Asian countries. The parasite rapidly acquired resistance and the geographical distribution of resistant *P. falciparum* widened. At present in India in all states, Pf should be considered to be resistant to chloroquine unless proved otherwise. *P. vivax* is susceptible to chloroquine in the vast majority of cases (Table 64.5).

RI resistance is likely to be missed as patients are not usually observed for disappearance of parasitemia with the relief of symptoms. Patients with severe malaria,

TABLE 64.5		
Grading of chloroquine resistance of <i>P. falciparum</i> (WHO 1973)		
Recommended Response symbol		
Sensitive	S	Clearance of asexual parasitemia within 7 days of treatment without any recrudescence
Resistance (mild)	R1	Clearance of asexual parasites within 1 week but reappear within 28 days (7-28)
Resistance (moderate)	R2	Significant regression but no clearance
Resistance (severe)	R3	No marked reduction or increase, with persistent symptoms

pernicious forms and/or increasing parasitemia should be straight away put on alternate effective combinations of anti-malarial drugs without losing time for assessing resistance.

TREATMENT

This can be considered under three heads

1. Control of overt attack-by schizonticidal drugs
2. Treatment of complicated forms of *Pf* by combinations of specific drugs and supportive measures.
3. Eradication of infection from the patient in order to prevent relapse and also to stop transmission to others.

The anti-malarial drugs available freely in India are given below.

Schizonticidal drugs: These act on the erythrocyte forms of the parasite and help to terminate the clinical attack of malaria.

Chloroquine

This is a 4-aminoquinoline drug. It destroys the trophozoite forms of all species of the parasite very effectively. Dose is 600 mg of chloroquine base given as single dose oral, followed by 300 mg six hours later and 150 mg twice a day for two more days, making the total dose at 25 mg/kg over 3-4 days.

The tablet contains 250 mg of chloroquine diphosphate and it provides 150 mg of chloroquine base. Drug sensitive organisms rapidly disappear on administering chloroquine and the blood smear may become negative for the parasite within 24-36 hours. Though the acute attack will subside the parasites will not be eradicated.

Chloroquine phosphate is available freely at a low cost; it is safe and well tolerated. Adverse side effects include gastrointestinal upset, allergic reactions, psychosis, convulsions, photosensitization and ocular-toxicity on long term use. Chloroquine gets deposited in the cornea and retina. These lead to visual impairment. Funduscopy examination is needed at all follow up visits to make early diagnosis. Corneal lesions resolve on withdrawing chloroquine, whereas retinal lesions tend to progress.

Ocular-toxicity is a major contraindication for continuation of chloroquine therapy.

Chloroquine hydrochloride is available as 200 mg doses for IM and IV therapy. This is seldom used at present for therapy of pernicious malaria.

Chloroquine is the drug of choice for *P. vivax*, and drug sensitive *P. falciparum*. Since drug resistance is widespread in *Pf*, in any severe form of malaria chloroquine may not be readily effective and so the present trend is to use more reliable and definitely potent drugs and drug combinations.

There are reports that avoidance of chloroquine in different countries over long periods has led to disappearance of chloroquine resistance.

Amodiaquine which is also a 4- aminoquinoline is schizonticidal and effective in treating overt attack of malaria. Chloroquine resistant *Pf* may at times be sensitive to amodiaquine. This drug is only seldom used in India.

Quinine

This is the most time-tested schizonticidal alkaloid drug obtained from cinchona bark, (cinchona is grown in India). The preparation is quinine sulphate available as 325 mg tablets, given orally. The dose is 650 mg b.d for 10 days or more. Quinine is effective against all species of parasites and this is a good alternative for chloroquine. *Pf* is generally sensitive to quinine but in many areas partial resistance has developed.

Adverse side effects include its bitter taste, cinchonism (tinnitus, deafness, nausea, blurring of vision and restlessness), hypoglycemia, myocarditis and peripheral neuropathy. Quinine- induced hypoglycemia can be fatal if unrecognized.

Combination of quinine with ciprofloxacin 500 mg bd or tetracycline 250 mg qid helps to overcome partial resistance. It is the better to use alternate more effective drugs, such as artemisinin if the patient's condition is serious.

Quinine ethyl carbonate is also available as tablets. It is less bitter. Doses and actions are similar to quinine sulphate.

Quinine hydrochloride is available for IV use in vials containing 600 mg/mL. This is given in doses of 10 mg/kg bw as IV injection diluted in 5% glucose given slowly or as IV infusion over 20 minutes. This dose is repeated 8 hourly till the patient can accept oral medication. In severe falciparum infections a loading dose of 20 mg/kg bw may be given initially.

Adverse side effects include anaphylactic shock, severe hypoglycemia, reactions at site of injection, and others.

Quinidine which is related to quinine has anti-malarial properties. It is seldom used for this indication at present. Several other drugs were in use from time to time as schizonticidal drugs. Due to their weak actions, non-availability and variable efficacy due to development of resistance these are seldom used as primary drugs in an overt attack. These include proguanil, pyrimethamine, sulfadoxin, sulphalene, mefloquine, dapsone and others.

The antibiotics tetracycline, ciprofloxacin, macrolides and co-trimoxazole all have schizonticidal properties, especially effective when combined with drugs like quinine. These combinations can be used for chloroquine resistant *Pf*. from the beginning.

TABLE 64.6

Preparations of Qinghaosu derivatives			
	Dose	Route	Effect
1. Artemisinin	80 mg day 1, 40 mg on days 2-4	IM injection, oral or rectal	Schizonticidal on all species including <i>Pf</i>
2. Artesunate, an ester of artemisinin	120 mg day 1 60 mg/for 4 days	Oral, IM and rectal	Effective particularly used for cerebral malaria
3. Artemether methyl ether derivative of artemisinin	80 mg bd for 3 days	IV IM and oral	Same as above
4. Arteether	150 mg/ day for 3 days	I M	Same as above + gametocidal

Qinghaosu Derivatives

These are derived from the plant *Artemisia annua*, initially studied extensively in the People's Republic of China and their anti-plasmodium effect was demonstrated in 1979. The available preparations are given in Table 64.6.

They are powerful schizonticides which act rapidly. The target of their action is *Pf* ATP. They also possess gametocidal properties.

Contraindications include G-6 PD deficiency, immuno-suppressed states, and first trimester of pregnancy. Adverse side effects include gastrointestinal upsets, neutropenia minor ECG changes, first degree heart block and transient rise in liver enzymes.

In severe or pernicious forms of *Pf* the World Health Organisation (WHO) recommends a combination regimen containing an artemisinin derivative. Chloroquine resistant *Pf* often reveals resistance to other drugs including mefloquine and sulfadoxine-pyrimethamine (multi drug resistance). WHO recommends artemether + lumefantrine or mefloquine+ artesunate as the first line drug combination. Lumefantrine-artemether tablets contain 120 mg and 20 mg respectively. The course consists of a total of 16 tablets over 4-5 days.

Availability of artemisinin group of drugs has been a real advance in the management of cerebral and other forms of pernicious malaria.

Chloroquine, amodiaquine, sulphadoxine-pyrimethamine, all can be combined with artemisinin drugs.

Due to the risk of development of resistance to artemisinin it is better to avoid monotherapy with this groups of drugs.

Fansidar

It is a long acting sulfonamide drug. Each tablet contains 500 mg sulphadoxine and 25 mg pyrimethamine. It is schizonticidal with a half life of 100 hrs or more. It can be given as an adjunct to quinine for suppressive therapy. It is effective against resistant *Pf* malaria. 3 tablets are given as a single dose. *Pf* may develop resistance to Fansidar.

Metakelfin

This is also schizonticidal. It contains sulphalene 500 mg + pyrimethamine 25 mg. Action is similar to that of Fansidar. 2-3 tablets may be given as single dose against resistant *P. falciparum*

Mefloquine

This is a quinoline methanol compound structurally resembling quinine. It is available for oral use. It is effective against all species of parasites. Dose is 15-25 mg/kg bw up to a maximum of 1g twice day given at 6-hourly intervals. The half life is 14-40 days. Mefloquine should not be given simultaneously with quinine.

Lumefantrine

This is an aryl amino alcohol similar to quinine. It acts on the intra-erythrocytic forms of the parasites. Each tablet contains 120 mg of the drug. Dosage is 1 tablet initially followed by 2 tablets at 8 hours, 3 tablets at 24 hours and 4 tablets at 48 hours.

Halofantrine

This is a phenanthrene methanol compound, active against multi-drug resistant *Pf*. The drug has a long half- life (1.3-6.6 days). The dose is 8 mg base/kg bw for 3 doses. In non-immunes the drug has to be repeated after 15 days.

Causal Prophylactic Drug

Pyrimethamine: This is a time-honoured drug used for more than seven decades. It is a weak schizonticide. It inhibits development of the sexual cycle of the parasite in the mosquito. This unique action helps to interrupt the transmission of the disease by the vector and hence the name *causal prophylactic*. It is available as 25 mg tab for oral use.

Drug used for Eradication

Primaquine is the available drug- It is an 8- aminoquino-line- each tablet contains 2.5 or 7.5 mg given orally in a dose of 15 mg/day for 14 days. It eradicates the exo-

erythrocytic cycle in the liver. It is also a weak schizonticide. It has gametocidal action.

Due to its gametocidal action it is given for all species of parasites even though *Pf* has no well defined exo-erythrocytic cycle. Primaquine is given orally as a single dose of 45 mg for its gametocidal action on *Pf*. The drug is available with the governmental malaria offices for free supply. Primaquine is toxic. It causes methemoglobinemia and hemolysis in G-6-PD deficient individuals.

General Directions for Treatment

Since several drugs are available and the disease spectrum differs depending upon the species of parasite and immune status of the individual the treatment has to be individualized, even though general consensus is available.

Non-immunes have higher morbidity and mortality. Therefore they require more powerful drug combinations. Pernicious forms of *Pf* demand combination therapy, with full supportive treatment without any delay. Delay in treatment leads to higher mortality and residual disability.

Overt Attack of Malaria

Drug of choice: Chloroquine is the drug of choice if parasites are sensitive. Pregnancy is not a contra-indication for chloroquine.

If *Pf* is resistant to chloroquine, artesunate+any powerful schizonticidal drug should be used.

Pernicious Forms

This demands parenteral administration of quinine. Quinine can be given safely during pregnancy also.

If the organisms are resistant *Pf*, artesunate drugs are to be added. Later, oral administration can be instituted. Specific supportive measures should be added depending on the system involved.

Multi drug resistant Pf has to be treated with Artesunate/Quinine+antibiotics – ciprofloxacin, amoxycillin or tetracycline. *Pf* is developing resistance to artemisinin derivatives in areas where it is widely used. Hence these drugs have also to be used with caution.

Recent report on a comparative study of dihydroartemisinin-piperaquine combination with artesunate-mefloquine for treatment of multi-drug resistant *Pf* malaria in Myanmar showed that the former combination was an equally effective, but less expensive drug regimen (\$ 1.5 vs \$ 3.0). Success rates were the same irrespective of whether the drug administration was supervised, or not.

Dose administered

group (1) dihydroartemisinin 2.1 mg/kg bw and piperaquine 16.8 mg/kg bw daily oral for 3 days

group (2) mefloquine 25 mg base/kg bw single dose on day 1 and artesunate 4 mg/kg bw daily oral for 3 days

Ref: Frank Smithius, et al. The Lancet 2006; 367:2075-85.

PREVENTION OF MALARIA

The departments of Health under the central and state governments have dedicated sections for control of malaria. Under the direction and technical and monetary help from the WHO, UNICEF, UNDP, World Bank and several other non governmental funding agencies including Bill and Melinda Gates Foundation, there are global efforts for control of the major infectious diseases- malaria, tuberculosis and AIDS in several countries- mainly African countries. India is also a beneficiary. The main thrust is on making available effective drugs, research on drug resistance of parasites, diagnosis, provision of preventive strategies such as insecticide-treated nets, interrupting transmission by the vector and development of anti-malaria vaccine. Already vaccines are at the stages of field trial. It is advisable that all doctors take the recommendation of the department of health in their areas, about the drug combinations, provision for supply of free medicines and epidemiological information available locally.

Reduction of malarial endemicity depends on the following strategies

1. Treatment of cases and eradication of the reservoir
2. Anti-vector measures
3. Individual protection by insecticide impregnated sleeping nets
4. Patient education on malaria and its prevention

Drug Prophylaxis

Drug prophylaxis is essential for the following categories of persons to prevent malarial infection.

1. Visitors including tourists entering malarious areas
2. All pregnant women in endemic areas
3. Patients having organ failure and risk of renal failure.

Drug Schedule

- a. If the prevalent *Pf* parasite is chloroquine sensitive: chloroquine 300 mg/oral once a week-start the drug one week prior to entry into the area and continue for 4 weeks after leaving the area.
- b. Area endemic for chloroquine resistant *Pf*: mefloquine 250 mg base once a week to be started 3 weeks earlier to entry and continued for 4 weeks after leaving the area.

Alternate schedule. Chloroquine 300 mg/week + doxycycline 100 mg/day.

To be started 2 days prior to entry and continued for 4 weeks after leaving the area (Table 64.7).

Note: Anti-malarial drugs available in the Indian market

TABLE 64.7

Special antimalarial drugs available in India			
Drug preparations	Manufacturer	Name of preparation	Formulation
Artesunate	Cadila Lab	Falcigo	Tablets 100 mg
	IPCA	LARIAGO	Tablets 100 mg
	"	"	IV or IM vials
Artemether	IPCA	LARITHER	120 mg/vial
			Injections IV.IM.
			80 mg/ mL/and
			capsules 40 mg.
	THEMIS	E-mal	150 mg oil-based
	chemicals		preparation /for
			deep IM injection;
Proguanil	IPCA Lab	Laveran	100 mg tablets
Primaquine	IPCA Lab	MALARID	7.5 and 15 mg tab
Fansidar	IPCA Lab	LARIDOX	500 mg +
		Pyralfin	pyremethamine 25 mg
Mefloquine	INFAS	MEFLOTAS	250 mg tab

Chloroquine and quinine are available freely, being produced by several drug manufacturers.

Leishmaniasis

V.P. Gopinathan, K.V. Krishna Das

GENERAL CONSIDERATIONS

Infection by the protozoan parasite of the genus *Leishmania* causes leishmaniasis. This may take several forms. In India, the infection is prevalent in almost all states sporadically. In the northern states it occurs in endemic and epidemic forms. The main clinical presentations seen in India are visceral leishmaniasis (kala-azar), post kala-azar dermal leishmaniasis and the primary cutaneous forms — tropical sore; known by different names. India contains 70% of the global burden of visceral leishmaniasis WHO has categorized leishmaniasis as a category 1 disease (i.e.) emerging and uncontrolled.

The parasite affects mainly the reticuloendothelial organs and the related endothelial cells primarily. Several vertebrate species may be affected by leishmania. In India, humans form the main reservoir of infection. In the Mediterranean areas, Africa and America other animals also harbour the parasites.

- a. *L. donovani* is the main species that causes visceral (VL) and post kala-azar dermal leishmaniasis in India. In other countries other species also produce the disease.
- b. *L. tropica*, *L. major*, *L. aethiopica* that cause oriental sore the primary cutaneous form
- c. *L. amazonensis* - Mucosal form,

All these species are morphologically similar but not immunologically. The parasite exists in two forms

- i. amastigote form, oval or rounded and nonmotile present in reticuloendothelial cells and
- ii. promastigote leptomonad or flagellate form seen in the vector – phlebotomus sand flies in which they develop and become infective in 7 days (Figs 64.6 to 64.9).

Visceral Leishmaniasis (VL)

Syn: Kala-azar

This is a prolonged febrile illness associated with progressive emaciation, anemia and hepatosplenomegaly caused by *Leishmania donovani* which parasitises the reticuloendothelial cells in the spleen, liver, bone marrow and other viscera. This disease has been in existence in India for centuries causing endemics and epidemics from time to time in the northern states. The disease exists in a smaller scale in several pockets in India and has been reported from almost all states including Kerala. The name **kala-azar** (black fever) is derived from the dark

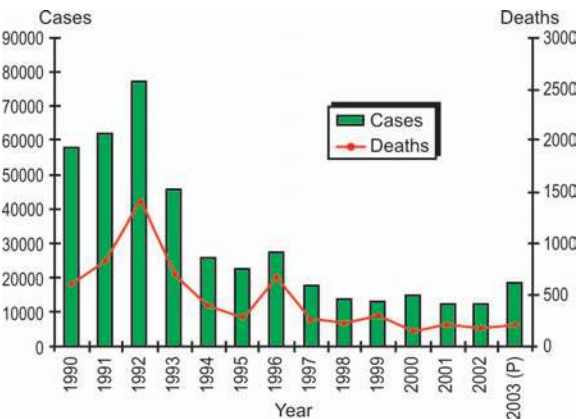


Fig. 64.4: Kala-azar situation in India

pigmentation that develops in the victims of visceral leishmaniasis. The parasite (L.D body) was discovered in 1903 simultaneously by Leishman in England and Donovan in Chennai. Recent work has shown that *L.tropica* may also produce visceral leishmaniasis occasionally.

Epidemiology

Though VL is endemic in more than 60 countries, most of the symptomatic visceral disease (> 90 %) is reported in rural areas of India, Nepal, Bangladesh, Brazil and Sudan, other African countries, Mediterranean countries, S. America and China. Rural surroundings and poverty favour the transmission of the disease. Contributory factors include:

- Altitude below 700 m
- High rainfall and humidity
- Alluvial soil
- Abundant vegetation and
- Rural settings

The previous decade witnessed a severe outbreak of visceral leishmaniasis in Bihar and the neighbouring states, which caused heavy mortality and morbidity.

With an organized centrally sponsored control program launched in endemic areas (1990-91), the disease declined at the rate of 70% annually. By 2003, deaths also could be reduced considerably by improved registration, follow up and intensified treatment strategy. At present the disease is more prevalent in Bihar and north eastern states where resistance to conventional pentavalent antimony compounds is reported to be about 60%, requiring other drugs for treatment (Fig. 64.4).

In the Mediterranean region, infants and children are almost exclusively affected. In other endemic areas including India, though the disease is more frequent in children and young people, older age groups are also susceptible. Males are affected more than females. Conditions which favour the multiplication of the main vector sandfly in India -*Phlebotomus argentipes*- and the presence of susceptible population determine the endemicity. Sand flies bite their victim during sleep. Over 20 species of sand flies can transmit the parasite in other parts of the world. Only female sand flies act as vectors. In India, kala-azar is a disease of humans and animal reservoirs are not reported. In other endemic areas dogs, raposa (a fox-like mammal) and rodents harbour the parasite. These form a natural reservoir from which man is infected. The parasites circulate in blood engulfed by macrophages and these are taken up by vector sandflies which suck blood and transmit them to others during their bites.

Transmission

Amastigotes of *L. donovani* reach the stomach of sandflies along with the blood meal. The parasite develops into the

flagellate leptomonad forms in the midgut of the vector. Within 5-7 days the organisms multiply heavily and extend anteriorly to the proboscis. During subsequent bites the promastigotes in its proboscis and pharynx are introduced into the bite wound. In the dermis the promastigotes become amastigotes and these are taken up by the macrophages. The parasite multiplies in the cytoplasm of the macrophages and when the host cells rupture, they are liberated into the tissue spaces. These are taken up by other macrophages and further proliferation occurs. Foci of parasitic multiplication consisting of parasitized macrophages, histiocytes and lymphocytes are formed. The parasitized macrophages pass into the circulation to reach several organs and develop further.

Pathology

The parasites *Leishmania donovani*, known commonly as Leishman-Donovan bodies (LD bodies) are the amastigote forms, which are found within the cytoplasm of macrophages and other RE cells, in the affected tissues and within monocytes and neutrophils in circulation. Maximum affection is in spleen, liver and bone marrow. In the Indian cases lymph nodes are less commonly involved. Most conspicuous changes are seen in the spleen, the liver and the bone marrow. The spleen is moderately enlarged and soft in an average case, but occasionally it may become very large and firm. Splenic infarcts and perisplenitis may occur in very chronic cases. Malpighian corpuscles are atrophic, macrophages containing LD bodies are seen in large numbers in the splenic pulp. Plasma cells, histiocytes and lymphocytes are seen in large numbers in the lesions. Extramedullary hematopoiesis may develop at times.

The liver is enlarged, pale, and shows fatty changes. Histology shows the Kupffer cells distended with LD bodies, vascular congestion and fatty change in the hepatocytes. The portal tracts show cellular infiltration and parasitized macrophages.

The bone marrow becomes hyperplastic. Yellow marrow in the shafts of long bones is replaced by cellular red marrow. Parasitized macrophages are seen in large numbers in the RE cells. Plasma cells may be increased. At times the lymph nodes, adrenal cortex and the intestinal mucosa may show parasites within macrophages. Lymph node involvement is more characteristic of the African and Mediterranean varieties.

Immunological Changes

In general cell mediated immunity (CMI) is impaired, especially so in those with malnutrition. Specific IgM and IgG antibodies are produced. These are not protective. Cellular immunity, dependent on T-lymphocyte is protective. With the production of gamma interferons (γ -IFN) and proliferation of natural killer cells immunity



Fig. 64.5: Patients with advance kala-azar— note the gross splenohepatomegaly and emaciation—adult 26 years

develops whereas TH2 lymphocytes producing interleukin 4 (IL-4) and interleukin 10 (IL-10) induce susceptibility. Even in cases which have been clinically cured, the parasite may still persist in vacuoles in the cytoplasm. Co-infection with HIV further lowers the CMI. It returns to normal with successful therapy.

CLINICAL FEATURES

There is wide variability in the clinical spectrum, depending on the host's immunity. Many cases may remain subclinical even while harbouring the parasites. The incubation period is usually 2-6 months and the onset may be insidious as in typhoid or abrupt as in malaria. Initially the disease may resemble typhoid fever, malaria or tuberculosis. Pyrexia and apyrexia may alternate for 2-3 weeks and fever may show double spikes on many days. This double spike of temperature is very suggestive diagnostically.

Progressive hepatosplenomegaly and anemia develop. Despite pyrexial spells, patients continue to feel 'well' without recognizing the fever. They may be having good appetite. The spleen and liver enlarge slowly and steadily, spleen reaching even upto right iliac fossa. These organs are usually non-tender. Mild or moderate lymphadenopathy may occur (Fig. 64.5).

As the disease progresses, weight loss, anemia (normocytic or microcytic), abdominal distension, and skin pigmentation develop. Emaciation, thin dry lusterless and brittle hair, dry rough skin, pigmentation around the face, pedal edema and bleeding tendency are late characteristic features. Death is due to bleeding, malnutrition and or intercurrent infection.

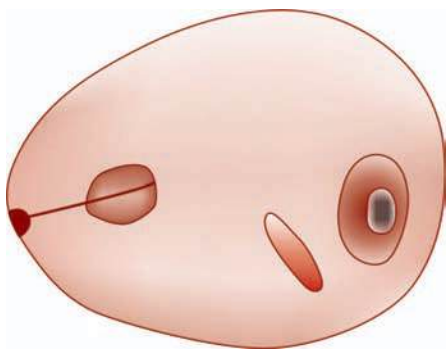


Fig. 64.6: *Leishmania donovani*—Leishmanial form (LD body) seen *in vivo* in man—general morphology (diagram)

Laboratory Investigations

Diagnosis is established by the demonstration of LD bodies in the bone marrow, splenic pulp, or lymph node aspirate. Marrow and splenic material are diagnostic in more than 95% of cases. Less commonly, an experienced observer may detect LD bodies in blood monocytes and neutrophils. LD bodies appear as oval or round 2-4 μ intracytoplasmic bodies. They have blue cytoplasm, pinkish red or violet nuclear structures, and rod like kinetoplast. In the majority of cases due to rupture of the macrophages during preparation of the slide, they are seen outside the cells (Fig. 64.7).

Associated features are leukopenia, thrombocytopenia, anemia, reversal of serum albumin globulin ratio and raised alkaline phosphatase. Features of hepatic dysfunction appear in advanced cases. The protein alterations are rise serum IgG and IgM with lowering of C3 complement levels. Reduction of eosinophils in peripheral blood was considered to be suggestive of the diagnosis of kala-azar.

Napier's aldelyde test is a simple bed side test which has been in vogue for more than seven decades. Though it lacks specificity, the ease with which it can be done in almost all hospitals, especially in rural settings may be a

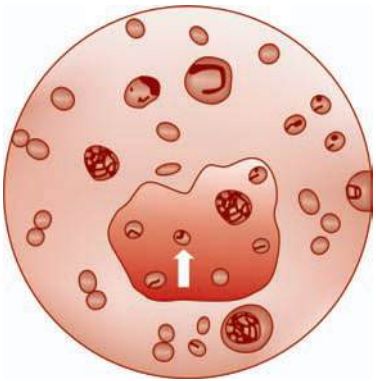


Fig. 64.7: *Leishmania donovani* in macrophages and outside cells (diagram)

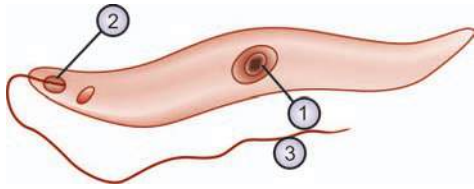


Fig. 64.8: Leishmaniasis-leptomonad form seen *in vitro* cultures and in the vector—diagram. Note (1) nucleus (2) kinetoplast (3) flagellum

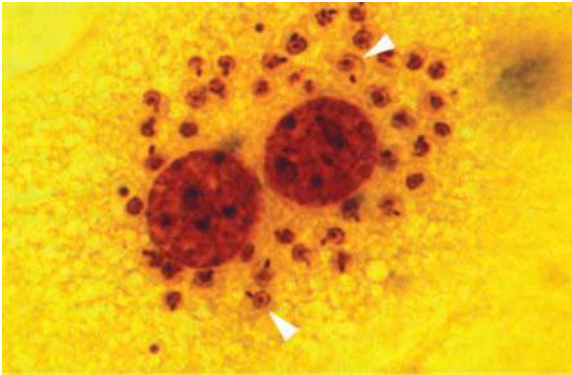


Fig. 64.9: Bone marrow smear LD bodies ($\times 1000$)

reason to employ this test in endemic areas even at present. Two drops of commercial formalin (formaldelyde 40%) is added to 1 mL of patients' serum. In a positive test, the serum becomes opaque, solid and white within 1 hour to 24 hours, depending upon the rate of positivity.

Culture of organism *Leishmania* can be grown in NNN medium using bone marrow or splenic aspirate material.

Direct agglutination tests using the antigen prepared by Harith et al has been found to be 100% sensitive and specific in early cases.

Ref: Jha TK et al JI. Ass Phys India 449.1996.

Anti – K 39 antibody demonstrable by a strip test is a very reliable diagnostic test in kala-azar and post-kala-azar dermal leishmaniasis. This can be done as a ready-to-use immuno chromatographic strip test which has been developed. In the Bihar epidemic this test using finger prick blood has been found to be extremely useful, giving positive results within five minutes and with specificity reaching 90-100 %, thereby enabling diagnosis early in the disease under field conditions.

Molecular Tests

Identification of the parasite DNA by PCR from blood or material collected from local lesions is a very reliable confirmatory test, available in advanced laboratories.

Skin test – leishmanin test of Montenegro has been used to elicit delayed hypersensitivity. It is negative in active kala-azar and PKDL, while it is positive in the primary cutaneous form. With the treatment of kala-azar and

recovery, the test becomes positive, indicating recovery of immunological function as well.

Diagnosis – Any chronic pyrexial disease associated with splenohepatomegaly occurring in an endemic area should raise the possibility of visceral leishmaniasis. Sporadic cases have been reported from all parts of the country, including a pocket in Trichur District of Kerala.

Differential Diagnosis

All chronic prolonged febrile illnesses and conditions producing hepatosplenomegaly enter the differential diagnosis. Important among these are enteric fever, malaria, acute military tuberculosis, brucellosis, septicemia, acute leukemias, and lymphoma. In India many places are endemic for malaria and leishmaniasis and these infections may co-exist.

Course and Prognosis

Untreated, the majority of patients suffer from chronic, recurrent febrile episodes, they undergo wasting and 70-80% die. Complications such as pneumonia, dysentery, hemorrhage, septicemia, *cancrum oris* and *noma* may develop and prove fatal. Co-infection with human immunodeficiency virus complicates the picture further.

Management

It is broadly divided into specific, supportive and symptomatic measures. Supportive treatment includes improvement of nutrition, treatment of concurrent infections and in selected cases, blood transfusion.

Specific therapy – The specific drugs are the time-honoured pentavalent antimonials and aromatic diamidines, still used in areas where the parasite is sensitive. These drugs are effective and relatively cheap giving cure rates up to 95%. Pentavalent antimonial drugs in common use are sodium stibogluconate, (Solustibostan, Stibatin and Pentostam) and methyl-1- glucamine antimoniate (Glucantime). Among the aromatic diamidines, pentamidine isethionate is more freely available and hence more commonly used in India. Other drugs include amphotericin B, paromomycin and miltefosine which are all highly effective even against resistant organisms.

Sodium stibogluconate is given as daily intramuscular injections initially in a dose of 5 mg/kg and increased up to 20 mg/kg for upto 28 days. Children and infants tolerate only lower doses. The drug is given under close medical supervision. Only up to a maximum of 300 mg /day for children and 200 mg /day for infants is given. Side effects are not infrequent. These include unpleasant and rarely life-threatening adverse effects such as sudden death,

cough, chest pain, abdominal colic, pain in the arms, vomiting, faintness and collapse. After a few injections allergic reactions may develop. Cardio - and hepatotoxicity, leukopenia, and thrombocytopenia may develop later. Delayed hypersensitivity reactions include fever, arthralgia and vague ill health. *In the Bihar epidemic only 30-40% of cases where sensitive to antimonials and therefore other drugs had to be employed.*

Pentamidine isethionate is available for IM or IV injection in doses up to a maximum of 3-4 mg/kg/bw daily or at longer intervals for 20-30 days. The full dose is reached after smaller test doses. Anaphylactic reactions may occur and resuscitative measures should be available at hand. Adverse side effects include nausea, diarrhea, vomiting, hyperglycemia and cardiotoxicity. A temporary diabetic state may occur in a few.

Other Drugs

More effective and safer drugs have been introduced though they are considerably more expensive. These include amphotericin-B, paromomycin, miltefosine and gamma interferon.

Amphotericin-B or its lipid formulation has been used with cure rates above 93%. The initial dose is 1 mg/kg bw given IV diluted in saline. The dose is gradually increased upto 2 mg/kg bw the total dose not exceeding 20 mg/kg bw over twenty days.

Liposomal amphotericin B: has been employed in doses of 1-3 mg/kg bw IV for 5 days. It gives better cure rates (90-100 %). As an alternative a single dose of 5-7.5 mg/kg bw given IV has been employed with 90% success rates. Adverse side effects include allergic reactions, anemia, hypokalemia, azotemia and others.

Paromomycin sulphate is an aminoglycoside which is less expensive and with only mild toxicity. It is given IV/1M in doses of 15-20 mg/kg for 21 days. It gives a cure rate of 93-97%. Adverse effects include ototoxicity infrequently, and local reaction at the injection site.

Miltefosine (Hexadecyl phosphocholine)

An oral drug, miltefosine has been developed with 98% cure rate. Adults are given 100 mg (50 mg 2 caps) daily for 28 days. Children are given the drug at a dose 2.5 mg/kg. Cure rates reach up to 100%. It is avoided in pregnancy, being teratogenic in experimental animals. Adverse side effects include nausea, vomiting, diarrhea, increase in liver enzymes and rise in serum creatinine.

Recombinant gamma interferon (γ - IFN) when given in a dose of 100 mg/m² body surface along with antimonials may improve immunity, and restore susceptibility of the parasite. It may reduce the incidence of future recrudescence.

Targeted delivery of drugs: Incorporation of antimonials or diamidines into liposomes help to increase the concentration of the drug at the local sites and to deliver higher doses to the phagosomes of the infected macrophages which contain the parasites. The therapeutic activity increases several folds even upto 700 times that of the parent drug, without increase in toxicity. Cure rates are much higher and duration of treatment is less.

The final word on the optimal management of visceral leishmaniasis is not available yet, considerable work is going on towards this goal. Availability of miltefosine has rendered the treatment of kala-azar simple and highly effective.

Results with Treatment

Successful treatment abolishes the fever in 2-4 weeks, the spleen becomes impalpable in three weeks, and anemia and leukopenia improve. Relapses may occur, usually within six months of apparent relief. Remission for periods exceeding six months indicate cure. Parasitological cure can be confirmed by appropriate tests. In many cases parasite may still remain dormant in the macrophages subclinically. This is not an indication for continuous therapy.

Prevention

Problems in the control and the spread of leishmaniasis are 1. prevalence of the vector, 2. resistance to pentavalent antimony, cost and the side effects of drugs, the inherent tendency for recrudescence, and 3. co-infection with HIV. Early detection of asymptomatic infection with the use of anti k 39 antibody by immunochromatographic strip test has helped early diagnosis. Use of insecticide (pyrethroid) impregnated bed nets (with narrow mesh < 25 holes/cm²), spraying of houses with insecticide, treatment of those with post kala-azar dermal leishmaniasis and regular follow up of treated groups form the essence of control programmes. Insecticide impregnated nets have to be repeatedly re-charged with insecticide. Nets with incorporated insecticide are effective for their life-time.

Prophylactic vaccines are not available yet.

POST-KALA-AZAR DERMAL LEISHMANIASIS

Syn: PKDL-Dermal Leishmanoid of Brahmachari

Definition

It is a chronic granuloma of the skin caused by *Leishmania donovani* following recovery from kala-azar. Maximum number of cases have been described from India and Bangladesh. In other endemic regions PKDL is rare or absent.

Etiology

PKDL develops as a sequel in 5-10% of cases of kala-azar, usually manifests 6 months to 5 years after apparent

cure. There is breakdown of cell-mediated immunity in the host so that the parasites in the dermis are not eliminated even after the visceral disease has been suppressed by chemotherapy or natural resistance.

Pathology

The lesions consist of granulomas in the dermis made up of parasitized macrophages, lymphocytes and plasma cells. The lesions do not ulcerate.

Clinical Features

Hypopigmented macules: Macular or erythematous lesions develop which are hypopigmented and flush with the surface, varying in size from pinpoint to large patches. These may involve the whole body leaving the regions of the belt, axillae and neck unaffected. The face, extensor surface of the limbs and lateral parts of the back show predilection. The whole face, and in rare instances the whole body may be affected.

Nodular lesions are commonly seen on the chin, other parts of the face except the ears, trunk, limbs, genitals and rarely the mucous membrane of the tongue and lips. Occasionally large tumour-like masses may appear on the face, limbs and trunk. The majority of cases of PKDL show more than one type of lesion. Constitutional disturbances are not present.

Laboratory Features and Diagnosis

Serum antileishmanial antibodies can be detected with standardized and sensitive assays. Diagnosis is confirmed by demonstrating LD bodies in the “slit and scrape material” obtained from the skin lesions, and stained by Leishman’s stain. Further, *L. donovani* may be grown in NNN medium from material aspirated from the nodules. The flagellate form (promastigote) is readily demonstrable after 7-10 days of incubation. PCR studies on material obtained from local lesions also give confirmatory evidence.

Differential Diagnosis

PKDL has to be differentiated from lepromatous leprosy, leucoderma, pityriasis versicolor, dermatitis, lupus erythematosus and neurofibromatosis.

Treatment

It responds to pentavalent antimonials as in the case of kala-azar. Three to four courses may be required.

Prognosis

If left as such, the lesions progressively worsen, and heal with heavy scarring. Cosmetic deformity results. With treatment, 50% clear completely and others may show

considerable improvement. Nodules and erythema readily respond, but the hypopigmented macules are more resistant.

CUTANEOUS LEISHMANIASIS

Cutaneous leishmaniasis is primary infection of the skin caused by direct inoculation of the parasites at the site of lesions by the appropriate vector sand flies. These are seen both in the old world and the new world. In India and the neighbouring countries the parasites are mainly *L. tropica* and *L. major*. In the American varieties the parasites are the *L. mexicana* species complex and the viannia sub-genus including *L. (V) braziliensis*. The parasites remain at the site of the ulcers or nodules, without causing systemic invasion, since cell mediated immunity is high.

Generally, the lesions are localized. They may be entirely cutaneous, e.g. oriental sore or mucosal, e.g. viannia sub-group. Diffuse cutaneous lesions may occur, e.g. *L. aethiopica* and *L. mexicana* complex species in other regions. Man and animal reservoirs such as gerbil provide the source of infection. Infection produces substantial immunity and, therefore, adults show resistance, whereas most of the victims are children. At the site of inoculation of pro-mastigotes lesions develop leading to granulomatous ulcers which are indolent and very chronic existing for several months to years. They are known by various synonyms such as *oriental sore*, *Delhi boil*, *Baghdad boil*, and others.

Oriental sore is a chronic granulomatous lesion of the skin and subcutaneous tissue which ulcerates to form an indolent ulcer. It is caused mainly by *L. tropica* and *L. major*.

The disease is present in the western part of India, Pakistan, Afghanistan, Iran, Iraq, the whole of Arabia, Egypt, Mediterranean region, coastal states of Africa, Sudan, Ethiopia, Niger, and asian parts of Russia.

The vectors are female sandflies belonging to several species in different areas. In India and Pakistan *Phlebotomus papatasi* is the main vector. Local lesion develops with the formation of a granulomatous ulcer. The organism remains at the ulcer site and can be demonstrated in imprint smears or aspirated material.

Clinical Features

Two patterns are seen. In the desert and semi-desert regions, the lesions are moist and tend to ulcerate early and the incubation period is 1-6 weeks. In the urban type, ulcerations is late and the lesions tend to be dry. In this form the incubation is prolonged to 8-24 weeks.

The ulcers are multiple and occur on exposed parts such as face, ears, extremities and the trunk. Early lesions start as itchy papules which enlarge to form nodules and ulcerate to form circular ulcers with clear cut margins.

The ulcers are covered with thin adherent scabs. Regional lymph nodes may enlarge due to spread. Bacterial infection supervenes in due course. The ulcers heal spontaneously in about six months to one year and produce deep scarring and depigmentation.

Diagnosis

In persons living in endemic areas and in those who have recently visited such areas the characteristic lesion should suggest the diagnosis. Other ulcerating lesions such as lupus vulgaris, leprosy, syphilis and rodent ulcer have to be differentiated. The organism can be demonstrated in smears made from scrapings of ulcer margin or in the tissue obtained for biopsy from the depth of the ulcer. The organism can be cultured in NNN medium from material obtained from the lesion.

Treatment

Local treatment is indicated when the sores are only a few. This consists of infiltration of the ulcer base by sodium stibogluconate 100 mg/mL solution. Infiltration is done at intervals of 3-4 days repeatedly and all the lesions heal by repeated sessions. A single small sore may heal with a single infiltration but larger sores heal only with 3-6 infiltrations. Oral drugs such as ketoconazole, 200-400 mg oral daily and itraconazole 100-200 mg oral daily are effective. Paramomycin, when applied as a local ointment gives relief in many cases. When the lesions are numerous or not easily accessible to infiltration therapy, systemic administration of sodium stibogluconate or methyl glucamine antimoniate is resorted to. The lesions heal with one or two courses of injections.

Prevention

Oriental sore can be prevented by adopting anti - sandfly measures, but these are difficult to implement under desert and semi-desert conditions. An ingenious method adopted by natives is to introduce the infective material in an area which is concealed. Natural immunity occurs when this lesion heals and further ulcers do not develop.

Vaccines against leishmania are being developed in several laboratories in India. Results are awaited.

American Cutaneous and Mucocutaneous Leishmaniasis

Syn: Espundiasis

Cutaneous and mucocutaneous leishmaniasis is prevalent in many countries of central and south America from Mexico to northern Argentina with the exception of Chile. The causative organisms are species of Viannic subgenus, especially *L. braziliensis* and *L. mexicana*. These different species show difference in isoenzyme patterns. They are not common in India.

Other Forms of Jungle Leishmaniasis

Several locally occurring forms of mucocutaneous leishmaniasis have been described in jungle regions lying between latitudes 22°N and 30°S. The causative organisms are species of viannia subgroups especially *L. braziliensis* and *L. mexicana*. They produce destructive lesions in the nasopharynx and nose leading to perforation of the nasal septum leading to deformity and disfigurement.

Lesions resemble those of oriental sore histologically. The organisms cause zoonoses among various species of rodents and are transmitted to man by sand flies. *Leishmania mexicana* leads to ulceration of the pinna of the ear and other exposed parts and this is known as “**chicleros ulcer**”, seen in persons who go into forests to collect gum. The pinna may be destroyed over several years.

African Trypanosomiasis

Syn: Sleeping Sickness

K.V. Krishna Das, V.P. Gopinathan

African trypanosomiasis or sleeping sickness is caused by two subspecies of *Trypanosoma brucei*, *T. gambiense* and *T. rhodesiense*. These hemoprotezoa are transmitted by the bite of infected tsetse flies (*Glossina*).

Geographic distribution: *Trypanosoma brucei gambiense* is found in West Africa, Congo, Southern Sudan and Uganda. *Trypanosoma brucei rhodesiense* is found in Central and Eastern Africa. Endemicity is closely related to the distribution of the vector tsetse flies and the reservoir hosts. The disease is not present in India.

Trypanosomes are hemoflagellates seen as actively motile spindle shaped organisms in peripheral blood. In Leishman stained preparations trypanosomes measure $14-33 \times 1.5-3.5$ microns. They possess a central nucleus and a kinetoplast situated near the posterior end. A flagellum arises from the blepharoplast situated close to the kinetoplast and passes forwards along the free margin of the undulating membrane and becomes a free flagellum protruding forward from the anterior end. Trypanosomes are seen actively moving in the plasma in fresh preparations. *Trypanosoma gambiense* and *Trypanosoma rhodesiense* are morphologically similar, but the latter is more virulent in laboratory animals (Figs 64.10 and 64.11).

Incidence

20,000 to 30,000 people are infected by Trypanosomes each year.

Transmission

The vectors are mainly *Glossina palpalis* (*G. fuscipes*) and *G. tachinoides* for *Trypanosoma gambiense* and *G. morsitans*, *G. pallidipes* and *G. swynnertonii* for

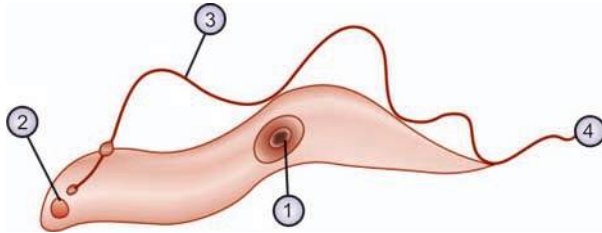


Fig. 64.10: Trypanosomes—General morphology. Note the nucleus (1), kinetoplast (2), undulating membrane (3) and the flagellum (4)

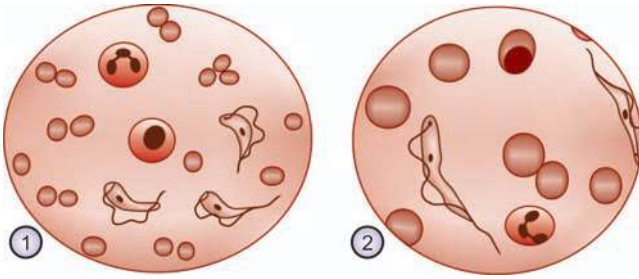


Fig. 64.11: Trypanosomes in peripheral blood
1. *T. cruzi*, 2. *T. gambiense*

Trypanosoma rhodesiense. Both sexes of tsetse flies suck blood and transmit the disease. They live for 2-5 months.

T. gambiense* and *T. rhodesiense are a widespread parasites of several herbivorous animals in endemic areas and these form the reservoir. Humans form the major reservoir for *T. gambiense* and animals form the major reservoir for *T. rhodesiense*.

Tsetse flies get infected by feeding on infected animals or man. The parasites multiply in the gut of the fly and pass anteriorly to the proventriculus and the salivary glands. The infective metacyclic forms develop and multiply there further and pass into the proboscis after 3-7 weeks. The fly remains infective for its life. The metacyclic forms are introduced into the host during the next bite. The metacyclic forms transform into trypanosomes within 48 hours and multiply in the tissue space. Ultimately, they pass to lymph nodes and the blood stream and then reach several organs.

Pathology

Lymph nodes and the central nervous system (CNS) show maximal lesions. There is localized or generalized lymph node enlargement. The nodes are congested and show hemorrhagic areas which contain trypanosomes. Later, these undergo fibrosis. In liver, Kupffer cell hyperplasia occurs with portal infiltration, but clinical hepatosplenomegaly is rare. Pancarditis occurs because of extensive cellular infiltration and fibrosis.

Affected organs show infiltration of the blood vessels by monocytes, macrophages and plasma cells causing endarteritis. This increases vascular permeability.

In the CNS the main lesion is leptomeningitis seen over the brain and spinal cord. Histologically there is perivascular cuffing with lymphocytes and plasma cells. Later, trypanosomes invade the brain tissue, particularly the frontal lobe, pons and medulla. Parasites are seen in the cerebrospinal fluid during the meningitic stage. Other changes include rise in pressure, moderate rise in protein and lymphocytosis. Complement-mediated hemolytic anemia may develop in some. IgM class antibodies are demonstrable in the serum and CSF.

Clinical Features

The incubation period varies from one to three weeks. Though the symptoms of *T. gambiense* and *T. rhodesiense* infections are broadly similar, the rhodesian type is usually more severe and runs a more acute course with a higher mortality. The initial lesion is the formation of a painless nodule at the site of bite (*trypanosomal chancre* or *trypanids*). This nodule occurs 5-15 days after the bite. *Trypanosomes* are seen in this lesion. Irregular fever and parasitemia occur within (1-2) weeks. Lymphadenopathy occurs usually after 3 weeks of the bite. Cervical, femoral and axillary groups of lymph nodes enlarge. Lymph nodes are more pronounced in the posterior triangle of the neck in *T. gambiense* infection. Enlargement of these groups of lymph nodes is called "*Winterbottom's sign*". The spleen is often enlarged. Anemia develops in due course due to slow inanition and hemolysis. Fever, lymphadenitis, anemia and debility continue for several months.

The CNS involvement is late in the gambian type while symptoms of the CNS involvement develop within a few months in the rhodesian type. The whole course runs over 2-3 years, but the course is shorter in the rhodesian type and death may occur in 6-9 months.

Several unusual manifestations may develop. These include circinate erythematous skin rashes, localized edema over the face, eyelids and neck, ulnar hyperaesthesia (Kerandel's sign) neuralgic pains, formication, myocarditis, pericardial effusion and jaundice. The sleeping sickness stage sets in when the parasites enter the CNS. The debility and languor increase, the gait becomes slow, shuffling and swaying, the speech becomes slurred, and tremors of the tongue and lips develop. The patient may become demented. Mask-like vacant expression, drooping of eyelids, tendency to fall asleep during day time and restlessness at night are all seen in endemic areas. The patient becomes severely emaciated and serious complications like pneumonia, dysentery, hyperpyrexia, convulsions and coma may supervene and prove fatal. Though untreated cases of sleeping sickness are generally fatal, the gambian type may recover spontaneously at times (Table 64.6).

TABLE 64.6

Comparison of disease caused by *T. Brucei gambiense* and *T. Brucei rhodesiense*

	<i>T.B. gambiense</i>	<i>T.B. rhodesiense</i>
Disease produced	Gambian sleeping sickness	Rhodesian sleeping sickness
Distribution	West and central Africa	East Africa
Vector	Glossina palpalis or tachinoides (riverine tsetse)	Glossina morsitans (Savanna tsetse)
Reservoir	Humans and domestic animals	Wild animals
Course	Slow—months to years. Less acute course	More rapid—up to one year. More acute course
CNS symptoms	More characteristic	Less marked
Results with treatment	Good	Not satisfactory
Chemoprophylaxis	Useful	Not reliable

Diagnosis

History of residence in an endemic area, irregular fever, enlargement of cervical lymph nodes and hepatosplenomegaly should point to this diagnosis. Trypanosomes are demonstrable in peripheral blood, lymph node aspirate and cerebrospinal fluid. Serological Tests such as indirect fluorescent antibody test and ELISA are helpful. Newer tests based on proteomics signature analysis are available. These are more specific and reliable for diagnosis and follow-up.

Drug Treatment

Early cases limited to blood and lymph nodes respond to suramin which is a derivative of urea. Dose is 20 mg/kg bw given IV as a 10% solution on days – 1, 3, 7, 14 and 21. the drug is nephrotoxic. Anaphylactic reaction may develop.

Late cases with neurological involvement respond to melarsoprol (Mel – B) which is a trivalent arsenical, combined with BAL (British anti lewisite). The drug has to be administered under supervision due to adverse side effects. The drug is quite effective in curing even late cases with neurological involvement. Resistance of the parasite to arsenicals may develop. Other drugs which are also effective include difluoromethyl ornithine (efflornithine) given in a dose of 200–400 mg/kg bw daily IV for 4 weeks and nitrofurazone given in a dose of 10 mg/kg given 8h orally for 10 days. With treatment, clinical and parasitological clearance occurs even in late cases. Patients should be watched for 2 years to ensure cure.

Prevention

Anti –tsetse fly measures including proper clothing and insect repellent creams (Di -meepol or diethyl benzamide and elimination of the reservoir hosts are effective. Drug prophylaxis with suramin or pentamidine are also available.

American Trypanosomiasis

Syn: Chagas Disease

K.V. Krishna Das, V.P. Gopinathan

GENERAL CONSIDERATIONS

The Brazilian Physician – Carlos R. J. Chagas discovered *Trypanosoma cruzi* in 1909. Chagas disease is caused by *Trypanosoma cruzi* (schizotrypanum) which is transmitted by species of reduvid bugs to man. It is seen in all countries of central and south America (Fig. 64.11).

Trypanosoma cruzi is a broad trypanosome about 20 µ in length and is C-shaped. The motile stage of the parasite is found only for a short period after infection. It soon develops into the leishmanial form that multiplies in the cells of mesenchymal origin. Reduvid bugs of the genera *Triatoma*, *Rhodinus*, and *Eratyrus* are the principal vectors. These bugs inhabit the floor and walls of rural houses. These come out at night and suck blood from the sleeping inhabitants. During the blood meal they defecate (Fig. 64.12). Reservoir hosts are formed by dogs, cats, opossums and armadillos. Reduvid bugs are infected by taking blood meal and in 6-15 days infective metacyclic forms are passed in feces. Organisms enter the body when the feces is smeared on to the bite wound. Other methods of transmission also exist. Infected mothers can transmit the disease to the fetus, giving rise to congenital Chagas disease. Spontaneous abortion may occur in many, but 2-5% of babies may manifest infection at birth.

Other vehicles for transmission of infection are blood or donated organs from infected individuals. Migration of population has led to introduction of this disease into several parts of the world which were free.

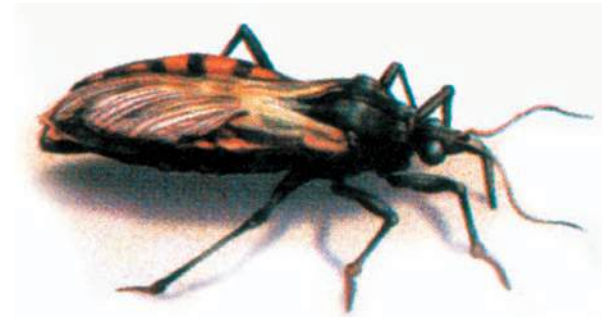


Fig. 64.12: Reduvid bug

Incidence

An estimated 16 -18 million people are infected in 18 Latin American countries. Chagas disease results in 45,000 to 50,000 deaths per year. Major cause of death is cardiac involvement. This disease is not reported from India.

Pathology

At the site of inoculation, the organisms multiply and produce a local lesion-Chagoma. They are seen in the blood stream for a short period. They are taken up by macrophages later. *Trypanosoma cruzi* multiplies and produces focal lesions in the cardiac and skeletal muscles and neuroglia. Cardiomyopathy develops as a result of cardiac involvement. From the foci of multiplication active trypanosomes enter the blood stream and are demonstrable.

Granulomatous lesions occur in the spleen, liver and lymph nodes. CNS involvement in children leads to meningoencephalomyelitis. Chronic Chagas disease manifests several years or decades later in 10-30% of cases. The direct effect of the parasite as well as immunological processes account for the late results. Common presentation is as cardiomyopathy. Pathological changes include biventricular enlargement, thinning of ventricular walls, apical aneurysm, mural thrombi and varying degrees of heart block. Parts of the alimentary tract are also affected.

In the esophagus and colon dilatation occurs giving a picture of acquired achalasia cardia and megacolon seen. The alimentary lesions are due to destruction of the Auerbach's plexus.

CLINICAL FEATURES

In children *Chagas disease* occurs in an acute form, presenting with fever, rash. without itching, and the rash clears in several days. Symptoms of the acute phase may also include malaise, myalgia, headache, asthenia, and anorexia. Mortality in the acute phase, is low (<5%) and it is due to acute myocarditis and/or meningoencephalitis, Children younger than 2 years suffer more.

Chagoma (furunculoid and peeling cutaneous lesion) which is nodular occurs at sites of entry of the parasite through the skin, generalized lymphadenopathy, myocarditis and rarely meningoencephalitis develop. The Romaña sign develops in 20-50% of cases in which the route of entry is through the conjunctiva. It is a painless, periophthalmic, unilateral edema of both palpebral conjunctiva, frequently accompanied by conjunctivitis and local lymph node enlargement. It persists for 30-60 days. The manifestations of the acute disease resolve spontaneously within 3-8 weeks in approximately 90% of individuals who are infected.

They enter the chronic, latent or indeterminate asymptomatic phase of the disease. A direct progression from the acute phase to the symptomatic chronic form of Chagas disease occurs in fewer than 5% of patients. In the chronic type cardiomyopathy and achalasia cardia and atonic dilation of the colon and the small intestine are seen. Approximately two thirds of cases develop cardiac manifestations leading to arrhythmias, cardiac failure, thromboembolic phenomena, and sudden death. In the endemic areas of south and central America Cardiomyopathy due to Chagas disease used to be a common cause of cardiovascular death among patients aged 30-50 years.

Involvement of the gastrointestinal tract leads to megaesophagus and/or megacolon in approximately one third of chronic cases, these chronic lesions do not resolve spontaneously.

Diagnosis

Direct microscopic examination of blood smears will demonstrate rapid movements of live *T. cruzi*. Quantitative Buffy coat also can be done for demonstration of parasite. Immunological tests such as detection of *T. cruzi* specific antibodies, indirect hemagglutination test, immunofluorescence and ELISA are also available. PCR test has been developed to demonstrate the parasite antigen.

ECG may show arrhythmias, heart block especially RBB and block of the anterior branch of the bundle of His.

Affection of the other systems can be demonstrated by appropriate tests.

Treatment

In acute phase, Benznidazole is the drug of choice. Benznidazole (Rochagan) is given as an oral dose of 6 mg/kg for 30-60 days. This has to be given under supervision. Primaquine has been found useful in a dose of 15 mg daily for about 6 months in acute Chagas disease. At present Nifurtimox (Lampit) a nitrofurantoin, is available for oral use. The dosage is 8-10 mg/kg/day for adults and 15-20 mg/kg/day for children and the drug has to be administered for 120 days. Cure rates of 80% in acute and 90% in chronic cases have been claimed. The drug is toxic and hence has to be given under supervision. Permanent lesions occurring in others organ systems demand management on their own merits.

Posaconazole which is a systemic antifungal agent shows promise as an anti *T. Cruzi* drug.

Control

Improvement in housing and sanitation, and use of insecticides limit the spread of the reduvid bugs. Treatment of active cases and attention to the animal reservoir reduce the reservoir pool.

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Amebiasis, Giardiasis, Balantidiasis, Toxoplasmosis and Cryptosporidiosis

K.V. Krishna Das, V.P. Gopinathan

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Chapter Summary

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Amebiasis

GENERAL CONSIDERATIONS

Fedor Aleksandrovich Losch in Russia first described amoebiasis in 1875. The term amebiasis includes all lesions caused by infection by the protozoan parasite *Entameba histolytica*. These amebae cause ulcerative lesions in the large intestine causing dysentery and from there they spread to several organs to produce necrotic lesions. There is a great tendency for the intestinal infection to become chronic and persistent for long periods. *E.dispar* is morphologically identical to *E. histolytica*, but nonpathogenic. It is genetically different. It is a commnsal. However, *E. histolytica* can also remain in the bowel for many years without causing major symptoms.

Amebiasis is worldwide in distribution, but it is very prevalent in tropical climates. In many parts of India, the infection rate used to be as high as 40 to 50%. Chronic carrier state, poverty, insanitary disposal of excreta, unhygienic food handling, and proliferation of flies are responsible for this high prevalence. Though all age groups are susceptible, adults suffer more often.

Due to the wide prevalence of intestinal parasitism and want of full information on the prevalence of other chronic gastrointestinal disorders such as irritable bowel syndrome and motility disorders there was a general tendency to overestimate the prevalence of intestinal amebiasis. In areas where the environmental sanitation has improved and the use latrines is popular the prevalence of amebiasis has considerably fallen. Intestinal endoscopic studies done in many institutions reveal that at present amebic lesions are relatively less common.

Parasitology

Amebae are widely distributed in nature. The common pathogen is *E. histolytica*. It exists in two forms—the *cyst* and the *trophozoite*. The cysts are round or oval in shape and measure 10 to 15 μ in diameter. In iodine-stained preparations the cysts show one, two or four nuclei depending on their maturity. Cysts resist adverse environment. In addition to the nucleus, one or more rod-like structures called chromidial bars, and a glycogen mass are also seen. Cysts are formed in the bowel when the environment becomes unfavorable for the trophozoite and are then passed out in feces. Cysts are responsible for transmission of the disease from person to person. The vegetative form (trophozoite) is actively motile by the aid of pseudopodia. It measures 20 to 50 μ in diameter. Invasive trophozoites are identified by the presence of ingested erythrocytes within them. Amebae multiply by binary fission. The trophozoite is the invasive form and is responsible for all lesions. A large number of trophozoites is seen in the feces of dysenteric patients. Trophozoites and cysts occur in the feces of carriers. Outside the body, the trophozoites survive only for an hour or so. Normal gastric juice destroys them in the stomach. Cysts survive external environment for long periods.

Transmission

Humans are the only reservoir for *E.histolytica*. Cysts are passed in the feces of cases and carriers. These are ingested along with food or water. Cysts resist acid

digestion in the stomach. Excystation occurs in the intestines, Trophozoites develop from cysts and they establish themselves in the colon, feeding on the bacteria and desquamated epithelial cells. They multiply by binary fission. These non-invasive forms may persist for long periods without producing any symptoms. Under favourable conditions these become invasive.

PATHOLOGY

Intestinal amebiasis: The invasive trophozoites adhere to colonic mucosa with the help of specific lectins and ulcerate the mucous membrane and penetrate deep into the submucosal layers of the colon. The basic pathological process is a lytic necrosis of tissue. This is due to an extra cellular cysteine kinase enzyme causing proteolytic destruction of the tissue, producing flask shaped ulcers. *E. histolytica* which produce lytic enzymes kills host cells which come into contact with them. The host cells become immobile on contact with *E. histolytica*, and the cells die. *E. histolytica* can also induce apoptosis in host cells. The cellular response consists of mononuclears and a few polymorphs. Amebae are seen in the invading margins of the lesions. Cecum, ascending and descending colon, and rectum are the sites of predilection. The appendix may be involved. The terminal ileum may be affected rarely. The ulcers have undermined edges and are covered by dense yellow or brown slough. The mucous membrane between ulcers is healthy. Ulceration may extend to blood vessels causing severe hemorrhage at times. Perforation of the bowel may occur, but it is rare. Sometimes **ameboma** or amebic granuloma develop due to repeated infection by ameba and bacterial pathogens. The acute inflammatory process has a tendency to subside spontaneously. In many patients chronic infection persists with microscopic lesions which harbour *E. histolytica* for many years. The lesions may heal in a few cases. Persistence of the chronic lesions accounts for the carrier state.

E. histolytica infection is associated with transient immunosuppression. Activated macrophages form the major defence against invasive amebae. Tumour necrosis factor (TNF) which is a cytokine derived from macrophages has parastical properties. The resistance against invasive amebiasis is mainly cell mediated immunity .

Extra-intestinal Lesions

Amebic liver abscess: Invasive amebae reach the liver through the portal blood stream from the colon which is the primary seat of infection. In the liver they multiply and cause colliquative necrosis of liver cells to produce abscess. Possibly malnutrition, alcoholism and consequent immunosuppression favour the development of liver abscess. Unlike pyogenic abscess, the wall of the amebic abscess is made up of necrotic and compressed liver tissue

and it is devoid of granulation tissue. Active amebae are found near the expanding margins. The pus is made up of necrotic tissue which shows amorphous material and erythrocytes. It is sterile on culture. In most cases the colour of the pus is reddish brown or chocolate. Amebae are seen only rarely in the pus aspirated from the center of the abscess, they are more often demonstrable in the pus aspirated from near the walls on subsequent occasions. The site of the abscess is more commonly the right lobe. It is usually single and may attain very large size. The abscess may enlarge progressively and spread by contiguity to the chest wall, colon, diaphragm, pleura, and pericardial cavities. Amebic abscess does not impair hepatic-function significantly. Jaundice is generally mild or absent, but pressure over a major hepatic duct can give rise to obstructive jaundice. On aspirating the pus the liver tissue comes into apposition and complete healing occurs without structural damage or fibrosis.

During acute amebic dysentery, the liver may enlarge as a result of diffuse inflammation caused by the products of inflammation of the colonic tissue and bacteria reaching the liver in the blood stream. The hepatic lesion clears up with cure of the dysentery. This lesion should not be mistaken for liver abscess.

Other foci for embolic lesions include the lungs, brain, spleen and other tissues. Direct invasion of the skin by active vegetative amebae leads to extensive spreading necrotic ulceration-cutaneous amebiasis.

CLINICAL MANIFESTATIONS

The incubation period varies from a few weeks to months.

Spectrum of illnesses caused by E. histolytica

Intestinal amebiasis

1. Asymptomatic infection
2. Symptomatic non-invasive infection
3. Acute proctocolitis (Dysentery)
4. Toxic megacolon
5. Chronic non dysenteric colitis
6. Ameboma
7. Peri anal ulcers

Extra intestinal amebiasis

1. Liver Absces
2. Pleuro -Pulmonary involvement
3. Pericarditis
4. Peritonitis
5. Brain abscess
6. Genito urinary disease

ACUTE AMEBIC DYSENTERY

This presents with sudden or subacute onset of lower abdominal pain and diarrhea with blood and mucus in stools. The frequency ranges from 3 to 10 in a day. At times watery diarrhea with large amounts of blood and

mucus may occur. Constitutional symptoms are mild and these include low grade fever and vague discomfort. Palpation of the abdomen reveals colonic tenderness and mild hepatomegaly. The feces is semisolid or liquid, showing fecal matter mixed with blood and mucus. Microscopic examination shows erythrocytes, a smaller number of leukocytes and trophozoites of *E. histolytica*. In the majority of cases, the condition subsides after several weeks even without treatment, to exacerbate again with dietary irregularity, psychological stress or other factors. Complications are rare but in a few cases extensive destruction of mucosa and submucosa may lead to severe hemorrhage and occasionally perforation. Rectal prolapse, intussusception and colonic stricture may develop in some. **Amebomas** may develop in the cecum or other parts of the colon and these may be mistaken for tumours. These resolve completely with specific treatment.

Non-dysenteric Amebiasis

This is a common mode of presentation in endemic areas. The condition starts insidiously with abdominal discomfort, flatulence, intermittent diarrhea with constipation, and the presence of mucus in stools. Asymptomatic intervals and periods of dyspepsia alternate for many months or years. Vague general symptoms like feverishness, mild depression, fear and anxiety may be prominent. Physical examination may reveal palpable tender cecum and sigmoid and sometimes tender hepatomegaly. An amebic granuloma (*ameboma*) may be felt as a sausage-shaped mass in the right iliac fossa and this may be mistaken for malignancy or tuberculosis. Mucosal ulcers may be seen on sigmoidoscopy. Examination of the mucus collected by sigmoidoscopy may show the active trophozoites. Repeated examination of fresh stool or sigmoidoscopic specimen may be necessary to establish the diagnosis. Sigmoidoscopic biopsy reveals the ulceration and the parasite in the mucosa.

HEPATIC AMEBIASIS

Hepatic involvement used to be very common, almost all patients give a history of alcoholism. Around 50% of patients suffering from hepatic amebiasis give history of dysentery. Liver involvement manifests as insidious onset of pain in the right hypochondrium or right lower chest with fever, chills and sweating. Loss of weight and anemia may be pronounced. In the early stage the liver is enlarged as a whole. The pathological process is not inflammatory, but it consists of multiple necrotic lesions caused by amebae diffusely distributed in the liver. In this stage the organ is enlarged as a whole and it is acutely tender. This stage may persist for varying periods and may resolve either spontaneously or with treatment, without

proceeding to abscess formation. At present the occurrence of liver complications has come down.

In those in whom abscess develops, the liver is considerably enlarged and tender. When the abscess spreads to the abdominal wall, there is superficial edema and severe local tenderness. The majority of liver abscesses are in the right lobe. Left lobe lesions are palpable over the epigastrium. Diaphragmatic involvement causes pleuritic pain in the right lower chest. Physical examination reveals diminished air entry, impaired percussion note and crepitations over the lower part of the right chest. Jaundice is rare. Blood shows mild to moderate leukocytosis (about 12-14.000/cmm) with polymorphonuclear cells dominating the field. The ESR is usually high. Fluoroscopy reveals elevation of the right dome of the diaphragm and diminished movement. Ultrasound, CT scan and isotopic scanning help to locate the site of the abscess.

Complications of liver abscess include rupture into neighbouring organs or cavities leading to peritonitis, right sided empyema, bronchohepatic fistula, and pericarditis. Untreated, the mortality may go up to 10%.

Cutaneous amebiasis occurs over the genitalia, perianal region, opening of sinuses and around colostomy wounds. Rarely metastatic lesions from the liver develop in the lungs and brain. Rupture of a liver abscess into the peritoneum causes the clinical picture of an acute abdominal emergency with shock.

Differential Diagnosis

Amebic dysentery has to be differentiated from bacillary dysentery, ulcerative colitis and tuberculous enterocolitis. Ameboma may closely resemble carcinoma. Chronic intestinal amebiasis may be mistaken for irritable bowel syndrome, diverticulitis, neurasthenia or malabsorption state. Hepatic amebiasis is a common cause of prolonged fever in the tropics and when liver enlargement and tenderness are not marked, it resembles enteric fevers, brucellosis or tuberculosis.

In an endemic area, enlargement and tenderness of the liver should suggest the diagnosis of amebic liver abscess. Other conditions such as alcoholic liver disease, primary and secondary tumours of the liver, subdiaphragmatic abscess and pyogenic liver abscess have to be differentiated. In case of doubt the diagnosis is confirmed by ultrasonography and later, aspiration. Prompt response to antiamebic drugs is a point suggesting a diagnosis of hepatic amebiasis.

Laboratory Diagnosis

Examination of the feces – Fresh stool examination by light microscopy invariably reveals *E. histolytica* in dysentery. Active *E. histolytica* shows characteristic ameboid movement and ingested erythrocytes. In chronic amebic colitis cysts are present in feces in varying numbers. These can be identified in saline preparations

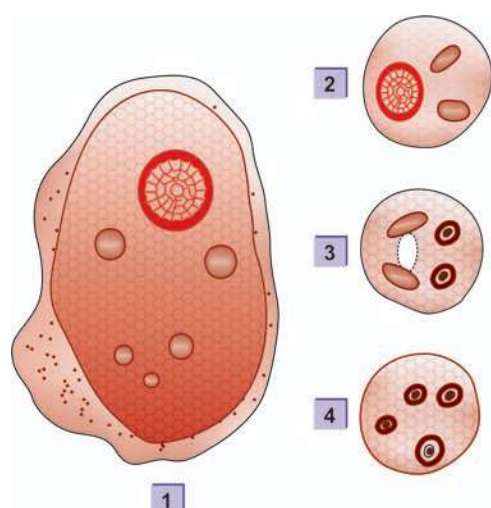


Fig. 65.1: *Entameba histolytica* in stools (diagram)

1. Trophozoite (vegetative motile form) with ingested erythrocytes
2. Uni- and bi-nucleated cysts
3. Chromatoid bars and glycogen vacuole
4. Mature cyst with four nuclei

but cellular details are better demonstrable in iodine stained specimen. Unlike bacterial dysentery, the feces does not contain innumerable leukocytes. Plenty of erythrocytes are present. Stool occult blood may be present in invasive intestinal disease. Stool enzyme immunoassay also will be useful (Figs 65.1 and 65.2).

E. histolytica has to be distinguished from the non-pathogenic *Entameba coli* by the following features.

	<i>E. histolytica</i>	<i>E. coli</i>
Saline wet smear		
1. Movement	Progressive	Non-
2. Ingested RBC	Present	Nil
Iodine stained preparation		
Nuclear Chromatin	Central	Eccentric
Number of nuclei in the cyst	1 or 4	1,2 upto 8
Chromidial bars	Short and thick	Filamentous

Apart from feces, vegetative *E. histolytica* can be demonstrated in the following specimen.

1. Liver abscess pus.
2. Sputum in pulmonary amebiasis.
3. Discharge from cutaneous amebiasis.

Serological tests – These tests are mainly used in extraintestinal disease. Indirect hemagglutination antibody test is positive in 95% of extraintestinal and 70% of intestinal amebiasis. Other tests also have been developed. Indirect immunofluorescence is positive in more than 60%

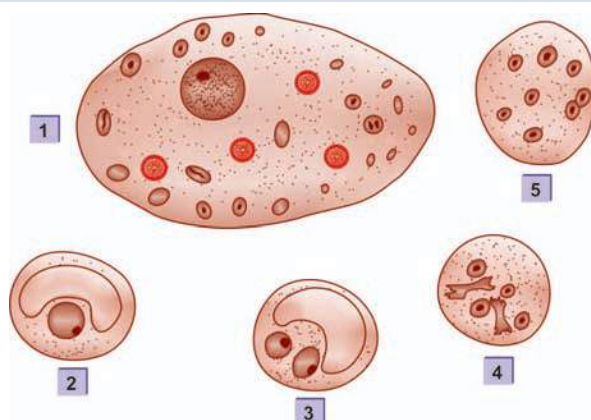


Fig. 65.2: *Entameba coli* in stools (diagram)

1. Trophozoite
- 2, 3 and 4. Uni-, bi- and quadrinucleate cysts with glycogen vacuole and chromidial bars
5. Mature cyst with eight nuclei

of cases. Countercurrent electrophoresis and agar gel diffusion are other methods employed.

Imaging studies: ultrasonography – A single lesion in the posterosuperior aspect of the right lobe of the liver is commonly seen. But, multiple abscesses may also occur in some patients. Deep seated abscess may be missed on clinical evaluation. Multiple abscesses should suggest the possibility of pyemic etiology.

CT scan – In cerebral amebiasis, CT may show irregular lesions without surrounding capsule or enhancement.

Other investigations – Blood counts may show mild anemia, leucocytosis, elevated ESR and elevated alkaline phosphatase.

Endoscopy – Rectosigmoidoscopy and colonoscopy may reveal small mucosal ulcers covered with yellowish exudates, and the intervening mucosa appears normal. For demonstrating vegetative amebae the fresh mucus exudates should be examined as a saline preparation, microscopically.

In chronic intestinal amebiasis the feces show amoebic cysts, when the disease is quiescent. With acute exacerbation, trophozoites appear from time to time. Charcot-Leyden crystals may be seen as a result of chronic bleeding foci. These crystals are needle shaped, refractile, and are made up of lysophospholipase.

TREATMENT OF AMEBIASIS

Drug treatment consists of amebicidal drugs. These may act on the parasites found in the lumen of the gut or on the invasive forms seen in the tissues. They are grouped as luminal amebicides and tissue amebicides. Some drugs, however, have action on both sites.

The most effective amebicides in current use are given in the following table.

1. Metronidazole 400 mg 3 times/day orally for 10 days (or) 800 mg tds for 5 days.
2. Tinidazole 600 mg 2 times daily for 5 days orally
3. Diloxanide furoate 500 mg 3 times daily for 10 days
4. Chloroquine 500 mg 2 times daily for 2 days
250 mg BD for 2–3 weeks

1. **Metronidazole:** This drug has effect on both trophozoites and cysts. It is well-absorbed after an oral dose to produce adequate tissue levels. It is effective for the treatment of acute and chronic intestinal amebiasis and in hepatic amebiasis. In severe cases the drug can be used intravenously in a dose of 500 mg twice a day as an infusion. Though side effects are not serious, they are common. These include distaste in the mouth, anorexia, nausea, abdominal discomfort, vertigo, dizziness and ataxia. Peripheral neuropathy may develop rarely. The drug is generally avoided during pregnancy on account of its possible teratogenic effects in laboratory animals.

2. **Tinidazole:** This drug belongs to the group of nitroimidazole derivatives, structurally related to metronidazole. The therapeutic spectrum is similar to metronidazole, but the drug is more potent, it is also better tolerated.

* Newer drugs in this group with more prolonged action are being introduced, e.g., Secnidazol 2 g single dose for intestinal amebiasis and 1.5 g as a single daily dose for five days for hepatic amebiasis.

3. **Diloxanide furoate:** It is a safe drug effective only on the intestinal forms of the parasite. It is used in the treatment of acute and chronic intestinal lesions in doses of 500 mg tds oral for 10 days. In amebic dysentery, the symptoms subside in 5-7 days. In chronic intestinal amebiasis clearance rates approximate 80-90%.

4. **Chloroquine:** It has amebicidal properties in hepatic lesions. This is brought about by the high tissue concentration of the drug obtained in the liver. It is effective in the treatment of hepatic amebiasis along with metronidazole or tinidazole. It has no action on the trophozoites or cysts in the intestine.

Acute amebic dysentery: Metronidazole, which produces symptomatic relief in 3-5 days, is the drug of choice. General management consists of the treatment of fluid and electrolyte imbalance, especially potassium loss. The diet should be soft, low residue type with high caloric value. After the full course of treatment, stool examination should be done to ensure parasitological cure.

Chronic intestinal amebiasis: When symptoms are mild and chronic, metronidazole or diloxanide furoate are the

drugs of choice. A single course may bring about parasitological cure in 80-90% cases. Repeated courses are required to completely eliminate the infection in most cases. Even with repeated courses some cases may prove to be resistant.

Hepatic amebiasis: Metronidazole and chloroquine are administered in full doses. During the acute phase metronidazole 500 mg infused IV twice a day till the pain and tenderness subside and then followed up by oral dosage is ideal. Addition of chloroquine is optional. Large abscesses should be aspirated 2-3 days after starting drug therapy.

Aspiration should be done at the site of maximum tenderness or edema of the chest wall. Ultrasonography helps to locate the exact site of the abscess for aspiration. Since there is no granulation tissue to wall off the cavity in amebic liver abscess, needle aspiration is adequate to remove the pus and favour healing. Most of the cases clear up with two to three aspirations. Emergency aspiration has to be done if the abscess threatens to rupture or has just ruptured. In case of left lobe abscesses aspiration under ultrasonographic guidance may be necessary to achieve full drainage.

The main complications of aspiration are hemorrhage, vasomotor collapse and introduction of infection into the cavity. Secondary infection should be treated with full doses of broad spectrum antibiotics. In uncomplicated liver abscess the pus is chocolate coloured or yellow, odorless, sterile and does not show predominance of pus cells on microscopy. When the abscess is infected the pus is yellow or greenish, foul smelling and microscopic examination shows predominance of pus cells. Gram staining and culture help in demonstrating the organisms. Small liver abscesses may resolve with medical treatment even without aspiration. In all cases of hepatic amebiasis a course of intestinal amebicides should be given to prevent relapse of the hepatic lesions and to clear the carrier state.

Other lesions: Amebic lesions of the brain, lung and skin respond to a course of metronidazole or tinidazole.

Dehydroemetine is indicated if the response is unsatisfactory. The dose is 60 mg/day by IM injection. The drug is toxic particularly causing myocarditis. A course should not exceed a cumulative dose of 600-900 mg. The drug is seldom used now.

Resumption of alcohol intake predisposes to relapse of liver abscess.

Asymptomatic cyst passers: It is advisable to treat them with metronidazole to avoid the risk of future hepatic amebiasis and to eradicate the carrier state. A full course of metronidazole or tinidazole given for 5-10 days clears 80% of cases. Repeated courses are needed for better results. Diloxanide furoate, either singly or in combination with metronidazole can also be employed with success.

Results of treatment: Both acute and chronic intestinal amebiasis respond satisfactorily to drug therapy. In endemic regions reinfection is quite common, unless proper hygienic measures are instituted. Complications like gut perforation and amebic peritonitis carry a high mortality if treatment is delayed. Prompt supportive measures and therapy with antiamebic drugs and antibiotics considerably improve the outlook. Mortality due to liver abscess is about 10% if the condition is not diagnosed and treated in time. Prompt treatment gives very satisfactory results. The liver recovers completely without residual damage. Amebic abscess of the brain clears up with specific therapy and other symptomatic measures, but it is fatal if missed.

Prevention: The most important steps are to observe food hygiene, provide safe drinking water and arrange for sanitary disposal of human excreta. Ordinary chlorination of drinking water does not kill the cysts. Cooks and food handlers should be periodically examined and the infection eradicated. Fruits and vegetables can be rendered safe by washing with soap and peeling off the skin wherever possible.

Primary Amebic Meningoencephalitis

K.V. Krishna Das

General Considerations

Some species of free-living soil amebae of the genus *Naegleria* may produce primary amebic meningoencephalitis, which is a rapidly fatal disease. The organisms are carried in the nose and throat to asymptomatic carriers. It is seen worldwide, occurring sporadically. The disease is present in India.

Naegleria gruberi is the common pathogen. The genus *Hartmanella* (syn: *Acanthamoeba*) can also affect man. In most of the cases a history of swimming or bathing in contaminated water may be obtained. The organisms enter through the roof of the nose and spread up the cribriform plate to reach the subarachnoid space. The brain is edematous and covered by a blood stained purulent exudate, especially in the basal cisterns. Amebae are also seen invading the grey matter.

Clinical Features

The incubation period is 2-14 days after a possible exposure. The clinical picture resembles acute meningitis. The CSF is under tension and it is turbid or blood stained. Microscopy shows erythrocytes, numerous polymorphs and motile amebae containing ingested erythrocytes which may be mistaken for macrophages. The species of ameba can be identified by suitable staining. CT scan shows generalized cerebral edema with increased vascularity in post-contrast study suggestive of meningitis.

Azithromycin in the dose of 7.5 mg/kg/day for 5 days has been tried with partial success. Amebic meningoencephalitis is associated with high mortality within 2-5 days. Present treatment is not fully satisfactory. In addition to meningoencephalitis occasionally granulomatous amebic encephalitis may develop. This is caused by *Acanthamoeba* species and *Balamuthia mandrillaris*, particularly in immunocompromised subjects.

Treatment

Amphotericin B given intravenously in a dose of 0.25 mg/kg daily for 8 days is partially effective against *Naegleria*. The drug can also be given intrathecally in a dose of 0.5 mg diluted in 5 mL of CSF, thrice a week.

Acanthamebae (*Hartmanella*) are free-living amebae seen in soil and water. These become pathogenic to immunocompromised hosts. They gain entry through the nasal mucosa, abrasions on the skin or eyes. Pathogenicity is similar to that of *Naegleria*.

Further reading: Tungikar SL et al. Primary amebic meningoencephalitis JAPI 2006; 34: 327-9.

Giardiasis

K.V. Krishna Das

Giardiasis is infection of the small intestine by the flagellate protozoon—*Giardia intestinalis* (*G. lamblia*). In the tropics and subtropics, this parasite is very widely prevalent, particularly in children.

Giardia lamblia is a flat pear-shaped organism 12-18µ in diameter with eight flagella, two nuclei and a large ventral sucker placed anteriorly. These flagellates are found in large numbers in the duodenum and jejunum in between the villi, and attached to them by their suckers. Occasionally biopsy specimens may show *giardia* between villi. With the aid of the flagella, giardia moves actively and this helps to identify the organisms in fresh stools or duodenal aspirates. Cysts are formed which are passed in feces (Fig. 65.3).

Transmission occurs by ingesting the cysts along with food and water. Infection rates are high in closed communities. New immigrants and travellers may get the infection from endemic areas. Hypochlorhydria and hypogammaglobulinemia predispose to heavy infection.

Pathogenesis

Though the exact mechanism is not known, it is possible that a large number of flagellates adhering to the mucosal surface may reduce the area for absorption. In addition, irritation of the brush border of the villi, alteration in bacterial flora in the small intestine; and invasion of the submucosa have been suggested as contributing factors. Many cases show increased intestinal motility.

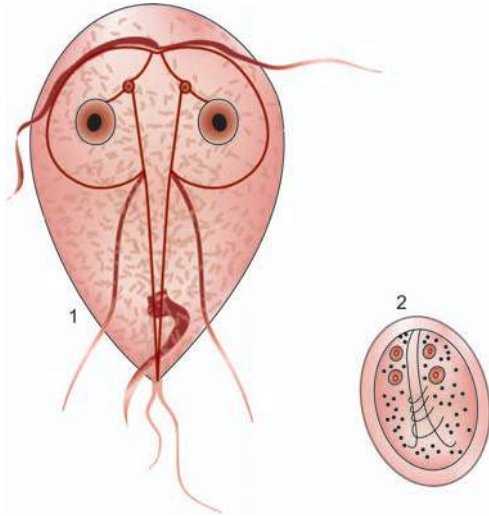


Fig. 65.3: *Giardia lamblia* seen in stools (diagram)

1. Actively motile form
2. Cyst

Clinical Features

Presenting symptoms range from mild abdominal discomfort to explosive diarrhea. Some infections may be asymptomatic but the majority are subacute or chronic. Nonspecific symptoms include failure to thrive, abdominal pain, epigastric distress, intermittent diarrhea and general ill-health. Features of malabsorption may occur, especially in children and this should suggest the possibility of giardiasis.

In some outbreaks explosive diarrhea with watery foul smelling stool may be the presenting symptom. Giardiasis is a frequent cause for traveller's diarrhea in endemic regions. The acute attack lasts for 3-4 days but in children the course may be prolonged for weeks or months and it results in malabsorption state. Many cases go into spontaneous remission and carrier state develops in them.

Diagnosis

Giardiasis is a common cause of diarrhea in children and vague abdominal discomfort in adults. Fresh feces should be examined for identifying the motile flagellate. Presence of the active flagellate in fresh stool or in the duodenal aspirate confirms the diagnosis. In many cases mixed infection with *Giardia* and other intestinal pathogens like *E. histolytica* or helminths is common. Clinical severity does not always correlate with the number of parasites seen in feces. In mild infections, repeated examination and concentration methods (formol-ether concentration method or Zinc sulphate floatation) may be required to establish the diagnosis. In some cases, when feces do not show the parasites, duodenal aspiration has to be done for recovering them. Presence of cysts indicates the carrier

state. These can be identified by examining iodine-stained preparations of feces.

Treatment

The drug of choice is metronidazole in a dose of 15 mg/kg/day given for seven days. In 80-90% of cases the infection is eliminated. In resistant cases this course can be repeated. Single administration of metronidazole in a dose of 30 mg/kg repeated after a week is also effective and it may be more suited for mass treatment on account of better patient compliance. Chloroquine 250 mg thrice a day for 5 days and tinidazole are also effective.

Giardiasis can be prevented by improving food hygiene and environmental sanitation. Heavy chlorination of water supply is required for killing giardia cysts.

Balantidiasis

K.V. Krishna Das

Balantidiasis is infection by *Balantidium coli* which affects the large intestine of man. *Balantidium coli* is a large ciliate (200 $\mu \times 80 \mu$), seen actively motile with the help of numerous cilia, in fresh specimens of stools. The cysts are rounded and smaller (Fig. 65.4). These are seen in carriers. Infection occurs when cysts are ingested. It is primarily a pathogen of pigs. Malnourished persons with low gastric acidity are more commonly infected. Compared to giardiasis and amebiasis, incidence of balantidiasis is very rare in India, but it is encountered from time to time.

Pathology

Balantidium coli primarily invades the colonic mucosa and produces flask-shaped ulcers which resemble amebic ulcers. Proteolytic enzymes and hyaluronidase are secreted by the organism. The mucosa shows infiltration by lymphocytes and polymorphs around the ulcers. Secondary infection and hemorrhage may occur as complications. In fulminant cases necrosis of the colon

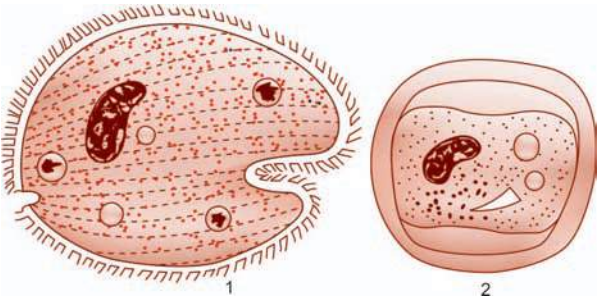


Fig. 65.4: *Balantidium coli* in stools (diagram)

1. Trophozoite—motile ciliate
2. Cyst

and perforation may result rarely. In addition to the colonic lesions, uterine, vaginal, and vesical lesions may also develop at times.

Clinical Features

These resemble cases of mild to moderately severe amebic dysentery. Mild infections may be asymptomatic.

Diagnosis

It is established by demonstrating the active parasite in feces or sigmoidoscopic aspirate material. Presence of cysts indicates the carrier state.

Treatment

Tetracycline given in divided doses of 10 mg/kg daily for 10 days eliminates the infection. Many cases show a tendency towards spontaneous remission and development of carrier state. Metronidazole is also effective but the results are not consistent.

Toxoplasma gondii

K.V. Krishna Das, V.P. Gopinathan

Infection by *Toxoplasma gondii* causes toxoplasmosis. This parasite undergoes its full life cycle only in cats and other canine hosts but it affects many mammals, birds, and reptiles chickens lambs and pigs may be affected. The parasite was first discovered in 1908 in a North African rodent—the gondii. *Toxoplasma gondii* is a crescent shaped organism $4.6 \times 2 \mu$ size demonstrable by Giemsa or Wright stain. It is seen intracellularly in endothelial cells, monocytes or tissue cells. It may be seen free in tissues and tissue fluids.

T. gondii is a sporozoan parasite which is intracellular. In its life cycle there is a sexual cycle in the intestinal epithelium of cats and other feline hosts. Immature oocysts develop into mature infective sporozoites in the environment within 2-3 days. When humans and other intermediate hosts ingest them trophozoites (also known as tachyzoites) are released. They invade the cells of the gastrointestinal mucosa and then disseminate through the circulation to most of the organs. In the nucleated cells the parasite proliferates. This leads to death of the host cell. If the host develops immunity the trophozoites encyst. Each cyst contains about 3000 organisms. Encystment protects the organisms. They persist through the life-span of the host. The dormant organism within the cysts are called bradyzoites. They are morphologically identical to tachyzoites, but they multiply slowly and are functionally different.



Fig. 65.5: Old choroido retinitis

Human infection is acquired by ingesting the oocysts passed in cat's feces or contaminated meat of animals and birds. *Toxoplasma gondii* may be found in the milk of infected animals. Transplacental transmission to the fetus from the mother occurs if she gets infection during early pregnancy. At times the maternal infection may be silent. Other rarer modes of transmission include inoculation of infected material into skin, blood transfusion, organ transplantation and entry through the respiratory tract. The disease is worldwide in distribution and limited serological surveys reveal that it is prevalent in India.

Pathology

The congenital form occurs in 3-5% of babies of infected mothers. If the fetus is affected heavily transplacentally during early pregnancy, abortion or stillbirth may result. If the fetus is affected in late pregnancy, the baby is normal at birth but symptoms develop after a few months. Lesions are seen widespread in the CNS, eyes, heart, lungs and adrenals. The parasite disappears from all tissues except the CNS and retina. Brain and spinal cord show extensive areas of necrosis, cyst formation and patchy calcification. Retina shows choroidoretinitis (Fig. 65.5).

In the acquired form, the parasite gets disseminated through the blood and lymphatics from the intestinal epithelium. Lymph nodes and spleen are commonly affected. Other tissues such as the liver, lungs, skeletal muscles, myocardium, meninges, and brain may also be involved.

Clinical Features

Congenital toxoplasmosis presents predominantly with neurological involvement. The child develops chronic encephalomeningomyelitis which results in hydrocephalus, microcephaly, convulsions, tremors, focal paralysis and contractures. Eye lesions include micro-

TABLE 65.1

Lesions in the different forms of toxoplasmosis

Congenital	Acquired
	Often asymptomatic detected by serological survey
a. Hydro- or micro- cephaly	a. Maculopapular rash
b. Convulsions	b. Fever
c. Ocular palsies	c. Hepatomegaly
d. Bilateral Choroido- retinitis	d. Lymphadenopathy-tender non-suppurative, anterior, and posterior cervical groups
e. Hepatosplenomegaly	e. Encephalitis
f. Jaundice	f. Myocarditis
g. Maculopapular rash	g. Choroidoretinitis rare, unilateral
h. Cerebral calcification	h. Pneumonia

6

phthalia, nystagmus, blindness and bilateral choroidoretinitis. In cases with meningoencephalitis, cerebrospinal fluid is xanthochromic with rise in protein and mononuclear cells but with normal sugar. *Toxoplasma gondii* may be demonstrable. Other manifestations such as hepatosplenomegaly with jaundice, thrombocytopenic purpura, lymphadenopathy and rashes have been described.

Unlike congenital toxoplasmosis, acquired toxoplasmosis may be symptomless in the vast majority, detectable only by serological tests (Table 65.1).

Symptomatic cases may occur in two forms—acute and chronic. The acute form presents frequently with fever, aches and pains, cough, pneumonitis, profound malaise and maculopapular rash. Rarely jaundice, myocarditis and meningoencephalitis may develop. In the chronic form there is generalized painful lymphadenopathy which is more marked in the cervical region, lymphocytosis with atypical lymphocytes in peripheral blood, hepatomegaly and rarely unilateral choroidoretinitis. In persons with latent infection or those who have undergone remission, depression of immune status of the individual results in recrudescence.

Toxoplasmosis in AIDS

Toxoplasmosis is one of the frequent opportunistic infection in HIV positive individuals. It mainly affects central nervous system. Toxoplasmosis occurs when CD₄ count falls below 100 cells/mL. It presents with fever, headache, focal neurological deficits like hemiparesis, aphasia and seizures. It also presents with pneumonia, pericarditis, and choroidoretinitis. For further details see chapter 48, pp 271.

Diagnosis

Strong clinical suspicion is necessary for recognizing the condition. Since the manifestations are protean,

toxoplasmosis should be considered in the differential diagnosis of a wide range of clinical situations. Demonstration of *T. gondii* in the CSF, lymph gland aspirate or in biopsy specimens, confirms the diagnosis. The organism can be recovered by inoculating the infective material into laboratory animals like mice, hamsters and guinea pigs. Isolation of the organism points to acute lesion.

When acute *T. gondii* infection is suspected in a pregnant woman, the diagnosis should be pursued. Toxoplasmosis usually is diagnosed on the basis of antibody detection. In acute infection, IgM and later IgG antibody levels generally rise within one to two week. IgM antibodies indicate the occurrence of recent infection. IgG antibodies develop later and persist for considerable periods.

Toxoplasmosis in Pregnancy

When a pregnant woman is found to be infected with *T. gondii*, the next step is to determine whether the fetus is infected. It is done by demonstrating polymerase chain reaction (PCR) testing of amniotic fluid to diagnose congenital toxoplasmosis. PCR testing of amniotic fluid is safer and more sensitive than fetal blood sampling, and it allows earlier confirmation of fetal infection. However, false-positive and false-negative tests may occur with PCR tests.

Other investigations like complement fixation test, neutralizing antibody test, indirect hemagglutination test and ELISA test are also available. The IgM-immunofluorescent antibody (IgM-IFA) test is particularly useful to detect recent infection. Immunocompromised subjects may not show rise in antibody titer. Ocular toxoplasmosis can be diagnosed by funduscopy on seeing typical lesion, associated with the positive serological tests.

The cerebral lesions can be visualized by contrast enhanced CT scan and MRI which show single or multiple ring-enhancing lesions near the basal ganglia, brainstem and subcortical region with space occupying effect, and surrounding edema.

In the investigation of pregnant women and neonates for infection, toxoplasmosis is always looked for.

Course and Prognosis

The lymphatic form tends to be mild and chronic which runs over several months, but is ultimately self-limiting. Congenital toxoplasmosis and acquired neurological lesions are associated with high mortality and morbidity. Congenital toxoplasmosis is a major cause of developmental anomalies.

Treatment

The organism is susceptible to a combination of pyrimethamine (daraprim) 25 mg/day and sulphadiazine

1 g every 6 hours for 14 days. Pyrimethamine is a folate-antagonist, and therefore, megaloblastic anemia may develop during prolonged therapy. In children the dose of pyrimethamine is 2 mg/kg. In acute cases large doses of pyrimethamine—i.e., a loading dose of 200 mg, followed by a maintenance dose of 25-75 mg/day, and sulphadiazine 100 mg/kg daily in three divided doses may be needed. At this dose, folinic acid 10 mg should be given daily to prevent the development of megaloblastic anemia. The course of treatment has to extend for 4-6 weeks.

Clindamycin is also effective and this can be combined with the standard drugs in resistant cases. The dose is 1200 mg/day in divided doses. Other drugs effective against *T. gondii* include azithromycin (250 mg bd) given with pyrimethamine (25 mg) or atovaquone monotherapy. In *Ocular toxoplasmosis* oral corticosteroid therapy given in addition to pyrimethamine—sulphadiazine is beneficial.

Treatment of Toxoplasmosis in Pregnancy

Women who are seropositive should be advised to take spiramycin 1 g qid for 4-6 weeks before undertaking pregnancy. This drug is safe for use during pregnancy. If the clinical features and laboratory investigations confirm that a pregnant woman has an active infection, the next step is to determine whether the fetus is infected. Prenatal tests including amniocentesis and ultrasound may help to determine whether the fetus is infected. If the fetus is infected. The mother is given pyrimethamine and sulfadiazine after the first trimester along with folinic acid in doses of 20 mg/day. Pyrimethamine is teratogenic and hence contra indicated in the first trimester of pregnancy. Other effective drug schedules include azithromycin + pyrimethamine or atovaquone monotherapy.

Cryptosporidiosis

K.V. Krishna Das

This is caused by infection by *Cryptosporidium parvum*. Cryptosporidia are coccoid protozoa. Distribution is world-wide. Domestic animals such as cattle, sheep, pigs and horses act as reservoir hosts. Infection occurs by

ingesting the oocysts. This infection has been reported in Kerala. In a study of stools in 148 diarrheal patients *C. parvum* was seen in 1.5% of cases. Maximum prevalence was in children below 2 years of age and in immunocompromised patients.

On reaching the small intestine, infective sporozoites are released from the oocysts. They undergo asexual development in the apical enterocytes of the small intestine. After two cycles of development sexual stages develop, with the formation of zygotes and more oocysts. The oocysts sporulate, mature fully in the gut and are passed in feces, ready to infect other hosts. Incubation period after ingestion ranges from 3-11 days.

Clinical Features

Onset is with acute watery diarrhea associated with fever and general malaise. In healthy individuals the disease runs a benign course and is self-limiting.

Cryptosporidiosis is a common opportunistic infection in AIDS. In such patients the disease runs a more aggressive down-hill course, leading to severe weight loss and general debility. Toxic dilation of the colon may occur in a few.

Diagnosis

Demonstration of oocysts using concentration techniques and modified Ziehl-Neelsen staining help to establish the diagnosis.

Treatment

No specific drug was available. Clindamycin, erythromycin, and spiramycin may reduce the severity of diarrhea.

In AIDS patients zidovudine clears the infection temporarily. Nitazoxanide in a dose of 7.5 mg/kg bw controls the disease when given for 5-7 days. This is a thiazolide drug, the active metabolite being tizoxanide. Adverse side effects are minimal.

Ref. Prevalence of parasite infection or with special reference to cryptosporidium. Anitha PM, Sudarsana J The J1 of the Academy of Clinical Microbiologists 2002. 4-2. 51-61.

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Helminthiasis: General Considerations

R.K. Shenoy, K.V. Krishna Das

Chapter Summary

General Biology 390

Pathogeneis 390

6

General Biology

Helminths constitute the most widespread parasites affecting humans all over the world. In India the problems of helminths is a serious one leading to considerable morbidity, mortality and economic retardation. *Ascariasis*, *ancylostomiasis*, *schistosomiasis* and *filariasis* are the most widespread helminthic parasites affecting extensive geographical belts and millions of people. The three main soil transmitted helminths *Ascaris lumbricoides*, *Trichuris trichura* and the hookworms-*Nectar Americanus* and *Ancylostoma duodenale* are common in most parts of India, where the soil is contaminated by human feces.

In many poor communities helminthiasis may be evident even at the age of 1 year, it reaches its maximum by the age of 10-12 years and then its severity declines. Helminths affecting man can be divided into *three groups* - *roundworms (nematodes)*, *tapeworms (cestodes)* and *flukes (trematodes)*. The helminths have well developed reproductive, excretory and nervous systems and many also possess alimentary tracts. They have complex life cycles and for the majority of parasitic helminths, the reproductive and transmission cycles require the presence of two or more hosts. Both the adults and the larvae are capable of producing disease depending on the parasite. Several mechanisms operate to produce lesions in different helminthic infections, examples of which are mentioned under pathogenesis. Allergy plays a part in producing symptoms during the stages of larval development. In many infections mild to moderate eosinophilia may develop. This reflects the immunological reaction of the host. Eosinophils have a protective role. They are seen to accumulate around helminthic larvae and destroy them, e.g. filaria.

Pathogenesis

Pathogenetic mechanisms in helminthiasis

1. Competition for nutrients in small intestine, e.g. *Ascaris lumbricoides* adults, *Diphyllobothrium latum*. They derive their nutrition by absorbing nutrients that pass through the intestines. Hook worms and whip worms get their nutrition and oxygen from the blood that traverse their intestinal tracts.
2. Ingestion of host's blood and causing blood loss from the intestine, e.g. Hook worms, *Trichuris trichura*.
3. Adults undergoing development in host's tissues and giving rise to tissue lesions, e.g. *Strongyloides stercoralis* and *Trichinella spiralis* in submucosa of small intestine, schistosomes in blood vessels, *Fasciola hepatica* in biliary passages, *Paragonimus westermani* in lungs.
4. Dilation of lymph vessels caused by adult parasites, which later becomes prone to secondary bacterial infection resulting in clinical disease, e.g. *Wuchereria bancrofti* and *Brugia malayi* filariasis.
5. Larval forms producing tissue lesions, e.g., migrating phase of round worms, hook worms and strongyloides producing pulmonary and other tissue lesions; larval forms of *Echinococcus granulosus* (hydatid cysts), *Taenia solium* (cysticercosis), *Trichinella spiralis* in muscles and *Onchocerca volvulus* in skin and eyes.
6. Tissue irritation by eggs, e.g. schistosomes.
7. Irritation by the presence of adults, e.g. *Enterobius vermicularis* over the perianal region, *Ascaris lumbricoides* in the intestinal tract, biliary passages and respiratory tract.
8. Allergic manifestations - both local and systemic, e.g. Loeffler's syndrome caused by larval forms of nematodes, larva migrans caused by *A. braziliense* and *Strongyloides*, tropical pulmonary eosinophilia caused by filariasis.
9. Give rise to severe functional damage to intestines to produce malabsorption state, especially in

immunocompromised hosts, e.g. strongyloidiasis, trichuriasis and ascariasis. Ascariasis may lead to lactose intolerance and malabsorption of Vit A.

- 10. Toxic effects due to absorption of the metabolites or products of dead worms e.g. round worms, microfilaria.
- 11. Risk of malignancy: Constant irritation by the adults or the ova in the tissues or natural passages has been associated with higher incidence of cancers in these sites, e.g. *Opisthorchis viverini* in Thailand, Laos and Malaysia and *Clonorchis sinensis* in Japan increase the risk of cholangiocarcinoma 25-50 times. *Schistosoma hematobium* is associated with the increased incidence of cancer of urinary bladder.

With the introduction of sanitary latrines and potable water supply, the prevalence of intestinal helminths has come down considerably in several communities, especially in Kerala but in many parts of India the soil transmitted helminths infection is very rampant. The problem with regard to tissue helminthiasis, especially lymphatic filariasis remains the same and larger and larger areas of India are now identified to be endemic for the disease.

Host parasite interaction: Several factors contribute to the survival and persistence of these worms in the human host. The worms produce anti-proteolytic substances which help them to escape the digestive enzymes. They modify the immune mechanisms of the host so as to avoid acute and formidable reactions in the host, thereby, enabling them to complete their life span in the human host including residence, feeding, and reproduction. Except *Enterobius vermicularis* and *Strongylus stercoralis* the others do not multiply in the same host. Increase in number is mainly due to continuous infection.

Helminths secrete substances which make them refractory to host immunity. Whip worms produce anti-inflammatory cytokines. They induce production of cytokines (interleukins 4,5,10 and 11), parasite specific immunoglobulin and nonspecific immunoglobulin E, and also expansion and mobilization of mast cells, eosinophils and basophils (TH₂ immune response).

Diagnosis

Helminthiasis is diagnosed in the vast majority of instances by the demonstration of the adults, larvae or eggs in appropriate specimens. Indirect methods include immunological tests like immunoelectrophoresis and enzyme-linked immunosorbent assay.

Treatment

Many subjects harbouring worms acquire heavy worm loads due to the long-life span of the parasites and

repeated infection. Effective anthelmintics can produce temporary reduction or elimination of the worm-load, but reinfection occurs if the subject continues to live in the same environment. Even regular periodic deworming fails to eradicate intestinal helminths from communities, unless simultaneous steps are taken to improve environmental sanitation.

Prevention

Strict personal hygiene, proper disposal of excreta and provision of potable water supplies are most important to ensure freedom from intestinal helminthic infestations. Whereas vector control assumes importance in infections caused by tissue nematodes. More recently mass drug administration to ‘at risk’ population in endemic countries is adopted as a measure to prevent transmission of filarial infection.

Important points

- 1. Helminths infecting man belong to the class nematodes, cestodes and trematodes.
- 2. Pathogenesis ranges from simple competition for nutrients to risk of malignancy.
- 3. Availability of broad-spectrum anthelmintics like albendazole and praziquantel has improved the ease and efficacy of treatment.
- 4. Good personal hygiene, vector control and mass drug administration are important to prevent different types of helminthic infections.

Choice of Drugs for Helminthiasis		
Worm	First choice of drugs	Alternatives
Round worm	1. Albendazole 2. Mebendazole 3. Pyrantel pamoate	1. Levamisole
Hook worm	1. Albendazole 2. Mebendazole 3. Pyrantel pamoate	1. Levamisole
Thread worm	1. Albendazole 2. Mebendazole 3. Pyrantel pamoate	—
Strongyloides stercoralis	1. Ivermectin 2. Thiabendazole	1. Albendazole 2. Mebendazole
Whipworm	1. Albendazole 2. Mebendazole	—
Trichinella spiralis	1. Thiabendazole 2. Albendazole	1. Mebendazole
Filariasis	1. Diethyl carbamazine	1. Ivermectin 2. Albendazole 3. Doxycycline
Tapeworm	1. Praziquantel 2. Albendazole	1. Niclosamide 2. Mebendazole
Hydatid disease	1. Albendazole 2. Mebendazole	—
Guinea worm	1. Metronidazole	—
Flukes	1. Praziquantel	1. Albendazole

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Ascariasis

Ascariasis is worldwide in distribution and is caused by the nematode *Ascaris lumbricoides*. In India it is one of the most widely distributed intestinal parasite.

Morphology and Habitat

The worm measures 20-35 cm in length. The female is larger than the male. The females lay several thousand eggs every day. The eggs are elliptical, 30-40 μ x 50-60 μ in size with an outer dense mammillated shell and a smooth translucent inner shell. They are passed in feces. They become embryonated and infective in the soil in 2-3 weeks and they can remain viable under optimum conditions for years.

Life Cycle

Embryonated eggs are ingested with food or water and the larvae hatch out in the small intestine (Fig. 67.1). They penetrate the intestinal mucosa to enter the venules or lymphatics and travel to the lungs, where they develop for about 10 days. They then enter the alveoli to be coughed up and swallowed. During the pulmonary phase the larvae undergo four moultings and become resistant to gastric acid. The larvae grow and mature in 2-3 months. Life span of this worm is 6-15 months.

Pathogenesis

During the stage of larval migration, pulmonary symptoms like cough, wheezing and hemoptysis may occur

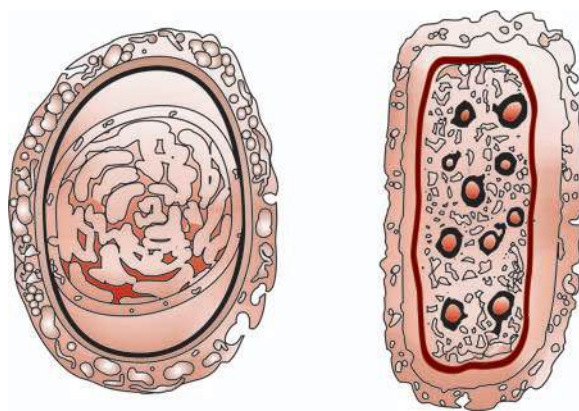


Fig. 67.1: Ova of *Ascaris lumbricoides* (diagram)
(a) Embryonated, and (b) Non-embryonated

(*Loeffler's syndrome*) and used to be a common cause of respiratory symptoms in children.

The adult worms ingest nutrients from the small intestine and lead to nutritional deprivation. Large number of adults may form tangled masses and obstruct the small intestines. The worm may migrate to ectopic sites like the stomach, nasal cavity, biliary tree, pancreatic ducts, respiratory passages, female genital tract or others.

Absorption of the products of living and dead worms lead to the development of allergy and toxic symptoms.

Clinical Features

Those due to larvae: Respiratory symptoms such as cough, hemoptysis or wheezing may develop 1-5 days after swallowing the eggs. Eosinophilia may be present. Clinical severity depends upon the worm load and reactivity of the host.

The liver may be enlarged and histology may show centrilobular necrosis. Rarely larvae may reach the brain, giving rise to convulsions. Other organs may also be affected.

Those due to adult worms: Light infestations are asymptomatic. Moderate worm loads produce abdominal pain, pica, diarrhea, abdominal distention and grinding of the teeth (bruxism). Infected children have voracious

appetite but they remain malnourished despite adequate intake of food. Migration of worms to biliary ducts or pancreatic ducts lead to obstruction. In heavy infection the masses of worms may lead to intestinal obstruction and they may be palpable.

Diagnosis

It is made from the history of passing round worms in the stool or the children may vomit round worms. Diagnosis is confirmed by demonstrating the characteristic ova in feces. In the rare event of infection by male worms alone, ova may not be present in feces. During the stage of larval migration, the diagnosis has to be presumptive.

Treatment

The adult worms respond to a variety of anthelmintics.

Effective, safe and polyvalent anthelmintics are preferred at present. In more than 30% of patients multiple helminths occur, common combination being roundworm, whipworm and hookworm and broad spectrum anthelmintics are more advantageous in them. Benzimidazole drugs which include albendazole and mebendazole bind to nematode β tubulin and inhibit parasite microtubule polymerisation which causes death of adult worms which may take a few days to complete.

Albendazole in single dose of 400 mg for adults and 200 mg for children is the drug of choice due to its safety, ease of administration and easy availability. **Mebendazole** in a dose of 100 mg twice a day for three days is another equally effective alternative. The worms are killed, and are eliminated in a partly digested manner. There is no danger of irritation of worms, exacerbation of symptoms or other untoward effects. The eradication rate of round worms after single dose reaches 80-90% and above 95% after two doses given at weekly interval. Albendazole is ideal for mass therapy in community practice on the merit of its effectiveness, ease of administration and safety. Adverse side effects include gastrointestinal upsets, nausea, vomiting, abdominal pain, dizziness and rarely granulocytopenia. Albendazole is contraindicated during pregnancy.

Pyrantel pamoate, in a dose of 11 mg/kg given as a single dose at bedtime is a limited broad-spectrum anthelmintic active against roundworm, hookworm and pinworm. The drug eliminates the worms in up to 50% of subjects. It is safe in children.

Ivermectin 200 μ g/kg in single oral doses is also effective against round worms.

Children with intestinal obstruction are managed conservatively with intravenous fluids, gastric suction and antibiotics for 24 hrs. If the mass of worms remains in the same position in the presence of severe abdominal colic and tenderness or if the general condition

deteriorates as indicated by rising pulse rate and toxemia etc. surgery is indicated. The worms are manipulated to break the mass without opening the intestine. Delayed surgery carries a high mortality.

Prevention

Improvement in nutritional status of children, health education, especially pertaining to personal hygiene and environmental sanitation reduce the infection rates. Mass deworming campaigns are helpful in endemic areas to reduce worm loads temporarily but reinfection within months is the rule.

Important points

1. No direct human-to-human transmission since *Ascaris* ova have to develop in the soil before they become infective.
2. There is a pulmonary phase in the developmental cycle.
3. No multiplication of roundworm in humans and the worm load depends on the number of eggs ingested.
4. Clinical symptoms could either be due to the larvae or the adult worm.
5. After administration of albendazole usually intact worms are not seen in the stools, as the dead worms are partly digested.

Hookworm Infection

Syn. *Ancylostomiasis*

Hookworm infection is prevalent in hot damp areas throughout the tropics and subtropics. Two species of hookworms - *Ancylostoma duodenale* and *Necator americanus* are seen to parasitize the small intestine of man. *Ancylostoma* is more harmful than *Necator* because it is more persistent in the environment and causes heavier blood loss. *Ancylostoma* is seen in the tropical and temperate zones whereas *Necator* is more widespread in the tropics.

In the rural communities in India, the prevalence for hookworm in adults ranges from 10 to 35%. In children with increasing age the prevalence rates also increase being 0.5% at 1 year of age to 10% in the 12th year. In 60-70% of affected persons *Ascaris lumbricoides* and *Trichuris trichura* may also be present. In almost all parts of India, Far East, Africa and South America both types of hookworms are seen. In South India, *N. americanus* predominates. Some persons show a special predilection to acquire and sustain different intestinal nematodes.

Morphology and Habitat

Man is the natural host. The adults remain in the small intestine. Eggs are passed in feces.

Adult worm of *Ancylostoma duodenale* is 8-13 mm long and is thread-like in thickness. The buccal cavity has

four pointed hook-like teeth. *Necator americanus* is smaller than *A. duodenale*. The buccal cavity contains two chitinous cutting plates (Figs 67.3 and 67.4).

The worms attach to the intestinal villi of the jejunum and duodenum by their mouthparts. They produce bleeding points from which the blood passes through the alimentary canal of the worm continuously. This blood is required for the nutritive and respiratory functions of the worm. Hook worms produce pathogenesis- related proteins which prevent clotting by combining with platelets and inactivating them. In addition, factors that inhibit factor Xa, V11a, and tissue factor are also secreted. Thus the worms ensure a continuous flow of blood through their intestinal tract. The loss of blood caused by a single ancylostome is estimated to be 0.1-0.2 mL per day. *Necator* causes a blood loss of 0.01-0.03 mL. Worm loads above 40 can give rise to significant iron deficiency anemia over a period of time if there is added malnutrition as well.

The fertilized female can lay up to 20,000 eggs a day. The eggs measure 40-60 μ and are embryonated when passed. *Necator americanus* lays fewer eggs than *A. duodenale*, but the eggs are larger (60-70 μ) (Fig. 67.2).

Rarely two other species of hookworms- *A. cyclonicum* and *A. braziliense* may infect man. *Ancylostoma cyclonicum* is a hookworm of cat found in the Far East, which occasionally reaches maturity in humans. *Ancylostoma braziliense* is a hookworm of dogs and cats, which may also infect man but does not reach maturity.

Life Cycle

Eggs are passed in feces and within 5 days they hatch in warm moist soil. The rhabditiform larvae come out and they moult twice on the third and fifth days and develop into filariform larvae, which develop a sheath. These are infective to man. The larvae can persist in the soil for two months, feeding on bacteria and other organic matter. On coming into contact with the skin of man, the sheath is shed and the larvae penetrate into the subcutaneous tissues and enter the lymphatics and venules.

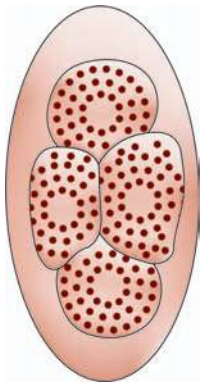


Fig. 67.2: Hookworm eggs. Note the segmented embryo (diagram)

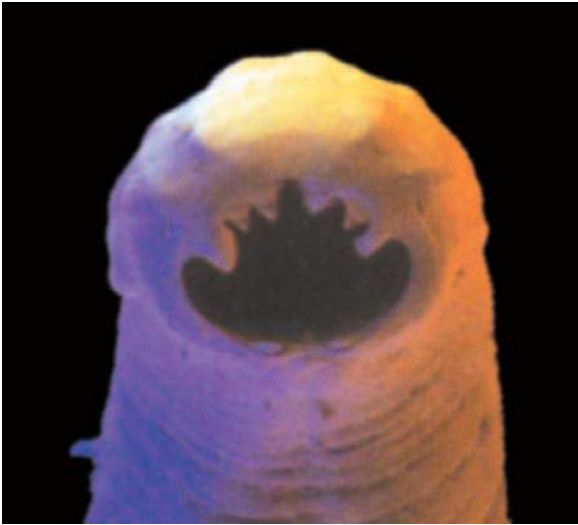


Fig. 67.3: Adult worm mouth parts A duodenae

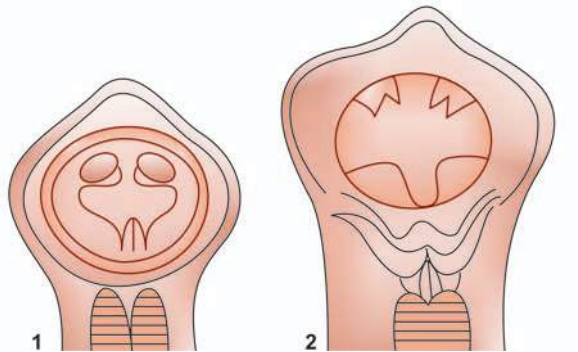


Fig. 67.4: Hookworms—Buccal capsules. (1) Necator americanus, (2) Ancylostoma duodenale—diagram

Within three days of entry into the skin, the larvae pass through the right side of the heart and the pulmonary capillaries to enter alveolar spaces. Foci of inflammation develop in the lungs. Then they enter the bronchi and pass up the trachea, larynx and back of the pharynx to be swallowed. In the oesophagus a third moulting occurs and a terminal buccal capsule is formed. In the small intestine they attach to the villi and grow into adults in 3-5 weeks. Average life-span of the worm is 2 years, but sometimes it may exceed 10 years.

Clinical Manifestations

Skin: The site of entry of the larvae becomes itchy and sodden. It ulcerates and becomes secondarily infected (ground itch). Common site for this lesion is the web of the toes.

Lungs: Larval migration through the lungs may lead to allergic symptoms, malaise, eosinophilia, dyspnea, cough and hemoptysis - *Loeffler's syndrome*.

Intestinal tract: Mild infections are usually asymptomatic. When the worm load is heavy, considerable blood loss occurs from the intestine. This leads to iron deficiency anemia, which is aggravated by coexistent malnutrition. Vague abdominal symptoms like pain resembling peptic ulcer or chronic intestinal amoebiasis may develop.

Heavy infection, apart from severe anemia, leads to stunted growth, apathy, reduction of learning abilities in children, frequent absence from work and school, diminished productivity, impairment of immune responses, frequent respiratory infections and increased susceptibility to tuberculosis.

Diagnosis

The diagnosis is established by demonstrating the ova in feces. Ova of *A. duodenale* and *N. americanus* are indistinguishable. The feces gives positive reaction for occult blood. The worm load can be quantitated by egg counting using Kato-Katz cellophane thick smear technique or by Stoll's method when there is heavy infection. Each worm produces 30 eggs per gram of feces per day. Identification of species is carried out by examining the adult worms passed after a vermifuge.

Treatment

Specific treatment can be administered directly if the hemoglobin is above 7 g/dL. In severely anemic patients proper diet and iron supplements are given to raise the hemoglobin to 5 g/dL or more before administering the anthelmintic. Though this is a golden rule to be followed in outpatient practice, specific anthelmintic treatment can be started much earlier using *albendazole* or *mebendazole*, which are considerably less toxic. Elimination of the worms leads to quicker recovery of the nutritional status as well.

Albendazole 400 mg single dose causes partial elimination of the worms along with other nematodes. Repeated doses may be required for complete elimination. The drug is best absorbed when given along with a fatty meal. It is available as 400 mg tablets and 200 mg suspension. Children above 2 years can be given the full doses. Younger children should be given 200 mg. Since the drug reaches several tissues it may act on tissue forms of helminths as well. *Albendazole* has become more acceptable for mass therapy on account of its effectiveness, safety and convenience of dosage. The side effects are mild including gastro intestinal upset, allergy, headache, alopecia and rarely convulsions. *Albendazole* is contraindicated in pregnancy due to risk of teratogenicity.

Mebendazole is given in the dose of 100 mg twice daily for three consecutive days after food (for adults). It is poorly absorbed from the intestine and therefore its

effects is mainly on the adult worms. This drug produces clearance of 80 % of worms in a single course and almost complete clearance if two courses are administered at an interval of 2 weeks. Due to risk of teratogenicity the drug is contraindicated during pregnancy and infancy.

Pyrantel pamoate, which is also a broad spectrum anthelmintic, given in a single dose of 11 mg/kg body weight is very effective in clearing the infection.

Prophylaxis

Personal measures include the use of proper footwear and sanitary disposal of excreta.

Important points

1. Ancylostomiasis is a geo helminth infection where skin lesions may be present at the site of larval entry.
2. There is a pulmonary phase during larval migration.
3. Clinical manifestations are mainly due to blood loss.
4. Occult blood may be present in stools in heavy infection.
5. Protective footwear, completely covering the feet is important in preventing transmission.

Trichuriasis

Syn: Whipworm infection

Trichuris trichiura is worldwide in distribution. It is especially prevalent in the tropics. The prevalence rate in India varies from 6 to 25 %, in different communities. There is considerable geographical variation. Co-infection with roundworm and hookworm is very common.

Morphology and Habitat

The adult worm measures 30 to 50 mm in length, the females being larger than males. The anterior three fifths is slender and filiform and the posterior two fifths is bulky and fleshy. The worms are seen in the caecum and large intestine with their anterior ends introduced into the mucosa to suck blood (Fig. 67.6).

The eggs are barrel-shaped, translucent, 20-50 μ in size, thick-walled, and possess knob-like ends (Fig. 67.5).

Life Cycle

The eggs become embryonated and infective in three weeks after being passed. They are ingested. Hatching occurs in the small intestine. The larvae get attached to the intestinal villi and after variable periods migrate to the large intestine where they mature in about 3 months. Though not exactly known, the lifespan of the worm is probably several years. The adults suck blood and lead to blood loss though in a smaller degree than hook worms. With the elimination of hookworms from many



Fig. 67.5: *Trichuris trichuria*—ovum (diagram)

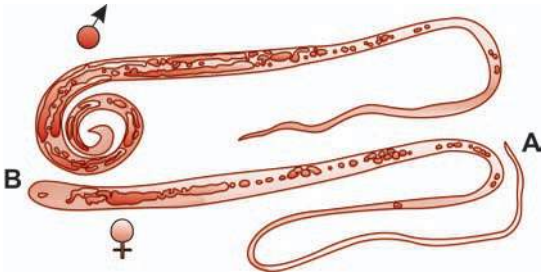


Fig. 67.6: *Trichuris trichuria*—adult. Note the slender anterior end (A) and the thick posterior end (B)

communities, whipworms have emerged as a major cause of intestinal blood loss.

Clinical Manifestations

Mild infections pass unnoticed and the diagnosis is made by routine examination of feces. Heavy infection, which is common in children and certain susceptible subjects, is accompanied by nausea, vomiting, diarrhea and dysenteric symptoms. Diarrhea with mucus and even blood-streaking may occur. Rectal prolapse may develop. Malabsorption leads to wasting and stunting of growth in children. Iron deficiency anemia may develop.

Diagnosis

Demonstration of the eggs in feces establishes the diagnosis. Adult worms may be seen hanging from the walls of the colon on sigmoidoscopy.

Treatment

Albendazole, the drug of choice, given in a single dose of 400 mg gives a clearance rate of 30 to 90%. Administration for 2 to 3 days continuously increases the clearance rate and this may be required in heavy infection.

Mebendazole 100 mg tablets twice daily for three consecutive days produces a cure rate of 50 to 80%. Repeated courses improve the clearance rate. This drug should be used with caution in children and pregnant women.

Ivermectin, a newly introduced anthelmintic, is also effective against trichuriasis.

Important points

- 1. Trichuriasis is a geo helminth infection.
- 2. There is no phase of larval migration.
- 3. Like hook worm infection, trichuriasis can cause blood loss and anemia.
- 4. Severe infections may be associated with symptoms of dysentery.

Strongyloidiasis

Strongyloidiasis is infection of the small intestine by *Strongyloides stercoralis*. Adult females are small measuring 2 mm in length. They live in the mucosa of the duodenum and lay eggs.

Life Cycle

The eggs are laid inside the mucous membrane. Soon the eggs hatch and the rhabditiform larvae enter the intestinal lumen by breaking the mucosa. These larvae are seen in fresh stools and their spring-like movement is diagnostic. *Strongyloides stercoralis* is known to take one of three life cycles (Figs 67.7 and 67.8).

- 1. **In the soil:** They develop into the infective filariform stage within three to four days. The larvae penetrate human skin to enter the blood vessels. An alternate mode of infection is accidental ingestion of infective larvae. They pass through the lungs and after a period of development, they are coughed up and swallowed. In the small intestine they mature and copulate. The fertilized female burrows into the mucosa of the jejunum while the males are passed in feces. Life span of the worm is not clearly known.
- 2. **Free living cycle:** *Strongyloides stercoralis* can develop as free-living worms in the soil. The



Fig. 67.7: Larva of *Strongyloides stercoralis* (diagram) (1) Gravid female, (2) Egg containing larva

rhabditiform larvae in soil may develop into free-living adults, which reproduce in the soil independent of the human host. Under favorable conditions, the free-living larvae can change into filariform larvae, which can enter the human skin and initiate a new cycle.

3. **Autoinfection:** By this life cycle the worm perpetuates itself without leaving the host. The rhabditiform larvae change into filariform larvae in the large intestine or in the perianal skin. The latter penetrate the mucosa or skin to enter venules and reach the pulmonary circulation and develop further. In this way the infection can persist in an individual for long periods even after leaving the endemic area.

Clinical Features

Clinical symptoms depend on the severity of infection and reactivity of the host. Mild infections may be asymptomatic. In immunocompromised subjects hyperinfection occurs which may be fatal.

Larval Migration

Local allergy and infection may appear at the site of penetration by the larvae. The progress of the larvae through the skin and subcutaneous tissue (**cutaneous larva migrans**) may produce linear streaks of urticaria, which progress at the rate of a few centimeters every hour. Crops of these urticarial lesions recur for considerable periods. Larva migrans caused by *Ancylostoma braziliense* and *A. caninum*, move at the rate of 1-2 mm/hour. The pulmonary phase of the larvae may be associated with cough, fever, breathlessness and asthmatic symptoms. Hemoptysis may occur rarely.

Symptoms Attributed to the Adult Worm

Heavy infection may cause epigastric pain, nausea, vomiting, and diarrhea. When the worm load is very high symptoms of enterocolitis develop. Meningeal irritation is seen in a few cases.

In immunocompromised individuals strongyloidosis may take a severe and fatal form of hyperinfection; may present as malabsorption syndrome or chronic diarrhea resembling Crohn's disease. Elimination of larvae in feces may be episodic and therefore the diagnosis may be missed by single examination of feces. Diagnosis can be confirmed by biopsy of small intestine. Extensive dissemination of the larvae can present with respiratory, cardiovascular, hepatic and central nervous manifestation rarely.

Diagnosis

It is established by demonstrating the larvae or adult worms. Larvae can be demonstrated in fresh fecal

samples. The larvae may be detected in the sputum during the pulmonary phase of migration. Accidentally the duodenal aspirate may reveal the larvae and intestinal biopsy may bring out the adult worm. During the phase of larval migration moderate to high eosinophilia may be seen. ELISA detecting antibodies to the excretory-secretory antigens of the parasite is shown to be highly specific and sensitive.

Treatment

Once the infection is diagnosed, treatment must be given, irrespective of the symptoms. *Ivermectin* is the drug of choice. It is given in doses of 200 µg/kg orally for 1 to 2 days. Cure rates reported range from 82-98%.

Thiabendazole, which is available as tablets or suspension is the alternative drug. This is given in a dose of 25 mg/kg twice a day for 3 days. *Thiabendazole* is generally safe, but vomiting and vertigo may occur at times, which are self-limiting. Clearance of the worms occurs in over 80 % of cases. Repetition of the drug after 3 months may be necessary if the larvae are demonstrable in feces or allergic manifestations persist.

Albendazole in a dose of 400 mg orally once a day is also effective. Repetition of 3 doses at weekly intervals gives higher clearance rates.

Prevention

The general principles mentioned in the case of hookworms are applicable in the case of strongyloides, but treatment has to be repeated to eradicate the infection due to the phenomenon of autoinfection.

Important points

1. *Strongyloides stercoralis* is known to have three different life cycles.
2. Infection tends to be severe and fatal in immunocompromised host.
3. Apart from lungs, larval migration can occur through the skin.
4. Only larvae (not ova) are seen in the stools.
5. Ivermectin is the drug of choice.

Enterobiasis

Syn: Oxyuriasis, Threadworm, Pinworm, Seat worm

Enterobiasis is caused by *Enterobius vermicularis* (also known as *Oxyuris vermicularis*), the adults of which inhabit the large intestine, especially the cecum, rectum and anal canal. The infection occurs worldwide and is seen more in children.

The female is 8-13 mm long and has the thickness of a thread. The male is 2-5 mm long. The egg, which contains a well-formed larva when passed, is plano-convex, 20 x 50µ in size and is infective when laid (Figs 67.9 and 67.10).

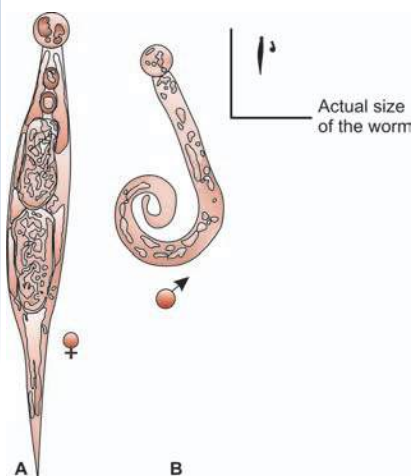


Fig. 67.9: *Enterobius vermicularis*—adult (diagram)

Life Cycle

The gravid female comes out of the anus to lay eggs in the perianal and perineal skin, usually during sleep. Intense itching results in scratching and the ova contaminate fingers of the host. These are swallowed accidentally by the same host or may be spread to others. The ova hatch in the intestine and the larvae migrate to the colon to mature. Life-span is 4-6 weeks. This infection can perpetuate itself in the same host for long periods.

Clinical Features

The patient may complain of passing pinworms in stools. Symptoms are produced by the adult female, which migrates to lay eggs. It results in perianal pruritus and excoriation due to scratching. In females, severe pruritus vulvae and mild vulvitis may develop. Children may suffer from nocturnal enuresis, insomnia and allergic manifestations.

Diagnosis

The condition can be diagnosed by observing the worms in the perianal region while the child is asleep or on the surface of the feces. Ova can be demonstrated by examining a scotch-tape swab prepared from the perianal skin. A cellophane tape is applied to the un-cleaned perianal region in the morning, with the sticky side up, to collect the ova. After removal it is placed on a clean glass slide, sticky side down with a drop of toluene over the slide and examined under the low power of the microscope to detect the eggs.

In heavy infections, material collected by digital examination of the rectum shows the ova.

Course

The infection is self-limiting if autoinfection is prevented, otherwise it persists for long periods due to reinfection. Members of the same household get cross infection.

Treatment

Single dose oral treatment with mebendazole 200 mg, albendazole 400 mg or pyrantel pamoate 10 mg/kg are all effective. The parasite can be eradicated from the household only if all affected persons are treated simultaneously. Some persons have a particular predilection to get the infection repeatedly. In them repeated deworming may be required.

Important points

1. Threadworm infection presents with nocturnal, perianal pruritus and in females pruritus vulvae.
2. Ova are not seen in stools and are demonstrated only by scotch tape technique.
3. Because of direct human infection members of whole household need to be treated.
4. Repeated courses of treatment necessary due to high incidence of reinfection.

Trichinosis

Syn: *Trichiniasis, Trichinellosis*

This is only rarely seen in India. Trichinellosis is caused by *Trichinella spiralis*, a nematode parasite of several animals such as the rat, pig, polar bear etc. Infection in humans occurs when meat containing infective larvae is ingested without proper cooking. The disease has been reported from many parts of Europe, North and West USA, African countries and China.

Common mode of infection is through partially cooked pork sausages. The pig acquires infection by eating infected rats or the offal of infected pigs. Both adults and larvae are seen in the same hosts, but two hosts are required to complete the life cycle.

Morphology and Life Cycle

The adult female varies in size from 3- 4 mm × 40-60 μm. The male is only half this length. When meat containing viable larvae is ingested, the larvae escape in the intestinal lumen, penetrate the mucosal cells of the duodenum and grow into adults in 5-7 days. After fertilization, the female discharges larvae, which embolize to many tissues. Those reaching the muscles encyst themselves in an oval capsule measuring 0.8 mm, grow, mature and become infective after 16 days. They remain viable for 6 months and thereafter die and become calcified. Each female may liberate 1000-1500 larvae during its lifespan. The male lives for about a week, while the female lives for 3-16 weeks. Intercostal muscles,

pectoral muscles, diaphragm and shoulder girdle muscles are heavily affected.

Clinical Features

Symptoms depend upon the heaviness of infection. Mild infection may be asymptomatic. Within the first 1-2 days after ingestion, fever, abdominal pain, nausea, vomiting and diarrhea may develop. Larval dissemination starts around the seventh day and is marked by urticarial rash, remittent fever, edema of the eyelids, conjunctivitis and subungual splinter hemorrhages. Neurological manifestations include polyneuritis, polio-like paralysis, myasthenia, meningoencephalitis and psychosis. The CSF does not show any abnormality. Myocarditis may occur. This is characterized by persistent tachycardia and congestive failure. In 20 % of cases ECG shows ST-T wave changes and conduction defects.

Diagnosis

Eosinophilia is a constant finding in the early stages. ESR is invariably normal. Serum muscle enzymes are elevated. Skin test using the larval antigen is not useful to diagnose active infection since it remains positive for even up to 20 years after infection. Useful serological tests are ELISA, Immunofluorescent test and bentonite flocculation test. Muscle biopsy from the deltoid or gastrocnemius shows encysted or calcified larvae and evidence of myositis (Fig. 67.11).

The acute stage of larval migration has to be differentiated from other conditions characterized by allergic manifestations and muscular pains such as dermatomyositis, other forms of polymyositis, polyarteritis nodosa, serum sickness and food poisoning.

Treatment

Available anthelmintic drugs are not proved to be effective once the parasite invades the muscles. They may be more effective during the intestinal phase of infection. Thus

albendazole 400 mg twice a day for 10 days; mebendazole 200-400 mg thrice a day for 10 days or thiabendazole 25 mg/kg given twice daily for 5-7 days are all effective. During the phase of muscle invasion, antihistamines, corticosteroids and analgesics may be required for obtaining symptomatic relief. The overall mortality is around 2 %.

Prevention

The larvae in meat can be destroyed by proper cooking or deep-freezing at -18°C for 24 hours.

Important points

1. Trichinellosis is rare in India.
2. This parasitic infection has to be differentiated from common collagen vascular diseases.
3. Eosinophilia associated with normal ESR is suggestive of *Trichinella spiralis* infection.
4. Anthelmintics are not proved to be of use in the muscle invasion phase.

Larva Migrants

Visceral Larva Migrants

The term “*visceral larva migrants*” is used to denote the manifestations produced by larvae of non-human ascarids, when they migrate through human tissues. Most often the ascarids of dogs and cats-*Toxocara canis* and *Toxocara cati*-are the common offenders. Possibly larvae of other helminths also may be causative. Though larvae migrate in human tissues for variable periods, the adults do not develop in man. The larvae migrate in the pulmonary and visceral capillaries evoking a granulomatous reaction in various organs. They die and the life cycle is terminated at this stage in non-canine hosts. However, in female dogs the larvae pass transplacentally into the fetus *in utero* and into the puppies through milk while suckling. The adults develop in the puppies. They eliminate the eggs in feces in the first few months.

Children between the age of one and four, who are in close contact with puppies, are at high risk of infection. The infection is acquired by ingesting dirt containing the ova. The larvae are liberated in the jejunum and they migrate into tissues like liver, lungs, heart, brain, ocular structures, kidneys and muscles.

Clinical Features

In the majority of cases the condition is asymptomatic. In a few, symptoms such as fever, cough, wheeze, abdominal pain, and pallor develop. Central nervous system may be involved leading to headache, visual disturbances, strabismus and convulsions. CSF pleocytosis with eosinophil predominance may occur. Nodular eruptions and urticaria may develop as skin manifes-

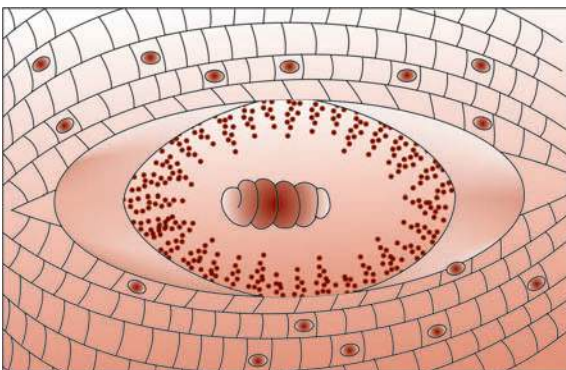


Fig. 67.11: *Trichinella spiralis* larva is striated muscle biopsy (diagram)

tations. Eye lesions include exudative endophthalmitis and retinal granuloma. These may impair vision considerably. Some children develop hepatomegaly.

Leukocytosis with marked eosinophilia is common during acute phase of infection. ELISA detecting larval antibodies is highly specific and sensitive.

Treatment

Visceral larva migrans is self-limiting, since the encysted larvae die out after varying periods. Involvement of liver, lung, brain or eyes calls for treatment.

Available anthelmintics are not proved to be effective in *visceral larva migrans*. Albendazole, mebendazole, thiabendazole and ivermectin are tried empirically. Albendazole 400 mg twice daily or mebendazole 200-400 mg twice daily are given for 21 days. Thiabendazole is given in a dose of 50 mg/kg body weight in divided doses daily for 2-3 days.

Antihistamines and corticosteroids are required to suppress the allergic response. Pulmonary lesion, chorioretinitis and neurological involvement are indications for corticosteroids. Ocular lesions may progress further even after specific anthelmintic therapy and, therefore, prolonged follow-up is necessary in such cases.

Larva migrans can be prevented by proper deworming of newborn pets and avoiding contamination of children's playground with the excreta of these animals.

Cutaneous Larva Migrans

The larvae of *Ancylostoma braziliense* and *A. caninum* (dog's and cat's hookworms) and *Strongyloides stercoralis* cause creeping eruption. The larvae, which are present in soil penetrate the intact skin and enter the tissues. In the subcutaneous tissues, they cause multiple, intensely pruritic serpiginous tracts. While the larvae of *A. braziliense* and *A. caninum* progress forwards at a rate of 2-3 mm per hour, those of *S. stercoralis* progress a few cm at a time. At the anterior end of the eruption the larva is present and a bleb may form. Since the larvae ultimately die, the lesions are self-limiting. The eruptions due to strongyloides tend to persist for several years, if left untreated.

Treatment

Albendazole 400 mg given orally for 5 days or ivermectin 200 µg/kg single dose are the treatment of choice on account of their safety. Antihistaminics help to suppress the pruritus.

Important points

1. Larva migrans in humans is mostly caused from accidental infection by helminths from animals.
2. Marked eosinophilia is common during active infection.
3. Anthelmintics are generally not proved to be effective.
4. *S. stercoralis* can cause rapidly progressing cutaneous larva migrans.

Chapter Summary

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General Considerations

Cestodes or tapeworms are segmented flat ribbon-like hermaphrodite worms that inhabit the small intestines of men or animals. The head (scolex) is at the anterior end and the body (strobila) is made up of segments. The head is small in size and it is provided with suckers, which help the worm to attach to the intestinal mucosa. The scolex contains hooklets in some species. The body consists of a short neck and a chain of successive segments

(proglottids). Every proglottid is a complete hermaphrodite unit. The proglottids are formed near the head as the worm grows. The segments near the head are immature, the intermediate ones are mature with fully developed gonads and the distal ones are gravid, filled by the uterus containing numerous eggs. Cross-fertilization occurs between adjacent segments. Tapeworms have no body cavity or digestive tract. Nutrients are absorbed by the surface. They require 2 or 3 hosts for completion of their life cycle. More than 30 species have been found to infect man but only six of them are common. These are *Taenia solium*, *T. saginata*, *T. echinococcus*, *Diphyllobothrium latum*, *Hymenolepis nana* and *H. diminutum*.

Taeniasis saginata

Syn: Beef Tapeworm, Unarmed Tapeworm

Taeniasis saginata is infection caused by *Taenia saginata*. This is the commonest among the large tapeworms found in man and is distributed worldwide. Prevalence is highest in areas where beef is a major source of meat. The adult worm grows to a length of 10 meters and may consist of over 2000 segments. It lies free in the jejunum and ileum, the head being attached to the mucosa. The scolex is 2 mm in diameter and bears no hooklets, but has four suckers. The gravid segments are actively motile and they come out in chains along with feces or wriggle out singly due to their intrinsic muscular action. The uterus has about 20 lateral branches.

The eggs are spherical measuring 30-45 μ in diameter and the egg shell is thick, striated and bile-stained. The embryo or onchosphere bears six hooklets and it remains viable for 4-8 weeks. The adult worm may live for 10-25 years.

Life Cycle

Man is the definitive host and *cattle and llamas* form the intermediate hosts. Eggs passed in feces contaminate soil. These are ingested by grazing cattle. The onchospheres are liberated in the intestine and they penetrate the mucosa, enter the blood stream, and reach various muscles, mainly those of the heart, tongue, shoulder, neck and loins. On reaching these sites the onchospheres lose their hooks and grow into the cystic stage known as *cysticercus bovis* in 60-70 days. The cysticercus is ovoid, measures 8 $\times$ 5 mm and contains a single sprouting scolex. Cysticercus remains viable for 1-3 years within the muscles. Heavily infected meat is easy to distinguish by the presence of numerous cysts.

On ingesting undercooked meat, the cyst wall is digested and the head attaches itself to the intestinal mucosa and rapidly grows to reach the adult size in 6-8 weeks. A host usually harbors only one or two worms.

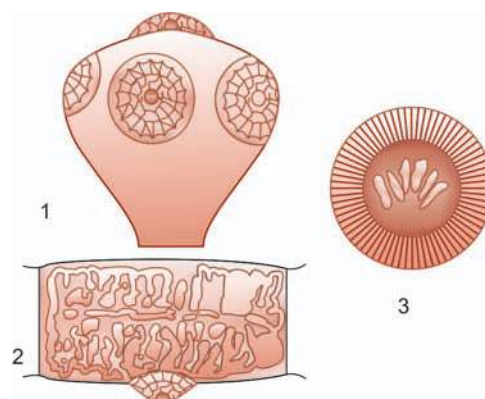


Fig. 68.1: *T. Saginata* diagram
1. Scolex. 2. Gravid proglottide, and 3. Ovum

Clinical Features

Majority is asymptomatic, though vague symptoms such as abdominal pain, diarrhea and increased appetite may occur in a few. The motile segments emerging out of the anus may cause pruritus and anxiety to the host. Appendicitis and biliary obstruction have been reported rarely.

Diagnosis

History of passing segments and seeing the segments in feces confirm the diagnosis. The species can be identified by observing the number of lateral branches of the uterus. An easy method is to press the segment between two glass slides and to hold it against light. *Taenia saginata* segment has more than 15 lateral branches, whereas *Taenia solium* has only less than 13.

Eggs can be demonstrated by microscopic examination of the feces or by examining perianal scotch tape swab. The eggs of *T. saginata*, *T. solium* and *T. echinococcus* cannot be differentiated from each other (Fig. 68.1).

Treatment

Both niclosamide (Yomesan) and praziquantel are effective against *T. saginata*. Niclosamide kills the scolex and segments on contact. Four tablets, each of 0.5 g, are given as a single dose to be thoroughly chewed in the morning with a gulp of water. The worm is passed partially digested 24-36 h later. If the whole worm including the scolex is not passed, the worm re-grows and segments reappear in stools within 3 months. In this case the drug is repeated in the same dose.

Praziquantel in a dose of 10-15 mg/kg body weight given as a single dose orally is adequate to dislodge the intestinal adult worm in almost all cases. The drug is generally safe. Side effects include dizziness, headache, vomiting and allergy. It is available as tablets of 500 mg and 600 mg. It is expensive, costing Rs. 330 per tablet.

Prevention

Taenia saginata infection can be prevented by avoiding infected beef, inspection of slaughterhouses and proper disposal of excreta.

Important points

1. *T. saginata* is the longest tapeworm infecting humans
2. Passing motile segments in stools is diagnostic.
3. Morphology of ova does not help to differentiate the different tapeworms.
4. There is no tissue invasion in humans

Taeniasis solium and Cysticercosis

Syn: Pork Tapeworm, Armed Tapeworm

The adult of *Taenia solium* inhabits the small intestine of man. The larval stage of *T. solium* may remain encysted in several tissues. This condition is called cysticercosis. *Taenia solium* is seen all over the world, especially in those countries where pork is a major source of meat. With the availability of computed tomography (CT) and magnetic resonance imaging (MRI) of brain, more and more cases of cysticercosis are being diagnosed in many parts of India. *T. solium* is present in all areas, though it is less common than *T. saginata* (Fig. 68.2).

Morphology

The adult worm is 3 meters in length and the proglottids are less than a thousand in number. The scolex is globular and 1 mm in diameter. It bears a rostellum with a row of hooklets and four suckers. The name solium is derived from the shape of the rostellum, which resembles the conventional figure of the sun.

The gravid uterus has a main stem with 8-10 compound lateral branches on either side. The worm has

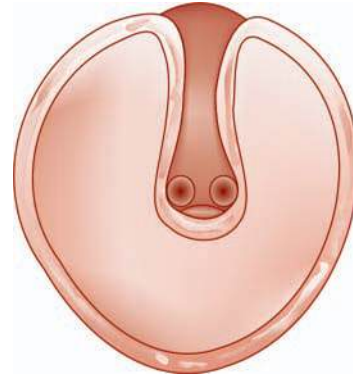


Fig. 68.3: *T. solium*—*cysticercus cellulosae* (diagram)

a long life span anecdotally stated as extending up to 25 years but, actually may be only up to five years. Eggs are indistinguishable from those of *T. saginata*. Larvae are found encysted in tissues. The cyst is oval in shape (5 × 20 mm) and contains an invaginated scolex (Fig. 68.3).

Life Cycle

Man is the definitive host. Pigs and occasionally man form the intermediate hosts. Segments containing eggs passed in the feces are eaten up by pigs. The hexacanth embryos liberated in the intestine of the pig penetrate the gut wall and reach several tissues through the blood stream. Muscles of limbs, tongue and neck are affected more. Within 60-70 days the embryos develop into cysts called *cysticercus cellulosae* (bladder worm). The cysticerci live up to 8 months after which they die. Heavily infected pork is known as “measly pork”. Man gets the infection by eating undercooked infected pork. The larvae are liberated in the intestines. They attach to the jejunal mucosa and grow into adult worms in 2-3 months after which segments are passed in stools.

Clinical Manifestations

Intestinal infection leads only to minimal symptoms or none at all. The patient may complain of passing segments in strips and this may lead to anxiety.

CYSTICERCOSIS

When man ingests the eggs or when the gravid segments with ova reach the stomach by reverse peristalsis, the eggshell is digested and larvae escape. The liberated embryo penetrates the mucosa. The larvae are disseminated to various tissues in the circulation and they develop into cysticerci. Cysticercosis is the result of a complex encounter between a highly sophisticated parasite and an elaborate immune response. This can lead to rapid elimination of the parasite in some cases. In others the parasites persist and grow. The cysts are found mostly in the subcutaneous tissues, eyes, brain and bones and they

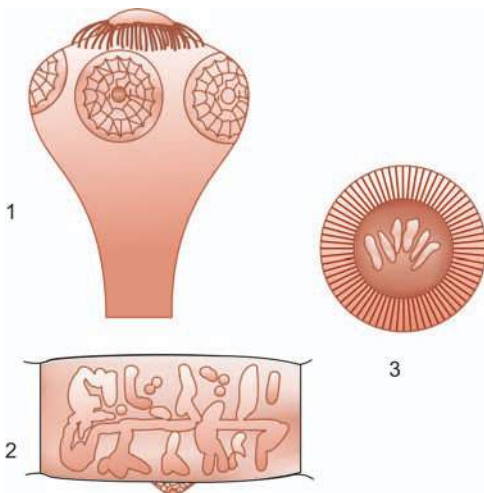


Fig. 68.2: *T. solium* (diagram)

1. Scolex, 2. Gravid proglottide. and 3. Ovum

remain viable for three years. Viable cysts do not cause any tissue reaction. When they die, the cysts swell up and provoke foreign body reaction in the tissues and general symptoms in the form of fever, eosinophilia, arthralgia and muscular pain. Ultimately, the cysts get calcified and can be seen in X-rays. The disease may be seen in strict vegetarians as well.

NEUROCYSTICERCOSIS

This has emerged as a common cause of seizures and intracranial space occupying lesion in many parts of India. The cysts developing in the nervous system may be situated in the parenchyma of the brain, subarachnoid space, meninges, ventricles or rarely in the spinal cord. They may present with focal or general neurological manifestations such as epilepsy, focal neurological deficits referable to brain or spinal cord, rise in intracranial tension and progressive or intermittent hydrocephalus. The commonest presentation is late onset epilepsy. The cysts in the brain do not calcify readily as in other tissues. In the eyes, the cysts provoke uveitis and retinal hemorrhage and they can be seen by ophthalmoscope. In the skin and muscles they are palpable as small nodules. Sometimes affected muscles undergo pseudo hypertrophy.

The advent of CT has revealed that cysticercosis exists in all communities irrespective of their dietary habits.

Diagnosis

T. solium is diagnosed by observing the gravid segments or eggs in feces. The gravid segment show distinctive features. The ova of all the taeniae are identical morphologically. Examination of the feces is quite adequate to diagnose the infection in almost all cases. Sophisticated tests to detect specific copro-antigen by ELISA are available. So also specific DNA based studies are available to detect carrier state.

Cysticercosis is suspected by history and clinical examination. Calcified cysts may be seen by radiological examination of soft tissues. Occasionally ocular cysticerci can be seen at funduscopy. CT scan and MRI scan are excellent methods to visualize cysticerci, which give diagnostic patterns. Both CT and MRI are reliable methods to diagnose neurocysticercosis and to follow up treatment results. Parenchymal cysticerci appear as multiple cortical and subcortical circumscribed lesions about 1 cm in diameter with perilesional edema appearing as a ring lesion. Contrast enhancement suggest active inflammation. The differential diagnosis includes tuberculosis and fungal infections. ELISA to detect antibodies to cysticercal antigens is helpful in diagnosis. Enzyme linked immunoelectrotransfer blot (EITB) is shown to be more specific and sensitive.

Treatment

Niclosamide is effective in killing the adult worms in a dose of 2 g, but the worm is disintegrated and this may liberate the ova. Due to the risk of cysticercosis, this drug is better avoided. Praziquantel in a single dose of 15-20 mg/kg is effective against the adult. It is preferable, since it has action against cysticerci too.

Treatment of Neurocysticercosis

The drug of choice is *albendazole* given orally in a dose of 15 mg/kg/day for 8 days. It is a benzimidazole compound, which is readily absorbed from the gut. *Albendazole* prevents glucose uptake by the parasite membrane, thereby leading to energy depletion. It reaches high concentration in most of the tissues and so it exerts wormicidal effects in tissue forms of helminths. It is easily available in India, cheaper than praziquantel and safe. The success rate is 80%. *Albendazole* can be safely administered with anticonvulsant drugs without affecting their efficacy.

Being embryotoxic and teratogenic, albendazole is contraindicated in pregnancy. Toxic effects include abdominal pain, nausea, vomiting, dizziness, headache, rashes, pruritus, leukopenia, alopecia, eosinophilia, jaundice and nonspecific rise of hepatic transaminases.

Praziquantel which is also a broad spectrum anthelmintic is effective against cysticerci when given in a dose of 50 mg/kg/day for 15 days. The success rate is 60-70%. It exerts its action by producing muscular paralysis and destroying the scolices. It is not freely available in India, but it can be procured for special cases, but at much higher cost than albendazole.

Treatment using albendazole or praziquantel should be started only after hospitalizing the patient. This is necessary since the dying parasites induce inflammatory reactions in the surrounding tissue resulting in features of meningism or signs of raised intracranial tension. These reactions require measures to reduce the inflammation and raised tension, along with antiepileptic drugs.

In late cases, where arachnoiditis and hydrocephalus have set in, results may not be fully satisfactory even after eradicating the cysticerci.

Symptomatic measures include the control of seizures by anti-epileptic drugs, control of cerebral edema and anti-inflammatory drugs. Rarely surgery may be required to relieve obstructive hydrocephalus. Corticosteroids are indicated when there is raised intracranial tension, signs of meningoencephalitis or ocular cysticercosis.

Prevention

The infection can be prevented by cooking pork thoroughly and by proper disposal of human excreta.

Important points

1. Cysticercosis can occur both in vegetarians and non-vegetarians.
2. Neurocysticercosis is a common cause of epilepsy and focal neurological deficits in endemic areas.
3. A high index of suspicion is required to make a clinical diagnosis of neurocysticercosis.
4. Treatment with albendazole or praziquantel should be given after hospitalization due to risk of inflammation induced by the dying parasites.

Echinococcosis

Syn: Dog Tapeworm or Hydatid Worm

Definition

Infection of human tissues by larval form of *Echinococcus granulosus* and less commonly *E. multilocularis* is termed echinococcosis. The disease is worldwide in distribution. It is more common in sheep-rearing countries both in the tropic and temperate zones. Close contact between man, dog and sheep favors this infection. *E. granulosus* is widely distributed in India and the disease is seen endemically or sporadically.

Morphology

The adult worm is small, measuring only 3-6 mm in length. The scolex bears four suckers and rostellum with two rows of hooklets. There are only three segments. The last segment is mature and gravid. Dogs pass the ova in their feces. The ova resemble those of *T. saginata* and contain the infective embryo. Larval forms occur within hydatid cysts. A single metastasized larva settles in tissues and grows to form a hydatid cyst. The germinal layer of the hydatid cyst gives rise to successive generations of embryos, ultimately leading to the development of several thousand infective larvae from a single egg (Figs 68.4 and 68.5).

Life Cycle

Definitive hosts are the dogs, wolves, jackals and other canines. Intermediate hosts are sheep, pigs, goats and humans. Sheep are the optimum intermediate hosts and they serve to perpetuate the natural life cycle of the parasite. The eggs passed in dog feces are ingested by the intermediate hosts. The embryos are liberated in the intestines. They penetrate the mucosa and enter the portal radicles to reach the liver. The larvae are arrested mainly in the liver and lungs but some may escape into the systemic circulation to reach other viscera like the brain, bones and kidneys. Within 3-6 weeks they grow into vesicles 5-10 mm in diameter and these are known as hydatid cysts (hydatids = drops of water). They grow to reach large sizes and the parasite multiplies in number.

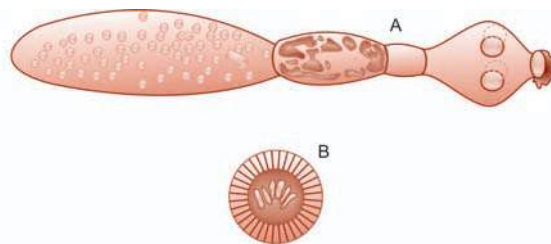


Fig. 68.4: *Echinococcus granulosus*
(A) Adult, and (B) Ovum

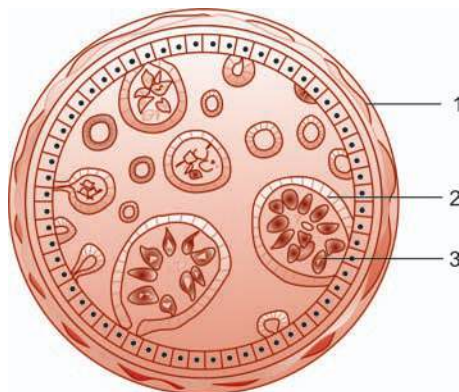


Fig. 68.5: Hydatid cyst (diagram)
1. Outer wall, 2. Brood capsules, and 3. Scolices

The hydatid cyst has a thick fibrous outer wall and an internal germinal layer, from which brood capsules containing budding scolices arise. These may separate from the capsule and float inside as daughter cysts. The hydatid fluid is a clear colorless fluid, which is highly antigenic. On keeping it a granular deposit forms at the bottom (hydatid sand), which contains free scolices and brood capsules.

When the hydatid cyst or scolices are ingested by the definitive hosts, they attach to the intestinal mucosa and grow into adults. Each animal may harbor many worms.

Clinical Features

Infected dogs are asymptomatic. In human hydatid disease, symptoms are due to allergic reactions and mechanical compression of the surrounding tissues. Local symptoms depend on the site and size of the cyst. Clinical features are those of an enlarging mass. Common presentation is with hepatomegaly, hemoptysis or neurological symptoms. In about 75% cases the right lobe of the liver is the seat of large cysts. Lungs, brain, orbits and bones are affected not uncommonly. An interesting physical finding is the hydatid thrill, which is elicitable by percussion over large hydatid cysts, particularly over the liver region. Place three fingers of the left hand firmly over the enlarged liver and percuss on the middle finger with the right hand, and feel the sensation over the other



Fig. 68.6: X-ray chest hydatid disease left lower zone

two fingers, produced by the movement of the free floating daughter cysts in the cyst cavity. This is called hydatid thrill.

Allergic manifestations occur either as non-specific allergy such as urticaria, eosinophilia or rashes. Sometimes rupture of a cyst and entry of the fluid into tissues evoke anaphylactic reactions.

Diagnosis

Strong clinical suspicion is necessary to suggest the diagnosis of hydatid disease.

1. **Blood:** Mild eosinophilia is invariably present.
2. **Casoni's reaction:** This intradermal test using sterile hydatid fluid used to be an important diagnostic test which was in vogue till three decades ago. It is no longer used because of poor specificity and cross reaction with other helminths.
3. **Immunological tests** such as hemagglutination test using sensitized sheep red cells and immunofluorescence are useful for screening.
4. **Immunoelectrophoresis and ELISA techniques** are specific, though technical difficulties restrict their wide use.
5. **X-rays:** The cysts are radiopaque and are seen as sharply outlined masses in the lungs (Fig. 68.6).
6. **Imaging:** Ultrasonography gives the most valuable information about the nature of the mass and its contents. CT and MRI are also useful imaging techniques. Calcification of the cyst wall on CT is suggestive of hydatid cyst. Isotope scans of the liver bring out cold areas.

Closed aspiration as a diagnostic procedure is generally contraindicated since escape of the contents may result in anaphylactic shock and secondary infection.

Treatment

Planned surgery offers the best chance of cure for symptomatic cysts as drug therapy fails to clear the mass fully. Due to problems associated with surgery, presently ultrasound guided percutaneous aspiration and infusion of scolical agents like ethanol or hypertonic saline followed by re-aspiration of the contents is recommended for uncomplicated cysts.

Albendazole, which is the drug of choice, is effective in sterilizing the scolices and reducing the size of the cysts. This drug is given pre-and post-operatively to sterilize the cysts and to prevent recurrence due to spillage during surgery. The dose is 800 mg given orally as two doses for 30 days. Pregnancy is a contraindication for this drug. Concurrent administration of corticosteroids help to reduce systemic reactions.

Praziquantel 50 mg/kg/day for 2 weeks is shown to destroy the protoscolices within the cysts but has no action on the germinal layer.

Prophylaxis

Care should be taken in handling dogs. Domestic dogs should be regularly dewormed. Monthly treatment with praziquantel 5 mg/kg eliminates *T. echinococcus* and *Hymenolepis nana* in dogs. Oxbendazole which is a vetnary drugs given a dose of 30mg/kg bw given orally, eradicates the infection in animals in > 95%.

Contamination of children's playgrounds with dog's feces should be avoided.

Important points

1. Hydatid cyst should be considered in the diagnosis of an otherwise asymptomatic space occupying lesion in the liver and lungs.
2. Ultrasound and CT findings are diagnostic, especially calcification in the cyst wall.
3. Aspiration of the cyst is associated with risk of spillage of the contents and anaphylactic shock.
4. Planned surgery is the definitive treatment since albendazole alone does not clear the cyst completely.

Diphyllobothriasis latum

Syn: *Diphyllobothrium latum*, fish tapeworm

Infection by *Diphyllobothrium latum* is extremely rare in India. It is more common in the USSR, Baltic regions, Switzerland and Japan. The adults are seen in human small intestine and may range in length from 3-10 meters. The eggs are operculated. Two intermediate hosts are required for completing the life cycle, the fresh water cyclops and fresh water fish. Man gets infected by eating uncooked fish. The parasite may compete for vitamin B₁₂ in the intestine, leading to vitamin B₁₂ deficiency in the host.

Both niclosamide and praziquantel are effective vermicides.

Hymenolepis nana

Syn: Dwarf Tapeworm

This is the smallest tapeworm found in man, measuring 1-4 cm in length. Children acquire infection by swallowing eggs. The larvae hatch out and grow in the small intestine. Niclosamide and praziquantel are very effective in clearing the infection.

Hymenolepis diminuta

This tapeworm is a parasite primarily affecting rats and mice. Man is accidentally infected by consuming the infective larva present in fleas, along with cereal grains. Both niclosamide and praziquantel are curative.

Dipylidium caninum

This is a tapeworm seen in cats and dogs. Many get infected accidentally by consuming the infective larvae present in fleas. Niclosamide and praziquantel are effective drugs.

Comparative morphology of the pathogenic tapeworms is given in Figure 68.7.

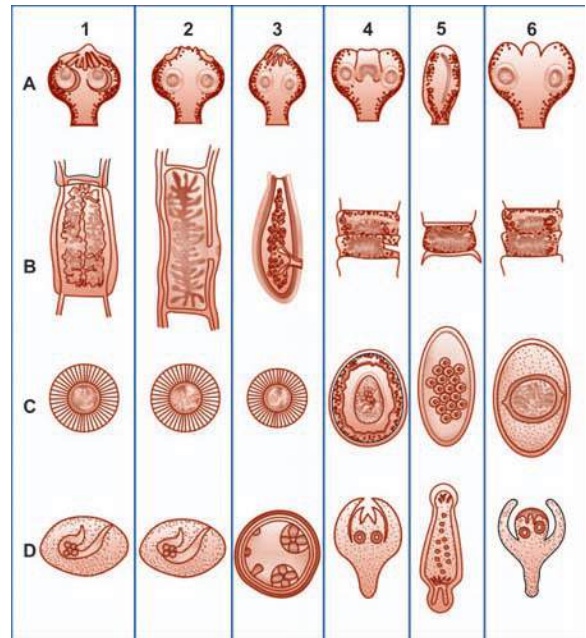


Fig. 68.7: Comparative diagram of tapeworms. (1) *T. solium*, (2) *T. saginata*, (3) *T. echinococcus*, (4) *H. nana*, (5) *D. latum*, and (6) *H. diminutum*. (A) Scolices, (B) Proglottides, (C) Eggs and (D) Larvae

69

Trematode (Fluke) Infections

R.K. Shenoy, K.V. Krishna Das

Chapter Summary

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Schistosomiasis 408

General Characteristics

Trematodes (flukes) are flat leaf-shaped unsegmented worms, which have a long life span. Except schistosomes all are hermaphrodites. Compared to the other worms, human fluke infection is rare in India.

The common features are:

1. Majority of them gains entry through the digestive tract except schistosomes;
2. Intermediate host is a snail and the infective metacercaria encyst on vegetables or develop in some aquatic animals which are ingested; and
3. The eggs are operculate except in the case of schistosomes.

General Life Cycle

Man and other mammals form the definitive hosts. Intermediate hosts are fresh water snails or molluscs. In addition, some have also a second intermediate host such as fresh water fish or a crustacean. The eggs hatch out

General characteristics of some of the common pathogenic trematodes		
Species of Flukes	Hosts	Habitat of adult
Intestinal flukes		
<i>Fasciolopsis buski</i>	Pig, occasionally dog, man	Duodenum and jejunum
<i>Heterophyes heterophyes</i>	Cat, dog, fox, man	Small intestine
<i>Metagonimus yokogawai</i>	Fish eating mammals, pelican, man	Small intestine
<i>Gastrodiscoides hominis</i>	Pig, man	Caecum and colon
Liver flukes		
<i>Clonorchis sinensis</i>	Dog, pig, cat and man	Biliary passages
<i>Opisthorchis felineus</i>	Dog, cat, fox, several other animals and man	Biliary and pancreatic passages
<i>Fascila hepatica</i>	Sheep, cattle, rabbit, man	Liver and biliary passages
Lung flukes		
<i>Paragonimus westermanii</i>	Tiger and other crab eating animals, man	Lungs
Schistosoma		
<i>S. haematobium</i>	Man	Urinary tract
<i>S. mansoni</i>	Man	Intestines, liver
<i>S. japonicum</i>	Man and other animals	Intestines, liver, lungs, brain

when liberated into water and give rise to the motile ciliated embryos called miracidium. These penetrate the body of particular species of snails and develop into sporocysts in the liver or lymph spaces. Rediae develop from the sporocysts. The rediae either develop into cercariae or a second generation of rediae. Asexual multiplication occurs at this stage and the number of parasites increases. The cercariae escape from the snails and either encyst as metacercariae over water plants or are taken up by the second intermediate hosts. Infection to man occurs due to ingestion of metacercariae on contaminated vegetables or by eating uncooked fish or crustacea (Table 69.1).

Fascioliasis
Syn: Sheep liver fluke

Fascioliasis is infection by *Fasciola hepatica*. It is essentially a parasite of cattle and sheep and is worldwide in distribution. Infection among cattle is not uncommon in India but human infection is less common.

Morphology, Life Cycle and Pathogenesis

This fluke measures 3.5 × 1.5 cm. The eggs measure 140 × 80 µm. They are operculate and are passed in feces. The snail vector is *Limnaea truncatula*. The cercariae encyst on aquatic vegetation. Man gets the infection by eating contaminated watercress. When ingested, the parasites excyst in the intestine and penetrate the wall to enter peritoneal cavity. They enter the liver by piercing the capsule. In the liver they mature into adults in the bile ducts. Ova appear in feces 3-4 months later.

Clinical Features

During parasitic invasion prolonged fever, abdominal pain, tender enlargement of the liver, urticaria and eosinophilia develop. Thereafter, the disease remains latent for months to years. The third stage is one of obstruction of the bile duct leading to jaundice and biliary cirrhosis.

Treatment

Triclabendazole given orally in a dose of 10 mg/kg body weight in 2 single doses, 2 days apart is the drug of choice. Bithional in a dose of 30-50 mg/kg given orally on alternate days for 10-15 days or Praziquantel in a dose of 75 mg/kg daily in three divided doses for 5 days is also effective.

Important points

1. Infection by *Fasciola hepatica* is one of the causes of obstructive jaundice and biliary cirrhosis.
2. Triclabendazole is the drug of choice.
3. In endemic regions watercress should not be eaten raw.
4. Cooking destroys the parasite.

Heterophyiasis

Heterophyes heterophyes is a small fluke found in large numbers in the small intestine of man, dog, cat and wolf. It is distributed widely in the Far East and Egypt. In India, it is occasionally seen in visitors or immigrants. The operculated eggs measure 13-16 µm in size and are passed in feces. They resemble those of *Clonorchis sinensis*. The snail vector is *Pironella conica*. The second intermediate hosts are the mullets and other types of fish, which are

infective when eaten raw or improperly cooked. Inflammatory reactions occur at the point of attachment to the intestinal mucosa. Heavy infections lead to diarrhea and abdominal pain. Ectopic worms and ova in the heart had been reported. These unusual sites are reached through the blood stream.

Treatment

Praziquantel given in a single oral doses of 20 mg/kg body weight clears the infection.

Clonorchiasis

Syn: *Chinese liver fluke*

Infection of the biliary passages by *Clonorchis sinensis* causes clonorchiasis. This disease is prevalent in the Far East among fish eating mammals such as dogs, cats, pigs and man. In India it has been reported among the Chinese immigrants.

Morphology, Life Cycle and Pathogenesis

This fluke is 11-20 x 3-4 mm in size. Eggs measure 30 to 16 µm and are passed in stools. The snail vectors belong to the *Bythinia* species. The cercariae are ingested by fresh water fishes (more than 40 species), which form the second intermediate hosts. Metacercariae develop in their muscles. When such fishes are ingested uncooked, the cyst wall is digested and the larvae are set free in the duodenum. They pass up through the ampulla of Vater to the smaller biliary passages and sometimes the pancreatic ducts. In course of time the biliary epithelium proliferates and the ducts dilate to form cystic cavities. The liver is enlarged and biliary cirrhosis, suppurative cholangitis and rarely malignancy may occur as complications.

Clinical Features

Include diarrhea, hepatomegaly, recurrent jaundice and eosinophilia.

Diagnosis

The eggs can be demonstrated in the feces or duodenal aspirate.

Treatment

Praziquantel in a dose of 75 mg/kg given in three divided doses for 1-2 days is curative. Bithionol given orally in doses of 50 mg/kg on alternate days for 2-3 weeks is also effective.

Important points

1. There are two intermediate hosts in the life cycle of *Clonorchis sinensis*
2. Clonorchiasis clinically presents with obstructive jaundice from cholangitis, biliary cirrhosis.
3. Chronic infection may predispose to the development of cholangio-carcinoma.
4. Proper cooking of fish prevents infection.

Schistosomiasis

Syn: *Bilharziasis*

Definition

Infection by *Schistosoma hematobium*, *S. mansoni* or *S. japonicum* constitutes schistosomiasis. *Schistosoma hematobium* affects the urinary tract. *S.mansoni* affects the large intestine, liver, lungs and also spinal cord. *S. japonicum* affects mainly the small intestine and upper part of large intestine, but the liver, lungs and the central nervous system are also affected frequently. *S. hematobium* and *S. mansoni* parasitize only man whereas *S. japonicum* may also affect other animals such as the dog, cat, rat, field mouse and cattle. More than 200 million people are affected by the worm, worldwide.

Morphology and Life Cycle

The life cycle of all the species is similar. Definitive host is man. Eggs are discharged in urine or feces. The eggs hatch out immediately in water and liberate free-swimming miracidia, which penetrate specific snail hosts within 24 h (genus *Bulinus* for *S. hematobium*, *Biomphalaria* for *S. mansoni* and *Oncomelania* for *S. japonicum*). Two sporocyst generations develop within the snail. Cercariae are formed within 4-6 weeks. These escape from the snail into water and remain infective for 2-3 days. A snail infected by one miracidium can shed thousands of cercariae daily for months. The cercariae penetrate intact human skin and the oral mucous membrane when there is a thin film of water. Infection is acquired by contact with fresh water containing the cercariae. After entry, the cercariae lose their tails and they reach the peripheral venules and lymphatics. Within 24 hours, they pass through the lungs, diaphragm and liver. Then they enter the systemic circulation. The parasites finally reach the portal venous system and develop into adult worms. The adult worms measure 1-2 cm in length and have a life span of 4-30 years. The male is broader and holds the female within its fold. The female is longer and more slender and cylindrical than the male (Fig. 69.1). Within 4-6 weeks of infection they reach their destination through the venules draining the pelvic viscera and start laying eggs. *Schistosoma japonicum* passes through the superior mesenteric vein and *S.mansoni* passes through the inferior mesenteric veins. Finally, they both reach the submucosal vessels of the intestine. *Schistosoma japonicum* affects the small intestine and the ascending colon, while *S. mansoni* lodges in the descending colon and rectum. *Schistosoma hematobium* reaches the bladder and other pelvic organs. They feed on blood and globulins by anaerobic glycolysis.

The females lay about 3000 eggs daily in the terminal blood vessels. The eggs contain ciliated miracidium larvae which secrete proteolytic enzymes which help them to

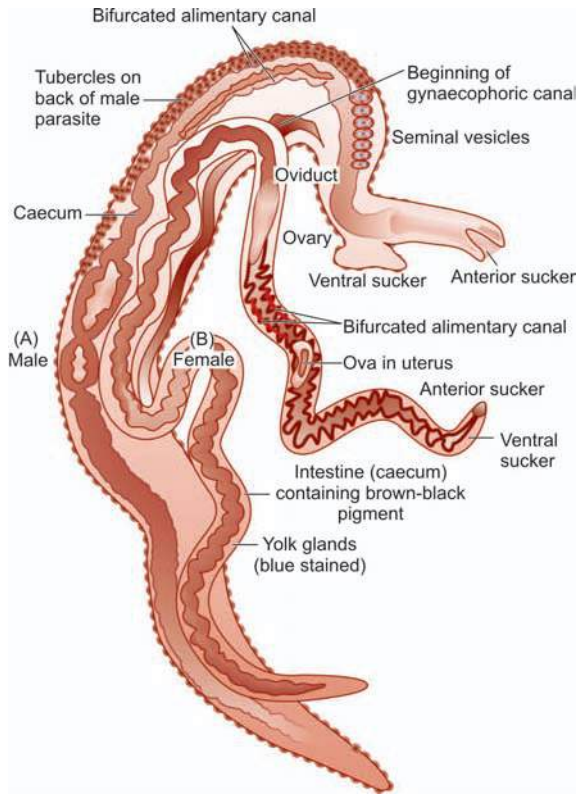


Fig. 69.1: Adult schistosome (A) Male, and (B) Female

migrate into the lumen of the bladder or the intestine. The worms slowly retreat as the terminal vessels get progressively blocked. The eggs remain viable for 1 week. The eggs of *S. hematobium* containing miracidia appear in urine. The eggs of *S. mansoni* and *S. japonicum* are passed in feces (Fig. 69.2).

Epidemiology

Though schistosomiasis is one of the more widespread helminthic infections affecting about 200 million people in 71 countries, it is only rarely reported from India. There is a pocket of infection by *S. hematobium* in Maharashtra state. Highest prevalence is in Africa and the Middle East. *Schistosoma hematobium* and *S. mansoni* occur in Africa, Middle East and South America. *Schistosoma japonicum* is prevalent among the field workers in China, Japan, Philippines, Celebes, Lagos, Thailand, Vietnam and Myanmar. Newer areas have become endemic with the construction of dams and irrigation projects.

Pathology and Pathogenesis

Eggs are laid in the tissues, but many are discharged into the lumen and are passed in urine or feces. About 50% of the eggs are retained in the tissues. The eggs produce proteolytic enzymes which lead to typical eosinophilic inflammatory and granulomatous reactions, leading to

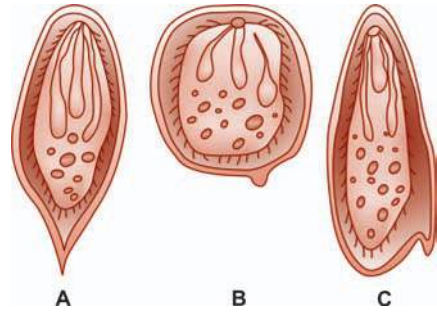


Fig. 69.2: Ova of schistosome (A) *S. hematobium*, (B) *S. japonicum* and (C) *S. mansoni*

fibrosis. Granulomatous lesions occur especially in liver, intestines, urinary bladder, uterus and lungs, resulting in complications. The tissue reaction is determined by the intensity of infection and the reactivity of the host. Ultimately further reinfection is limited by immunity developed by the host in endemic areas.

Clinical Features and Complications

Three phases are recognizable.

1. **Earliest lesion** is caused by penetration of the skin by cercariae. It results in itching and papular rashes at the sites of penetration (**swimmer's itch, cercarial dermatitis**). This phase is more common in infections caused by non-human schistosomes.
2. In about 4-6 weeks the **second stage** starts with fever, severe toxemia and allergic reactions. Marked eosinophilia develops in about 4-6 weeks. This stage is called **Katayama syndrome**. This serum sickness like reaction is seen during oviposition and it is most severe in *S. japonicum* infection.
3. **Late complications** are seen three months to several years after the initial infection. These are due to granulomatous lesions and fibrosis occurring in various organs. The manifestations of this stage differ in the three species.

Schistosoma hematobium (*Genitourinary schistosomiasis*) affects the urinary bladder, ureters and the prostate in males, whereas vagina, cervix and uterus are also involved in females. Urinary symptoms predominate depending on the stage of the disease. *S. hematobium* infection predisposes to vesical carcinoma.

Schistosoma mansoni infection (*Intestinal schistosomiasis*): The early stage is characterized by abdominal pain and dysenteric symptoms. The lesion extends to the liver due to retrograde passage of eggs into the portal system and the liver. Periportal fibrosis resulting in presinusoidal portal hypertension develops in the liver. Massive splenomegaly may occur. The ova may reach all organs through the portal-systemic collaterals. The ova in the brain lead to neurological symptoms. *Schistosoma mansoni* infection favors the development of carrier state for *Salmonella typhi*. There is no rise in the risk of cancer.

***Schistosoma japonicum* infection (Katayama disease, Asiatic schistosomiasis):** Since this worm produces more eggs than the others, its pathogenicity is greater. Major pathological lesions are seen in the small intestine, mesentery and ascending colon. This leads to ulcerations, fibrous thickening, and polyp formation. Early symptoms are abdominal pain and bloody mucoid stools. Cirrhosis liver develops with all its attendant complications. Five percent of cases develop ectopic foci of infection, especially in the lungs and central nervous system. Symptoms include Jacksonian epilepsy, focal paralysis, paraplegia and coma. Embolization of eggs in the pulmonary circulation leads to obstruction of small arterioles resulting in pulmonary hypertension. Granulomas develop in the lungs, which result in fibrosis. Such patients present with asthma, bronchitis, or pulmonary emphysema.

6

Diagnosis

Schistosomiasis is diagnosed by demonstrating the eggs in appropriate specimens or in tissue biopsy. Concentration technique like Kato-Katz quantitative method is useful to enhance the egg count results. Investigation for *S. hematobium* includes plain X-ray abdomen for bladder calcification, excretory urograms and cystoscopy with biopsy, especially when there are no eggs or miracidia in urine. Rectal biopsy, sigmoidoscopy, barium enema and colonoscopy with biopsy are necessary to diagnose *S. mansoni* and *S. japonicum*. Serological tests like ELISA and Immunoblot are available for diagnosis.

Modern investigations such as ultrasonography, CT and MRI help to assess lesions in the liver, portal venous system, kidneys, bladder, brain and spinal cord. With the availability of these facilities structural lesions can be diagnosed and appropriate corrective treatment instituted.

Treatment

It should be the aim to start treatment early since at this stage lesions are reversible. *Schistosoma hematobium* is most susceptible and *S. japonicum* is more resistant to drug therapy.

Praziquantel

This is an acylated quinoline-pyrazine derivative. It is given as a single oral dose of 30-45 mg/kg and the drug is effective

against the adult worms in all types of infections. Cure rates of 72-95% have been reported and side effects are few, spasmodic abdominal pain being the most common. Being effective in a single dose, it can be utilized for mass therapy. Therefore at present it is the drug of choice. *S. hematobium* responds to 30 mg/kg body weight, whereas *S. mansoni* and *S. japonicum* require above 40 mg/kg for proper response. The drug is available as 600 mg tablets. After a single dose 70-100% of patient cease to discharge eggs. A follow-up dose repeated 6-12 week later ensures killing of developing pre-patent worms as well. Katayama fever is primarily treated with corticosteroids and praziquantel.

Oxamniquine is a quinoline derivative specific for *S. mansoni* infection. It is given orally in a dose of 20-30 mg/kg/day for 3 days. Fever and eosinophilia may develop 2-3 days after completing treatment.

Metrifonate: This is an organophosphorous compound specific for only *S. hematobium*. It is given orally in a dose of 10 mg/kg every 2 weeks for a total of 3 doses.

Preventive measures should aim at:

1. Proper environmental sanitation and health education;
2. Mass therapy with oral drugs to reduce the worm load;
3. Destruction of snails by proper control of water and use of molluscicides and
4. Avoidance of infection by wearing protective clothing.

Important points

1. In schistosomiasis the pathology is caused by the ova deposited in the tissues.
2. *S. hematobium* infection predisposes to vesical carcinoma.
3. *S. mansoni* infection favors carrier state for *Salmonella typhi*.
4. Neurological manifestations are caused by both *S. japonicum* and *S. mansoni*.
5. *S. japonicum* infection may result in pulmonary hypertension.
6. Mass drug administration using praziquantel is one method of parasite control in endemic regions.

Further reading: Bruno Gryseels et al. Human Schistosomiasis, seminar the Lancet 2006; 368:1106-18.

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Tissue Nematodes

R.K. Shenoy, K.V. Krishna Das

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Lymphatic Filariasis 411**Loiasis 418****Onchocerciasis 418****Other Filarial Infections 419***M. perstans* 419*M. streptocerca* 419*M. ozzardi* 419**Dracontiasis 420****Filariasis**

R.K. Shenoy

General Considerations

Infection by nematodes belonging to the superfamily filarioidea constitutes filariasis. *Wuchereria bancrofti*, *Brugia malayi*, *Brugia timori*, *Loa loa*, *Onchocerca volvulus*, *Dipetalonema perstans*, *Dipetalonema streptocerca* and *Mansonella ozzardi* parasitize man. The distribution of these parasites depends upon the geographical and climatic conditions and the prevalence of the appropriate vector. In India the two species prevalent are *W. bancrofti* and *B. malayi*. The parasites are distributed in different parts of Africa, South America and possibly other areas. The morbidity burden caused by filariasis in India is considerable. Extensive areas are endemic for this disease.

Lymphatic Filariasis

This is caused by *W. bancrofti*, *B. malayi* and *B. timori*. The first two infections are considered in this chapter since *B. timori* is rare and is confined to a few islands in Indonesia. The adult worms living in the lymphatic vessels are responsible for the lesions and hence the name.

Epidemiology

It is estimated that 120 million people throughout the world are infected with *W. bancrofti* or *B. malayi*. Out of this disease burden, India and Sub-Saharan Africa account for about 38% and 34% respectively. Infection by *W. bancrofti* is endemic between latitudes 41° north and 30° south involving most parts of India, Myanmar, Africa, South-East Asia, West Indies, Central America, the Pacific Islands and eastern coastal plains of South America. Infection due to *B. malayi* is restricted to South-East Asian countries and several pockets in India particularly along the coastal and backwater regions of Kerala and Andhra Pradesh. It is now becoming clear that many areas hitherto unsuspected, coastal, midland and even mountainous, are endemic for bancroftian filariasis.

Morphology

The adults of *W. bancrofti* are 4-10 cm long, whereas those of *B. malayi* are only 3-5 cm. The males are smaller than females. The adults are seen coiled in clusters in the lymphatic vessels and their life-span ranges probably from 7-15 years. Periodically, the female worm discharges numerous embryonated eggs (microfilaria) into the lymphatics. These circulate in blood. In India the microfilaria (mf) are most numerous in the peripheral blood at night, whereas in other geographical areas like the Pacific Islands they are present during daytime as well. This phenomenon probably corresponds with the biting habits of the vector mosquitoes and the sleep rhythm of the patients.

When they are not present in peripheral blood, the microfilaria remain in the central parts of circulation in the lungs, liver and spleen. The microfilaria are sheathed, vary in length from 200-300 µ, and are actively motile. The mf of *B. malayi* differ from those of *W. bancrofti* by certain characteristics like increased length of the cephalic space, secondary kinks in the curvature and presence of terminal nuclei in the tail. These help to identify them morphologically. Man is the only known definitive host for *W. bancrofti*, but animals like monkeys and wild carnivores also harbor *B. malayi*.

Life Cycle

The microfilaria are ingested by the vector mosquitoes during blood meals. For *W. bancrofti* many species of *Culex* and some species of *Anopheles* mosquitoes act as vectors. *B. malayi* is transmitted by *Mansonia* and *Anopheles* mosquitoes, the former being more important. The adult worms do not multiply in the host, nor do the larvae multiply in mosquitoes, so that the extent and severity of infection ultimately depend on the number of bites by the infective vector. Further development occurs when the mf are ingested by the appropriate mosquito vectors. In the mosquito the mf shed their sheath, reach the wing muscles, become shorter and thicker, moult twice, and develop further to become the infective form. Depending on the temperature and humidity of the environment and species of the mosquitoes this takes 10-14 days. The infective L3 larvae, which measure 1.4-2 mm x 18-23 μ migrate to the proboscis-sheath to be deposited at the bite wound caused by the mosquito. The larvae enter the skin at puncture sites and reach the lymphatics to grow, mature and mate. Microfilariae appear in circulation 6-12 months after entry of the larva. The severity of infection is determined by the number of adult worms harbored by the host. The microfilaria remain viable for 2-3 months after which they die and are removed by the macrophages of the liver and the lungs (Figs 70.1 and 70.2).

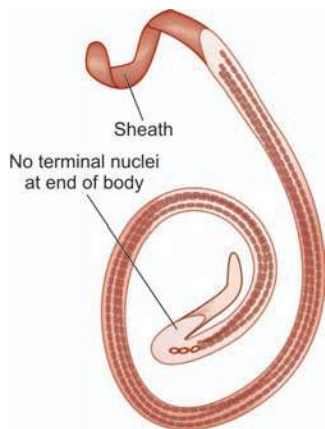


Fig. 70.1: Microfilaria *W.bancrofti*

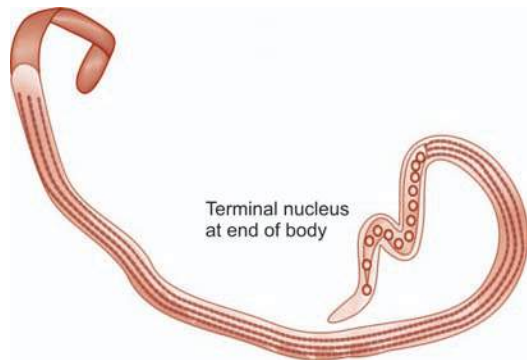


Fig. 70.2: Microfilaria *B.malayi*

Pathology

The adult worms living in the lymph vessels are responsible for the early changes in these vessels. The severity of the pathology depends on the number of adult worms, their location and the host immune response. At one end of the disease spectrum there are many who, in spite of repeated exposure, do neither have microfilaremia nor any lesions. The largest group of affected individuals are asymptomatic who harbour the adult worms and show mf in their peripheral blood, but without clinical disease. The commonest clinical presentation is lymphedema involving the extremities or occasionally the genitalia in both sexes and rarely breasts in the females. At the other end of the clinical spectrum is tropical pulmonary eosinophilia syndrome, which results from an exaggerated immune response of the host. It is classified under occult filariasis.

Spectrum of disease in lymphatic filariasis

- Endemic normals
- Asymptomatic microfilaremia
- Clinical disease
- Tropical pulmonary eosinophilia syndrome

Recent studies have revealed that the earliest lesion in lymphatic filariasis is dilatation of the lymph vessels harboring live adult worms. This is demonstrable by ultrasound scan and lymphoscintigraphy, in even asymptomatic patients harbouring microfilaria. Dilatation is responsible for the later lymphatic dysfunction and lymph stasis. It predisposes to secondary bacterial infections and development of lymphedema in the affected regions. The alterations in the immune response of the host and the parasite products probably contribute to the lymphatic dilatation (Figs 70.3 to 70.6).

Infection by *Str. haemolyticus* and occasionally other bacteria produces recurrent episodes of acute adenolymphangitis (ADL), also termed acute dermato-



Fig. 70.3: Filarial lymphedema with acute adenolymphangitis



Fig. 70.4: Late stage of filarial lymphedema of leg



Fig. 70.7: Fungal infection in the interdigital web space in a case of filarial lymphedema



Fig. 70.5: Warty excrescences in a filarial foot



Fig. 70.6: Large nodular excrescences in a filarial leg

lymphangio-adenitis (ADLA) because of the sequence of events i.e., inflammation of the skin, lymph vessels and then lymph nodes. These involve the limbs or sometimes

genitalia, where there is underlying lymphatic damage. ADL presents as acute febrile episodes. In most patients with acute ADL attacks, sites of entry for the bacteria are demonstrable in the limb involved (Fig. 70.7). These include fungal infections of the interdigital spaces, minor injuries or other lesions that damage the skin barrier allowing entry of bacteria. Moisture and damp environment favor the development of the skin lesions. This accounts for their greater frequency during rainy season. Repeated ADL attacks lead to progression of the lymphedema and later elephantiasis of the affected region. In elephantiasis the edema is non-pitting. There is thickening of the skin and gross hypertrophy of the subcutaneous tissues. The skin may show warty or nodular excrescences.

In the early stages of lymphedema there is evidence of subacute inflammation in the affected tissues and in the draining lymph nodes. There is predominant polymorphonuclear infiltration. As the disease advances there is further dilatation of lymphatics, proliferation of the lymphatic endothelium and new lymph vessel formation. Late stages of lymphedema show obstructive changes, gross thickening and fibrosis.

The dilation and rupture of the lymphatics lead to oozing of lymph - lymphorrhage. This favors secondary infection. Common sites of lymphorrhage are the scrotum (lymph scrotum) and lower extremities (Lymphorrhage). Rupture of lymph varices around the renal pelvis leads to presence of chyle in the urine (chyluria). Rupture of peritoneal lymphatics leads to chylous ascites i.e. the presence of chyle in the ascitic fluid, which makes it milky. Dilatation leading to dysfunction of lymphatics of the spermatic cord and the para-aortic lymphatics leads to collection of fluid in the tunica vaginalis testes - hydrocele. Similarly chylocele may occur due to the rupture of these lymphatics.

When the adult worms die this leads to granulomatous changes with predominant eosinophilic infiltration. The dead worms may get calcified.

Immunology

Immune mechanisms play the major role in the pathogenesis and clinical manifestations of filariasis. The adult worms remain in the host for long periods without evoking host defense response by producing anti-inflammatory substances. The T lymphocyte responses lead to production of interleukins 4 and 5 (IL4 and IL5). *B. lymphocytes* are stimulated to produce IgE and IgG4 which are associated with eosinophilia. IgG4 blocks the action of IgE, thereby reducing the host immune response. In the tropical pulmonary eosinophilia syndrome the hyperimmune response with high levels of IgE is characterized by increase in eosinophils in the absence of microfilaria in peripheral blood.

6 Role of Wolbachia in Lymphatic Filariasis

Recent studies have shown the presence of endosymbiotic bacteria of the genus *Wolbachia* in the adult filarial worms. *Wolbachia* are required for the homeostasis of their hosts. Destruction of these bacteria by drug intervention results in profound effects on the development, viability and fertility of the adult parasite. The role of these bacteria in the pathogenesis of filariasis and the inflammatory episodes is currently under investigation.

CLINICAL FEATURES

The incubation period is from 5 to 12 months. There are acute and chronic clinical manifestations.

ACUTE MANIFESTATIONS

Attacks of adenolymphangitis (ADL) are the commonest acute clinical manifestations, which may occur both in the early and late stages of the disease. These are characterized by fever, lymphangitis, lymphadenitis or epididymo-orchitis. Fever is usually moderate and intermittent but sometimes it may be high, associated with severe rigor, sweating and delirium. The affected area is painful, tender, warm, red and swollen. Inguinal, axillary and epitrochlear lymph nodes, lower and upper limbs or genitalia are frequently affected. In *B. malayi* infection genital involvement is rare, and lower limbs below the knee and upper limbs below the elbow alone are involved. These acute ADL attacks recur many times a year in patients with lymphedema. Common sites for lymphangitis are the inner aspects of the thighs, legs, and arms. Repeated episodes of lymphangitis lead to distal edema, which resolves initially but later on tends to persist. Other acute manifestations are funiculitis, orchitis and epididymitis. Rarely scrotal pain, abscess formation in the breast in females or lymphadenitis in the abdomen resembling a picture of acute appendicitis or psoas abscess may occur. Hematuria, usually microscopic is seen sometimes in patients with microfilaremia.

Acute manifestations directly caused by adult worm death are usually rare and they occur when the adult worms are destroyed in the body either spontaneously or by drugs like diethylcarbamazine or albendazole. These true attacks of *acute filarial lymphangitis* (AFL) are characterized by formation of small tender nodules at the location of adult worms either in the scrotum or along the lymphatics in the limbs. Lymph nodes may become tender. Inflamed large lymphatics may stand out as long tender cords underneath the skin, usually along the lateral aspect of chest or upper arm and axilla associated with painful restriction of movement of affected limb. Unlike ADL, these episodes are not associated with fever, toxemia or evidence of secondary bacterial infection.

Manifestations of lymphatic filariasis	
1. Early silent phase:	Clinically asymptomatic Microfilaria present in peripheral blood Dilatation of lymphatics demonstrated by ultrasonography and lymphoscintigraphy
2. Acute manifestations:	Acute adenolymphangitis Acute epididymo-orchitis, funiculitis Acute onset hydrocele due to inflammation Abscess formation Acute abdominal lymphadenitis Hematuria
3. Chronic manifestations:	Lymphedema/elephantiasis of extremities, genitalia and breasts Hydrocele Lymph scrotum Chyluria, Chylocele, Chylous ascites Lymph node enlargement Lymphadeno-varix

Chronic Manifestations

The commonest permanent sequel of the disease is lymphedema, which may be pitting on pressure in the early stages. But in later stages it is non-pitting leading on to elephantiasis, which may attain enormous sizes. Lower limbs, external genitalia in males and upper limbs are affected in the order of frequency. In females, the breast and the genitalia may develop elephantiasis at times. This feature is rare in India. Repeated ADL episodes are responsible for the progression of lymphedema.

Hydrocele of the tunica vaginalis is a common manifestation resulting from involvement of the para-aortic group of lymphatics. The skin of the scrotum may be covered with vesicles distended with lymph giving a soft velvety feel known as lymph scrotum. Chylous ascites and chyluria, often associated with hematuria may result from rupture of dilated peritoneal or perirenal lymphatics. Spongy lymphadeno-varix is another chronic manifestation. In this condition, the lymph nodes, usually in the groin are enlarged, soft and spongy, the swelling becoming prominent in erect posture. Usually there is associated lymph scrotum, chylocele or chyluria.

Lymphatic Filariasis in Children

Infection acquired in childhood: It is now known that filarial infection is first acquired mostly in childhood. Lymphedema of the limbs, hydrocoele and ADL attacks are known to occur in children and young adults in endemic areas. Recent studies have indicated the extent of microfilaremia and circulating filarial antigens in children aged 3 years and above. Lymphoscintigraphy has demonstrated lymph vessel dilatation and ultrasound has shown presence of adult worms in lymph nodes and lymph vessels in children. The current understanding is that lymphatic dilatation once established is irreversible and promotes future progression of the disease. Most children with microfilaremia or lymph vessel dilatation are asymptomatic. Acute ADL attacks and lymphedema are later manifestations, which may be the first clinical presentation.

Diagnosis

The diagnosis is evident when a patient presents with unilateral or asymmetrical bilateral edema of the limbs of long duration associated with recurrent febrile episodes of lymphangitis in an endemic area or if there is history of residence in an endemic area. But diagnosis of filarial infection is not possible clinically in the early asymptomatic phase. The following tests help in the diagnosis of lymphatic filariasis in its various stages.

Differences between chylous and pseudochylous urine		
Characteristics	Chylous urine	Pseudochylous urine
a. Appearance	Milky	Cloudy
b. On keeping for hours	Fat containing high triglycerides float on top	Pus and debris settle in the bottom
c. Triglyceride content	>110 mg/dL	<110 mg/dL
d. Mixing with ether, or other fat solvents	Fat dissolves, urine becomes relatively clear	No change
e. Microscopy	RBCs, lymphocytes, fat, microfilaria	Cellular debris, pus cells or malignant cell

Microfilaria Detection Tests

Due to the periodicity of the parasite, mf are detected usually by examination of peripheral blood at night. They are detectable in the early stages of the disease even before clinical manifestations develop. Once lymphedema develops microfilaria are rarely seen in the peripheral blood. But hydrocele may be associated with microfilaremia.

Examination of a blood smear obtained by finger prick method from the patients between 10 PM and 2 AM and stained with Leishman or Geimsa stain helps in the identification of the parasite and species. Motile mf are generally seen in fresh thick wet films and this helps in rapid diagnosis. Concentration methods and techniques to filter the mf through nuclepore membrane filters are available to enable easy detection even when mf counts are low and also to quantify the load of infection.

A moderate rise in eosinophils (up to 20 %) is usually present, though this is not invariable. Chylous urine and hydrocele fluid may show microfilaria.

Sometimes pyuria with disintegration of the cells may superficially appear milky. This is termed pseudochylous urine.

Histological examination of lymph nodes or swellings may reveal the adult worms.

Immunochromatographic Test (ICT)

Both card and ELISA based ICT are highly specific and sensitive for the diagnosis of *W.bancrofti* infection. This is a filarial antigen detection test, which can be done on blood collected even during daytime. This test is positive in early stages of the disease when the adult worms are alive and becomes negative once the worms are dead. This test is not currently available commercially.

For *B. malayi* infection a recombinant antigen-based ELISA and its modification, the ‘Brugia Rapid’ dipstick test, are currently available. This test detects filariasis specific IgG4 antibody in *B. malayi* infection. Both these tests are highly sensitive and specific.

Ultrasonography: Live *W.bancrofti* adult worms can be visualized in the scrotal lymphatics of microfilaremic males by ultrasonography using special techniques. ‘Filarial dance sign’ is the demonstration of the wriggling movements of the live adult worms on ultrasonography.

Lymphoscintigraphy: Another imaging modality of the lymphatics is lymphoscintigraphy. This procedure has shown dilatation of lymph vessels in the limbs of amicrofilaremic, asymptomatic individuals including children. Lymphoscintigraphy is also useful in advanced lymphedema to delineate the pathology in the lymph channels and to determine their patency to plan lympho-venous shunt procedures (Figs 70.8 and 70.9).

Even though several tests are available for laboratory diagnosis, in the present situation in India, the diagnosis has to be arrived at by clinical findings, geographical considerations and probability. The fact that microfilaria are seen in the night blood only in the asymptomatic phase and that too in around 30% of the cases, makes early diagnosis difficult.

Definite differentiation between filariasis due to *W.bancrofti* and *B.malayi* is possible only during the early

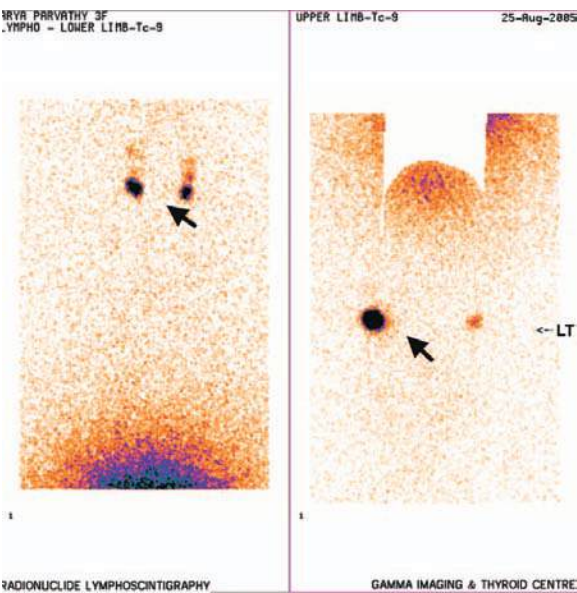


Fig. 70.8: A normal lymphoscintigram of the lower and upper limbs after injecting Tc99m tagged Sulphur colloid in the interdigital spaces. The inguinal and axillary lymph nodes are imaged. Normal lymph vessels are not visualized

asymptomatic microfilaremic phase, by examining the morphological characteristics of the microfilaria. The ICT helps in the diagnosis of *W.bancrofti* infection when the adult worms are alive. The table below lists some of the differences between the diseases produced by these two species.

Differences between <i>W.bancrofti</i> and <i>B.malayi</i> infection		
Characteristics	<i>W.bancrofti</i>	<i>B.malayi</i>
a. Global prevalence	106.2 million	12.9 million
b. Global distribution	Tropical regions of Asia, Africa, China, Pacific and Americas	China, India and other South-East Asian countries
c. Distribution in India	12 States and Union Territories	7 States only
d. Incubation period	5 to 12 months	2 to 12 months
e. Sites of involvement	Extremities, Genitalia and breasts	Only extremities: Lower limbs below knee Upper limbs below elbow
f. Immunology tests	ICT card test and ELISA for circulating filarial antigen	Brugia Rapid and ELISA for filariasis specific IgG4
g. Sensitivity to drugs	Less sensitive to DEC	More sensitive to DEC

Mixed infections by both the parasites are encountered occasionally in some endemic regions where both are

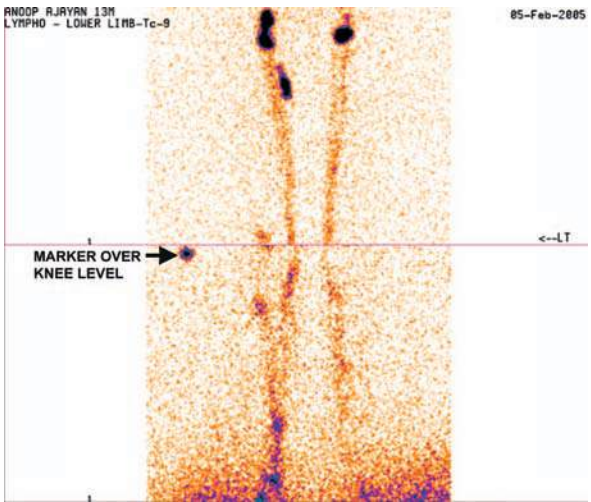


Fig. 70.9: Lymphoscintigram showing dilated lymph vessels in both legs of a child with asymptomatic microfilaremia. Dilation of the lymph vessels is caused by the adult worms

known to co-exist, while blood is examined for microfilaria. The diagnosis of mixed infection is possible only at this stage since mf are not generally seen once symptoms appear.

Differential Diagnosis

Filarial aetiology should be considered in the differential diagnosis of the following clinical situations:

- Repeated or single attacks of lymphangitis, lymphadenitis or cellulitis
- Unilateral or asymmetrical bilateral swelling of limbs
- Swelling of the scrotum, funiculitis, epididymo-orchitis
- Fever with chills, rigor and delirium
- Persistent eosinophilia

Lymphedema and elephantiasis are also known to occur in other conditions where there are congenital anomalies of the lymphatics, following irradiation to the lymph nodes for treatment of malignancies or following surgical excision of the lymph nodes. Lymphedema of the legs simulating filariasis may also be seen in late stages of carcinoma cervix or carcinoma of the prostate with pelvic floor secondaries. Rarely still, damage to the lymphatics following absorption of particles like silica in certain geographic areas also result in lymphedema. In all the above situations where there are abnormalities in the lymphatics, recurrent ADL episodes are known to occur in the affected limbs due to secondary bacterial infections, thus worsening the edema leading on to elephantiasis, indistinguishable from that of filarial etiology.

MANAGEMENT

Treatment of lymphatic filariasis is described under following heads:

1. Use of drugs acting against the parasite
2. Treatment and prevention of acute ADL attacks
3. Treatment of lymphedema, elephantiasis and hydrocele
4. Control and prevention of filariasis

Drugs acting against the filarial parasite:

There are three drugs now available in this group:

- a. Diethyl carbamazine
- b. Ivermectin
- c. Albendazole

a. Diethyl carbamazine (DEC) is the drug of choice, which is effective in destroying microfilaria even in single annual doses of 6 mg/kg. It is easily available, effective, cheap and has a high safety profile. DEC is shown to kill only over 50% of the adult worms in those who harbor them. By ultrasonography it is shown that even single doses of DEC kill the adult worms when they are sensitive to the drug. If insensitive, even repeated doses do not produce any effect on the adult parasite. This drug does not act directly on the parasite and its action is mediated through the host immune system.

The earlier recommended dose of this drug was 6 mg/kg given daily for 12 days. The rationale of this dosage is under scrutiny in the light of above recent observations. The sustained microfilaricidal effect of this drug even in annual single doses makes it a good tool to prevent the transmission of this disease. The adverse effects produced by the drug in patients with microfilaremia are due to the rapid destruction of the mf and are associated with fever, headache, myalgia, sore throat or cough lasting for 24 to 48 hours. They are usually mild and self-limiting, requiring only symptomatic treatment with analgesic and antipyretic drugs. Direct adverse effects related to the drug are very rare. DEC is known to produce unpleasant side effects in microfilaremia of *O. volvulus* and *Loa loa* infections.

DEC is indicated when there is active filarial infection as evidenced by presence of microfilaria in blood or in hydrocele fluid, demonstration of adult worms by ultrasonography or positive antigen/antibody tests. Single dose of 6 mg/kg is as effective as the 12 days dose both against microfilaria and adult worms. In cases of established lymphedema and ADL, usually there are no adult worms or microfilaria. Recent studies have clearly shown that the ADL attacks respond promptly to antimicrobials and local treatment and that the role of specific antifilarial drugs is not substantiated.

DEC is also the drug of choice in the treatment of tropical eosinophilia syndrome where the drug is to be given for longer periods of 3 to 4 weeks.

b. Ivermectin: This drug acts directly on the microfilaria and in single oral doses of 200 to 400 µgm/kg keeps the blood mf counts at very low levels even at the end of one year. The adverse effects noticed in microfilaremic patients are similar to those produced by DEC but milder due to the

slower clearance of the parasitemia. Ivermectin is not effective against the adult parasite, during ADL attacks or in tropical eosinophilia. So this drug has no role in the treatment of clinical manifestations of lymphatic filariasis. Other benefits of ivermectin are clearance of lice infestation, scabies and some of the intestinal helminths.

c. Albendazole: When given in doses of 400 mg bid for two weeks, this drug is shown to destroy the adult filarial worms, inducing severe scrotal reactions which is the common site in where the adult worms are killed.

Albendazole has no direct action against the microfilaria. But when given in single dose of 400 mg in combination with DEC or ivermectin, the microfilaricidal action of the these drugs becomes more pronounced and sustained. Because of this effect and its action against many intestinal nematodes, albendazole combination with DEC or ivermectin is currently recommended for the Global Programme for the Elimination of Lymphatic Filariasis.

Use of antibiotics against Wolbachia: Studies in animals and recent trials in humans indicate that treatment targeted at Wolbachia, which are intracellular symbionts in the filarial worms may be useful to destroy the adult parasites. Treatment with tetracycline and doxycycline daily for 4 to 6 weeks results in elimination of the bacteria with profound effects on the adult worms like dysembryogenesis and death.

The utility of this form of treatment in lymphatic filariasis is still under trial.

Treatment and Prevention of Acute ADL Attacks

Systemic antibiotics, particularly ampicillin-cloxacillin combination should be instituted. Microbiological examination of the local infective sites help to select the suitable antibiotic. Attention to local site of entry of the organisms is important. Bed rest, analgesics and NSAIDs give symptom relief.

Prevention of further attacks is crucial to reduce the morbidity and economic loss from this disease. Proper foot-care has to be instructed to all patients. We have found the following regimen to be very effective, giving statistical significant results.

- i. The feet should be washed with soap and water daily and wiped dry before going to bed, with special attention to the interdigital folds, cracks and abrasions. Presence of moisture in inter digital spaces promotes fungus infections and excoriation of skin inducing ADL.
- ii. Keep the nails short, clean and promptly clipped.
- iii. Antiseptics such as povidone iodine or chlorhexidine ointment should be applied over cuts and wounds. Antifungal drugs like Whitfield's ointment or clotrimazole cream should be applied over sites predisposed to fungal infection.
- iv. Proper footwear should be worn.

- v. Edematous limb should be kept elevated during sleep.
- vi. Light exercise of the affected limb promotes lymph drainage.

Local care will not be perfect when there is gross elephantiasis with excrescences, warty growths and so on. Such cases may benefit from short or long term systemic antimicrobial therapy.

Treatment of Lymphedema, Elephantiasis and Hydrocele

Use elasto-crepe bandage or tailor made stockings while ambulant. The patient should be instructed to apply the bandage effectively. ADL should be prevented by proper foot hygiene measures.

There are various surgical options like lymph node-venous shunts, omentoplasty and excisional surgery available for established cases of elephantiasis. In elephantoid scrotum and breasts, the thickened skin and subcutaneous tissue can be surgically excised and reconstructed.

Surgery for hydrocele: Surgery is the treatment of choice for patients with persistent hydrocele due to filariasis.

CONTROL AND PREVENTION OF FILARIASIS

Once the clinical disease is established lymphatic filariasis cannot be cured. This is due to the irreversible damage to the lymph vessels caused by the adult worms. So prevention assumes great importance. **The Global Programme for the Elimination of Lymphatic Filariasis**, which has been started in countries with endemic filariasis, from 2000 AD consist of two arms.

- i. Mass chemotherapy using combinations of either DEC or ivermectin with albendazole in single annual doses for 4-6 years or regular use of DEC medicated cooking salt and
- ii. Alleviation of disability in those who have the disease.

Annual mass treatment with the above drug regimens for prolonged periods reduces the microfilaria counts to very low levels, thereby reducing the transmission rate. Mosquito control measures have to be instituted on a long-term basis. Personal protection against mosquito bites can be achieved by the use of bed nets and insect repellents.

Important points

1. Adult worms are responsible for the basic pathology. Microfilaria do not cause any symptoms.
2. Acute ADL attacks are caused by secondary bacterial infection and not by the adult worms.
3. Acute filarial lymphangitis due to adult worm death is very rare.
4. In chronic disease neither the adult worms nor microfilaria are usually present.
5. Once established the pathology cannot be reversed by treatment with antifilarial drugs.
6. Mass drug administration is a feasible way to control transmission of lymphatic filariasis.

Loiasis

Loa loa is prevalent in West and Central Africa and this is commonly known as the African eye worm. The adult worms migrate in the subcutaneous tissues of several parts of the body including the eyes. Adult female measures 70 mm in length whereas the male measures only 30 mm. The thickness ranges from 0.3-0.4 mm. They live for 10-15 years. Sheathed microfilaria are produced and these appear in the blood during day time. This infection is transmitted by *Chrysops* (*C. silacea* and *C. dimidiata*), which act as vectors. In many endemic areas monkeys form the reservoir.

The disease manifests as Calabar swellings, which are recurrent localized allergic inflammatory swellings. The swellings may overlie the adult worms at times. They commonly appear over the limbs or trunk. When the eyes are affected, intense lacrimation and pain may result. The adult worm may be seen in the eye during its subconjunctival migration. Endomyocardial fibrosis is more prevalent in areas endemic for loiasis. Rarely the microfilaria invading the nervous system may result in encephalitis, myelitis or focal seizures. The examination of CSF may show the larvae. Diagnosis usually clinical, is confirmed by demonstrating the characteristic microfilaria in the blood during daytime. Eosinophilia is invariably present.

Treatment consists of the administration of diethyl carbamazine, which kills both adults and microfilaria. The dose is 6 mg/kg given for 14 days. Treatment with this drug may produce severe reactions, including encephalitis, in people with heavy microfilariaemia. So ivermectin or albendazole are suggested for initial treatment of patients with high microfilaria counts.

Onchocerciasis

Syn: African river blindness

This is a cutaneous form of filariasis caused by *Onchocerca volvulus* prevalent throughout tropical Africa, Mexico, Guatemala, Eastern Venezuela and Northern Brazil. This disease has not been identified in India.

The female worm measures 35 - 70 cm and the male 2-3 cm in length. The adult worms lie tangled together in the subcutaneous nodules and they live for 7-15 years. The microfilaria, which are unsheathed, are widely distributed in the adjacent skin. The vectors are female black flies belonging to the genus *simulium*.

Pathology

The lesions are caused by the microfilaria. Inflammatory and allergic processes play their roles in pathogenesis. The adults form local granulomas, which appear as subcutaneous nodules. The microfilaria are distributed around these nodules. Their extent and density vary. Dead

or dying microfilaria are responsible for the pathological changes occurring in both anterior and posterior chambers of the eye leading to permanent blindness. The role of *Wolbachia*, obligate intracellular bacteria of filarial parasites, in the causation of ocular pathology is under investigation.

Clinical Features

The adult worms give rise to subcutaneous nodules, which are 0.5-5 cm in diameter. These are firm, non-tender, freely movable and are most commonly seen around the head and shoulders or the pelvic girdle. The skin manifestations are intensely itchy lesions, which in the early stages are seen as papulo-erythematous rashes. Later, the skin becomes thickened, hyperkeratotic (crocodile skin) and depigmented. The penis and scrotum may show elephantoid changes.

Ocular lesions develop especially if the adult worms are numerous over the head and neck. These are punctate keratitis, iridocyclitis and rarely choroidoretinitis, all of which ultimately lead to blindness.

Diagnosis

Demonstration of microfilaria in the skin shavings or skin snips taken from the affected area or the adults in biopsy of the nodules, establishes the diagnosis. Antifilarial antibodies may be detected in 95 percent of cases.

Treatment

The microfilaria are rapidly destroyed by diethyl carbamazine but the drug is ineffective on adult worms. The drug is started in a low dose and gradually worked up to 100 mg given thrice daily for 7-10 days. Severe allergic reactions may complicate the initial phase of therapy. Diethyl carbamazine is no more used in the treatment of onchocerciasis due to the severe systemic and ocular reactions induced by rapid destruction of microfilaria.

Presently **ivermectin** is the drug of choice for the treatment of onchocerciasis. Ivermectin given in a single dose of 150- 200 µg/kg body weight orally is very effective in destroying microfilaria and clearing the systemic and ocular lesions. Thereafter the drug dose is repeated every 6 months or yearly intervals. In the vast majority lesions clear up within six months. This drug is safe and side effects due to destruction of microfilaria are mild and do not adversely affect the eyes.

The drug suramin, a complex urea derivative, is effective against the adult worms. It is given intravenously in doses of 1 g weekly for five to six weeks. Due to complexities of dosage and toxic effects like renal damage this drug is not routinely used.

Recent animal and human studies have indicated that tetracycline or doxycycline given for 6 weeks has macrofilaricidal effect. This is due to the action of these drugs in clearing *Wolbachia* bacteria, endosymbionts of *O. volvulus*.

Ocular lesions have to be treated with mydriatics and topical steroid applications. The adult worms are removed by excision of nodules wherever they are accessible.

Control of infection in endemic areas is achieved by antivector measures, personal prophylaxis and recently, mass therapy for endemic population. Regular administration of ivermectin 150- 200 µg/kg repeated every 6 months or yearly intervals helps to reduce microfilaria rates and transmission from person to person.

Other Filarial Infections

MANSONELLA PERSTANS

This parasite is prevalent in central Africa, South America and the Caribbean. Adults are seen in the subserosal layer of viscera. The pleura, pericardium and peritoneum are involved. In many cases the mesentery is a frequent site. The microfilaria are unsheathed, non periodic and are demonstrable in blood. The vectors are the blood sucking midges-*Culicoides*. Though in the majority of cases infection is asymptomatic, some cases may develop fever, pruritus, skin rashes and abdominal pain. Demonstration of the microfilaria in peripheral blood confirms the diagnosis.

Treatment

Diethyl carbamazine is generally ineffective. Repeated doses of ivermectin effectively reduce the blood microfilaria levels. Success has been reported with mebendazole given in a dose 100 mg twice daily for 30 days and albendazole 400 mg twice daily for 10 days.

MANSONELLA STREPTOCERCA

It is prevalent in parts of Africa. It is transmitted by *Culicoides*. Adult worms are seen in the dermis and subcutaneous tissues. The microfilaria are nonperiodic and they are seen surrounding the adult worms and are demonstrable in skin snips taken from the lesions. Clinical features consist of pruritic papular rashes, edema and hypopigmentation. This worm responds to diethyl carbamazine in the usual doses. Ivermectin 150 µg/kg single dose causes sustained suppression of microfilaremia.

MANSONELLA OZZARDI

This infection has been reported from the tropical regions of South America. Adult worms are found in the visceral

adipose tissue. Microfilaria are nonperiodic and are seen in peripheral blood. Vectors include *Simulium* and *Culicoides*. In the majority of cases this infection is nonpathogenic, though fever, lymphadenopathy and erythematous skin rashes may occur at times. Treatment with diethyl carbamazine is generally ineffective. Single dose of ivermectin is shown to be effective in the treatment of this infection.

Dracontiasis

Syn: Guinea worm, Serpent worm, Dragon worm

Infection by *Dracunculus medinensis* used to be seen in several endemic pockets in India, Pakistan, Iran, Middle East, West Indies, South America and East, West and Central Africa. In India the disease was common in Punjab, Madhya Pradesh, Gujarat, Maharashtra, Andhra Pradesh and Tamil Nadu. At present India has been declared disease-free by the WHO. Endemic pockets are present in some African countries.

Morphology and Habitat

Adult male is 2.5 cm long and is short lived. The female worm is 60-100 cm long and 1.5-1.7 mm in diameter, cylindrical, white and is viviparous. The posterior end is tapering and hook-shaped. Opening of the uterus is at the anterior end. Adult females may live up to one year. Larvae are discharged in batches when the anterior end of the worm comes in contact with water.

Life Cycle

The larvae are taken up by fresh water cyclops, belonging to the family *crustacea* and these form the intermediate hosts. The larvae become infective to man in 10 days. Man gets infected by ingesting the cyclops in water. The larvae are liberated in the intestine and these migrate to the subcutaneous connective tissues to grow into adults in 9-18 months. After fertilization, the females come to lie subcutaneously under those parts of the body, which come in contact with water. A blister develops in the skin where the anterior end of the worm lies, which breaks down to form an ulcer. When the part comes in contact with water the worm protrudes its anterior end through the ulcer and discharges a milky fluid containing a large number of larvae. Over a period of 3 weeks the worm is extruded and the ulcer heals. Infection is generally acquired when the drinking water source is infested with cyclops and people with open lesions contaminate it.

Clinical Features

Initial symptoms include urticaria, eosinophilia, wheezing, nausea, vomiting and diarrhea. Formation of the blister is accompanied by local pain, itching and inflammation. The tissue around the blister may become red, tender, and edematous. Secondary infection of the ulcer is common. Periarthritis and pyoarthrosis may occur if the worms are in the neighborhood of joints. The ulcer may even act as a portal of entry for *Clostridium tetani*. Sometimes the female worm may be palpable in the subcutaneous tissue. Worms that fail to reach the surface die and get calcified. Aseptic abscesses may develop around the worms.

Diagnosis

It is easy to diagnose if the worm is seen in the center of the ulcer, which is characteristic. The worm can be induced to discharge the larvae by applying water over its anterior end. Under the microscope the motile larvae are demonstrable in the discharge from the ulcer. X-ray may demonstrate calcified worms. Blood shows eosinophilia.

Treatment

Local dressing and administration of antibiotics serve to minimize local infection. Removal of the worm is achieved mechanically. The worm is induced to discharge its larvae in water for a few days by which process it protrudes more and more. As the anterior end comes out progressively it is tied with a fine silk thread and rolled up over a matchstick till it is extracted fully over a course of 15-20 days. Live worms are easier to extract. If the worm breaks and its anterior end retracts, the track is likely to be infected. Surgical measures are indicated when conservative treatment fails.

Drug Therapy

Thiabendazole given in a dose 25 mg/kg for 3 days or metronidazole 400 mg daily for 10-20 days offer relief of symptoms, but do not kill the adult worms.

Prevention

The transmission of *D. medinensis* can be interrupted by public education; avoidance of contamination of drinking water source by persons with infective lesions; vector control by chemical treatment of water source and boiling or proper filtration of drinking water. India launched the National guinea worm eradication programme in 1984 with technical assistance from WHO. Since 1996 no fresh case has been reported.

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Sporadic cases of exotic helminthic infections are reported from time to time, man being accidentally infected by helminths parasitizing animals. These include *multiceps*, *intestinal capillariasis*, *anisakiasis*, *angiostrongyliasis*, *gnathostomiasis* and *sparganosis*.

Multiceps Multiceps

This is a tapeworm, the adults of which live in the intestines of dog. The larvae (bladder worm) are seen in the brain of sheep and other herbivores-*Coenurus cerebralis*. Accidentally man may be infected when the brain or eye harbor the larvae.

Intestinal Capillariasis

This has been described from Thailand and Philippines. The adults (*Capillaria philippinensis*) parasitize birds. Fish and crustaceans are the possible intermediate hosts. Infection is acquired by eating raw or partially cooked intermediate hosts. The larvae mature and live in the crypts of the small intestines. They multiply in large numbers and lead to malabsorption state or protein losing enteropathy. Eggs are passed in feces and their identification helps to establish the diagnosis. Prolonged treatment using mebendazole and albendazole is effective.

Anisakiasis

This is caused by *Anisakis* species, which are intestinal nematodes of marine animals. Several species of fish act as intermediate hosts and infection occurs by eating raw or partially cooked fish. Cases have been reported more often from Japan, Netherlands and Scandinavia. The larvae penetrate the stomach wall or intestinal wall, giving rise to pain and symptoms, sometimes simulating acute abdomen. No drug is effective against this parasite. Albendazole is reported to be useful.

Angiostrongyliasis

Man may become infected by *Angiostrongylus costaricensis* or *Angiostrongylus cantonensis*. Adults parasitize several species of rats. *A.costaricensis* is described from central and South America. Man acquires the infection by eating mollusks, which act as the intermediate hosts. Symptoms include abdominal pain, which may even resemble acute abdomen.

A. cantonensis is described from Far East and also from India. Man gets infected by eating molluscs, prawns or crabs, which harbor the larvae. The larvae migrate in tissues. Some reach the brain to give rise to meningitic symptoms. Spinal fluid may show lymphocytes and eosinophils. In the vast majority the disease is self-limiting.

There is no specific treatment available. Angiostrongyliasis can be prevented by proper cooking of crabs, prawns and molluscs before consumption.

Gnathostoma spinigerum

This is an intestinal nematode affecting dogs and cats. The intermediate hosts are fish, which when consumed uncooked leads to human infection. Infection is reported

Diseases Caused by Infections

from Far East, especially Thailand. The larvae do not develop into adults in man, but migrate and lead to the development of eosinophilic granulomas, mostly seen in subcutaneous tissue and brain. Eosinophilia may develop. CNS involvement leads to neurological features. Biopsy of subcutaneous nodules may help to give a histological diagnosis. Serological diagnosis can be made by ELISA testing. Treatment with Ivermectin 200 µg/kg for two days and albendazole 400 mg twice a day for 21 days is effective.

Sparganosis

Sparganum is the second larval stage of tapeworms of the genera *spirometra* and *Diphyllbothria* that are common

in various canines and felines. The ova are ingested by cyclops and the first stage larvae (*proceroids*) develop in them. The *sparganum*, which is the second stage larva, develops in frogs, crustacea and fishes that ingest cyclops. Man may acquire sparganosis by ingesting infected cyclops or by the application of infected frogs or fish as poultices over wounds or inflamed eyes. The condition is seen in Far East. The larva (*Sparganum mansonii*) grows and forms a cyst, which appears as nodular lesion. Treatment is to remove the nodules surgically.

7

Fluid and Electrolytes

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Abnormalities of Water and Electrolyte Balance

R. Kasi Visweswaran

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General Considerations

Water constitutes approximately 60% of body weight. As fat contains less water, obese persons have proportionately less body water compared to lean individuals. Thus, the proportion may vary from 80% in the newborn to 60% in lean and young males and 40% in obese and elderly women. The water in the body is distributed in 2 major compartments, intracellular fluid (ICF) 66% and extracellular fluid (ECF) 34%. The ECF compartment is further subdivided into interstitial fluid (65%), intravascular fluid (25%) and transcellular fluid (10%). In the intravascular compartment, only 10% is in the arterial system. Majority of the fluid is distributed in the capillary system (55%) and venous system (35%). About 10% of extracellular fluid is distributed as CSF, gastrointestinal fluid, serosal fluid, fluids in the eye and others. This is the 'transcellular' fluid. The intracellular fluid constitutes the remaining part of the body water. The composition of the fluid in the intra and extracellular compartment are markedly different.

The total number of anions and cations are equal in all these compartments. Sodium (Na⁺) is the predominant extracellular cation and potassium is the most abundant intracellular cation. The intracellular concentration of magnesium (cation) is also high. Chloride and bicarbonate are the major anions in the extracellular compartment. Phosphates, sulphates and protein contributes to the anions of the intracellular fluid compartment (Table 72.1).

Water Homeostasis

Under normal circumstances, water intake and water elimination are equal and the osmolality of the body fluids

TABLE 72.1

Composition of intra and extracellular fluid compartments		
Substance	ICF	ECF
1. Sodium Na ⁺	10 mmol/L	140 mmol/L
2. Potassium K ⁺	150 mmol/L	4 mmol/L
3. Chloride Cl ⁻	2 mmol/L	104 mmol/L
4. Bicarbonate HCO ₃	6 mmol/L	24 mmol/L
5. Calcium Ca ⁺⁺	50-100 nanomoles/L	2.25-2.65 mmol/L
6. Magnesium Mg ⁺⁺	0.5 mmol/L	0.75-1 mmol/L
7. Phosphates,	1.4 mmol/L	0.8-1.5 mmol/L

Note: For univalent ions the mEq and mmol are the same

is maintained. Water balance is regulated by formation of concentrated or dilute urine. The diluting mechanisms permit the excretion of up to 12-15 litres of urine daily whereas the urinary concentrating ability can achieve full elimination of the daily metabolic waste in as little as 500 mL urine. In health, the urine osmolality could vary from 50 and 1200 mosm/kg. The water intake is mainly regulated by the thirst mechanism. When the plasma osmolality increases by 3-5 mosm/kg, the osmoreceptors in the medulla oblongata are stimulated resulting in thirst. Hypovolemia, hypotension and angiotensin II are also stimuli for thirst. The antidiuretic hormone (ADH or vasopressin) regulates the concentration of urine. In the presence of ADH the collecting tubule becomes more permeable to water and more of water is reabsorbed leading to higher concentration of urine. When the fluid in the collecting tubule traverses the renal medulla, water is reabsorbed into the hypertonic medullary area through these permeable tubules. The increased permeability is achieved by the insertion of water channels called aquaporin channels into the cell membrane of the tubule cells. In addition to the renal losses which can be regulated to some extent, water loss occurs through the skin, lungs and gastrointestinal tract. The loss through the skin and lungs depends upon the climate, exercise and body temperature. Under normal circumstances, the gastrointestinal loss is approximately 120-160 mL per day. If

the daily water loss in a person remaining indoors with outside temperature of 32°C is 200 mL, the loss during heavy exertion outside at temperature over 40°C may be even 5–6 litres.

When there is excess water in the body, the volume expansion results in stretching of the atria, release of atrial natriuretic peptide and promotion of natriuresis and diuresis. The ADH secretion decreases. The collecting tubules become less permeable to water (the aquaporin channels are delinked from the cell membrane) and the dilute tubular fluid is passed out as urine. Thus, the excess water in the body is eliminated.

Sodium Homeostasis

In a healthy adult, the total body sodium is approximately 5,000 mEq. About 90% is in the extracellular compartment. The main function is to maintain the ECF volume, osmolality and blood pressure. Under normal circumstances, the salt intake and excretion are equal. The salt intake of individuals or communities is highly variable. The daily salt requirement is about 6 g or 100 mEq (one level teaspoon = 6 g). In addition to the diet, sodium intake could occur through parenteral fluids or sodium containing drugs. Sodium concentration in the sweat is low. Significant sodium loss could occur in those with excessive sweating and in diarrhea. In health, the kidney is the main route for elimination of ingested sodium. In diseases, sodium loss could occur through other sources also.

Sodium is freely filtered by the glomerulus. The concentration of sodium in the glomerular filtrate is the same as in blood. As the filtrate traverses the proximal tubule, 60–65% of sodium and water are reabsorbed. Thus, the glomerular filtrate remains iso-osmotic at the end of proximal tubule. The next segment contributing to sodium reabsorption is the thick ascending limb of the loop of Henle where the negatively charged chloride (Cl^-) is actively reabsorbed. The sodium-potassium-2 chloride co-transport pump is active in this segment. Sodium (Na^+) which is positively charged accompanies the chloride so as to maintain the electro-neutrality. About 25–30% of sodium is reabsorbed here. As this segment of the tubule is impermeable to water, the fluid leaving the loop of Henle is hypo-osmolar (osmolality < 100). The remaining 10% of the sodium reabsorption occurs in the distal tubule and collecting duct. The reabsorption here is mediated through sodium and chloride co-transporter and $\text{Na}^+ \text{K}^+ \text{ATPase}$. This reabsorption is regulated by aldosterone which causes reabsorption of sodium in exchange for potassium. The fine tuning of the sodium excretion occurs in these segments. Thus, the urine may contain only < 1% of the filtered sodium. In those with high salt intake and normal renal sodium regulation, the urinary sodium excretion will be high.

The controlling mechanism for renal sodium excretion is mediated through afferent and efferent limb. The afferent impulses are from the receptors in atria and pulmonary vascular bed. Activation of these receptors by distension, stretching or pulmonary congestion cause decrease in sympathetic outflow, decreased renal sympathetic tone and natriuresis. Conversely, low central venous pressure leads to sympathetic stimulation and sodium reabsorption. The efferent limb consists of the sympathetic system, hormones and the forces acting on the starling equilibrium. The ‘Starling forces’—the capillary hydrostatic pressure, tissue oncotic pressure, capillary oncotic pressure and tissue hydrostatic pressure play a significant role in the reabsorption of Na^+ in the proximal tubule. The sympathetic stimulation causes increased cardiac output, blood pressure, activation of renin angiotensin system and these enhance sodium reabsorption. The hormonal factors include angiotensin II, atrial natriuretic peptide, prostaglandins and arginine vasopressin.

Disorders of Sodium and Water Balance

The ECF fluid volume and osmolality are maintained in a narrow range despite wide variations in the intake of salt and water. Disorders in water balance result from abnormalities of concentrating or diluting capacity of the kidney. The major causes include renal disease, abnormalities in vasopressin release or action and defective thirst mechanism. Urinary concentrating ability is diminished both in central and nephrogenic diabetes insipidus (DI). Both present with polyuria and dilute urine. The other disorders of urinary concentration include renal insufficiency, solute diuresis, water diuresis, use of osmotic diuretics, loop diuretics, and severe protein malnutrition.

Urinary diluting capacity is diminished in conditions like renal failure, cirrhosis liver, nephrotic syndrome capillary leak syndrome, congestive cardiac failure and conditions associated with decreased arterial blood volume. Severe chronic hypokalemia, hypothyroidism and syndrome of inappropriate ADH secretion are other important causes.

Syndrome of inappropriate ADH (SIADH) release is a common cause of hyponatremia in hospitalised patients. Disorders of urinary dilution often manifest as hyponatremia.

Hyponatremia

Hyponatremia is a common problem in hospitalised patients and is defined as plasma sodium of less than 135 mmol/L. Before confirming the diagnosis of hyponat-

TABLE 72.2

Classification of hyponatremia based on ECF volume status

1. Hyponatremia with decreased ECF volume and low total body sodium (hypovolemic hyponatremia)
 - a. Due to renal losses
 - i. Diuretic use
 - ii. Salt losing nephropathy
 - iii. Osmotic diuresis
 - iv. Cerebral salt wasting
 - b. Due to extra renal losses
 - i. Vomiting
 - ii. Diarrhea
 - iii. Burns
 - iv. Pancreatitis—third space loss
 - v. Trauma
2. Hyponatremia with increased ECF and high total body sodium (hypervolemic hyponatremia)
 - i. Cirrhosis liver
 - ii. Congestive cardiac failure
 - iii. Nephrotic syndrome
 - iv. Advanced chronic renal failure
3. Hyponatremia with normal ECF and normal total body sodium (euvolemic hyponatremia)
 - i. Glucocorticoid deficiency
 - ii. Hypothyroidism
 - iii. Severe potassium depletion
 - iv. Postoperative administration of salt free fluids
 - v. Drugs such as antipsychotics, nicotine, tolbutamide, chlorpropamide, chlorpromazine, carbamazepine and others
 - vi. Syndrome of inappropriate antidiuretic hormone secretion (SIADH)

remia based on low plasma sodium level, **pseudohyponatremia** and **translocational hyponatremia** must be excluded. **Pseudohyponatremia** is a condition characterised by low serum sodium readings when plasma is tested in patients with hyperlipidemia and hyperproteinemia. This occurs because the ‘solid phase’ of plasma is increased and the sodium is low when the plasma is assayed. The osmolality is often normal. This fallacy can be overcome by using potentiometry which measures the true liquid based sodium. Substances like glucose, mannitol or glycine increase serum osmolality while decreasing serum sodium. For every 100 mg increase in blood glucose level, the serum sodium decreases by 1.6 mmols and is due to movement of water from the intra to extracellular fluid compartment due to high sugar. This is an example of **translocational hyponatremia**. Although there may be no symptoms till the level of sodium falls < 120, proper identification and appropriate treatment are necessary.

Hyponatremia could occur acutely (within 48 hours) or may be chronic (over 48 hours). It is classified depending on the ECF status (Table 72.2).

Hyponatremia with decreased ECF volume and decreased total body sodium occurs due to selective loss of intravascular fluid and extracellular fluid.

Hyponatremia with increased ECF volume and increased total body sodium occurs in conditions associated with fluid retention and edema. In these conditions, there may be sodium retention and increase in total body sodium and the disproportionately high water retention causes the hyponatremia. This is predominantly a ‘dilutional’ hyponatremia.

Hyponatremia associated with normal ECF volume and normal total body sodium is a common disorder. Although the ECF volume may be slightly higher, there is no edema and the water is distributed throughout intra and extracellular fluid compartments.

SYMPTOMS AND SIGNS

Most patients are asymptomatic and the diagnosis is based on low sodium levels detected by biochemical tests. The signs and symptoms depend on the rate of onset of hyponatremia and its severity. Mild and moderate cases are generally asymptomatic. Symptoms of acute symptomatic hyponatremia are due to cerebral edema. Cellular edema occurs because the intracellular compartment is hypertonic compared to ECF. Therefore water moves into the cells causing edema. When symptoms occur, they may be nonspecific and vague. Anorexia, lethargy, nausea and headache followed by muscle cramps, drowsiness coma and convulsions may occur.

The early clinical signs of hypovolemic hyponatremia include postural tachycardia and postural hypotension, dryness of the mouth, lack of sweating in axilla and poor skin turgor. The urine volume may be reduced and there may be elevation of urea and uric acid. Urinary sodium is more than 20 mmol/L in renal causes and less than 20 mmol/L in extrarenal causes of hypovolemic hyponatremia. Clinical edema occurs when more than 5 L of fluid accumulates in the interstitial fluid compartment.

Management of Hyponatremia

In acute symptomatic hyponatremia developing in < 48 hours aggressive correction is warranted in view of the possible complications due to cerebral edema. Correction should be done with normal saline or hypertonic (3%) saline. Total correction to ‘normal blood level’ of around 140 mmol/L is not necessary. Initially, hyponatremia may be corrected to achieve blood level of 120 mmol/L. The rate of correction should not be over 1.5-2 mmol/L/hour and the correction is given till symptoms improve or a correction of 10 mmol/L in 24 hours is achieved. It is not safe to correct hyponatremia by more than 10 mmol/L in 24 hours. The amount of sodium required can be calculated from the formula ($120 - \text{present serum Na}^+ \text{ level}$) $\times 0.6 \times \text{body weight in kg}$. 1 litre of 3% sodium chloride provides 512 mmol Na^+ and 1 litre of 0.9% sodium chloride (normal saline) provides 154 mmol of Na^+ . If a person weighing 54 kg has serum sodium 110 mmol/L and is symptomatic, the aim is to correct at 1.5 mmol/L/hr initially up to a maximum of 10 mmol/L per day. The

total volume of 3% sodium chloride to be administered is calculated as follows. Level of Na^+ to be achieved (120) minus present level of Na^+ , i.e.) $110 \text{ mmol} \times 0.6 \times 54 \text{ body weight (54)} = 324 \text{ mmols}$. This is contained in 630 mL of 3% saline. This amount of fluid should be infused within 16-24 hours.

In chronic asymptomatic hyponatremia, aggressive correction is not required. Aggressive correction of chronic hyponatremia may lead to osmotic difference between intra and extracellular compartments resulting in movement of water from intracellular to extracellular space. The changes of cellular dehydration manifest mainly in the CNS and present as osmotic demyelination syndrome (central pontine myelinolysis). Chronic symptomatic hyponatremia evolves in more than 48 hours. Correction must not be aggressive. Initial correction of 10% (approximately 10 mmol/L) is achieved over 24-48 hours. This is followed by correction at the rate of 1-1.5 mmols/L/per day. Hypertonic saline should be avoided. Fluid restriction is the mainstay in chronic asymptomatic hyponatremia. The underlying problems like hypothyroidism, adrenal insufficiency, SIADH or intake of drugs like lithium should be looked for and corrected.

Hypertatremia

Hypertatremia is a disorder of sodium and water homeostasis associated with serum sodium level of more than 145 mmol/L. It may be symptomatic or asymptomatic. Hypertatremia may occur when there is more water loss than sodium loss or more sodium gain than gain of water in the body. As in hyponatremia, hypertatremia can be associated with ECF volume contraction, ECF volume expansion or normal ECF volume (Table 72.3).

TABLE 72.3

Causes of hypertatremia

- A. Hypertatremia associated with low ECF volume (more water loss compared to sodium loss)
 - i. Hyperosmolar nonketotic diabetic coma
 - ii. Use of osmotic diuretic – mannitol
 - iii. Tube feeding with high osmolar fluid
 - iv. Hot humid weather, febrile convulsion, excessive sweating
 - v. Post-obstructive diuresis and recovering acute tubular necrosis (ATN)
 - vi. Gastroenteritis
 - vii. Peritoneal dialysis with high concentration dextrose solutions
- B. Hypertatremia with hypervolemia (higher salt intake compared to water)
 - i. Excessive intake of NaHCO_3
 - ii. Excessive infusion of normal/hypertonic saline
 - iii. Salt water drinking/drowning
- C. Hypertatremia with normal ECF volume (mainly due to loss of free water and defective thirst mechanism)
 - i. Central diabetes insipidus (DI)
 - ii. Nephrogenic DI
 - iii. Psychogenic/polydipsia

CLINICAL MANIFESTATIONS

Infants, elderly patients, those with underlying polyuria, hypertonic fluid infusions, osmotic diuretics, those on mechanical ventilation, or uncontrolled diabetes are at increased risk for hypertatremia. Since hypertatremia represents a hyperosmolar state, the signs and symptoms are related mainly to the CNS.

Since hypertatremia often occurs in hospitalised sick patients and in predictable clinical settings, careful monitoring and prevention is very important. The mortality in children due to acute hypertatremia varies ($50 \pm 20\%$). Many of the survivors may have long-term neurological sequelae. The mortality in chronic hypertatremia is about 10%.

Management of Hypertatremia

The primary aim of therapy is to restore the serum tonicity. If hypovolemic hypertatremia is associated with hypotension or orthostatic hypotension, initially these patients are given IV normal saline till the systemic hemodynamics and hypotension are corrected. Subsequently, administration of half normal saline (0.45% NaCl infusion) or 5% dextrose can be used to replace more water than sodium.

In hypervolemic hypertatremia, the aim is to eliminate the excess sodium but at the same time administering water. Use of diuretics combined with 5% dextrose IV can achieve this. Those with renal impairment may need dialysis because the response to treatment may not be prompt. In euvolemic hypertatremia, the water loss from the body is in excess of salt loss. These patients can be managed by 5% dextrose infusion or encouraging oral intake of plain water. the dietary sodium and protein are restricted. Thiazide diuretics cause more natriuresis than water diuresis. The correction of hypertatremia should be gradual and not at a rate greater than 1.5 mEq/L/hr and the total correction can be achieved over 48-72 hours.

Disorders of Potassium Homeostasis

Potassium (K^+) is the major intracellular cation. The body contains approximately 3,500 mmol of K^+ (roughly 50 mmol/ kg) and is distributed as 90% intracellular, 8% in bone and 2% is in the ECF and serum. The presence of K^+ in the ECF is critical for cellular depolarisation and the serum potassium is maintained between 3.5 and 5.5 mmol/L. The level of serum K^+ does not reflect the total body potassium. The average normal intake of potassium is 60-80 mmol/day. This is eliminated mainly through urine (80%), gastrointestinal tract (15%) and sweat (5%). Fruits, fruit juices, dry fruits, tender coconut water, beans, chocolates and vegetables are rich in potassium. Dietary potassium is absorbed and it is driven into the cells by insulin. The sodium potassium ATPase pump in the cell wall constantly shifts the potassium to the inside and sodium out of the cell. In the kidneys, the potassium is

completely filtered by the glomerulus. The potassium in glomerular filtrate is conserved or eliminated depending on the needs of the body. About 65-70% of potassium is reabsorbed in the proximal tubule. About 25% reabsorption that occurs is in the thick ascending limb of the loop of Henle and is mediated by the $\text{Na}^+ \text{K}^+ \text{Cl}^-$ co-transport system on the luminal side of the tubular cells. The fine control of renal potassium elimination occurs in the collecting duct. There are two types of cells in cortical collecting ducts—*The principal cells and the intercalated cells*. Principal cells are concerned with K^+ secretion. This is enhanced by increased luminal flow rate, sodium concentration, aldosterone and pH. In the intercalated cells, potassium reabsorption occurs in exchange for H^+ ions through the $\text{K}^+ - \text{H}^+$ ATPase. Thus, the normal kidney regulates the serum K^+ level. In hypokalemia, urinary loss of > 30 mmol/day reflects renal potassium wasting and in hyperkalemia urinary loss of < 30 mmol/day suggests primary renal disease.

Trans-tubular potassium gradient (TTKG) provides an indirect measurement of the net K^+ secretion in the distal nephron. It is calculated as follows:

$$\text{TTKG} = \frac{\text{Urinary potassium}}{\text{Serum potassium}} \times \frac{\text{Serum osmolality}}{\text{Urinary osmolality}}$$

Normal TTKG is 5 to 10.

In hypokalemia, if the kidney is functioning normally, the TTKG will be less than 5. If the TTKG is > 10 it suggests inability of kidney to reabsorb potassium and hypokalemia is due to primary renal disease, e.g. renal tubular acidosis (types I and II) and Bartter's syndrome.

In hyperkalemia if the kidneys are normal, TTKG will be more than 10. In hyperkalemia due to aldosterone deficiency or resistance to aldosterone, and in renal failure, TTKG will be less than 5 indicating inability of the kidneys to excrete K^+ ions.

HYPOKALEMIA

In hypokalemia, the serum potassium (SK^+) level is less than 3.5 mmol/L. In early stages, it is asymptomatic and is incidentally detected by investigations. Many conditions are associated with development of hypokalemia.

Common causes includes:

1. **Diuretic therapy:** Most diuretics except the K^+ sparing diuretics can lead to hypokalemia.
2. Pyloric stenosis and continuous gastric drainage will lead to HCl loss, alkalosis and volume contraction. Renin angiotensin—aldosterone axis is activated due to hypovolemia. Aldosterone causes sodium reabsorption and potassium excretion and leads to hypokalemia.
3. **Alcoholism:** The hypokalemia that occurs in alcoholism is due to poor intake, gastric loss due to vomiting and urinary loss.

4. **Renal tubular acidosis:** Both distal (Type I) and proximal (type II) are associated with urinary K^+ loss and hypokalemia.
5. **Antibiotic induced hypokalemia:** Antibiotics like penicillin, carbencillin and gentamicin cause hypokalemia due to excessive secretion of K^+ by renal tubules.
6. Amphotericin B produces type I (distal) RTA and hypokalemia.
7. **Hyperaldosteronism:** Any condition causing primary and secondary hyperaldosteronism causes hypokalemia.
8. **Bartter's syndrome,** a syndrome characterised by hyperreninemia, hyperaldosteronism, metabolic alkalosis and hypokalemia is associated with hyperplasia of juxtaglomerular apparatus. It is associated with failure to thrive, polyuria and muscle cramps.

Other conditions causing hypokalemia are acute leukemia, magnesium deficiency, chronic diuretic or laxative use, salt losing nephropathies, familial hypokalemic periodic paralysis, Cushing's syndrome, steroid therapy, ectopic ACTH secretion, insulin administration, use of Beta 2 adrenergic agonists (salbutamol) and metabolic alkalosis.

CLINICAL MANIFESTATIONS

Even though the laboratory report may show low levels of K^+ , most patients are asymptomatic till Serum K^+ levels are below 3 mmol/L. In hypokalemia, major manifestations are due to functional cellular abnormalities in skeletal muscle, smooth muscle, cardiac muscle and renal cells. Initially, the motor power is diminished particularly in the lower limbs. This is followed by weakness or paralysis. The deep tendon reflexes may remain normal initially. The severe myopathy may progress to rhabdomyolysis, myoglobinuria and acute renal failure. Paralysis of respiratory muscles may also occur. The manifestations relating to cardiac muscle involvement is more in digitalised patients or those with ischemic heart disease. The electrocardiographic changes are non-specific ST-T changes and more specific U wave changes (Fig. 72.1). In the kidney there is vacuolation of renal tubular cells, leading to polyuria, polydipsia, metabolic alkalosis, increased ammonia synthesis and increased acid excretion in urine. The presence of acid urine in the setting of metabolic alkalosis is called **paradoxical aciduria** and it is a common feature in hypokalemic states. The other renal manifestations include reversible renal failure due to the changes in the renal tubule, phosphaturia, hypophosphatemia, hypocalcemia and water retention. In hypokalemic states, the release of insulin from pancreas is blunted resulting in hyperglycemia. In the gastrointestinal system, severe hypokalemia, often associated with hypomagnesemia below 1 mg/dL, results in paralytic ileus.

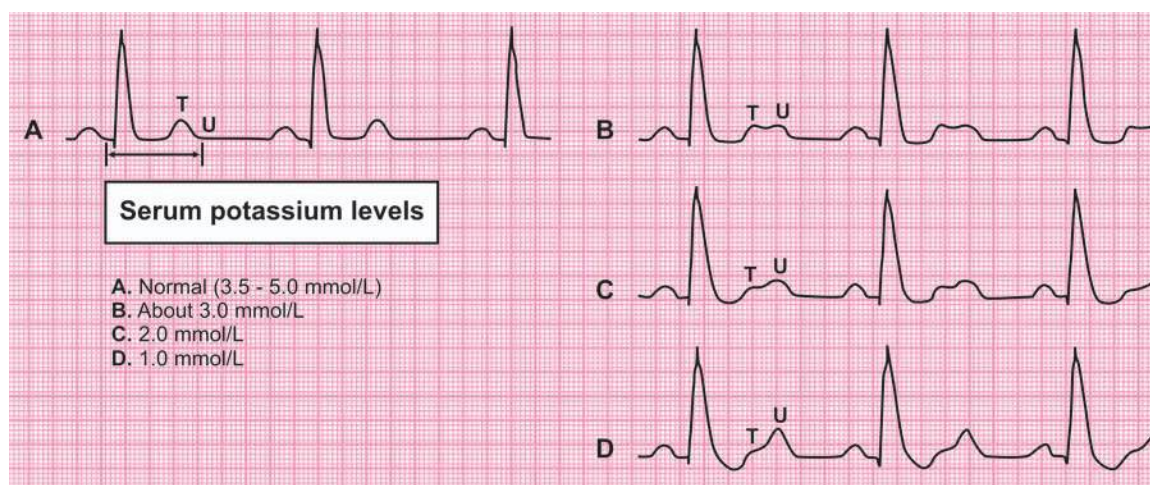


Fig. 72.1: Hypokalemia—ECG.

Note: (1) Flat/inverted T waves, (2) Prominent U waves (3) Prolonged QT interval

MANAGEMENT OF HYPOKALEMIA

While attempting to correct hypokalemia, certain important guidelines are followed. The normal intake of about 60 mmol/day of potassium often prevents the development of hypokalemia. However, cardiac patients on long-term diuretics, digitalis therapy, those on large doses of steroids, ischemic heart disease, and postoperative patients may need higher potassium intake. Since potassium is an intracellular ion, serum potassium level does not truly reflect the total body potassium. One mmol/L fall in serum potassium level represents approximately a total body deficit of 200-400 mmol. If the serum potassium is <2 mmol/L the deficit may be > 600 mmol of potassium. Administration of potassium should be carefully monitored in those receiving potassium sparing diuretics, angiotensin converting inhibitors or angiotensin 2 receptor blockers, and patients with renal failure or oliguria and anuria since this can precipitate hyperkalemia. Oral route is sufficient in most situations. In severe hypokalemia, with paralysis, potassium is given as IV infusion.

Potassium should never be given as a bolus injection or rapid IV infusion since it may cause cardiac arrest and instantaneous death. Intravenous potassium infusions are given only in intensive care units where monitoring facilities are available. The rate of infusion should not exceed 10 mmol/hour and the administration and response should be continuously monitored.

If intravenous potassium administration is needed for severe hypokalemia and in those with symptoms or signs like cardiac arrhythmia, paralytic ileus, respiratory muscle paralysis, severe myopathy or familial periodic paralysis, 100 mEq potassium chloride in 1,000 mL normal saline is given over 10-12 hours. The subsequent dose is decided based on response and blood level. Appropriate supportive measures including ventilatory/respiratory assistance should be available. The correction must be steady and gradual. If the response is not adequate in 48 hours,

concomitant hypomagnesemia must be looked for and corrected with oral or IV magnesium. The 2 important causes for non-responsive nature of hypokalemia are ongoing K^+ loss and associated hypomagnesemia. Potassium supplements are continued as a long-term treatment for those with constant urinary potassium loss.

Once the acute stage is corrected and the renal functions are normal potassium-sparing drugs can be used as adjuvant therapy. Often, it is not necessary to give potassium supplements along with K^+ sparing diuretics like spironolactone, amiloride and triamterene.

If the serum K^+ is between 3 and 4 mmol/L and the patient is asymptomatic, no aggressive treatment is necessary. However, if the patient is receiving diuretic, or laxative or has chronic diarrhea, appropriate potassium supplements in the form of fruits and vegetables or oral potassium chloride supplements may be given. In patients with ischemic heart disease or on digitalis, K^+ level should not be allowed to drop below 3.5 mmol/L as it may induce life-threatening arrhythmias. Serum K^+ level of < 3 mmol/L requires treatment. Oral K^+ replacement is adequate in most patients. Potassium chloride is used for correction of hypokalemia associated with alkalosis. Potassium chloride dissociates into K^+ and Cl^- and is absorbed in the gut instead of Na^+ and HCO_3^- respectively. Thus, the alkalosis and hypokalemia are corrected. The dose is 20 to 40 mmol orally, 2-4 times a day. In those with hypokalemia and acidosis (renal tubular acidosis types I and II) potassium bicarbonate or potassium citrate-based replacement solution may be used. The recommended oral dose is 20-40 mmol of KCl four times a day. During therapy, serum and urinary potassium levels are monitored daily.

Spironolactone, in doses of 25-50 mg, 3-4 times a day is given till the potassium level reaches 4 mmol/L. Thereafter, the dose may be reduced and smaller doses of 25 mg daily are given as maintenance dose. Triamterene and amiloride are other potassium sparing diuretics used.

Since hypomagnesemia, hypophosphatemia, hypokalemia and alcoholism are associated with chronic hypokalemia, correction of the primary conditions is necessary on long-term management. In rare situations of acidosis with hypokalemia, potassium supplements are administered initially to correct hypokalemia before attempting to correct acidosis with IV bicarbonate. For diluting potassium chloride, normal saline is preferred to 5% dextrose. Ringer lactate contains potassium. Most oral rehydration fluids also contain potassium.

HYPERKALEMIA

In hyperkalemia, serum potassium is greater than 5 mmol/L. It is considered moderate if K^+ level is between 5.5 and 6.5 mmol/L and severe if > 6.5 mmol/L. Severe hyperkalemia causes cardiac arrest. A functioning kidney is able to eliminate the potassium from the body efficiently and so most cases of hyperkalemia are due to renal failure. Pseudo-hyperkalemia may be due to errors in blood collection, hemolysis of the sample, leukocytosis or thrombocytosis. In such cases, plasma potassium is re-checked using a properly collected specimen. Though potassium is excreted mainly by the kidney, when the kidney function deteriorates gradually as in chronic renal failure, the gastrointestinal excretion increases and potassium homeostasis is maintained. The risk of hyperkalemia increases when such patients develop oliguria, infection, sepsis, or they consume potassium rich diets or use potassium retaining drugs. Stored blood, fruit juice, angiotensin converting enzyme inhibitors, spironolactone or potassium containing drugs may precipitate hyperkalemia in patients with milder degrees of renal failure.

- Hyperkalemia in these situations may be due to following mechanisms:
 - Kidney diseases:** Failure of excretion of potassium could occur either due to decreased glomerular filtration or due to defective tubular secretion of potassium. Both acute and chronic renal failure cause hyperkalemia. Defective potassium secretion is due to either deficiency or cellular unresponsiveness to aldosterone. Since the kidney cannot eliminate the K^+ rapidly, any rapid increase in exogenous potassium intake invariably causes hyperkalemia.
 - Rapid release of potassium from the intracellular compartment may occur with rhabdomyolysis, tumour lysis syndrome, intravascular hemolysis, trauma causing crush injury, infection and transfusion of stored blood. In most patients with normal renal function and normal urine output, the excess K^+ is eliminated gradually.
- Redistribution of K^+ from intracellular to extracellular compartment as in diabetic ketoacidosis, use of drugs like beta adrenergic blockers, and digitalis overdose can cause hyperkalemia.

- Hypoaldosteronism may be primary or secondary as in diabetes with tubulointerstitial disease. In these patients, the hypoplasia of the juxtaglomerular apparatus leads to hyporeninemia, hypoaldosteronism and hyperkalemia. When the tubular cell is unresponsive to aldosterone as in sickle cell anemia, SLE, amyloidosis or following renal transplantation, hyperkalemia occurs.

Clinical Manifestations and Diagnosis

Hyperkalemia is very often asymptomatic and the diagnosis is made by investigation. Muscular weakness and paresthesias may be the only initial symptoms. Rarely hyperkalemic periodic paralysis may occur. Mild to severe chest discomfort resembling cardiac pain may be the only symptom when the patient presents with ventricular fibrillation or cardiac arrest.

The diagnosis is confirmed by demonstrating serum $K^+ > 5.5$ mmol/L. Electrocardiographic changes characteristic of hyperkalemia evolve through the following stages as the serum potassium level increases from 5.5 to > 9 mmol/L. The relationship between the ECG changes and blood levels is quite variable. The ECG changes are:

- Tall peaked T waves (Serum K^+ 6-7 mmol/L)
 - Prolongation of PR and absent p wave (Serum K^+ 7-8 mmol/L)
 - Widening of QRS (Serum K^+ 7-8 mmol/L)
 - Sine wave, ventricular tachycardia, ventricular fibrillation (Serum K^+ 8-9 mmol/L)
 - Cardiac arrest (Serum $K^+ > 9$ mmol/L) (Fig. 72.2).
- In patients with recurrent chronic hyperkalemia, the following points should be particularly looked for:
- History of intake of potassium in diet, or as potassium supplements.
 - Drugs causing hyperkalemia such as potassium sparing diuretic, beta blockers, Ace inhibitor, H_2 receptor blockers, NSAIDs.
 - The combination of hyperkalemia with hyponatremia should suggest Addison's disease.

Management of Hyperkalemia

In mild and moderate hyperkalemia, attention to potassium intake, avoidance of drugs causing hyperkalemia and correction of acidosis are often sufficient. Cation exchange resins such as sodium or calcium polystyrene sulfonate given orally or as retention enema exchanges sodium/calcium for potassium and helps to eliminate K^+ from the body. 2 g of resin exchanges 2 mmol Na or 1 mmol of calcium for 2 mmol potassium. For oral administration, the resin is given in 20% sorbitol. For retention enema—10% dextrose is used as the vehicle.

Severe hyperkalemia is a medical emergency and is managed as follows:

Step 1-A: 20 mL of 10% calcium gluconate is given as a steady slow intravenous injection over 5-10 minutes and

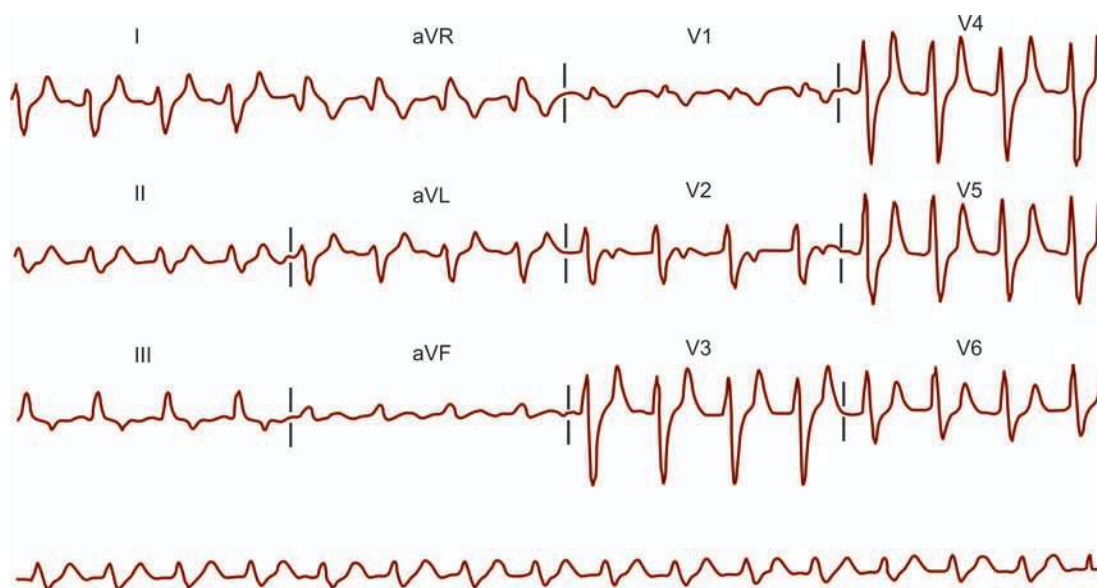


Fig. 72.2: Hyperkalemia—ECG
Note: Read with description in test

repeated once if necessary. The solution should not be injected rapidly as a bolus. Calcium stabilizes the myocardial membrane against the arrhythmias caused by K^+ but the effect is very transient.

Step 1-B: If the patient is acidotic, 100 mL of 7.5% sodium bicarbonate is given IV. 10 mL normal saline should be given after bicarbonate injection before starting IV calcium. Calcium salts and sodium bicarbonate are physically incompatible and they form calcium carbonate when they come into contact with each other. Sodium bicarbonate causes temporary reversal of acidosis and reduces serum K^+ level by causing movement of potassium into the intracellular compartment. This is used only if the patient is clinically acidotic.

Step 2: 100 mL of 25% glucose along with 5 units of regular (crystalline) insulin is infused in 2 hours. Insulin also promotes entry of K^+ into the cells and controls hyperkalemia. Thus, it helps to gain time for initiation of dialysis.

Step 3: High doses of adrenergic agonists such as albuterol or salbutamol (5 mg/mL) when given as nebulisation in doses of 10-20 mg over approximately 10 minutes also shifts the K^+ to the intracellular compartment, thereby reducing serum K^+ level.

Step 4: Both hemodialysis (HD) and peritoneal dialysis (PD) help to remove K^+ rapidly from the body. HD does it faster and more efficiently. The potassium concentration of the HD concentrate or PD fluid can be altered depending on the clinical circumstances.

Step 5: If dialysis facility is not available, removal of K^+ from the body can be achieved by the regular use of

sodium/calcium polystyrene sulfonate. The recommended dose is 15 g 6 hourly orally and it is continued till the serum potassium falls below 5.5 mmol/L. Thereafter smaller doses are given to prevent rise in potassium levels. In all patients with renal failure, low potassium diet and avoidance of offending drugs are necessary.

Hyperkalemia suggests mainly impaired potassium elimination by the kidney and is an asymptomatic “silent killer”. So, early diagnosis and prompt treatment are life saving.

Disorders of Calcium and Phosphate Homeostasis

CALCIUM

Calcium plays a crucial role in cellular functions and is an important ingredient of the bone. Calcium exists in 2 forms, bound and free forms. The bound calcium which constitutes more than 99% of the body's calcium is in bones. The free calcium may be in the ionised or non-ionised forms. It is present in the intra and extracellular fluid compartments. The plasma concentration of total calcium is 9-11 mg/dL. About 50% of this is in the ionised form and is important for cellular functions. The non-ionised fraction of calcium in serum is bound to Albumin. So, a change in serum albumin level alters the proportion of bound and free forms of calcium in blood. The serum calcium level should be corrected for any reduction in serum albumin < 4 g/dL. Corrected serum calcium = Actual serum Ca + 0.8 (4-serum albumin/dL), e.g. if the serum calcium is 10.7 and the serum albumin is 3 g/dL, the corrected calcium will be : $10.7 + 0.8 (4-3) = 10.7 +$

0.8 = 11.5 mg/dL. The plasma concentration of ionised calcium is tightly regulated by parathormone, calcitriol $1,25(\text{OH})_2\text{D}_3$ and calcitonin. The ionic calcium is influenced by the acid-base status, estrogens and prolactin. Alkalosis causes fall in ionised calcium. The dietary calcium, approximately 800-1100 mg/day, is absorbed from the intestine and transported to the ECF compartment. In the extracellular space, it is deposited in the bone or eliminated via the kidney. The entry and exit between the skeletal and non-skeletal compartments are equal under steady-state conditions. The kidneys, intestine and skeleton are important in the short, mid and long-term homeostasis respectively.

HYPERCALCEMIA

Hypercalcemia is defined as total serum calcium more than 11 mg/dL. Hypercalcemia results from an increased intestinal calcium absorption, stimulation of bone resorption or decrease in urinary calcium excretion (See section 11 Chapter: 99).

The clinical manifestations of hypercalcemia depend on the degree and rate of its development. Symptoms like fatigue, muscle weakness, nausea, vomiting, constipation, polyuria, headache, amnesia stupor and coma may occur. Soft tissue calcification, nephrocalcinosis and nephrolithiasis occur with longstanding hypercalcemia. The electrocardiogram shows shortening of QT interval, reduction or absence of ST segment, slight increase in QRS duration and prolongation of PR interval (Fig. 72.3). It also amplifies digitalis toxicity. Presence of hypercalcemia can be confirmed by estimating serum calcium level. The underlying causes like primary or secondary hyperparathyroidism, neoplastic disorders and granulomatous diseases should be investigated for.

Severe symptomatic hypercalcemia requires aggressive management with rehydration using saline, use of loop diuretics, correction of acid base imbalance, and use of bisphosphonates.

The use of calcitonin and mitomycin are reserved for malignant hypercalcemia with serum calcium above

15 mg/dL. Steroids may be used in hypervitaminosis D, sarcoidosis and hematopoietic tumours such as myeloma, lymphoma and solid tumours like breast cancer. A new class of calcium receptor (CaR) agonists or calcimimetics are used in primary and secondary hyperparathyroidism.

HYPOCALCEMIA

Hypocalcemia is defined as serum calcium below 8.5 mg/dL. Acute hypocalcemia may occur following acute hyperventilation and respiratory alkalosis. Chronic hypocalcemia is caused by hypoparathyroidism, pseudohypoparathyroidism, vitamin D deficiency states, chronic renal failure and magnesium deficiency (See section 11 Chapter 99).

The diagnosis is confirmed by corrected serum calcium level of < 8.5 mg/dL. If hypocalcemia is associated with high plasma phosphorus, conditions like hypoparathyroidism, pseudohypoparathyroidism and advanced renal failure are the possibilities. In steatorrhea, vitamin D deficiency, acute pancreatitis and recovering acute renal failure, combination of hypocalcemia and hypophosphatemia is seen.

The ECG signs of hypocalcemia include prolongation of the QT interval, flat or inverted T waves in severe hypocalcemia, slight decrease in QRS duration and ST segment lengthening (Fig. 72.4).

PHOSPHORUS

Phosphorus is present in the intra and extracellular fluids. It participates in most metabolic processes including the release of energy from ATP. Apart from being an abundant component of skeleton along with calcium, it is also present in various tissues and cell structures. The plasma phosphorus level is controlled by hormones like PTH and calcitriol. Long-term maintenance of phosphate homeostasis is regulated by renal tubular reabsorption. About 60% of the dietary phosphate is absorbed by the intestine. There is a constant turnover daily between blood and bone phosphorus. The daily renal phosphate excretion equals the intestinal absorption.



Fig. 72.3: Hypercalcemia—ECG. Note: (1) ST segment short or absent, (2) short QT interval, (3) slight increase in QRS duration, (4) PR interval may be prolonged



Fig. 72.4: Hypocalcemia—ECG. Note: (1) prolongation of the QT interval, (2) flat or inverted T waves in severe hypocalcemia, (3) slight decrease in QRS duration, (4) ST segment lengthening

Hyperphosphatemia

Hyperphosphatemia is defined as serum phosphorus > 5 mg/dL. The most common cause is reduced renal excretion as seen in renal failure. Normally, 85-90% of filtered phosphorus is reabsorbed. When the GFR is declining, even though the remaining nephrons eliminate 90% of phosphorus, the serum phosphorus increases because of decrease in the number of functioning nephrons. Other causes of hyperphosphatemia include, hypoparathyroidism, chronic hypocalcemia, acromegaly, hypercatabolic states (tumour lysis and crush injury) and vitamin D intoxication.

Severe hyperphosphatemia decreases serum calcium level which in turn stimulates PTH. This causes increased phosphate excretion and normalisation of hyperphosphatemia. The occurrence of severe hypocalcemia with tetany and ectopic calcification is the most severe manifestation of hyperphosphatemia.

Treatment of the underlying cause of hyperphosphatemia is most important. Low phosphate diet, low protein diet, oral phosphate binders like calcium acetate and magnesium salts may be used. Aluminium containing phosphate binders should be used cautiously in CRF because of toxicity due to aluminium accumulation. A new non-absorbable aluminium and calcium free phosphate binding resin—*sevelamer* is now available and can be used in doses of 800 mg in 3 divided doses.

Hypophosphatemia

It is defined as plasma phosphate level of less than 2.5 mg/dL. It may be caused by genetic diseases or acquired conditions. Inherited hypophosphatemia include Fanconi's syndrome, X-linked hypophosphatemic rickets and distal renal tubular acidosis.

Acquired conditions include malnutrition, alcoholism, diabetic ketoacidosis, acute respiratory alkalosis, oncogenic osteomalacia and total parenteral nutrition. The clinical manifestations depend on the severity of hypophosphatemia. Metabolic encephalopathy, muscle weakness, rhabdomyolysis, hemolysis, thrombocytopenia and leukocyte dysfunction may occur. The cause of hypophosphatemia is identified and treated appropriately. Oral phosphate supplementation is achieved by increasing intake of milk products. Joule's solution containing disodium hydrogen phosphate buffered in phosphoric acid may be used orally for long-term treatment. In severe symptomatic deficiency parenteral potassium phosphate infusions may be given.

Disorders of Magnesium Homeostasis

Magnesium is predominantly an intracellular cation. It is involved in metabolic processes like protein synthesis, regulation of mitochondrial function, and immune and inflammatory processes. It is also involved in the maintenance of vasomotor tone, neuronal activity, cardiac

excitability and neuromuscular transmission. The dietary magnesium averages about 12 mmols/day. Only about 50% is absorbed. The plasma magnesium concentration is maintained between 0.75 to 1.0 mmols/L (1.8-2.4 mg/dL). The absorbed magnesium reaches the intracellular fluid and is either deposited in the bone or soft tissue. The renal elimination approximately equals the intestinal absorption and the magnesium homeostasis is maintained.

Hypermagnesemia

It is defined as serum magnesium level more than 1.9 mg/dL (or 1 mmol/L). The common cause are renal failure and use of magnesium containing drugs. The signs and symptoms are due to the effect of magnesium on the CNS and CVS. Mild cases are asymptomatic. When the serum level increases to 7 to 9 mg/dL (3 mmols/L), deep tendon reflexes are lost. When the level is > 12 mg/dL (5 mmols/L), respiratory paralysis, hypotension, cardiac conduction abnormalities and loss of consciousness occur. The initial step in the emergency management of symptomatic hypermagnesemia is administration of IV calcium.

Hypomagnesemia

It is defined as decrease in total body magnesium content. Malabsorption syndrome and massive resection of small intestine, excessive use of laxatives, chronic alcoholism and uncontrolled diabetes mellitus are the causes of hypomagnesemia. Use of drugs like gentamicin, cisplatin, cyclosporin and overuse of diuretics may also lead to hypomagnesemia. Moderate to severe magnesium depletion may result in general weakness, neuromuscular hyperexcitability with hyper-reflexia, carpopedal spasm, tremor and rarely, tetany. The ECG changes include widening of QRS, prolongation of QT interval, ST depression, low or inverted T wave and occasional U waves (Fig. 72.5). Treatment is by using oral magnesium salts. In emergency, parenteral magnesium sulphate may be used. 1.5 to 3.0 g of magnesium sulphate is given by deep intramuscular route. It provides 150-300 mg of elemental magnesium.

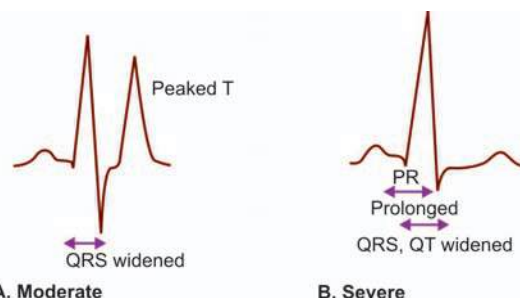


Fig. 72.5: ECG changes in hypomagnesemia (1) Peaked T waves, T wave amplitude falling progressively in severe deficiency, (2) QRS widened, QT widened, (3) P-R interval prolonged, (4) 'U' waves may develop, (5) ST segment depressed.

Hypermagnesemia: It is uncertain whether hypermagnesemia *per se* leads to any pathognomonic ECG changes

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Abnormalities of
Acid-base Balance

R. Kasi Visweswaran

Chapter Summary

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General Considerations

The pH of the blood and extracellular fluid must be maintained constantly between 7.35 and 7.45 for the viability, normal metabolism and enzyme functions of the cells in the body. The diet contributes to the normal intake of acids and alkali. Metabolism of amino acids like lysine, arginine, methionine, cysteine or organophosphates yield acid. Some amino acids like glutamate and aspartate or substances like acetate and citrate yield alkali on metabolism. Generally, non-vegetarian diet gives rise to more acid production. In addition, the body produces small quantities of organic acids like acetic acid, lactic acid and pyruvic acid. The endogenous acid production is approximately 1 mEq per kg per day. The acids are added to the body as volatile acids and non-volatile acids. They are immediately buffered and transported to the lungs and kidneys for elimination. Carbonic acid (H_2CO_3) is a volatile acid since it dissociates into carbon dioxide and water ($H_2CO_3 \rightleftharpoons H_2O + CO_2$). The lungs help to eliminate approximately 15,000 millimoles of CO_2 daily and regulate the CO_2 concentration. The kidneys excrete the non-volatile acids as titrable acids and ammonium. For each milliequivalent of acid excreted by the kidney, the body gains one milliequivalent of bicarbonate. Thus, the kidneys regulate the bicarbonate concentration.

The buffer systems in the body are very important in preventing the shift of pH of the extracellular fluid. The bicarbonate-carbonic acid buffer system is the most important buffer system in the ECF. The other buffer

systems include hemoglobin, plasma proteins, phosphate ions and the bone. Since the dissolution of the bones provides alkaline calcium salts and adds bicarbonate to the ECF, the bone buffers are utilized in chronic metabolic acidosis.

When the pH of blood falls < 7.35 , the condition is called acidemia and when it rises > 7.45 , it is called alkalemia. The term acidosis and alkalosis are used to denote the pathophysiological process causing the shift in the pH. Hypercarbia is carbon dioxide retention (high $PaCO_2$) and hypocarbia is carbon dioxide washout (low $PaCO_2$). Hypoxemia is low PaO_2 levels in blood.

From the above, we can visualize four primary disturbances in the acid-base equilibrium.

- a. Fall in bicarbonate $\rightarrow$ metabolic acidosis
- b. Rise in bicarbonate $\rightarrow$ metabolic alkalosis
- c. Rise in $PCO_2 \rightarrow$ respiratory acidosis
- d. Fall in $PCO_2 \rightarrow$ respiratory alkalosis

If there is a fall in bicarbonate, the body tries to compensate by achieving a fall in PCO_2 so that the degree of shift in pH is minimized. If hyperventilation is the primary event causing a fall in PCO_2 , the body tries to compensate with lowering of HCO_3 by increasing bicarbonate excretion in urine.

In order to recognize and interpret the acid-base disorder, four parameters are used.

- 1. $PaCO_2$ —from arterial blood gas analysis (ABG) by ABG machine using “anaerobically” collected heparinised arterial blood.
- 2. pH—from ABG or pH meter
- 3. HCO_3 —Measured or calculated from pH and PCO_2
- 4. Anion gap (AG)— $Na^+ - (HCO_3 + Cl)$.

The normal values for above parameters (at sea level) are

pH	—	7.4 ± 0.05
$PaCO_2$	—	40 ± 4 mm Hg
HCO_3	—	24 ± 2 mmol/L
Na^+	—	140 ± 5 mmol/L
Cl^-	—	99 ± 3 mmol/L
AG	—	$8 - 12$ mmol/L

Approaches and interpretations of acid-base disorders is done by correlating the four parameters. A simplified approach is given below.

1. First, look at the pH and decide whether there is acidemia or alkalemia. (pH less than 7.36 is acidemia and pH more than 7.44 is alkalemia).
2. Look at HCO_3^- and decide whether the deviation in HCO_3^- will explain the deviation in pH. If the pH and HCO_3^- both are lowered or increased, the condition is of metabolic origin.
3. Look at PCO_2 and decide whether the deviation in PCO_2 will explain the deviation in pH. If the pH is high and PCO_2 is low, it suggest respiratory alkalosis. If the pH is low and PCO_2 is high, it suggests respiratory acidosis.

Example 1

PH = 7.32, $\text{HCO}_3^- = 18$, $\text{PaCO}_2 = 38$

- Step 1 $\rightarrow$ (pH < 7.35) $\rightarrow \therefore$ Acidemia
 Step 2 $\rightarrow$ HCO_3^- low $\rightarrow \therefore$ metabolic
 Step 3 $\rightarrow$ PCO_2 'normal' $\rightarrow \therefore$ not primary respiratory disorder
 $\therefore$ Metabolic acidosis

Example 2

PH = 7.48, $\text{HCO}_3^- = 24$, $\text{PaCO}_2 = 22$

- Step I $\rightarrow$ (pH > 7.45) $\rightarrow \therefore$ Alkalemia
 Step 2 $\rightarrow$ HCO_3^- normal $\rightarrow \therefore$ Not metabolic
 Step 3 $\rightarrow$ $\text{PCO}_2 = 22$ $\rightarrow \therefore$ Markedly low
 $\therefore$ Respiratory alkalosis

The body 'compensation' follows the "same direction rule" in relation to the numerator and denominator of the

pH equation $\text{pH} \propto \frac{\text{HCO}_3^-}{\text{PCO}_2}$. Thus, the compensatory

response for the four primary disorders are.

a. Metabolic acidosis	Respiratory alkalosis
b. Metabolic alkalosis	Respiratory acidosis
c. Respiratory acidosis	Metabolic alkalosis
d. Respiratory alkalosis	Metabolic acidosis

Anion Gap

The number of cations and anions in the body fluids are equal and neutralize each other. Sodium, potassium, calcium and magnesium are the cations. Bicarbonate, chloride, sulphate, phosphate, organic acid and albumin are the anions. Only sodium, bicarbonate and chloride are taken into consideration for the calculation of anion gap. Anion gap = $\text{Na}^+ - [\text{HCO}_3^- + \text{Cl}^-]$. The gap consists of the anions that are usually not measured or included in the calculation. The normal value for anion gap is approximately 12 ± 2 mmol/L. For the purpose of calculation of anion gap, unmeasured anions (UA) as well as unmeasured cations (UC) and potassium are discarded (Fig. 73.1).

Since albumin is negatively charged, it contributes to the anion gap significantly. The normal anion gap is

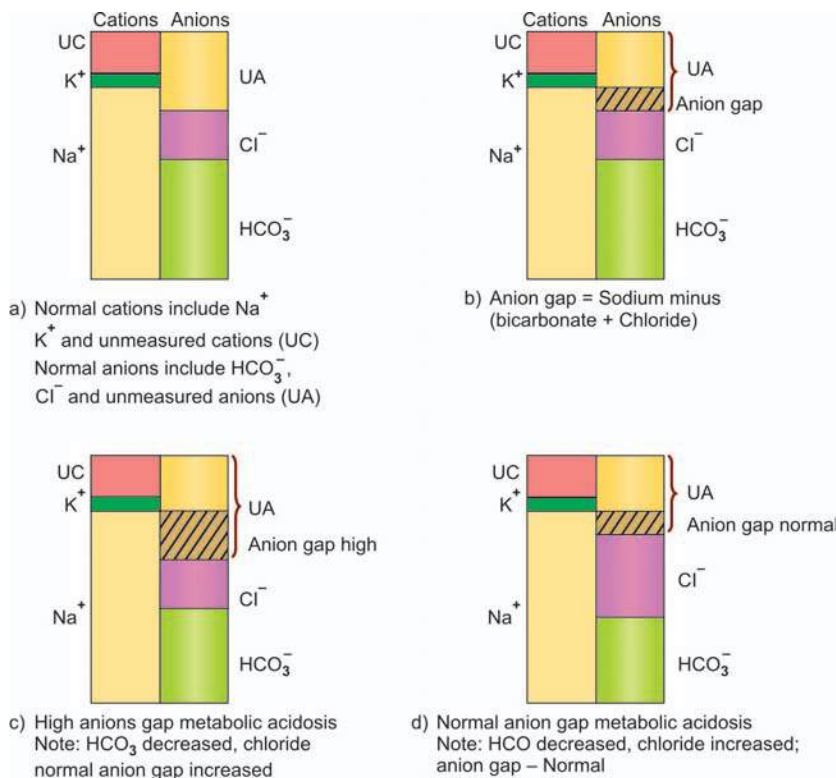


Fig. 73.1: Showing anions, cations, anion gap and types of metabolic acidosis

approximately three times the serum albumin level. Therefore, if the patient has hypoalbuminemia the interpretation of anion gap has to be modified as anion gap is decreased.

If acidosis (low bicarbonate), is associated with high chloride, the anion gap is unaltered. This is hyperchloremic or normal anion gap metabolic acidosis. In such cases the accompanying H^+ ions will be chloride. If the anion accompanying the H^+ ion is not chloride, the low bicarbonate will be compensated to an equal extent by accumulation of an anion other than chloride, e.g. ketoacid, lactic acid, etc. This causes a rise in the anion gap.

A clear understanding of the acid-base equilibrium, the primary disturbances, the 'compensatory' mechanisms, interpretation of ABG results, and identification of mixed acid-base disorders are all absolutely necessary to give the appropriate treatment in emergency situations.

Metabolic Acidosis

Metabolic acidosis occurs when acid is added to the body or when alkali is lost from the body. The metabolic acidosis is broadly classified as high anion gap metabolic acidosis and normal anion gap 'hyperchloremic' metabolic acidosis. Both may occur due to renal or extrarenal causes.

Classification

A. *Metabolic acidosis with high anion gap*

- i. Renal causes – Uremic acidosis due to accumulation of uremic anions occurs when the GFR is < 20 mL/min.
- ii. Extra-renal causes
 - a. Accumulation of lactic acid - (due to incomplete carbohydrate oxidation) lactic acidosis, e.g. shock, sepsis, cirrhosis, malignancies, phenformin and very rarely metformin.
 - b. Accumulation of ketoacids due to incomplete oxidation of fat, e.g. diabetic ketoacidosis, starvation ketoacidosis, alcoholic ketoacidosis.
 - c. Poisoning, e.g. ethylene glycol, methanol, ethanol, isopropyl alcohol, salicylate.
 - d. Gain of exogenous acid, e.g. hydrochloric acid, ammonium chloride, methionine and intravenous hyperalimentation.

B. *Metabolic acidosis with normal anion gap*

- i. Renal causes:
 - Proximal renal tubular acidosis (Type II RTA)
 - Distal renal tubular acidosis (Type I RTA)
 - Hyperkalemic distal RTA (Type IV RTA)
 - Chronic kidney disease with mild renal insufficiency.
- ii. Extrarenal causes:
 - Diarrhea (loss of bicarbonate)
 - Pancreatic/biliary fistula (loss of bicarbonate)

Uretero sigmoidostomy leading to reabsorption of H^+ ions and ammonia in exchange for bicarbonate in the gut.

Use of cholestyramine.

Clinical Features and Diagnosis

The clinical features of metabolic acidosis are similar irrespective of the etiology. In mild degrees of acidosis, increase in respiratory rate and in severe acidosis, deep sighing respiration (Kussmaul's breathing) occurs. A careful history of recurrent stone disease, diabetes, alcoholism, drug therapy, poisoning or overdose should be elicited.

The confirmation of diagnosis is by analysis of ABG along with anion gap.

Management

Management depends on the correction of the underlying disorder. Correction with IV sodium bicarbonate is indicated if acidosis is symptomatic and severe ($pH < 7.2$ and $HCO_3^- < 12$). The dose of bicarbonate is calculated by the formula. Bicarbonate required = $0.3 \times \text{bodyweight in Kg} \times \text{deficit}$. The deficit is calculated by noting the difference between required HCO_3^- (usually 12 to 16) and observed bicarbonate (available lab value). The correction is achieved within 2 to 4 hours and ABG is repeated. In high anion gap metabolic acidosis due to intoxications, removal of the toxins by appropriate measures may be undertaken.

Metabolic Alkalosis

Metabolic alkalosis may be initiated by loss of acids from the body or gain of alkali. Normally, such events are effectively handled by the kidney by removing the excess bicarbonate from blood. Therefore, certain additional factors are required for maintaining metabolic alkalosis. *If metabolic alkalosis is associated with low extracellular fluid (ECF) volume* as in vomiting or diuretic use, there is prompt correction of alkalosis with administration of chloride. This is called chloride responsive metabolic alkalosis. *Metabolic alkalosis is associated with normal or increased ECF* in hyperaldosteronism and Cushing's syndrome respectively. In these conditions alkalosis will be sustained only if renal functions are markedly reduced or alkali loading is very high. Such alkalosis persists despite chloride administration and it is called "*chloride resistant alkalosis*". The urinary chloride helps to distinguish between these two types of metabolic alkalosis. In chloride responsive type, the urinary chloride is less than 10 mmol/L and in chloride resistant alkalosis, the urinary chloride is more than 10 mmol/L. The body

tries to minimize the degree of metabolic alkalosis by reducing ventilation and increasing PaCO_2 .

Classification

The metabolic alkalosis is classified as chloride responsive, chloride resistant, and miscellaneous.

A. Chloride responsive metabolic alkalosis

- a. Gastric acid loss
 - i. Vomiting
 - ii. Gastric drainage
 - iii. Pyloric stenosis
- b. Urinary loss—Diuretic therapy (thiazides, metolazone, frusemide, torsemide, bumetanide and ethacrynic acid)
- c. Fecal loss—Congenital chloride diarrhea, villous adenoma of colon
- d. Recovery from chronic hypercapnia

B. Chloride resistant metabolic alkalosis

- a. Hyperaldosteronism
 - i. Conn's syndrome
 - ii. Cushing's syndrome
 - iii. Bartter's syndrome
 - iv. Liddle's syndrome
 - v. Liquorice ingestion

C. Miscellaneous

- a. Alkali administration
 - i. Milk - alkali syndrome
 - ii. Massive blood transfusion, due to excess of citrate
 - iii. Alkali supplements
- b. Hypercalcemia
- c. Poorly absorbable anion administration (e.g. antibiotic like carbencillin).

Clinical Features

Metabolic alkalosis is generally, well tolerated and patients are not symptomatic. The symptoms are generally related to hypoxemia, hypokalemia, hypocalcemia and alkalemia. Symptoms like lethargy, confusion or stupor are often related to hypoxia and hypoventilation, and are particularly worse in those with chronic obstructive airway disease. The clinical manifestations related to hypokalemia are weakness, ECG changes or even flaccid paralysis. Tetany may occur due to fall in ionic calcium level.

Diagnosis

The finding of serum bicarbonate of > 30 mmol/L associated with hypokalemia is pathognomonic of metabolic alkalosis. Although HCO_3 may be high in chronic respiratory acidosis, it is not associated with hypokalemia. Since metabolic alkalosis may co-exist with other acid-base disturbances, mixed acid-base disorders should be looked for. A single measurement of urinary

chloride in a spot sample of urine is sufficient to classify if it is chloride responsive or chloride resistant metabolic alkalosis.

Management

The primary disorder is identified and treated accordingly. In chloride responsive metabolic alkalosis, the aim is to replace the chloride deficit and normalize the sodium and potassium concentrations. Thus, the mainstay of treatment is sodium chloride infusion with additional potassium orally or intravenously. The amount of sodium chloride required depends on volume contraction and is guided by CVP monitoring. Usually, with the correction of chloride, the kidneys effectively eliminate the excess bicarbonate. In patients with cirrhosis liver, digoxin therapy or respiratory failure, the alkalosis may have to be corrected by exogenous administration of acids or acid precursors. Treatment includes administration of dilute intravenous 0.1 normal hydrochloric acid, ammonium chloride or arginine hydrochloride. Dialysis with low bicarbonate dialysate is the treatment modality of choice in severe cases associated with renal failure.

Respiratory Acidosis

Respiratory acidosis is characterized by a primary rise in PCO_2 and is invariably due to alveolar hypoventilation. CO_2 retention is invariably associated with hypoxemia and may even cause death before PCO_2 levels reach over 80 mmHg. In acute respiratory acidosis, for every 10 mmHg increase in PCO_2 , the bicarbonate will increase by 1 mmol/L. In chronic respiratory acidosis, the renal mechanisms play a role and cause elevation of HCO_3 by 4 mEq/L for every 10 mmHg rise in PCO_2 .

Causes of Respiratory Acidosis

1. Neurologic causes:

- a. Inhibition of respiratory center (central)
 - General anesthesia
 - Sedative overdose
 - Head injury/cerebrovascular accident/tumours
 - Encephalitis/brainstem lesions
- b. Neuromuscular causes:
 - Spinal cord injury
 - Poliomyelitis
 - Multiple sclerosis
 - Muscular dystrophy
 - Guillain-Barré syndrome
 - Status epilepticus
 - Amyotrophic lateral sclerosis

2. Respiratory muscle paralysis:

- Tetanus, botulism
- Myasthenic crisis
- Periodic paralysis

Diaphragmatic paralysis
Myopathies
Succinyl choline administration
Organophosphorus poisoning

3. Upper and lower airway obstruction

Obesity
Sleep apnea
Aspiration
Laryngeal edema / vocal cord palsy
Bronchoconstriction
Emphysema
Chronic interstitial lung disease
Pleural thickening/lung stiffening
Thymoma/aortic aneurysm

Clinical Features

Hypercarbia (CO_2 retention) and hypoxemia (low PaO_2) often coexist. The usual symptoms include severe breathlessness, disorientation, confusion, tremor, myoclonus, headache, asterixis, incoherence and drowsiness. Blurring of optic disc, papilledema and symptoms of increased intracranial pressure are due to vasodilatory effects of CO_2 . Sometimes, injudicious administration of high flow O_2 may precipitate coma. The vascular manifestations are due to vasodilatation. Congestive cardiac failure and cardiac arrhythmias may occur. These patients may also develop salt and fluid retention.

Treatment

Hypoxemia is mainly responsible for the mortality. Therefore, careful O_2 administration is the mainstay in the treatment. Injudicious O_2 administration may lead to worsening of hypoxemia due to suppression of respiratory drive particularly in patients with chronic obstructive airway disease. In acute respiratory acidosis, the treatment principles include maintenance of airway, administration of oxygen and judicious use of antibiotics, bronchodilators and corticosteroids. Noninvasive ventilation or intubation and mechanical ventilation may be used for more severe cases with $\text{pH} < 7.0$ and $\text{PCO}_2 > 80$. Bicarbonate administration may be necessary to bring the pH to 7.2.

Respiratory Alkalosis

Respiratory alkalosis is characterised by a primary fall in PCO_2 . The rate of production of CO_2 in the body is relatively constant. Therefore, any fall in PCO_2 can only be due to alveolar hyperventilation. It is a common acid-base disorder and occurs in normal pregnancy and at high altitude. It also occurs in critically ill patients as a simple disorder or as a part of mixed disorder. The primary fall in PCO_2 does not increase pH to levels above 7.55 and severe alkalemia is unlikely.

Causes of Respiratory Alkalosis

A. CNS stimulation and hyperventilation

Voluntary/psychogenic/ anxiety/pain
Pregnancy
Brainstem lesions
Encephalitis
Salicylate intoxication
Sepsis
Cirrhosis of liver.

B. Stimulation of intrathoracic receptors

Pneumothorax, hemothorax, flail chest, pneumonia, asthma, pulmonary edema, pulmonary embolism, pulmonary fibrosis, acute respiratory distress syndrome.

C. Stimulation of peripheral chemoreceptor

High altitude hypoxemia
Hypotension, severe anemia
Drowning, aspiration, pneumonia

D. Drugs

Respiratory stimulants (doxapram, nikethamide)
Salicylates
Nicotine
Epinephrine/nor-epinephrine.

Clinical Features

The clinical features are variable and depends on the primary disorder, rate of onset and severity of the respiratory alkalosis. The usual initial symptoms include tingling sensation in the extremities, and circumoral region, lightheadedness and confusion. Later, muscle cramps, carpopedal spasm and brisk deep tendon reflexes may be noted. Cardiac arrhythmias and seizures may also occur in severe cases. The occurrence of symptomatic respiratory alkalosis or $\text{PCO}_2 < 20\text{--}25$ mmHg in critically ill patients suggests a grave prognosis.

Diagnosis and Treatment

The diagnosis can be established by the history, physical examination and laboratory data including ABG. The treatment is directed towards the underlying cause. Often, no treatment is required for mild respiratory alkalosis if it is not associated with symptoms. In psychogenic hyperventilation, rebreathing into a closed bag can be tried. Acute mountain sickness can be prevented by slow ascent, pretreatment with acetazolamide and oxygen therapy. In the case of salicylate intoxication, the first step is to remove unabsorbed salicylate from the gut. This is achieved by inducing emesis or gastric lavage, absorption may be prevented by administration of activated charcoal, with sorbitol. The absorbed salicylates can be removed from blood by alkaline diuresis or hemodialysis. In patients on assisted ventilation with respiratory alkalosis, appropriate adjustments in the mode of ventilation

may have to be undertaken. In hypoxemia, oxygen therapy is useful.

If the pH is more than 7.55 and patient has hemodynamic instability, or altered mental status, more aggressive measures are warranted. Attempts must be made to bring the pH to less than 7.5. This can be achieved by either reducing HCO_3^- or increasing PCO_2 . The bicarbonate can be reduced by the use of acetazolamide, ultrafiltration or hemodialysis using low bicarbonate dialysate or by isotonic saline replacement.

The PCO_2 can be increased by rebreathing into a closed system or by giving controlled hypoventilation using a ventilator.

Mixed Acid-base Disturbances

When two or more acid-base disorders occur simultaneously, the condition is called mixed acid-base disorder. This can be two or three disorders combined. The usual compensation of the body to a primary acid base disorder is not considered as a mixed disorder. Mixed acid-base disorders are commonly observed in hospitalised patients particularly in the intensive care units. The clinical settings in which they occur include cardiorespiratory arrest, sepsis, drug intoxication, complications of diabetes mellitus, renal, hepatic, pulmonary or cardiac failure and those on artificial life support. A few examples are enumerated and explained below.

- a. Respiratory acidosis and metabolic acidosis
For example: Chronic obstructive airway disease with sepsis or cardiopulmonary arrest.
- b. Respiratory alkalosis and metabolic acidosis
For example: Salicylate intoxication, gram-negative sepsis, pulmonary edema, hypoxemia and mechanical hyperventilation.
In salicylate intoxication, the stimulation of central respiratory center by salicylate, stimulates hyperventilation and respiratory alkalosis. Accumulation of pyruvic acid and lactic acid or salicylic acid itself leads to metabolic acidosis.
In gram-negative septicemia, sepsis induces hyperventilation and respiratory alkalosis, and shock causes lactic acidosis.
- c. Metabolic acidosis and metabolic alkalosis
For example: Diabetic ketoacidosis with vomiting, Renal tubular acidosis with vomiting, Protracted vomiting/nasogastric suction with uremia, or alkali therapy for cardiopulmonary resuscitation.

Prolonged vomiting and nasogastric suction can cause metabolic alkalosis and when this occurs in a patient who has metabolic acidosis due to any cause, this mixed acid-base disorder can occur.

- d. Metabolic alkalosis with respiratory acidosis
For example: Chronic obstructive pulmonary disease and diuretics.
Combination of conditions with chronic obstructive pulmonary disease (respiratory acidosis) with conditions causing acid loss (vomiting) or alkali gain (diuretic therapy, exogenous bicarbonate administration) can lead to this mixed disorder.
- e. Metabolic alkalosis with respiratory alkalosis
For example: Hyperemesis gravidarum, congestive heart failure and diuretic use.
In hyperemesis gravidarum, the respiratory alkalosis occurs as a part of normal pregnancy. It is complicated by metabolic alkalosis, when loss of gastric acid occurs due to hyperemesis.
In congestive cardiac failure, the respiratory alkalosis may occur due to tachypnea and metabolic alkalosis due to diuretics.
- f. Mixed metabolic acidosis
Metabolic acidosis may be high anion gap or 'normal' anion gap (hyperchloremic). They are caused by different pathogenic mechanisms and they occur under different circumstances. Therefore, they can be combined and may coexist with other disturbances as well.
For example:
 - i. Combination of two types of high anion gap metabolic acidosis-uremia and diabetic ketoacidosis.
 - ii. Combined high anion gap metabolic acidosis due to diabetic ketoacidosis and sepsis (lactic acidosis).
 - iii. Normal anion gap (hyperchloremic) metabolic acidosis as in renal tubular acidosis may be combined with sepsis and lactic acidosis.
 - iv. Diarrhea in a patient with renal tubular acidosis may lead to normal anion gap metabolic acidosis due to two independent mechanisms.
- g. Mixed metabolic alkalosis
Different pathogenetic mechanisms causing metabolic alkalosis may be occur together in a patient at the same point of time.
For example: Vomiting and diuretic therapy
Potassium deficiency + mineralocorticoid excess.

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Disturbances of Osmotic Equilibrium

K.V. Krishna Das, R. Kasi Visweswaran

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Introduction

The water combined with various solutes and electrolytes contributes to the tonicity of the body fluids which is maintained within a narrow physiological range. Osmolality represents the number of osmotically active solutes in the one kilogram of water. The osmolality of plasma varies from 285-290 milliosmoles/kg. In health, plasma osmolality is closely related to sodium level. Substances like mannitol, methanol, ethanol, high levels of glucose, ethylene glycol and conventional radiocontrast agents increase the osmolality. Osmolality of plasma can be measured using an osmometer, which measures the osmolality from the freezing point. A solution with osmolality 1 (1000 milliosmoles) freezes at the temperature of 1.86°C. Plasma osmolality can also be calculated from the concentration of electrolytes, glucose and urea using the formula:

Osmolality = $2 \times Na \text{ (mmol/L)} + \frac{B. \text{ urea (mg\%)}}{6} + \frac{Blood \text{ sugar (mg\%)}}{18}$

Disturbances of Osmolar State

Osmolar disturbances also accompany disturbances of fluid and electrolytes. Serum sodium is the chief determinant of plasma osmolality. In intracellular fluid potassium does the same function. Conditions which lead to hyponatremia or absolute water retention produce hypo-osmolar states. The dilutional hyponatremia of congestive heart failure, edema in cirrhosis liver and fluid retention due to psychogenic polydipsia give rise to hypo-osmolar states whereas water depletion and hypernatremia give rise to hyperosmolar states. Diabetes insipidus is associated with hyperosmolality. Abnormally high levels of glucose

TABLE 74.1

The quantitative and molar composition of different solutions used for infusion

Solution	Chemical composition
1. 2,5,10,40% dextrose	Corresponding number of g% of dextrose
2. 0.85% NaCl (normal saline)	145 mmol/L of Na and Cl
0.45% NaCl	77 mmol/L of Na and Cl
3.0% NaCl	513 mmol/L of Na and Cl
3. 15% potassium chloride (10 mL ampoules)	2,000 mmol/L of K and Cl or 2 mmol/ml of K and Cl
4. 1.5% Na HCO ₃	178 mmol/L of Na and HCO ₃
7.5% Na HCO ₃	890 mmol/L of Na and HCO ₃
10 mL ampoules	roughly 1 mmol/mL
5. 1/6 molar lactate or (1.87% NaC ₃ H ₃ O ₃) Ringer's lactate	167 mmol/L of Na and HCO ₃
NaCl	130 mmol/L
Sodium lactate	27 mmol/L
KCl	4 mmol/L
CaCl ₂	4 mmol/L

can cause hyperosmolality as seen in nonketotic hyperosmolar coma of diabetes. Infusion of large doses of mannitol or fructose given therapeutically also lead to hyperosmolar states.

Hyperosmolar states are corrected by the administration of 0.45% saline. The underlying condition like hyperglycemia or uremia should also receive attention. Hypo-osmolar states are corrected by eliminating water by diuresis, with supplementation of salt, or by the administration of hypertonic saline (1.5 or 3% NaCl).

Osmotic pressure of body fluids plays a major role in transfer of fluid and chemical constituents across semipermeable membranes and cell walls in several tissues. Gross changes in osmotic equilibrium lead to severe abnormalities in fluid and electrolyte transfer resulting in metabolic disturbances. Estimation blood osmolality is an important investigation in critical care medicine. The composition of the commonly used IV fluids is given in Table 74.1.

TABLE 74.2

Equivalent of 1 g of solute

<i>Solute</i>	<i>mmol</i>
NaCl	17.24
KCl	13.3
CaCl	9.0
CaCO ₃	10.0
MgSO ₄	8.3
NaHCO ₃	11.9
Na ₂ HPO ₄	7.0
NaH ₂ PO ₄	8.2

Estimation of serum osmolality should be undertaken in the following conditions:

- dehydration,
- syndrome of inappropriate secretion of antidiuretic hormone (SIADH),

- hyperosmolar nonketotic coma in diabetes, and
- for the identification of low molecular weight substances in plasma.

Whenever possible, osmolality should be measured by osmometer and also calculated from the estimation of sodium, potassium, glucose and urea in the plasma (see formula above). If the measured osmolality exceeds the calculated one by 10 mosms or more the following conditions should be suspected:

- diminution of water content in the plasma as occurring in hyperlipidemia and hyperproteinemia, and
- presence of low molecular weight substances such as methanol, ethanol, ethylene glycol, etc.

Table 74.2 gives the amount of solutes expressed as millimoles in each gram of the substance.

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Digestive Organs: General Considerations

K.R. Vinaya Kumar, K.V. Krishna Das

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Applied Anatomy and Physiology

ESOPHAGUS

Esophagus is a muscular tube ranging in length from 25 to 30 cm extending from the cricopharyngeal sphincter to the lower esophageal sphincter above the cardia of the stomach. Its immediate relations are the trachea, left main bronchus, the aortic arch, and the left atrium. The blood supply is derived from the small branches of the descending thoracic aorta. The inferior thyroid artery supplies the uppermost part and the left gastric artery supplies the lower end. Veins from the upper part drain into the superior vena cava, those from the middle third drain into the azygos system and the veins of the lower third drain into the portal system through the gastric veins. These veins are interconnected. The vagus nerve, fibers of which anastomose with the Auerbach's plexus, acts as the chief motor nerve. The cervical sympathetic ganglia and the fibers from the thoracic sympathetic ganglia provide sympathetic innervation. The cervical lymph nodes receive lymphatics from the upper third, mediastinal nodes from the middle-third, and the celiac and gastric lymph nodes from the lower third. The lymphatics anastomose freely. The upper one third of the esophagus contains striated muscle and the lower two-third contains smooth muscle. The esophagus has no serous coat. It is lined by stratified squamous epithelium. Under abnormal conditions when gastric acid regurgitates into the esophagus, the lining of the lower end undergoes metaplasia, to resemble columnar epithelium resembling the gastric mucosa.

Physiology

444 The cricopharyngeal sphincter remains tonically closed except during swallowing. On swallowing, a wave of

peristalsis (called primary peristalsis) sweeps down. Secondary peristalsis is set up when gastric contents regurgitate into the esophagus. On swallowing, the lower esophageal sphincter (LES) relaxes and the food bolus passes into the stomach. Reflux of gastric contents into the esophagus is prevented by the LES. This sphincter is controlled by inhibitory and excitatory neural influences. Several other factors also influence the LES tone. Prostaglandins, cholinergic agents, metaclopramide, cisapride, alkalies and high protein meal increase the tone, whereas secretin, cholecystokinin, alcohol, chocolate, smoking, and gastric acidity lower it. The esophagus acts as an active conduit for food from the pharynx to the stomach.

STOMACH

The stomach is the most distensible part of the gastrointestinal tract. Capacity of the adult stomach is 1-1.5 liters. Stomach wall is made up of mucosa, submucosa, muscle coat and serosa. Branches of the celiac axis, and to a lesser extent branches of superior mesenteric artery provide arterial blood. Veins accompany the arteries and drain into the portal circulation. Lymphatic drainage is into four main groups of lymph nodes, left gastric, pancreaticosplenic, right gastroepiploic and pyloric. From these primary nodes, further drainage occurs into the celiac group of preaortic nodes and then into cisterna chyli. The stomach receives sympathetic and parasympathetic nerves. The two vagus nerves which are parasympathetic, reach the stomach through the esophageal hiatus and anastomose with the ganglion cells in the layers of the organ. Parasympathetic stimulation leads to gastric secretion, contraction of the stomach, and relaxation of the pylorus. The sympathetic fibers derived from T6-T10 segments reach the stomach through the celiac ganglia and celiac plexus. Sympathetic stimulation constricts blood vessels, contracts the pylorus, and inhibits secretion and motor activity.

Structure

The gastric glands differ in the three regions of the stomach and are called the cardiac glands, oxyntic glands

and the pyloric glands. The oxyntic glands have four cell types—the chief cells, oxyntic or parietal cells, mucous neck cells and endocrine cells. The chief cells produce pepsinogen, the parietal cells produce hydrochloric acid and intrinsic factor, and the mucous neck cells produce mucus. The cardiac and pyloric glands have predominantly mucus-secreting cells. The pyloric glands have, in addition, endocrine cells producing gastrin.

Physiology

The proximal part of the stomach acts as a reservoir to receive ingested food and the distal portion (*antral mill*) churns the food and converts it into chyme. Gastric emptying is controlled by the antral contractions. Liquids leave the stomach faster than solids. The antrum contracts at the rate of 3/min. Gastric emptying depends on factors such as volume and composition of the meal and by the activity of the duodenum and small bowel which is mediated through neurohumoral mechanisms. Gastric emptying is slowed by *glucagon*, *gastrin*, *secretin*, *cholecystokinin*, *vasoactive intestinal polypeptide* (VIP) and *gastric inhibitory polypeptide* (GIP). Noxious stimuli like pain may also inhibit gastric emptying.

The gastric juice contains *hydrochloric acid*, *pepsinogens*, *intrinsic factor* and *mucus*. The endogenous stimulants of gastric acid secretion are gastrin, histamine and acetylcholine. Food is the most important physiologic stimulus for gastric acid secretion. Distension of the stomach enhances acid secretion through cholinergic reflexes. Amino acids and peptides in the stomach induce acid secretion through the release of gastrin. *Pepsins*, which are the proteolytic enzymes in the gastric juice, are stored as inactive precursors, the *pepsinogens*, which are converted to pepsin in the presence of acid. *Cholinergic reflexes*, *gastrin* and *histamine* stimulate secretion of pepsin. *Intrinsic factor* is produced by the parietal cells and normally the quantity of intrinsic factor far exceeds the amount required for vitamin B₁₂ absorption. *Intrinsic factor secretion* is stimulated by vagal stimulation, cholinergic agents, histamine, and gastrin.

SMALL INTESTINE

The small intestine is 6-7 meters long (range 300-850 cm). If the length is reduced below 200 cm, it leads to 'short bowel syndrome'. The widest part is the duodenum and it is fixed. The rest of the small intestine is arbitrarily divided into jejunum and ileum without any sharp demarcation. The small intestine derives its arterial supply from the celiac and superior mesenteric arteries. Its veins drain into the portal system. The vagus provides parasympathetic innervation. Sympathetic fibers originate from T9 and T10 segments. The wall of the small intestine has four layers. They are *mucosa*, *submucosa*, *muscular*

layer and *serosa*. The small intestine is the main site of digestion and absorption. The mucosa is thrown into convoluted folds, the *valvulae connentes*, which are more numerous in the jejunum. The luminal surface is covered by villi which are taller in the jejunum than in the ileum. The villi are lined by a single layer of tall columnar epithelial cells. The area between the villi is occupied by the crypts. The crypt epithelial cells are the precursors of the villous epithelial cells. In addition, the crypt contains *Paneth cells*, *goblet cells* and *endocrine cells*. The crypt epithelial cells migrate towards the villi where they mature and are finally shed off from the tip. The villus epithelium is constantly being replaced and the migration time from crypt to villus is 2-6 days. In addition to the tall columnar cells, the mucosa contains goblet cells which secrete mucus and enterochromaffin cells with endocrine function. The luminal end of the epithelial cells has the brush border, composed of tall closely packed microvilli. This region contains the enzymes for digestion of carbohydrates and proteins. The paneth cells are trapezoid cells with basophilic cytoplasm seen at the base of the crypts. They secrete growth factors, antimicrobial peptides and digestive enzymes.

The Brunner's glands are seen in the submucosa of the duodenum. They secrete alkaline mucus, epidermal growth factor and pepsinogen II.

The *lamina propria* contains blood vessels, lymphatics, nerve fibers, lymphocytes, plasma cells, eosinophils, macrophages, and mast cells. The lymphocytes and plasma cells of the lamina propria and the epithelium form part of the immune system. *Peyer's patches* are aggregations of lymphoid tissue seen in the submucosa of the ileum.

Motility of the Gastrointestinal Tract

The stomach and intestines undergo regular co-ordinated peristaltic movements. Motility and intraluminal pressures can be recorded by manometry at different levels.

Movement occurs in three phases

Phase 1— quiescent phase

Phase 2—occurs after eating in which the fasting pattern gives place to the fed pattern in the stomach and small intestine. At this stage the migratory pattern stops and bursts of contractions occur which help to mix the contents and enhance digestion and absorption.

Phase 3—this occurs during fasting. The movements are known as **migrating motor complex (MMC)**. Regular motility occurs at the rate of 3 cycles per minute in the duodenum and pass down the intestine.

The peristaltic activity is controlled by mechanical and neurohumoral factors. Chyme is mixed up by segmenting movements and propelled forwards by peristaltic movements. Movement of chyme is faster in the jejunum than in the ileum.

Two major functions of the small intestine are: (i) digestion and absorption of food and (ii) barrier function against luminal microorganisms and toxins. Intestinal failure leads to three major problems:

1. Malnutrition,
2. Sepsis,
3. Symptoms which impair the quality of life—diarrhea, vomiting and abdominal pain.

Lesions and resection of the distal parts of the small intestine produce greater abnormalities of digestion and absorption. Removal of long segments of the small intestine also leads to secondary hypersecretion in the stomach as a result of decrease in the production of the inhibitory hormones.

LARGE INTESTINE

Syn: Colon

The large intestine, which begins at the ileocecal junction and ends at the anal canal, is 90-125 cm long. The caliber of the colon diminishes progressively from cecum to the sigmoid. The portion proximal to the midtransverse colon is derived from the midgut and it derives its blood supply from the superior mesenteric artery. It is absorptive in function. The distal half is derived from the hindgut and it derives its blood supply from the inferior mesenteric artery and its main function is storage. The lower end of the rectum and anal canal is supplied by paired middle and inferior rectal arteries which arise from the internal iliac artery. The veins accompany the arteries and ultimately reach the portal system through the superior and inferior mesenteric veins. The rectum provides a site for portal-systemic anastomosis. The lymphatics of the colon and rectum accompany the superior and inferior mesenteric vessels. Lymphatics from the anus drain into the superficial inguinal nodes. Sympathetic and parasympathetic nerves supply the colon. Sympathetic fibers arise from T11 to L2 through the sympathetic ganglia and splanchnic nerves and finally reach the colon along with the blood vessels. Parasympathetic fibers arise from the vagus and the sacral outflow.

Colonic mucosa is lined by a single layer of columnar epithelial cells which are flat. The surface of the mucosa shows the *crypts of Leiberkuhn*. There are numerous goblet cells in the mucosa. The crypts show argentaffin cells also. The luminal surface of the epithelial cells shows villi. The lamina propria contains blood vessels, lymphatics, nerve fibers, lymphocytes, plasma cells, and histiocytes.

Physiology

The essential function of the large intestine is to process the intestinal wastes, to store them and to discharge them at periodic intervals. In addition, it plays an important role in the maintenance of fluid and electrolyte balance. The

colon absorbs water, sodium and chloride and nutrients, and secretes potassium and bicarbonate. The motor activity of the colon consists of segmenting and propulsive movements. The segmenting movements facilitate the absorption of water and electrolytes. Due to the absorption of water the liquid contents are transformed into solid material as the contents pass down. Distension of the rectum initiates the defecatory reflex. The goblet cells of the mucosal surface secrete mucus, which lubricates the feces and facilitates propulsion.

The amounts of water and the major electrolytes entering and leaving the colon in 24 hours are as follows.

	Entering	Leaving
Water	1500-1800 mL	100-150 mL
Sodium	180-220 mmol/L	5 mmol/L
Potassium	5 mmol/L	9-13 mmol/L
Chloride	117-157 mmol/L	2 mmol/L

Upto 400 calories can be provided through the colon by intracolonic infusion. Colonic function supplements function of the small intestine. If the colon is normally functioning, a patient can be maintained even with only 50 cm length of small intestine. At least 100 cm of small intestine is absolutely necessary to manage a patient whose colon is nonfunctional.

Digestion and Absorption

Digestive processes start in the mouth and proceed as the food passes down. The ultimate function of the gastrointestinal tract is the assimilation of ingested nutrients. The food materials which are in macromolecular form have to be broken down to smaller molecules before they can be absorbed. This process is called digestion. Absorption is the process of transfer of digested nutrient molecules across the mucosal epithelium from the intestinal lumen into the tissues. Digestion and absorption are closely interrelated. A part of the digestion occurs in the stomach. Exocrine pancreatic secretion and the bile salts aid in the process of digestion. The digestive processes of some of the nutrients continue in the brush border of the small intestinal epithelium. Small intestine is the major site of absorption of nutrients, and most of the water and electrolytes. Calcium and iron are preferentially absorbed in the duodenum. Vitamin B₁₂ and bile salts are absorbed mainly from the ileum. The rest of vitamins, minerals, and nutrients in the diet are absorbed from the jejunum. The large intestine absorbs mainly water and electrolytes.

Digestion and Absorption of Fat

The pancreatic lipase splits the triglycerides into monoglycerides and fatty acids. The bile acids help to bring these insoluble products into soluble form which is

absorbed. The products of digestion of fat are incorporated into the center of the micelles formed by bile salts to form mixed micelles. The brush border of the intestinal epithelium absorbs monoglycerides and fatty acids from the mixed micelles. The fatty acids are again converted to triglycerides in the epithelial cells and covered with a lipoprotein coat to form chylomicrons. The chylomicrons are discharged into the lacteals from where they reach the systemic circulation. Medium chain triglycerides are those composed of short chain fatty acids. They are more readily absorbed and they enter the portal vein directly instead of the lacteals.

Digestion and Absorption of Carbohydrates

Starch, sucrose, and lactose constitute the important carbohydrates in the diet. Salivary amylase initiates digestion of carbohydrates in the mouth, but dietary carbohydrates are mainly digested in the upper small intestine with the help of pancreatic amylase. Starch is broken down to *maltose*, *maltotriose* and *alpha limit dextrins*. These products and other disaccharides like sucrose and lactose are broken down further into monosaccharides by the *disaccharidase enzymes* located at the brush border of the intestinal epithelium. On further breakdown, glucose is formed from maltose, maltotriose, and alpha limit dextrins; glucose and fructose are formed from sucrose, and glucose and galactose are formed from lactose. Glucose and galactose are actively absorbed. Fructose is absorbed by facilitated diffusion.

Digestion and Absorption of Proteins

Digestion of proteins starts in the stomach where pepsin is present. However, the major site of digestion of dietary protein is the upper small intestine. This is effected by the pancreatic enzymes.

The *proteolytic enzymes* are secreted as inactive precursors, and are activated by the duodenal mucosal enzyme—*enterokinase* and by *trypsin*. The proteolytic enzymes break down the proteins to produce small peptides of 2-6 amino acids. These small peptides are further broken down by the *oligo peptidases* in the brush border of intestinal epithelium. Dipeptides and tripeptides may be actively taken up as such into the epithelial cell. They are hydrolyzed to free amino acids in the cell before they pass into the portal circulation.

Vitamins: Jejunum is the main site of absorption of all the vitamins except vitamin B₁₂, which is absorbed in the ileum.

Water and electrolytes: About nine liters of fluid (2 liters intake plus 7 liters of gastrointestinal secretions) pass through the alimentary tract daily. Only 100-200 mL is excreted in the stools. Water is transported in the

alimentary tract passively by the osmotic or hydrostatic pressure gradient generated by active solute transfer.

Sodium is absorbed mainly in the small intestine and its active transport is linked with the absorption of glucose.

ENDOCRINE FUNCTIONS OF THE GUT AND THE REGULATORY PEPTIDES

General Considerations

The term hormones (derived from the Greek word for “I arouse to activity”) is used to describe the chemical messengers acting at a distance. The other mechanism of control of bodily functions is neural. These two apparently different mechanisms of control of bodily functions act in an integrated manner. The same active principles (regulatory peptides) can be produced and released by endocrine and neural tissues and these may act as circulating hormones, local regulators, neurotransmitters or all these. The term *regulatory peptides* has been coined to describe active peptides capable of exerting their effects in one way or the other. Though these regulatory peptides were originally identified in the gut, brain or both, it is now realized that their distribution is much wider and that they are present practically in all the tissues.

Gastrointestinal Hormones

The regulatory peptide system of the gastrointestinal tract has received particular attention in recent times. Some of the regulatory peptides are secreted either by the endocrine cells interspersed among the mucosal cells or the enteric nerves, while others are present in both sites.

The peptidergic nervous system is a complex system composed of different types of peptidergic neurons. The cell bodies of the neurons lie either in the submucosal plexus or the mesenteric plexus. These neurons can cause gut movements independently and these belong to the noncholinergic, nonadrenergic class of autonomic nerves. Several peptides including *VIP*, *substance P*, *somatostatin*, *enkephalin*, and others have been identified in these nerves. Table 75.1 gives the regulatory peptides.

Gut Flora in Health and Disease

Human alimentary tract normally contains about 100 trillion microorganisms. It is sterile at birth; but soon after delivery, it gets inhabited by the microbial flora mainly from the fecal organisms of the mother and those from the surroundings. There are over 400 different species of microbes in the normal gut flora and they may reach a few hundred grams. The microbial density is less in the stomach and upper small intestine due to the presence of

TABLE 75.1

Regulatory peptides		
Peptide	Main distribution	Established actions
1. Gastrin	Stomach, duodenum	Stimulate gastric acid secretion
2. Cholecystokinin	Duodenum, jejunum and brain	Stimulate contraction of gallbladder and secretion of pancreatic enzymes
3. Secretin	Duodenum and jejunum	Stimulates secretion of pancreatic bicarbonate
4. Vasoactive intestinal peptide (VIP)	Central and peripheral nervous system and gut	Stimulates muscle relaxation, vasodilatation, secretion
5. Gastric inhibitory polypeptide (GIP)	Small intestine (duodenum and jejunum)	Stimulates secretion of insulin, inhibits secretion of gastric acid
6. Glucagon, enteroglucagon	Pancreas, gut, brain, ileum and colon	Regulates carbohydrate metabolism (pancreatic glucagon), trophic to gut (enteroglucagon)
7. Motilin	Small intestine	Stimulates gut motility
8. Pancreatic polypeptide	Pancreas	Inhibits pancreatic enzyme secretion and gall bladder contraction
9. Substance P	Central and peripheral nervous system	Sensory and vasodilatory role, stimulates muscle contraction
10. Neurotensin	Ileum, adrenal, brain	Vasodilatory, inhibits gastric acid secretion
11. Bombesin	Gut, brain, lung	Stimulates release of peptides (? antagonistic to somatostatin)
12. Somatostatin	Gut, pancreas, thyroid, brain	Inhibits release and action of many peptides
13. Enkephalins and endorphins	Gut, brain, sympathetic nervous system, carotid body, adrenal	Opiate effects
14. Thyrotrophin releasing hormone (TRH)	Brain and the gut	Endocrine action and bioactivity on the brain
15. Insulin	Pancreas, gut	Carbohydrate, lipid and other metabolic functions
16. Miscellaneous: ACTH, growth hormone, angiotensin II	mainly endocrine tissue	Probable activity on the gut and brain

gastric acid and intestinal peristalsis. Anaerobes far outnumber aerobes.

In addition, peptococcus, peptostreptococcus, klebsiella, proteus and others may also occur (Table 75.2).

Physiological Role

Gut flora are metabolically very active. They synthesize vitamin K and B-complex vitamins. They metabolize unabsorbed lipids to short chain fatty acids (SCFA) which are the main energy source for colonocytes. They ferment nondigestible dietary residues and endogenous mucus. They help absorption of calcium, magnesium and iron. In the proximal colon the pH is 5-6 (acid). The microbial growth is maximum and saccharolysis is predominant. In the rectum and distal colon the pH is neutral, bacterial growth is slow and proteolysis is predominant.

They also reduce cholesterol to coprostanol which is unabsorbable and thus they play an important role in

cholesterol balance. They are also responsible for deconjugating conjugated bile salts, converting unabsorbed protein and urea to ammonia and fermentation of dietary fibres. The gut flora stimulate and favour the spread of migrating motor complex (MMC) of the gut. Trophic functions include the control of epithelial cell proliferation and differentiation and homeostasis of the immune system. They play a role in the maintenance of normal gut endocrine function and detoxification of dietary carcinogens.

Protective function against pathogenic bacteria is achieved by preventing their growth and colonization. Adherent non pathogenic bacteria prevent the attachment and subsequent entry of pathogens into the epithelial cells.

Gut Flora in Disease

Excessive proliferation leads to malabsorption, bloated feeling due to fermentation: and nutritional deficiencies

TABLE 75.2

Bacterial contents in the normal gastrointestinal tract

Parameter	Stomach	Jejunum	Ileum	Colon
bacteria	streptococci staphylococci fungi	streptococci staphylococci lactobacilli	coliforms bacteriodes bifidobacterium clostridium	bacteriodes bifidobacterium clostridium enterococci
Bacterial density (per mL of contents)	10 ⁰⁻³	10 ⁰⁻⁴	10 ⁵⁻⁹	10 ¹⁰⁻¹²
pH	2-4	6-7	7.5	6.8-7.3

(bacterial overgrowth syndrome). It may play an important role in the pathogenesis of inflammatory bowel diseases (IBD), especially Crohn’s disease and irritable bowel syndrome (IBS). Bacterial translocation is an important factor in the pathogenesis of spontaneous bacterial peritonitis (SBP), necrotizing pancreatitis and systemic sepsis following surgery, shocked states, major injuries and burns.

Probiotics and Prebiotics

Probiotics are live microorganisms which, when administered, confer a health benefit to the host. They are approved by WHO for clinical use. *Saccharomyces boulardii* and *Lactobacillus delbrueckii* are the main probiotics in clinical use. Prebiotics are non-living nutrient elements which are not broken down by the intestinal enzymes. They nourish the probiotic flora to enhance their function.

Disorders where probiotics may be beneficial include;

- ulcerative colitis
- pouchitis
- irritable bowel syndrome
- antibiotic associated diarrhea and
- acute pancreatitis

Symptoms in Alimentary Disorders

Ptyalism: There is excessive salivation in this condition. This is a frequent complaint and it develops due to the local causes in the mouth such as dentures, dental fillings, gingivitis or other painful lesions. Excessive salivation may occur reflexly in peptic ulcer, esophagitis and other lesions of the upper GI tract. Ptyalism may be troublesome in parkinsonism. Excessive salivation in association with distaste is a common side effect of drugs like parasympathomimetic agents, antibiotics and iron salts.

Dryness of the mouth (Xerostomia): This may be a prominent accompaniment of dehydration, diabetes mellitus or drugs like atropine. Mouth breathing, chronic sialadenitis and Sjögren’s syndrome are local conditions which make the mouth dry. Mouth and conjunctiva are

dry in sicca syndrome. Dryness of the mouth predisposes to infection and interferes with speech and deglutition.

Halitosis: Bad odor of the mouth is commonly caused by poor oral hygiene, periodontal sepsis or infections in the paranasal sinuses. Deep seated lesions like lung abscess, bronchiectasis or achalasia cardia may also give rise to halitosis. The bad smell is produced by anerobic organisms multiplying in these areas.

Bleeding from the gums: Bleeding on brushing the teeth is usually caused by gingivitis and periodontal infections like pyorrhea alveolaris. Spontaneous bleeding occurs in hemorrhagic disorders and scurvy.

Bruxism: It is grinding of the teeth, especially during sleep. This is more common in children. Reflex irritation from the digestive organs may give rise to this symptom, though in many cases no cause is detectable.

Dysphagia: It is difficulty in swallowing which may be due to mechanical or neurogenic causes. *Odynophagia* is painful swallowing.

Mechanical causes are due to surgical conditions like carcinoma, stricture, diverticula and foreign bodies in the esophagus, or pressure from without as in mediastinal tumors, enlarged left atrium, retrosternal goitre or mediastinitis. The obstruction is gradual in onset and difficulty is more during the swallowing of solids than liquids.

The swallowing mechanism is deranged in paralysis of the lower cranial nerves or affection of the muscles. Neurological causes of dysphagia are paralysis of 9th, 10th or 12th cranial nerves, myasthenia gravis, motor neuron disease and cranial myopathies.

Hunger: It is an unpleasant awareness of the desire to eat when the stomach is empty. It is accompanied by irritability and a sensation of abdominal discomfort.

Appetite: It is a pleasurable desire to eat food and it may not bear any direct relationship to hunger. Many factors like emotions, social customs and training modify appetite. Satiety is the feeling of fullness after the ingestion of food.

Anorexia: It is a morbid loss of desire to eat. Unlike satiety, which occurs only on taking food, anorexia may be present even when the person is hungry. Anorexia may accompany gastrointestinal and liver diseases, infections like tuberculosis or psychological disturbances like depression.

Nausea and vomiting: Nausea is the feeling of impending desire to vomit. It is usually associated with salivation, inhibition of gastric peristalsis, and rise in tone of the duodenum and proximal jejunum. Duodenogastric reflux occurs. The spasmodic and abortive respiratory movements in the presence of a closed glottis cause retching. During retching the distal part of the stomach contracts and the proximal part relaxes. The gastric contents are forcibly ejected through the mouth. Vomiting is controlled by the two medullary centers—the vomiting center and the chemoreceptor trigger zone.

Weight loss: This is not a phenomenon specific to gastrointestinal diseases, but in many alimentary disorders considerable weight loss occurs. Diminution of food intake, malabsorption, loss of nutrients, accelerated metabolism and parasitism may contribute to the weight loss. Diseases like gastrointestinal and hepatic malignancy and liver cirrhosis may present with considerable weight loss before the local symptoms develop.

Abdominal pain: Abdominal pain may be classified into: (i) *visceral pain*, (ii) *parietal pain*, and (iii) *referred pain*. Pain arising from the abdominal organs is visceral pain.

Visceral pain: It is carried by the C fibers and, therefore, it is poorly localized. Visceral pain is evoked by stretching, rise in tension in the wall of hollow organs due to spasm and dilatation, or traction on the mesentery or the blood vessels.

Pain from solid organs is caused by stretching of the capsule, inflammation, ischemia or neoplastic infiltration of the free nerve endings. Pain from solid organs tends to be of constant dragging, lancinating or throbbing nature, aggravated by movements and respiration. Pain arising from hollow viscera such as the esophagus, intestines, biliary tract and urogenital tract tend to be intermittent, often associated with contraction of the viscus against resistance or hyperperistalsis. The nature is colicky, in which the pain starts, works up to a maximum and passes off after varying periods, with relief. These episodes tend to recur at intervals. The pain is described as gripping, twisting or squeezing. The site of pain may correspond to the dermatomal distribution of the organ, or may be over its surface marking.

Biliary colic arising from the gallbladder tends to be a steady pain despite its name. It is severe and intermittent. It starts abruptly and lasts up to five hours in uncomplicated cases. It may be felt over the right hypochondrium

and epigastrium or may radiate to the right scapula or shoulder.

Parietal pain: Pain arising from the parietal peritoneum is generally more intense and more precisely localized because it is transmitted by overlying somatic nerves.

Referred pain: Sometimes pain felt in the abdomen may be referred from other sites such as the pleura, lungs or heart or it may result from spinal root irritation (T₇-T₁₂).

Diarrhea: Diarrhea is defined as the passage of stools of fluid consistency more frequently than is usual (usually more than 3 times per day). The wet weight of the stool is increased. Diarrhea results from several factors like intestinal hypermotility, malabsorption of water and electrolytes, inflammation of the gastrointestinal tract or use of laxatives. In addition to the development of dehydration and malabsorption state, diarrhea and vomiting along with abdominal pain impair the quality of life. Acute diarrhea clears up within two weeks. Chronic diarrhea exceeds two weeks in duration. The presence of fresh blood in stools is called hematochezia.

Infections or irritants cause acute diarrhea whereas chronic diarrhea may result from many causes.

Constipation: It is the condition of infrequent evacuation with harder consistency of feces. Any reduction in frequency of normal bowel movement in an individual should be considered as constipation. There is no single definition for the term constipation. Different attributes include one or more of the following: - hard stools, infrequency (less than thrice a week) excessive straining, sense of incomplete evacuation, excessive time taken for defecation and unsuccessful defecation. Common causes are reduction of dietary bulk, dehydration, lack of exercise, recumbency, social factors like change of place and travel, drugs reducing intestinal motility, increased intracranial tension in children, myxedema, megacolon, intestinal obstruction, and psychiatric disorders. Both diarrhea and constipation should receive more attention when they are of recent onset since they may be the warning signals of serious underlying diseases such as malabsorption or cancer.

Investigations in Alimentary Disorders

Examination of Feces

Wherever possible, examination of the total quantity of feces passed at a time should be done. This helps in assessing the volume, colour, consistency, and abnormal constituents of feces. On an average Indian diet the weight of feces ranges from 250 to 500 g/day. The consistency may vary from semisolid to hard even among normal individuals. The colour is derived from products of bile pigments. Clay coloured stools are seen in obstructive

jaundice. Presence of altered blood makes the feces black and tarry (*melena*). Black colour may be due to ingestion of heavy metals or other dietary articles.

Microscopic examination: The microscopic examination of fresh feces helps in identifying protozoa such as *E. histolytica* and *G. lamblia*. Other abnormalities commonly seen are helminthic ova and larvae, cellular exudates, fat globules, and muscle fibers. Protozoal cysts and helminthic eggs are better detected by concentration techniques and staining with aqueous iodine.

Microbiological investigations: These are done for the identification of pathogenic bacteria, fungi or viruses. Fresh fecal specimens, rectal swabs, or material obtained during proctoscopic examination are used for this purpose.

Biochemical tests: Occult blood may be present in stools and is detected by the *o-toluidine blue* or *guaiac* test. As a rule, it is better to avoid iron containing drugs and consumption of meat for 3-5 days before collecting feces for occult blood test. Presence of occult blood points to a bleeding source in the gastrointestinal tract such as benign ulceration or malignancy. Absence of occult blood in feces on repeated testing is a strong point against such lesions.

Quantitative estimation of the fat content of the stool helps to establish steatorrhea. Other biochemical tests such as estimation of the electrolytes, pH value, nitrogen content, stercobilinogen, porphyrins, etc. are done at times in special situations.

Digital Examination of the Anal Canal and Rectum

This is a very valuable method which gives information on the pathology in the anal canal, rectum and even the lower parts of the sigmoid colon. Digital examination is done with the gloved index finger, properly lubricated with vaselaine, keeping the patient in the left lateral decubitus or in the knee chest position. Proper explanation to the patient is necessary to ensure his co-operation. The external parts of the anus, tone of the anal sphincter and mucosal surface of the anal canal and rectum are systematically palpated. Fissure-in-ano, hemorrhoids, carcinoma, other growths, abnormalities of the prostate and other pelvic organs can all be diagnosed with reasonable certainty. Fecal masses and foreign bodies can be identified. Examination of the material on the finger helps to diagnose bleeding from upper or lower gastrointestinal tract. Microscopy of the material and further studies help to diagnose dysentery and other ulcerative lesions.

The findings on digital examination can be further clarified by proctoscopy, ano-rectal manometry and further imaging procedures.

Gastric Acid Analysis

The time honoured method of fractional test meal has been replaced by measurement of basal and maximal acid output. Maximal acid secretion is obtained by stimulating with histamine (0.04 mg/kg), histalog (1.5 mg/kg), or pentagastrin (6 µg/kg) given parenterally. Acid output values are expressed as mmol/h.

The test: Anticholinergic drugs should be avoided at least for 48 h before the test. After fasting overnight a tube is passed through the mouth and its tip is positioned at the junction of the lower and the middle-third of the stomach under fluoroscopic control. Basal secretion is collected by continuous suction and histamine is given subcutaneously. The gastric juice is collected by continuous suction and four 15-minute samples are collected separately. Volume of each specimen and the amount of hydrochloric acid are determined. For Indians basal acid output (BAO) varies from 1-4 mmol/h and maximal acid output (MAO) from 6-30 mmol/h. By using insulin as the stimulant, the test can be employed to assess the completeness of vagotomy (*Hollander test*). With the advent of endoscopic studies, the value of gastric secretory studies in the diagnosis of gastric and duodenal ulcer and gastric carcinoma has come down. In these conditions the acid levels show considerable overlap and, therefore, may be misleading. However, very high gastric acid values are valuable clues in the diagnosis of Zollinger-Ellison syndrome and complete absence of gastric acid (achlorhydria) is suggestive of pernicious anemia.

Sampling of Intestinal Contents

Sampling of intestinal contents from various levels has been employed for chemical and microbiological studies in conditions such as malabsorption states, and hepatic and pancreatic diseases. Contents of the gastrointestinal tract can be aspirated by using special tubes, the tip of which can be accurately positioned at the particular site under fluoroscopic control. Endoscopy has revolutionized the procedure for aspiration. Conventional methods using tubes or biopsy capsule blindly have been totally replaced by aspiration or biopsy from specific areas, under vision.

Radiological Examination of the Digestive System

These time-honored studies are of considerable help in diagnosis. Diagnostic accuracy has been considerably improved by several technical refinements. Endoscopy is more reliable to visualize mucosal lesions, and to take biopsies. But to demonstrate other structural lesions, displacements, fistulae, etc. and for studying the progress of the contrast medium, radiological studies are regularly undertaken.

Plain X-ray of the abdomen: Liver, spleen, kidneys, and tumours can be identified in a plain X-ray and their size determined. Calculi in the gall bladder, bile duct, urinary tract or pancreas, calcification of organs such as the pancreas and adrenals; and radiopaque foreign bodies and fetal parts are all classically demonstrable in a plain radiograph.

A plain X-ray of the abdomen taken in the erect posture after proper bowel preparation may show the presence of gas under the diaphragm, gas in organs such as gallbladder, biliary tree and liver, that normally do not contain gas. Presence of gas under the diaphragm indicates perforation of a hollow air-containing viscus such as the stomach or intestine. Gas in the biliary tree and gallbladder should suggest fistula formation with the gallbladder, perforation or infection by gas-forming organisms. Intestinal obstruction gives rise to the presence of multiple dilated loops with fluid levels.

Contrast studies of the gastrointestinal tract: Several contrast materials have been employed to visualize different organs.

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Barium swallow: Barium swallow is done to visualize the esophagus. After overnight fast the patient is made to swallow a thick freshly prepared paste of barium sulfate as rapidly as possible. Since most patients swallow considerable amounts of air also simultaneously, the air distended esophagus is well visualized. Barium swallow brings out lesions such as strictures, neoplasms, diverticula, esophagitis, ulcers, tears, esophageal varices, and external compression. The function of the esophagus and the lower sphincter can be assessed from the passage of the barium downwards and the pattern of peristaltic waves.

Barium meal: For barium meal studies a large quantity (250-500 mL) of freshly suspended emulsion of barium sulfate is swallowed rapidly. The rate of transit of the barium and the contours of the stomach and intestines can be assessed by fluoroscopy or television. Pictures are taken at regular intervals to delineate the different parts. Double contrast technique using air and barium helps to bring out even minute mucosal abnormalities. Barium meal studies for stomach and duodenum are indicated in suspected peptic ulcer, neoplasms of the stomach, mucosal erosions, obstructions, persistent vomiting, and vague upper abdominal symptoms.

The intestines are visualized by taking pictures in the intestinal phase of the meal. The time taken for the passage of barium, pattern of distribution in the intestinal lumen and morphological abnormalities can be assessed. Several newer techniques have helped in increasing the diagnostic efficiency and minimizing the discomfort to the patient.

Enteroclysis (Small Bowel Enema)

Barium contrast is administered directly into jejunum through a tube introduced through the nose or mouth and

positioned under fluoroscopy across the duodenum. In conventional barium study adequate quantity of barium may not enter the jejunum freely, due to the action of the pyloric sphincter. Better delineation of the small intestine can be obtained by enteroclysis.

Hypotonic duodenography: The medial wall of the duodenum, which is closely apposed to the pancreas, can be better visualized by instilling barium after using a relaxant drug such as propantheline bromide (probanthine) 30-60 mg intramuscularly or 15 mg intravenously.

Barium enema: The large intestine up to the ileocecal junction can be visualized by barium enema. Meticulous preparation of the large bowel before examination is absolutely essential to ensure accuracy. The patient should be on a low residue diet for 2 days prior to the examination. Evacuation is achieved by a purgative and, if needed, a thorough bowel wash. Barium sulfate suspension is given as an enema to fill the whole large intestine and the progress of barium is watched under the fluorescent screen. Pictures of the barium-filled colon are taken. After evacuation of the barium, air is pumped through the anal canal to fill the colon and further pictures are taken. This double contrast study helps to demonstrate mucosal lesions clearly. Barium enema is indicated in lesions of the colon and rectum such as carcinomas, ulcerative colitis, diverticulitis, polyposis, strictures, and megacolon.

Gastrointestinal Endoscopy

The advent of flexible fiberoptic endoscope has revolutionized endoscopy. Incorporation of video screens in which magnified images can be seen simultaneously has made the procedure much more efficient. Almost all parts of the stomach, many parts of the duodenum and small intestine, and almost the whole of the colon can be visualized using endoscopes which are capable of manipulation to bring to focus several areas such as the fundus of the stomach, cecum, ileocecal region and others which could not be fully visualized by the earlier endoscopes. At present the procedure is very reliable, freely available in many centers, and almost noninvasive. Endoscopy enables direct examination of the lesions, biopsy, cytology of suspicious areas, and documentation by photography. Therapeutically, endoscopes are used to remove polyps and foreign bodies, dilate strictures and cauterize ulcers and bleeding points. At present all parts of the alimentary tract are accessible to endoscopy.

Upper alimentary endoscopy: Examination of the esophagus, stomach and duodenum is done by a panendoscope. Upper alimentary endoscopy is indicated in patients with upper gastrointestinal bleeding, all types of chronic dyspepsia, and when lesions are demonstrable by X-ray but their pathological nature is not clear.

Whenever facilities are available, endoscopic examination should be undertaken to confirm the nature of mucosal lesions. Endoscopic esophageal variceal injection, variceal ligation, percutaneous feeding gastrostomy and similar procedures are commonly undertaken in gastroenterology departments at present. Endoscopic ultrasonography is a technique which gives more precise data from locations usually inaccessible to conventional ultrasound. It gives better imaging of the pancreas and even tumours less than 3 cm in diameter can be detected. Endocrine adenomata and cancer with vascular invasion arising from pancreas, and small lesions arising from other parts of the gastrointestinal tract are particularly well seen by endoscopic ultrasonography.

Special Types of Endoscopes

1. *Capsule endoscope* – A battery powered computer chip camera is assembled inside a capsule. Patient swallows it orally and the signals are recorded, which can be viewed in the monitor screen. The cost of an endoscopic capsule may come to Rs.30, 000.
2. *Zoom endoscopes* — The lesions can be zoomed to 50 to 150 times magnification.
3. *Laparoscope assisted pan-endoscopy (LAPE)*— Endoscope is introduced per orally and the small intestine is sleeved on to the endoscope with the help of the laparoscope. The entire small intestine can be visualized. It is very useful in obscure gastrointestinal bleeding.

Proctoscopy: Anal canal and rectum are visually examined with the proctoscope. Digital examination of the rectum is mandatory before introducing the proctoscope. Proctoscopy is contraindicated in severely painful lesions and strictures of the anal canal. Digital examination and proctoscopy help to diagnose the vast majority of lesions in the rectum and anal canal. These procedures should be done as part of the clinical examination in all patients presenting with symptoms pertaining to the lower alimentary tract.

Digital examination is contraindicated in the first 3-4 days following myocardial infarction, since there is the risk of triggering off serious arrhythmias.

Further refinements in the study of the anal sphincter mechanism especially in the investigation of fecal incontinence, are ultrasonography to detect tears of the external sphincter muscle, pudendal nerve latency to assess nerve conduction and anal canal manometry.

Proctosigmoidoscopy: The anal canal, rectum, and distal sigmoid colon can be visualized through a sigmoidoscope. Rigid and flexible sigmoidoscopes are available. The simplicity of the procedure and availability of the instrument in all hospitals have contributed to widespread use of this procedure. Hemorrhoids, polyps, acute and

chronic inflammatory bowel disease, neoplasms, ulcerating lesions, and sources of bleeding can be diagnosed by sigmoidoscopy and biopsy.

Colonoscopy: Flexible fiberoptic colonoscopes are available and the whole of the large intestine can be examined with them. Proper bowel preparation using an osmotically active cathartic is mandatory to clear the colon of fecal matter and enable full visualization.

Indications for colonoscopy are:

1. In lower gastrointestinal bleeding not accessible to the sigmoidoscope.
2. In inflammatory bowel disease, to assess the extent.
3. In the evaluation of radiologically demonstrable abnormalities in the large bowel situated beyond the reach of the sigmoidoscope.
4. Therapeutically, these instruments are used to remove polyps and foreign bodies and to arrest bleeding points.

Peritoneoscopy (Laparoscopy): Examination of the peritoneal cavity is safely carried out using a peritoneoscope (laparoscope). Under aseptic precautions, air is introduced into the peritoneum and the laparoscope is introduced through a small incision on the anterior abdominal wall. Liver, spleen, gallbladder, omentum, loops of intestines, pelvic organs and peritoneum can be seen directly. Localized lesions can be biopsied under vision through the peritoneoscope. Laparoscopy is indicated for detecting the cause of ascites, diagnosing liver diseases and in detecting metastatic carcinoma. Surgical procedures can also be undertaken through the laparoscope. Heart disease, acute infections, hemorrhagic diatheses, and peritoneal adhesions are contraindications for laparoscopy. Rarely complications such as hemorrhage, peritonitis and perforation of organs may occur.

Choledochoscopy: In this procedure an endoscope is passed into the biliary tree, usually during surgery. It helps to visualize the major biliary passages, remove stones and release obstructions.

Endoscopic retrograde cholangiopancreatography (ERCP): This is a procedure undertaken to delineate the common bile duct and pancreatic duct. After fixing the endoscope at the ampulla of Vater, the ampulla is cannulated using special catheters and several procedures can be performed. These include collection of the respective digestive juices, contrast injection and visualization of the duct pattern, removal of stones and growths, sphincterotomy and others.

Angiography: Abdominal angiography may be required for the investigation of several gastrointestinal diseases. With the help of suitable catheters, the celiac, superior and inferior mesenteric arteries and their branches can be selectively cannulated and contrast injected. Angiography

is indicated to detect the site of acute and chronic gastrointestinal bleeding, determine the cause of ischemic bowel disease, and in other vascular disorders of the gastrointestinal tract. Therapeutic indications include the administration of vasoconstrictor drugs (e.g., pitressin), clotting factors or microemboli to arrest bleeding, and local cytotoxic drugs for neoplasms.

Ultrasound Imaging

Ultrasound scanning is a safe, noninvasive, simple and relatively inexpensive examination. It is useful in imaging solid, cystic or air-containing tissues and organs. Ultrasound examination is indicated in hepatobiliary diseases like primary or secondary tumours, liver abscess, differentiation of medical from surgical jaundice, cholelithiasis, and various lesions of the pancreas. In skilled hands, ultrasound examination is a very reliable procedure. This has become a primary investigation to establish hepatobiliary disease, organomegaly, ascites, pregnancy, and others. Ultrasound-directed percutaneous biopsies from lesions, and aspiration of pus from abscess cavities are undertaken regularly at present. The average cost for ultrasonography of the abdomen is around Rs. 400.

Computed Tomography (CT) Scan

This technique is widely employed in the investigation of diseases of abdominal organs. Solid tissues like liver, pancreas, kidneys, adrenals, and tumors of lymph nodes and fluid-containing masses like cysts and abscesses produce diagnostic images. It is also useful in the investigation of biliary tract disease, and in the differentiation of medical from surgical jaundice. With the help of CT scan, percutaneous biopsy needles can be accurately positioned to get biopsies. This investigation has the advantage of being noninvasive, but its high cost and nonavailability in smaller cities and towns are disadvantages. The cost of CT scanning of the abdomen is around Rs. 3000. Several newer techniques using CT scanning have been introduced.

Virtual colonoscopy is a CT technique which generates high resolution two-dimensional axial images from which three-dimensional images of the colon resembling those seen on colonoscopy are reconstituted.

The reliability of this imaging procedure in detecting colonic lesions including cancer is being investigated.

Magnetic Resonance Imaging (MRI)

MRI scans are increasingly used in complicated abdominal conditions. MRI is more useful than CT scan

in defining soft tissue lesions and is especially useful in conditions like internal intestinal fistulae.

Isotopic Investigations

These are of great value in diagnosis. Absorption and fecal elimination of many substances such as cyanocobalamin and fats can be studied by using suitable isotopes. Functions of several organs can be assessed.

Biopsy

Histology is a valuable aid in confirming the diagnosis. The advent of flexible endoscopes have made all parts of the alimentary tract accessible for biopsy.

At present endoscopic biopsy is preferred for all the tubular organs. For solid organs such as the liver, pancreas, lymph nodes and solid tumors ultrasound directed or CT directed biopsy is done on account of its reliability and safety.

Laparoscopy: This is the procedure to visualize intra-abdominal and pelvic structures in vivo using appropriate laparoscopes. Several refinements and modifications have resulted in the manufacture of sophisticated instrument and development of techniques which make it possible to inspect almost all organs in the peritoneal cavity. Laparoscopy is safe and minimally invasive. In experienced hands the findings are quite reliable. Biopsy procedures and surgical interventions can be undertaken at the same time.

However, when the other non-invasive tests are not conclusive, and particularly so when malignancy is suspected, early laparotomy has to be undertaken. In some centers, mini laparotomy is used as a diagnostic tool in the investigation of jaundice and other hepatobiliary problems. By this procedure, after exposing the left lobe of the liver, liver biopsy, transhepatic cholangiography, portal manometry, and collection of bile for cytology can be carried out.

Investigative techniques have reached a high level of perfection. With the availability of modern facilities it is possible to arrive at a proper diagnosis in almost all cases, without resorting to surgery. These investigations also help the physician in assessing the functions of organs accurately, so as to plan the therapy more objectively. The proper selection and interpretation of the tests demands the diagnostic skills of the physician and a very meticulous clinical examination.

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Diseases of the Mouth and Tongue

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Inflammation of the Salivary Glands**Syn:** Sialadenitis**Causes of Generalized Sialadenitis**

- Bacterial infections:** *Staph. aureus*, *Ps. aeruginosa*, *Strep. viridans*, and rarely pneumococci and *E. coli*.
- Viral infections:** Mumps.
- Other conditions:** Sjögren's syndrome, leukemia, lymphoma, sarcoidosis (*Heerfordt's syndrome*), lupus erythematosus, tuberculosis, other mycobacteria, actinomycosis, obstruction of the ducts, salivary calculi, and rarely Reiter's syndrome.

Causes of Parotid Enlargement

- Reaction to drugs** such as iodides, guanethidine, chronic toxicity by copper, lead or mercury.
- Alcoholism, Laennec's cirrhosis and calcific pancreatitis.**
- Suppurative parotitis:** This may complicate prolonged fevers like typhoid. Infection reaches the gland from the mouth through the duct. Dehydration and poor oral hygiene predispose to infection. An abscess develops in the parotid gland. Once the abscess forms, pus has to be drained by incision. Suppurative parotitis is prevented by proper care of the mouth in predisposed individuals.

RECURRENT APHTHOUS ULCER**Syn:** Cancer sore, Mikulicz aphthae, Aphthous stomatitis

Aphthous ulcers are the most common lesions affecting the oral mucous membrane. The exact etiology is unknown. Recent observations suggest an autoimmune etiology. Microscopically, the lesion shows a non-specific ulcer with necrosis of subepithelial small blood vessels.

Clinical Features

Crops of painful ulcers occur periodically at intervals of weeks to months. The ulcers can be divided into minor (60-70%) and major aphthae (30-40%).

Minor Aphthous Ulcers

These occur mainly on the labial, buccal, and tongue mucosa. They are shallow, measuring 2-4 mm in diameter. The floor is covered with fibrin and the periphery is erythematous. Rarely, the ulcers may become secondarily infected, but they heal without scarring.

Major Aphthous Ulcers

These appear commonly in the soft palate and lower labial mucosa. They are larger, measuring over 1 cm in diameter, and are deep and indurated. They persist for more than 4 weeks and heal with scar formation. Other clinical features are similar to those of minor aphthae.

Diagnosis is clinical. Minor aphthae have to be differentiated from the oral manifestations of herpes simplex, agranulocytosis, infectious mononucleosis and cyclic neutropenia. Major aphthae showing induration should be differentiated from malignancy.

Treatment

There is no specific treatment. Topical application of steroids in the initial phase may abort an attack. Pellets of glucocorticoids or 0.1% triamcinolone in orabase applied locally four times daily are effective in 2-3 days. Rarely systemic corticosteroids may be required.

Other modalities of treatment include tetracycline mouth wash and 2% anesthetic ointment or jelly. Castor oil 5-10 mL administered at bed time in milk for 3-4 days helps in shortening the duration and aborting an attack (personal observation-KVK).

Oral Submucous Fibrosis

Submucous fibrosis is commonly seen among all races inhabiting South-east Asia. It is common in South India. There may be an increase in incidence in those who chew betel nut continuously for several months. Recent studies have shown a high content of copper in some of the nut preparation available commercially. The significance of this finding needs further study.

Pathology

Pathological changes include ribbon-like atrophy of subepithelial collagen and moderate infiltration by chronic inflammatory cells. There may be dysplastic changes in the epithelium and many cases develop squamous cell carcinoma on follow-up.

The disease starts insidiously and runs a chronic course. Early symptoms include burning sensation of the mouth and difficulty to tolerate spicy foods. Gradually, fibrosis sets in, and this may interfere with opening of the mouth. In advanced cases the uvula becomes fibrotic and small. The fibrotic process may rarely extend to the pharynx and esophagus in advanced cases. Later on, recurrent erosions and ulcers develop which heal slowly. Carcinoma develops from these erosive or ulcerated areas and not uncommonly it is multicentric.

Clinical diagnosis is based on the symptoms and the leathery inelastic feel of the oral mucosa. Diagnosis is confirmed by biopsy.

Management

There is no specific treatment. Smoking and chewing of tobacco and betel nut should be stopped. Repeated submucous infiltration of 25 mg of hydrocortisone hemisuccinate into the fibrous areas may help in resolving early lesions and improving the mobility of the lower jaw and tongue. All patients have to be followed up and suspicious lesions biopsied. If malignancy is detected, it is treated by irradiation.

Orofacial Granulomatosis

Oral lesions are common in patients suffering from Crohn's disease of the intestines. These include aphthae, diffuse swelling of lips and cheeks, chronic inflammatory hyperplasia with fissuring of the mucosa, mucosal tags, vertical fissuring of lips, and hyperplastic gingivitis. Sometimes similar lesions may occur even in the absence of the intestinal lesions.

Outlook for orofacial granulomatosis is variable. Some cases are self-limiting. Drugs which are found to be partially effective include danazol and clofazamine.

Non-specific Inflammatory Diseases of Periodontium

Limited surveys reveal that periodontal disease occurs in up to 90% of several communities in India. Periodontium comprises gingiva, periodontal membrane, and the alveolar bone which support the teeth. All the non-specific infections together are called as **pyorrhea**. Pyorrhea is common in persons past middle age. Dental infection is the most common focus of sepsis in any individual. The infection takes the form of gingivitis in the beginning and then it progresses to periodontitis, and finally the teeth fall off. Many local and systemic factors influence the course of the disease. Local factors that aggravate the progress of periodontal disease are traumatic occlusion, malalignment of teeth, mouth breathing, calculus, illfitting appliances and xerostomia. Systemic conditions include protein malnutrition, puberty, pregnancy, menopause, diabetes, anemia, scurvy, granulocytopenia, drugs like phenytoin, and immunodeficiency states.

The earliest change is the formation of a bacterial plaque in the cervical margin of the tooth. The plaque contains *Streptococcus viridans*, *Staph. albus*, *Staph. aureus*, lactobacilli, *Helicobacter pylori* and actinomycetes. The toxins produced by the bacteria evoke an inflammatory response in the gingival crevice. The gingiva and interdental papilla become edematous and bleed on palpation. Further bacterial proliferation and toxin formation occur and inflammation progresses.

The gum attachment migrates apically. The periodontal fibers undergo degeneration and the alveolar bone also undergoes resorption. This stage is called periodontitis. At this stage an acute periodontal abscess may form. Continued inflammation and resorption of alveolar bone leads to loosening and loss of teeth.

Clinical Features

Gingivitis may be symptomless except for halitosis and painless bleeding from gums on brushing. The gingiva are red and the normal stippling is absent. Periodontitis is characterized by dull pain. Periodontal abscess causes throbbing pain which increases when the patient is recumbent. Pus can be expressed from the gingival crevice.

Diagnosis

The diagnosis of non-specific periodontal disease is made by clinical examination. Depth of the gingival pocket can be measured by a periodontal probe.

Intraoral *bite wing X-rays* are useful in assessing the pattern and extent of bone loss. In all cases of severe periodontal disease full clinical examination and investigation should be done to exclude the underlying systemic disorders.

Management

The disease can be prevented by avoiding the formation of dental plaques. Plaques can be removed by regular brushing and flossing. The calculus formed should be removed by scaling. Analgesics and antibiotics are required to control pain and infection respectively. Acute gingival or periodontal abscess has to be drained. If there are deep pockets, gingivectomy has to be done. Loose teeth have to be extracted if they cannot be refixed by appropriate dental management.

Dental Caries

Dental caries is defined as the local destruction of susceptible hard tissues by acidic byproducts formed by bacterial fermentation of dietary carbohydrates. Caries may affect the crown or the root of the tooth.

Dental caries is one of the most widespread diseases present all over the globe, but shows wide variation in prevalence among different communities. In several parts of India the prevalence is 65-70% among the general population. It results from demineralization and dissolution of the enamel and dentine. The etiology of dental caries is complex and several factors serve to start off the process. Factors which affect the extent and progress of the disease are the composition of the enamel, food habits, content of carbohydrates in the food, oral hygiene, heredity, and fluoride intake in food and water. Food debris and bacteria accumulate on the pit and fissure surface of the teeth to form a plaque consisting of bacteria, mucus, and desquamated epithelial cells. Refined carbohydrates like sugars adhere to the plaque and help in liberating acid products by action of the mixed bacterial flora, the most important among them being *Streptococcus mutans*. The infant acquires *Streptococcus mutans* from the mother or other primary care givers. Under the plaque, the pH is lowered below 5.3 and this causes demineralization of the enamel. The calcium salts are removed, leaving the tooth surface rough and chalky white. At this stage the proteolytic organisms destroy the protein matrix of enamel rods. This process proceeds towards the dentine and a cavity is formed. In the dentine the progress is faster and the pulp is reached. The response of the pulp depends upon the age and general resistance of the individual and virulence of the organism. Either an acute pulpitis with necrosis may develop or the inflammation may become chronic. Secondary dentine may be formed from the pulp in an attempt to limit the infection. At times the pulp may undergo hyaline degeneration and calcification.

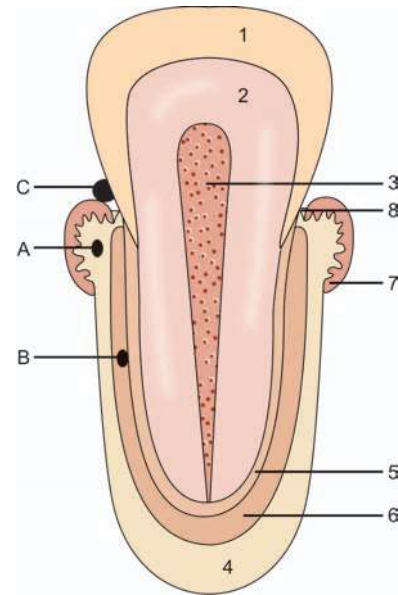


Fig. 76.1: Tooth and gum

1. Enamel
 2. Dentine
 3. Pulp
 4. Soft tissues
 5. Cementum
 6. Alveolar bone
 7. Gingiva
 8. Gingival crevice,
- (A) and (B) Site for periodontal abscess.
(C) Site of accumulation of plaque.

Finally, the bacteria and their toxins reach the periapical tissues and produce acute periapical periodontitis and progress to acute periapical abscess. If the host resistance is poor, the infection can spread to adjacent tissues, maxillary sinuses, base of the skull, and through the bloodstream. More often the inflammation becomes chronic leading to the formation of a granuloma which acts as a chronic focus of sepsis. An inflammatory cyst may be formed (Fig. 76.1).

Clinical Features

In children caries is usually seen in the pit and fissures of the occlusal surfaces whereas in elderly persons it is noticed more in the cervical margins of the teeth, though any surface may be affected. The whole process may proceed slowly over the years or can be rapid to develop within months. Widespread acute caries involving all surfaces of several teeth is referred to as *rampant caries*.

The condition remains asymptomatic till the lesion reaches the dentinoenamel junctions, since there are no nerve endings in the enamel. Early lesions appear as chalky white areas on the enamel surface which can be detected by a probe. These are translucent on X-ray examination. Later, the chalky areas become brown or black. Initial symptom is *sensitivity* to sweet, cold or hot drinks produced by stimulation of nerve endings in the dentine. Pain develops when the pulp becomes hyperemic.

Acute pulpitis causes unbearable pain, often described as toothache, on the affected side. The pain is only poorly localized and the patient may not be able to pinpoint the affected tooth. As the acute condition subsides, pain becomes dull. If the pulp undergoes necrosis, pain is abolished and the condition remains symptomless for a while. As the inflammation extends outside the tooth, pain returns. Exacerbations and remissions alternate for considerable periods of time.

Treatment

Powerful analgesics give moderate relief of pain in the acute stage. Prompt relief is obtained by injection of a local anesthetic. A broad-spectrum antibiotic like ampicillin 250 mg 6 h or ciprofloxacin 500 mg b.d is required for 3-5 days to control infection. Abscesses have to be drained surgically. Since appropriate dental care is to be instituted, the case should be immediately referred to a dental surgeon.

Caries is incurable once it is established, since the dentine is not capable of undergoing repair. Early lesions are treated by removal of the affected parts and filling up the defect with suitable materials. Technical advances in dentistry have been remarkable and even grossly affected teeth can be restored to functional stage, without recurrence of pain. If the tooth is grossly damaged beyond repair, it has to be extracted. At present the policy is to restore the tooth to normal functions and preserve it as far as possible.

Prevention

Dental caries is an easily preventable disease. Prevention should start during pregnancy, when the teeth of the fetus are getting mineralized. Adequate supplements of calcium, vitamin D and other nutrients to mothers during pregnancy and later to the child, ensure proper teeth formation. Inclusion of fresh vegetables and fruits which require proper mastication helps to keep the teeth and gums healthy. The habit of allowing the baby to sleep with the milk feeding nipple in the mouth helps to promote caries. Soft drinks which contain sugar favour the growth of organisms and promote the development of caries. Proper brushing of the teeth and massage of the gums before the child goes to bed is an effective preventive measure against caries.

Fluoridation of community water supplies at 1 ppm reduces the incidence of caries. Fluoride applied topically either directly or by using fluoridated tooth pastes or chewing gums improves local resistance of the teeth. Fluoride tablets containing 2.2 mg of sodium fluoride (equivalent to 1 mg fluorine) have been used to supplement the intake in babies. One tablet is dissolved in 1.25 L water and this water is used for making up milk formula and cooking for children below the age of three years. Above the age of three years

one tablet may be administered daily. Periodic dental check-up of preschool and school children and education of the mothers are absolutely essential to lower incidence of caries in the community. In many parts of India where the fluoride content of drinking water is high, additional supply of fluoride through toothpastes has been incriminated as a factor aggravating fluorosis. This has to be borne in mind while making recommendations for fluoride supplementation.

Vincent's Infection

Syn: Vincent's angina, Acute necrotizing ulcerative gingivitis

It occurs as a painful condition caused by a mixed bacterial flora consisting of *fusiform bacilli* and *Vincent's spirochetes*. It may be associated with extensive necrotizing ulcerative mucositis, or acute pseudomembranous lesions of the pharynx or tonsils. The condition is predisposed to by poor oral hygiene, food impaction, excessive smoking, and local trauma.

The gums are painful, swollen, hemorrhagic and foul smelling. A serious complication is noma which begins at the corners of the mouth and proceeds to rapid necrosis of the entire thickness of the cheeks. Rarely septicemia and meningitis may occur.

Treatment

The organisms respond dramatically to penicillin in the usual dosage. Metronidazole 200 mg given orally thrice daily for 7 days gives good relief and is a satisfactory alternative.

Diseases of the Tongue

Glossitis: It is inflammation of the tongue and in general denotes soreness and redness of the tongue. The tongue appears beefy red and the papillae are prominent. In some cases the papillae may be ironed out. Glossitis may result from deficiency of B complex vitamins, megaloblastic anemia, cirrhosis of liver, irritants like alcohol, excessively spicy foods, and all causes of stomatitis. Specific lesions of syphilis, gonorrhea, tuberculosis, actinomycosis and AIDS may start in the oral cavity.

Leukoplakia: This is a chronic lesion characterized by the presence of white, firm, smooth patches over the tongue present over a variable extent. Though painless at first, it may become fissured and painful later. Being a precancerous condition, persons who develop leukoplakia have to be regularly followed up.

Geographical tongue: It is the name given to chronic migrating superficial glossitis. Though it appears fierce, it is not clinically significant. The cause is not clear.

Glossodynia: It is pain arising from the tongue, which is apparently normal.

Atrophy of the tongue (bald tongue): Mucosal atrophy occurs in iron deficiency anemia, pellagra, vit B₁₂ deficiency, or syphilis. The tongue may be sore. Lesions of the hypoglossal nerves or their nuclei cause atrophy of the muscles. In this condition the tongue shows longitudinal furrows.

Pigmentation of the tongue and oral mucosa: Main causes of this condition are given below.

1. Poor oral hygiene.
2. Irritation due to dentures or extensive metal fillings.
3. Addison's disease.
4. Side effects of drugs like phenothiazines and oral contraceptives.
5. Peutz-Jeghers syndrome.
6. Accumulation of heavy metals like lead, mercury and bismuth.
7. Malignant melanoma.

Fissured tongue (scrotal tongue): The dorsal and lateral surfaces of the tongue are covered by deep fissures which are soft, painless and often asymptomatic except for the appearance. This may cause anxiety to the patient.

Hairy tongue: This abnormality develops due to elongation of the filiform papillae at the dorsum of the tongue, as a result of failure of the keratin layer to desquamate normally. Staining by food, tobacco, "pan" or chromogenic microbes gives this a black or brown color.

Oral Cancer

This is the most frequent form of cancer in Indian subjects, especially males. More than 95% cases have squamous

cell carcinoma. The sites of predilection are the lips, posterior two-third of the tongue, inner aspects of the cheek and gingival margins. The growth is single in the majority of cases but cancer arising from submucous fibrosis may be multiple.

Etiology

Excessive chewing of tobacco in the form of *pan* (betel leaf, lime, and tobacco) and retention of the cud in the mouth are closely associated with oral cancer in India. Other associations are cigar or pipe smoking, smoking with the lighted end of the cigar or *beedi* inside the mouth (as in Andhra Pradesh), and keeping snuff in the mouth.

Conditions like submucous fibrosis, alcoholism, syphilitic glossitis, chronic irritation by malaligned teeth and *Plummer-Vinson syndrome* are associated with higher risk of cancer. Leukoplakia is a common precancerous lesion.

Since the early lesions are painless, there may be considerable delay in seeking medical aid. Presence of induration of the ulcer or growth should draw attention to the possibility of cancer. All chronic ulcerating or indurated lesions in the mouth should be examined carefully by palpation and biopsied without delay to detect carcinoma and the case may be referred to the appropriate speciality services.

Treatment

Mainly local irradiation is advised. Surgical measures are employed in special circumstances.

Regular attempts to educate the public and training of volunteers to detect oral cancer in the community by the Regional Cancer Center, Trivandrum has served to bring oral cancer cases at a much earlier stage for therapy.

77

Diseases of the Esophagus

K.R. Vinaya Kumar, K.V. Krishna Das

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Symptoms in Esophageal Disease

Diseases of the esophagus manifest as esophageal pain and/or dysphagia. The esophagus is not readily accessible to physical examination and in the ordinary case the examiner has to satisfy himself with interrogation regarding these symptoms. Investigations include contrast radiography using barium swallow, esophagoscopy, and biopsy from different regions under vision.

Esophageal Pain

It may be of three types:

1. *Heart burn*—burning sensation produced by reflux of acid gastric contents into the esophagus.
2. *Odynophagia*—pain during deglutition which is due to inflammation of the esophagus.
3. *Colicky pain*—caused by vigorous contraction or distension of the esophagus. Esophageal pain may arise either because of obstruction by food or diffuse esophageal spasm. Esophageal pain may be mistaken for angina pectoris. Presence of dysphagia suggests that the pain arises from the esophagus. Autonomic disturbances like sweating may accompany these attacks. Nitrates may relieve the pain of esophageal spasm.

Dysphagia

460 It may be oropharyngeal or esophageal.

Causes of Oropharyngeal Dysphagia

Neuromuscular disorders: Lower cranial nerve paralysis, myasthenia gravis, oropharyngeal myopathies, motor neuron disease, hydrophobia, and iron deficiency states.

Mechanical obstruction: Tumors, stricture, diverticula or webs as in iron deficiency anemia.

Esophageal dysphagia: This can be distinguished by the onset of dysphagia when the patient initiates swallowing. The passage of food is delayed. Though some degree of localization of the pain is possible, on many occasions it is referred to other regions like the suprasternal notch. Mechanical causes lead to obstruction to solids whereas neuromuscular causes lead to difficulty in swallowing solids and fluids.

Neuromuscular causes: These include achalasia cardia, diffuse esophageal spasm, vagal paralysis, progressive systemic sclerosis and Chagas' disease.

Mechanical causes: These may be intrinsic or extrinsic.

Intrinsic causes: These include: (i) carcinoma, (ii) strictures, (iii) diverticula, and (iv) esophageal rings and webs, e.g. the mucosal or muscular ring at the junction of the squamous and columnar epithelium (*Schatski ring*).

Extrinsic causes: These include compression by mediastinal masses like lymph nodes, tumors, enlarged left atrium, aortic aneurysm, mediastinitis, or infiltration by bronchogenic carcinoma.

Dysphagia should be fully investigated to find out the cause. If none is detected, the investigations should be repeated after a suitable interval. Carcinoma of the esophagus may present with bizarre symptoms for long periods of time and a high index of suspicion is necessary to make an early diagnosis.

Vomiting

Vomiting is a forceful expulsion of the gastric contents through an open mouth. This has to be distinguished from

regurgitation which is the effortless entry of the gastric or esophageal contents into a closed mouth. This may be spat out or swallowed.

Vomiting may be caused by different mechanisms. The common causes of vomiting are given below:

Gastric causes: Irritant foods, drugs or other chemicals, bleeding into the stomach, gastritis, and pyloric obstruction.

Neurological causes: Rise of intracranial tension, intracranial bleeding, inflammation of brain or meninges, vertebrobasilar ischemia and migraine.

Metabolic causes: Uremia, hepatic failure, diabetic ketoacidosis, lactic acidosis, acute intermittent porphyria, and poisoning.

Endocrine causes: Hypoadrenal crisis, hyperparathyroidism, hyperthyroidism, and pheochromocytoma.

Reflex causes: Labyrinthine stimulation occurring in motion sickness, ocular causes.

Psychogenic vomiting: Anxiety state, hysteria, depression.

Pregnancy: Hyperemesis gravidarum.

Drugs

Several drugs lead to nausea and vomiting as prominent side effects. This may be due to local irritation as in the case of anti-rheumatic drugs, antibiotics and iron salts or vomiting may be caused by stimulation of the medullary centers. Anti-cancer drugs, oral contraceptives and estrogenic steroids come under this group.

Vomiting is a very unpleasant symptom due to the associated autonomic phenomena such as sweating, salivation, palpitation and tachypnea. Severe vomiting leads to dehydration, hyponatremic hypokalemic, hypochloremic alkalosis and ketosis. Repeated vomiting may also lead to gastro-esophageal tears (Mallory-Weiss syndrome), esophageal rupture, subconjunctival hemorrhage or even intraocular and intracranial hemorrhage.

Precise diagnosis of the underlying condition and specific treatment is required in all cases. Correction of the metabolic derangement should be instituted in severe vomiting as in hyperemesis gravidarum. In severe cases infusion of intravenous normal saline should be started without delay. Further management depends upon the degree of electrolyte and acid base disturbances. Infusion of fluid should be started as soon as the patient is first seen. Even in the presence of moderately severe vomiting, frequent small sips of fluids (30 mL given every 10 min) help to retain some fluid and in many cases this is very beneficial.

Fluid can be administered rectally. Up to 1.5 L of normal saline can be given in 24 hours by this route. The fluid is given through a narrow bore urinary catheter introduced high up in the rectum and given at the rate of

75-100 mL/hour. The infusion bottle should be suspended 30-50 cm above the bed. If fluid is given at greater pressure into the rectum the fluid may be ejected. Prokinetic agents such as metoclopramide, domperidone and cisapride can restore normal gastric motility and give good symptomatic relief. Antihistamines such as pheniramine 25-50 mg oral are useful to prevent vomiting in motion sickness. Phenothiazines such as trifluoperazine hydrochloride 5-10 mg oral are effective in mild forms of vomiting due to neurological causes. In more severe forms injection of procloperazine maleate 12.5-25 mg IM may be required. Vomiting can be very disturbing in cancer chemotherapy. Selective 5-HT receptor antagonists such as ondansetron 4-8 mg given slowly IV before starting chemotherapy prevents this complication.

Esophagitis

Inflammation of the esophagus may occur in several diseases, some of which are listed below:

1. *Irritants*—corrosives, alcohol, spicy foods and drugs.
2. *Infections*—systemic infections like influenza, cytomegalo virus, HIV, measles and chickenpox, and local infections like herpes simplex and candidiasis.
3. *Peptic esophagitis*—associated with gastroesophageal reflux.
4. *Specific infections*—tuberculosis, syphilis, gonorrhea.
5. *Post-irradiation esophagitis*.

Management: When a specific cause is identified, it should be removed. Small feeds given frequently and administration of demulcents and antacids gives symptomatic relief. Omeprazole 20 mg oral bd given for 3-4 days may help. If swallowing is difficult, ranitidine injection 50 mg IM 8 h will be beneficial.

In the case of infections, specific anti-infective agent is indicated. Management of corrosive poisoning is given in Section 4.

Achalasia Cardia

Syn: Cardiospasm

In this disorder there is abnormality of lower part of the esophagus which results in failure of relaxation of the sphincter when food reaches the lower end. The esophagus progressively dilates and becomes atonic. The dysfunction is due to degeneration in the Auerbach's plexus and vagal fibers (Fig. 77.1).

Clinical Features

The presentation may be varied. There may be dysphagia, recurrent respiratory infections or vague upper abdominal symptoms. Even with dysphagia the general health is preserved. At the end of the meal the patient exerts pressure which opens the sphincter and the food material

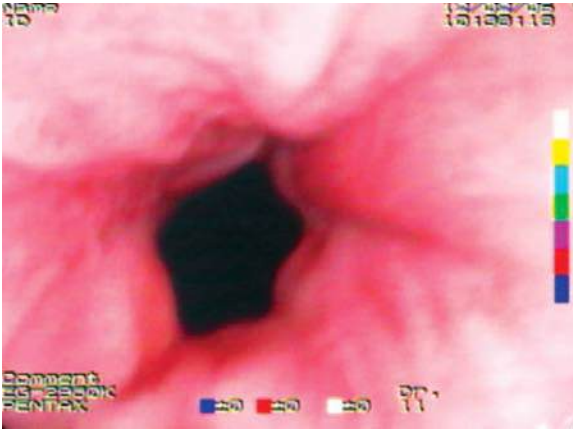


Fig. 77.1: Achalasia cardia dilated esophagus

passes down to the stomach with a gurgle. Food collected in the dilated esophagus undergoes fermentation. Repeated aspiration of this material into the respiratory tract results in recurrent bouts of respiratory infection. Carcinoma may supervene on achalasia cardia.

In some cases of achalasia there may be vigorous contractions of the esophageal muscles causing chest pain (*vigorous achalasia*).

Diagnosis

Clinically, the condition should be diagnosed when long-standing dysphagia is accompanied by good general health. Some cases may be identified for the first time from chest radiographs. The presence of a mediastinal shadow with a horizontal fluid level produced by the dilated fluid-filled esophagus should draw attention to this condition. Barium swallow confirms the diagnosis (Fig. 77.2). In all cases, esophagoscopy and biopsy should be done to exclude stricture and carcinoma. Other conditions which produce esophageal lesions similar to achalasia are gastric carcinoma infiltrating into the lower end of the esophagus, amyloidosis and Chagas' disease.

Treatment

Conservative management consists of dietary adjustment such as frequent small feeds, anticholinergic drugs like propanthine 15-30 mg thrice a day 15 minutes before meals, and attention to general health. Calcium channel blockers such as nifedipine have been tried with limited success.

Pharmacotherapy is often unsatisfactory and unpredictable. All symptomatic patients require a definitive therapy such as balloon dilatation, injection of botulinum toxin or surgical cardiomyotomy (Heller's operation). Balloon dilatation under endoscopic or fluoroscopic control is a quick and safe procedure which gives lasting relief. It is the first choice in many centers. Endoscopic injection of botulinum toxin also gives similar results for varying

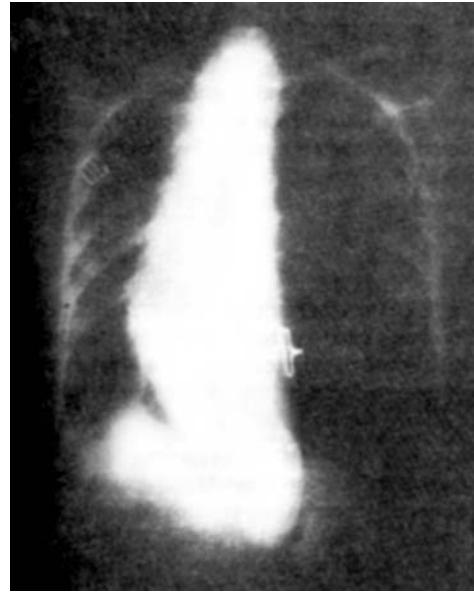


Fig. 77.2: Achalasia cardia: Barium swallow. Note the grossly dilated esophagus

periods. It has to be repeated. Surgery gives permanent relief but regurgitation is a complication.

Diffuse Esophageal Spasm

Syn: Corkscrew Esophagus

This is caused by disordered peristalsis. Multiple contractions occur simultaneously in addition to normal contractions induced by deglutition. The disorder may be primary or secondary to esophagitis and carcinoma. The lower esophageal sphincter is normal. Emotional stress and hurried eating precipitate symptoms. These patients complain of retrosternal pain induced by swallowing.

Barium swallow demonstrates the irregular peristalsis. Motility studies confirm the diagnosis. Carcinoma has to be ruled out by endoscopy.

Treatment

Nitroglycerine in a dose of 0.5 mg sublingually relieves the spasm, and it also helps in relieving the pain if given before eating. General measures to allay anxiety, education in proper eating habits, and reassurance, clears symptoms in most cases.

Esophageal Hiatus Hernia and Peptic Esophagitis

The lower esophageal sphincter may be incompetent and regurgitation of gastric contents into the esophagus may occur in a variable proportion of normal subjects, but in a few cases it causes symptoms. The sphincteric action is assisted by the intra-abdominal pressure which helps in closing of the sphincter with increase in pressure. In hiatus

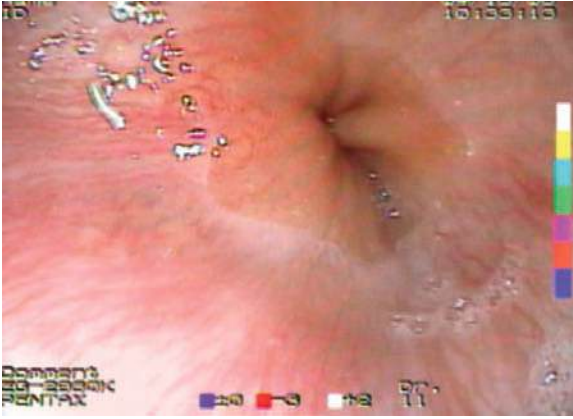


Fig. 77.3: Normal gastro-esophageal junction

hernia, the esophagogastric junction slides above the diaphragm and reflux occurs into the esophagus when intra-abdominal pressure rises.

Gastric acid, pepsin, and bile lead to inflammatory changes in the esophagus. The lower end of the esophagus may show metaplasia of the epithelium and the lining may resemble gastric mucosa (*Barrett's esophagus*). Peptic ulceration and adenocarcinoma may develop in such metaplastic epithelium as late complications. Peptic esophagitis may be complicated by hemorrhage, stricture formation and perforation (Fig. 77.3).

Hiatus hernia is more common in obese females. This may be of two types. In the *sliding type hernia*, the esophagogastric junction slides through the *diaphragmatic* hiatus. In the *paraesophageal type of hernia*, a knuckle of the fundus of the stomach passes up to the thorax alongside the esophagus. These hernias as such may be symptomless but symptoms start appearing when peptic ulceration develops.

Clinical Features

The common symptoms is heart-burn felt at the lower part of the sternum, when the patient lies down flat, stoops forward as in tying the shoe lace or lifts heavy objects. The pain is relieved by adopting the erect posture. Certain foods aggravate this pain. Rarely gastric contents may regurgitate into the mouth or may be aspirated into the respiratory tract.

Diagnosis

It is confirmed by radiology and esophagoscopy. The lesion is demonstrable by barium meal taken in the Trendelenberg position.

GASTRO-ESOPHAGEAL REFLUX (GER)

This term denotes the reflux of the acidic gastric contents into the esophagus. It is not a disease. It is seen in many subjects, especially children. Normally the lower esophageal sphincter maintains a pressure 15 mm Hg

above the gastric pressure and so, there is no regurgitation of gastric contents into the esophagus.

Gastro-esophageal Reflux Disease

GER becomes a disease when it is causing symptoms such as heart burn, or when it is associated with endoscopic changes or histopathological changes in the esophageal mucosa. It is a common disease and about one third of the adult population have symptoms at some point in their life time. Obesity and smoking are weakly associated with GERD. Males suffer more.

Heart burn and regurgitation are the common symptoms of GERD. Dysphagia chest pain, dysphonia and globus are also seen in severe cases. Laryngitis, reflux bronchospasm, precipitation or aggravation of asthma and strictures and ulcerations of the lower end of esophagus are seen as complications. Severe disease may be associated with Barret's esophagus. Ambulatory PH monitoring done with a PH probe positioned 5 cms above the gastroesophageal sphincter records the GERD though out the day.

Endoscopy and PH metry are the diagnostic investigations. Endoscopy can assess the severity of the illness and can also detect complications such as strictures, Barret's lesions, ulceration and esophageal adenocarcinoma (Fig. 77.4).

Treatment

The medical treatment of GERD and esophageal hiatus hernia is similar in the early stages and hence they are described together. Mild cases require only dietary regulation, elevated position of head during sleep and antacids. Weight reduction and short courses of treatment with prokinetic drugs such as metoclopramide 10-15 mg bd or mosapride 10 mg bd help to relieve symptoms. H₂ receptor blockers such as ranitidine or famotidine are useful, but protein pump inhibitors such as omeprazole 40 mg bd or pantoprazole 40 mg bd are more effective. Severe cases require high doses of PPI for long duration

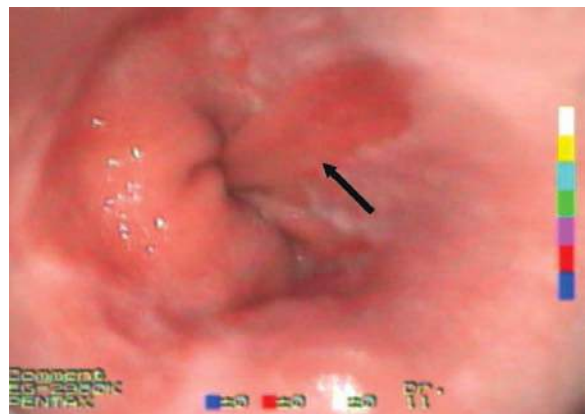


Fig. 77.4: Barrett's esophagus. Note: gastric metaplasia in the esophagus (arrow)

(several years). Cases resistant to medical therapy may be benefited with surgical interventions such as laparoscopic fundoplication. Complications such as esophageal strictures are managed with endoscopic balloon dilation.

(Further reading: Paul Magyed. L. Nicholas Talley. Gastro-intestinal reflux disease. The Lancet 2006;367:2086-2100).

Paraesophageal hernias: These may not be symptomatic in many cases since the lower esophageal sphincter is intact but sometimes large hernias may produce symptoms like cardiac arrhythmias, dyspnea, and dysphagia. Gangrene or perforation may present as surgical emergencies at times.

Carcinoma of Esophagus

This is common in India, especially in the southern states. 30-40% of all esophageal carcinomas occur at the lower end of the esophagus—95% is squamous cell carcinoma and 5% is adenocarcinoma. In many countries the proportion of adenocarcinoma is increasing. Etiological factors include smoking, alcoholism, Barret's esophagus,

obesity, poverty, burns of the esophagus and Plummer Vinson syndrome.

Due to the absence of serous coat, esophageal cancer disseminates early. The growth may be ulcerating, polypoid or annular.

Progressive dysphagia, initially to solids and later to fluids as well, is the time honoured description, but in a minority of cases symptom may be vague and atypical. Loss of weight is an early symptom. Barium swallow, esophagoscopy and biopsy confirm the diagnosis. These investigations must be undertaken in all patients with symptoms referable to the esophagus.

Treatment

Lesions in the distal third are more amenable to therapy. Surgical resection and irradiation are beneficial in early cases. In advanced cases irradiation may give symptomatic relief. A feeding gastrostomy may prolong life, but the miserable condition of the patient after the surgery is a strong point against palliative surgery. Self expandable metallic stents are available which can be introduced endoscopically. Radiation can be applied over the stent.

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Diseases of the Stomach

K.R. Vinaya Kumar, K.V. Krishna Das

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Gastritis

Definition

“Gastritis” denotes inflammatory process of various etiological factors involving the wall of the stomach, particularly the mucosa.

Classification

There are two types of gastritis—(i) acute gastritis, and (ii) chronic gastritis. Chronic gastritis is further classified into: (a) chronic superficial gastritis, (b) atrophic gastritis, (c) granulomatous gastritis, (d) eosinophilic gastritis, and (e) hyperplastic gastritis.

Acute Gastritis

Chemicals like strong acids or alkalies, drugs such as salicylates and indomethacin, ethanol, ionizing radiations, acute mental and physical stress, shock, hypoxia and renal failure may cause acute gastritis. The pathological change leads to breakdown of gastric mucosal barrier. The hydrogen ions diffuse into the mucosa from the lumen. Vascular damage occurs. Acute hemorrhagic gastritis may be localized or diffuse. Superficial erosions may develop due to necrosis of the epithelium and extravasation of blood from the damaged vessels in the lamina propria.

Symptoms include upper abdominal pain, nausea, vomiting, hematemesis and melena. Endoscopy reveals edema of the mucosa, hyperemia, surface erosions, and hemorrhages. Proper treatment results in complete recovery within a few days.

Treatment

Removal of the cause, bland frequent diet, antacids and correction of fluid and electrolyte levels give relief. Hematemesis may develop which demands emergency management. H_2 receptor blockers such as ranitidine 150 mg oral b.d or famotidine 40 mg oral b.d help to bring early relief. Proton pump inhibitors (PPIs) such as omeprazole 40 mg bd are very effective.

Chronic Gastritis

Chronic gastritis can be subdivided into types A and B. Type A gastritis is probably an immune-mediated disorder. Some of these cases develop pernicious anemia. *Helicobacter pylori* is causally associated with type B or chronic bacterial gastritis. Many drugs such as NSAIDs and others may produce chronic chemical gastritis. Attention to these factors helps to relieve the condition in many cases.

Chronic superficial gastritis: In this form the gastric glands are normal but cellular infiltration consisting of lymphocytes and plasma cells occur in the lamina propria adjacent to the surface and the gastric pits. The body and fundus of the stomach are affected leaving the antrum free.

Chronic atrophic gastritis: This is more common as age advances. It is associated with pernicious anemia, diabetes mellitus, thyroid disorders, Addison's disease and iron deficiency anemia. Mucosa over the body and fundus is diffusely affected. Mucosal cells atrophy partially or completely resulting in variable thinning of the mucosa. Gastric epithelium may undergo metaplasia and be transformed into intestinal type of epithelium. There is also infiltration by lymphocytes and plasma cells. Acid secretion falls. Majority of cases are symptomless, but pernicious anemia or gastric bleeding may develop in some. Parietal cell antibodies are demonstrable in 60% of cases. Carcinoma of the stomach is more common in

these patients, treatment is only symptomatic. The atrophic epithelium does not generally recover.

Granulomatous gastritis: Several granulomatous disorders such as tuberculosis, Crohn's disease, sarcoidosis, syphilis and others may be associated with gastritis. The gastric mucosa shows chronic inflammation, ulceration and hypertrophy. Treatment of the underlying condition leads to regression of the gastric lesions as well.

Eosinophilic gastritis: This is part of widespread eosinophilic infiltration of the gastrointestinal tract, the cause is not evident in many cases. Peripheral blood may show increase in eosinophils. Treatment with corticosteroids and antihistamines is often successful.

At times larval forms of nematodes such as *Anisakis marina* may cause infestation of the gastric mucosa. This is associated with secondary eosinophilic infiltration.

Hypertrophic gastritis: This is characterized by large hypertrophic folds of gastric mucosa. There are two varieties:

1. This causes hypersecretion of gastric juice poor in acid and rich in protein. This is called *Menetrier's disease*. The excessive protein loss may lead to hypoproteinemia and edema. Treatment consists of high protein diet and symptomatic measures.
2. In the other variety, gastric juice is rich in acid and low in protein. This hyperacidity responds to H_2 blocker drugs or omeprazole.

Other rarer causes of gastritis include infections caused by pyogenic bacteria or anaerobes and *Candida albicans*. External irradiation leads to both acute and chronic gastritis.

PEPTIC ULCER

This term refers to nonmalignant ulceration of gastric or duodenal mucosa as a result of acid-peptic influences. These are seen in the stomach, duodenum or other sites where gastric type mucosa may be present, e.g. lower end of esophagus or Meckel's diverticulum. Peptic ulceration may be acute or chronic. **Acute peptic ulceration** may result from ingestion of corticosteroids, non-steroidal anti-inflammatory drugs, corrosive agents and unwholesome food. Severe stressful conditions such as mental stress, burns, shock and others may lead to acute mucosal ulceration and these present as hematemesis and melena complicating the primary disease.

Chronic peptic ulceration generally affects the stomach or duodenum and less commonly other ectopic sites of gastric mucosa. Normally, the ulcerogenic effect of acid and pepsin is counteracted by the mucosal resistance of the gastroduodenum. Ulceration results when this equilibrium is upset.

Duodenal Ulcer

This is 10 to 20 times more common in males than females, and it is 12 to 30 times more common than gastric ulcer. Chronic duodenal ulcers occur in the first part of the duodenum just distal to the pyloro-duodenal junction. 50% are on the anterior wall. Multiple ulcers occur in 10-15%. In 10% duodenal and gastric ulcers coexist. The pathogenesis of duodenal ulcer is not completely understood. It is more common in the rice-eating population of India.

Hereditary factors, dietary habits, heavy smoking and chronic use of drugs like aspirin, antirheumatic drugs and corticosteroids may predispose to this disorder. Psychological stress aggravates ulceration and precipitates bleeding. Duodenal ulcer is associated with HLA B₅ as reported from the west. It is also more common in blood group O nonsecretor subjects. The ulcer is sharply demarcated and the site of predilection is the first part of the duodenum. The role of *Helicobacter pylori* in the pathogenesis of ulceration has been established.

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Helicobacter pylori

It is a Gram-negative spiral organism which is now accepted as the major causative factor in chronic duodenal ulcer, gastric ulcer and chronic gastritis. It plays a role in the pathogenesis of gastric carcinoma and mucosa associated lymphoid tissue (MALT) lymphoma of the stomach. It is demonstrable in almost all cases of duodenal ulcer and over 80% of cases of gastric ulcer. About 50% of the adult population is infected with *H. pylori* and this is possibly one of the most common bacterial organisms colonising humans. Some cases of pernicious anemia are also closely associated with the presence of *H. pylori*. *H. Pylori* infection is more prevalent in the low socioeconomic groups. Spread of infection is by the oral route, ingestion. Family contacts, especially children are affected more. Once infection occurs, spontaneous elimination of the organism is rare.

H. pylori moves under the mucus layer in the stomach by its flagella and thrives in this location. Presence of urease helps the organism to produce carbon dioxide and ammonia from urea and this mechanism protects it from gastric acid. *H. pylori* produces a vacuolating cytotoxin (VACA) which enters the epithelial cells. Its pathogenic role is not fully known. *H. pylori* causes inflammation of duodenal mucosa, hyperacidity and duodenal ulcers. Inflammation of the stomach may lead to hypochlorhydria and predispose to gastric carcinoma.

The organism is demonstrable beneath the mucus layer adjacent to the cells, mainly in the mucosa of the gastric antrum and duodenum, especially if there is gastric metaplasia of the mucosa. Only some types of *H. pylori* are pathogenic. It is also known that *H. pylori* which can

cause gastric adenocarcinoma can protect against esophageal adenocarcinoma. There are reports that *H. pylori* may even protect against reflux esophagitis. So eradication is indicated only under appropriate situations. The indications for investigation to demonstrate *H. pylori* are listed below:

1. All patients with peptic symptoms <45 years of age.
2. Patients <45 years with alarm symptoms. Endoscopy is also indicated.
3. Patients <45 years with recent onset of symptom. They also require endoscopy.

Alarm symptoms indicating need for endoscopy include the following:

1. Unintentional weight loss
2. Dysphagia
3. Odynophagia
4. Persistent vomiting
5. Hematemesis, melena
6. Recent onset iron deficiency state
7. Epigastric mass
8. Previous gastric surgery
9. NSAID use

In NSAID induced ulcers and Zollinger-Ellison syndrome, *H. pylori* has no major pathogenic role.

Helicobacter heilmannii is a native organism in animals. Rarely it may infect humans. It may cause mild gastritis. This infection is more associated with MALT lymphoma.

H. pylori is detected non-invasively by the urea breath test which is an isotopic test. Indirect evidence of infection is by demonstration of antibodies. Biopsy of the ulcers can be done for demonstrating the organism.

CLINICAL FEATURES OF PEPTIC ULCER

The classical feature is the hunger pain felt in the epigastrium, relieved by food. Pain starts within three hours of eating food and it may be described as burning, aching, pressure, fullness or as a sensation of hunger. The pain comes on every day for a few weeks and then subsides for considerable periods. Pain may be more prominent at night. The pain is usually relieved by food, antacids, or even by vomiting. A small proportion of ulcer subjects may be asymptomatic. Occurrence of complications may be the first sign of disease in them. Compared to the disabling symptoms, physical signs are only minimal. Physical examination may reveal tenderness in the epigastrium or to the right of the midline. Ulcer patients are able to localize the pain and this feature helps to distinguish them from cases of functional dyspepsia.

Differential Diagnosis

Epigastric pain is a common symptom in several alimentary disorders such as gastric carcinoma, pancreatic

carcinoma, pancreatitis, biliary tract disease, peptic ulceration of the esophagus, duodenitis and ancylostomiasis. The pain of irritable bowel syndrome may mimic peptic ulcer.

Diagnosis

The history of pain coming on with hunger and relieved by hot fluids or antacids is suggestive, but final diagnosis depends on the demonstration of the ulcer by gastro-duodenoscopy. Endoscopy confirms the presence of ulcers. Since the clinical features of benign ulcers show considerable overlap with those of malignancy, upper gastrointestinal endoscopy should be done to see the lesion and confirm it histologically in all cases, where the clinical presentation is not straightforward. Duodenal ulcer is seen as an ulcer crater in the proximal part of the duodenal bulb in the barium meal. The duodenal bulb may show marked deformity (trifoliate appearance). Indirect demonstration of the lesion is by barium meal examination.

There is a great tendency to recur after initial healing. It is seen even after surgery. The persistence of *H. pylori* infection is the most common cause for recurrence.

Course and Complications

Chronic duodenal ulcer persists with exacerbations and remissions over several years. Precipitating factors are change in diet and lifestyle, drugs and mental stress. Complications include hematemesis, melena, pyloric obstruction, and perforation, and pancreatitis due to posterior penetration.

Management

Aims of Therapy

1. Relief of pain as early as possible
2. Favour healing of ulcer
3. Prevent complications and
4. Avoid recurrence.

General Measures: The patient should be advised to take food regularly at 2.5 to 3 hour intervals to avoid pain. A cup of milk taken at bed time often helps to abolish nocturnal pain in many cases. Sometimes patients report that milk leads to worsening of acidity. Excepting highly spiced food, there is no choice between the various foods to be avoided. Till the advent of H_2 receptor blocking drugs, one of the mainstay of management was strict dietary therapy. In some cases dietary adjustment itself may give considerable relief and even help in gradual healing of the ulcer. It is important that persons who are predisposed to develop peptic ulcer should maintain this dietary discipline for life, to avoid relapse.

Tobacco smoking should be stopped forthwith, since it favours ulcerogenesis and hinders ulcer healing. Resumption of smoking is a common cause for relapse of ulcer-symptoms. Alcohol should be avoided, especially the spirits. It is advisable to restrict coffee to two cups daily or less.

Drug Therapy

Several drugs are available for treating peptic ulcers. Table 78.1 shows the available groups of drugs, their main actions and major side effects. Antiulcer drugs are among the most widely used drugs in modern medical practice.

Specific drugs should be started along with the general measures. Choice of drugs depends on the individual case. Though antacids are effective in relieving pain and are cheap, they achieve ulcer-healing only in a smaller proportion of cases. Therefore, it is better to add an H_2 receptor blocker or proton pump inhibitors concurrently. These drugs are available as tablets for oral use. They are very powerful inhibitors of gastric acid, giving pain-relief within a few days of administration. Cimetidine 300 mg and ranitidine 50 mg are also available as IM or IV injections and they are indicated when oral medication is not possible or when more urgent relief is needed as in hematemesis or melena. Both H_2 -receptor blockers and proton pump inhibitors favour ulcer-healing when given for 3-6 weeks. Their role in preventing relapse of ulcer is less definite. Still, long-term continuation of treatment may help to reduce relapse rate in those who are otherwise prone to relapse. In the vast majority these drugs can be stopped after 6-12 weeks of therapy. Newer H_2 receptor blockers are rizatidine 300 mg hs oral for 4-5 weeks and rextidine 150 mg hs for 4-6 weeks. Proton pump inhibitors in common use are omeprazole 20-40 mg oral daily lansoprazole 15-30 mg oral daily and pantoprazole 20-40 mg daily, esomeprazole 20 mg bd and rabeprazole 20 mg bd. Adverse effects of proton pump inhibitors include gastrointestinal upsets, allergy and susceptibility to food and water borne infections. Rarely inhibition of absorption of vitamin B_{12} may occur, if treatment is prolonged.

Eradication of *H. pylori*

Though *H. pylori* is very sensitive to many antibiotics *in vitro* it is difficult to eradicate it due to its location in the mucus layer of stomach where antibiotics do not reach readily. Multiple drugs are required for prolonged duration. Present day triple therapy given for 10-15 days gives an eradication rate of 95%.

A common regimen effective in the vast majority of cases is listed below:

Omeprazole	20 mg bd or 40 mg od
Amoxycillin	1g bd
Clarithromycin	500 mg bd, all given for 10 days consecutively

TABLE 78.1

Drugs used for peptic ulcer			
Drugs	Action	Dose for oral administration	Major side effects
Antacids			
Aluminium hydroxide Magnesium hydroxide Magnesium trisilicate Magnesium carbonate	Neutralizes gastric acid	15-30 mL of suspension one and three hours after each meal and at bed time, for 6 weeks	Diarrhea or constipation, inhibition of absorption of iron, calcium and phosphates, and milk-alkali syndrome
Mucosal protecting agents			
Sodium alginate	Coats the mucosa	0.5-1 g after food and at bed time	Nil
Carbenoxolone sodium		100 mg tid for 4-8 weeks	Retention of sodium and loss of potassium
Sucralfate (aluminium salt of sucrose-octa sulfate).	Coats the mucosa	1 g four times a day	Nil
Antihelicobacter agents			
Colloidal bismuth: tripotassium dicitrato-bismuthate (De-nol) Omeprazole, amoxycillin, clarithromycin preventing relapse	Eliminates <i>H. pylori</i> , thereby hastening ulcer-healing and	20 mL three or four times a day for 30 days	Unpleasant taste, staining of mouth and teeth
H₂-receptor blocking agent			
	Suppression of acid secretion and favour ulcer-healing		Drowsiness, allergy, gynecomastia, impotence and inhibition of gastric intrinsic factor
Cimetidine		200 mg 6 h and 400 mg bed time	Reduction of gastric acidity may predispose to Salmonella infection
Ranitidine		150 mg bid or 300 mg bed time	
Famotidine		20 mg bid or 40 mg bed time	
Proton-pump inhibitor			
Omeprazole lansoprazole, pantoprazole, esomoprazole and rabeprazole	Inhibits H+K+ ATPase, and suppresses acid secretion,	10-20 mg twice a day and 20 mg bed time favours ulcer-healing	Very few, Diarrhea, skin rashes headache, impotence and gynecomastia 30 mg od
Prostaglandins			
Misoprostol	Cytoprotection and reduces acid production	200 mg four times a day	Diarrhea
Note: Antacids and acid inhibiting drugs are continued for 4-8 weeks in full doses and then maintenance treatment is given depending on the individual response.			

Elimination rate is about 95%. Repeated courses and quadruple therapy including metronidazole or tinidazole to the triple drug regimen may be slightly more effective. Colloidol bismuth augments the efficacy of this regimen.

Metronidazole resistance is widespread in India. In resistant cases and in relapses, quadruple therapy including tetracycline 500 mg 6 h and tinidazole 300 mg t.i.d are effective.

It is ideal to assess the success of treatment by endoscopy which will reveal healing of the ulcer. Apart from specific treatment aimed at the local problem in the stomach, other drugs including analgesics such as dextropropoxyphene 65 mg, parasympatholytic drugs such

as propantheline bromide 10-20 mg, and anxiolytic drugs such as chlordiazipoxide 10 mg, may be required to control symptoms.

Surgical Measures

At present treatment of peptic ulcer is by and large a medical problem. More than 90% of ulcers heal with proper treatment. Surgery is indicated in a small proportion of cases which fail to heal or where there is suspicion of malignancy. The usual procedure is highly selective vagotomy in which the vagal fibers supplying the parietal cell bearing area of the stomach are interrupted, leaving the rest of the nerve intact. This operation

serves to reduce the acid secretion and thereby favour ulcer-healing.

Indications for Emergency Surgery

- 1. Bleeding of the ulcer, not responding to conservative management.
- 2. Perforation of the ulcer. This is an urgent indication.
- 3. Pyloric stenosis and gastric outlet obstruction.
- 4. Frank carcinoma or atypical features on histology of the ulcer.

Complications

If left untreated, peptic ulcers lead to complications. Acute complications include severe ulceration with intractable hematemesis, and perforation. Major chronic complication is the development of cicatricial stenosis of the pylorus resulting ‘in pyloric obstruction. Penetration of the ulcer outside the peritoneum leads to development of adhesions with the omentum and neighbouring viscera and ulceration of the structures adjacent to the posterior wall of the stomach and duodenum, especially the pancreas.

Hematemesis presents as an acute medical emergency. It is often precipitated by the use of nonsteroidal antirheumatic drugs, corticosteroids or aspirin. Perforation presents with sudden onset of severe pain, tenderness over the epigastrium, rigidity of the abdominal wall, signs of peritonitis and presence of gas under the diaphragm, demonstrable by X-ray taken in the erect posture. If this emergency is not recognized, the condition rapidly proceeds to local and general peritonitis with its associated high mortality. Ideal treatment is to close the perforation surgically at the earliest opportunity.

Pyloric obstruction develops 10-20 years after onset of duodenal ulcer. When this develops the clinical picture changes. Once pyloric obstruction is established surgical treatment becomes inevitable.

Gastric Ulcer

Gastric ulcers occur in the mucosa of the stomach, 90% being located along the lesser curvature. Gastric ulcers are seen more frequently in males, in the sixth decade of life. Chronic analgesic users are affected more. Most of the benign ulcers are single and 90% are located in the antrum immediately distal to the junction of the antrum with the acid secreting mucosa of the body of the stomach.

The exact mechanism of ulcerogenesis is not known. Unlike as in duodenal ulcer gastric ulcer patients have only normal or low acid levels. NSAIDs and *H.pylori* are the two most common causes. Corticosteroids and acute stress may cause acute ulceration manifesting frequently as hematemesis.

Clinical Features

Gastric ulcer patients present with epigastric pain of long duration. The pain is generally precipitated by intake of food but in many cases it is indistinguishable from that of duodenal ulcer. Nausea, vomiting, and significant weight loss may be present. Physical examination is unrewarding in the majority of cases.

Diagnosis is confirmed by endoscopy which should not be delayed if symptoms persist for a few weeks or more. Endoscopy and biopsy should be performed in all cases. Not infrequently gastric ulcers are malignant. It is, therefore, important to establish the exact nature of the ulcer before starting therapy. Carcinoma of the stomach may start as ulcer or very rarely malignant change may supervene on a benign ulcer. Gastric ulcer in association with achlorhydria is almost always suggestive of malignancy.

Indirect demonstration of the ulcer is by barium meal imaging, by which the ulcer crater and abnormal patterns in the gastric mucosa can be demonstrated. With the advent of gastroduodenoscopy and biopsy, barium imaging in gastric lesions has lost its prime importance. But, in the diagnosis of motility abnormalities, gastroesophageal reflux and stasis, barium studies are still extremely helpful. Size of the ulcer as revealed by X-rays is not a reliable guide to the nature of the lesion. Table 78.2 gives the radiological differences between benign and malignant ulcers.

Management

Dietary regimen is similar to that for duodenal ulcer. Antacids, ranitidine and omeprazole constitute the sheet anchor of treatment. Over 90% of ulcers generally heal in about six weeks. Drugs which encourage healing of duodenal ulcer are very effective in benign gastric ulcers as well. Repeat endoscopy is essential to confirm ulcer

TABLE 78.2	
Radiological differences between benign and malignant ulcers	
Benign	Malignant
1. Flat, broad or conical crater with smooth margins	Irregular crater with fissure-like expansions and a nodular contour of its base
2. Radiating gastric folds converge on the ulcer and they arise from the margins of the ulcer crater	Radiating folds are absent due to tumor infiltration of gastric wall
Note: Even in the presence of slightest doubt proceed to endoscopy.	

healing. If the ulcer has not healed by three months or if the ulcer size has increased at the end of four weeks, surgery may be considered. The recommended surgical procedure is antrectomy with Billroth I anastomosis. General management, indications for surgery and complications are similar to those described under duodenal ulcer. If there is evidence of *H. pylori* infection, it should be eradicated.

Zollinger-Ellison Syndrome

This syndrome consists of recurrent ulceration of the stomach, duodenum and jejunum and marked increase in gastric acid secretion caused by a gastrin secreting tumour, commonly arising from the non- β cells of the islets of Langerhans. Most common site is the duodenum (70%). Others include the pancreas (25%) and extra intestinal areas (5%).

About 60% of gastrinomas are malignant, the rest are benign. Around 90-95% of patients with gastrinomas show marked hyperacidity and ulceration of the gastrointestinal tract. Majority of the ulcers occur in the first part of duodenum or the stomach. Multiple ulcers are common. The ulcers are generally fulminant, progressive and resistant to medical therapy. Symptoms include abdominal pain, features of recurrent gastric ulceration, diarrhea and evidence of malabsorption. Due to the very high gastric acid, the intestinal pH remains low and therefore several nutrients do not undergo proper digestion and absorption.

Diagnosis

By maximal histamine test the basal acid output exceeds 10 m mols/h and this should suggest the diagnosis. Increased levels of serum gastrin can be demonstrated by radioimmunoassay. Normally, fasting serum gastrin level is below 160 pg/mL. Values above 1000 pg/mL are diagnostic of gastrinoma. Injection of secretin in normal individuals results in the fall of serum gastrin levels, but in gastrinomas, there is a paradoxical rise, which is specific. Location of the tumour can be made in some of the cases by CT scan or MRI. Endosonography, selective angiography, MR angiography and operative sonography are useful for precise localization. Selective catheterization of portal venous blood enables to identify the source of gastrin production.

Management

Medical treatment consists of large doses of antisecretory drugs. Large doses of H_2 receptor antagonist drugs or proton pump inhibitors help to give symptomatic relief and ulcer healing in some cases. Surgical treatment of choice is total gastrectomy or excision of the gastrinoma if it can be identified.

Carcinoma of the Stomach

Gastric carcinoma is common in Indians. Men are affected more than women. Atrophic gastritis and gastric polyps predispose to gastric carcinoma. It is more common in persons with blood group A. The growth may be polypoid, ulcerative, diffuse or infiltrative, and superficially spreading. Gastric carcinomas are mostly adenocarcinomas.

The antrum or body of the stomach may be equally affected. Around 10-20% involve the cardia. Extension of the tumour may occur by direct spread in the gastric wall and to the perigastric tissues. Lymphatic metastases develop in the perigastric, para-aortic, portal, and splenic nodes. Spread through the thoracic duct leads to enlargement of the left supraclavicular lymph nodes (*Virchow's sign*). Distant metastases, especially to the liver, occur through the blood stream.

Clinical Features

Upper abdominal discomfort or pain, anorexia, and weight loss are the prominent features. When antral tumours produce pyloric obstruction, they lead to vomiting of stale food. Affection of the cardia around the esophageal opening causes dysphagia. Late features include anemia and widespread metastasis.

Physical Examination

Physical examination may reveal tenderness in the epigastric region or a mass in advanced cases. A gastric mass has to be distinguished from hepatic enlargement and other organs in the epigastrium. Barium meal examination helps to demonstrate the tumour. Final diagnosis can be made by endoscopy and biopsy, or exfoliative cytology. Routine upper gastrointestinal endoscopy and cytology helps in diagnosing the lesion before the tumour is demonstrable radiologically. Treatment of the tumour at this stage gives considerably better results. Gastroscopy, therefore, should be performed without delay in all cases of persistent upper abdominal symptoms. When endoscopy is available this is the investigation of choice for early and definitive diagnosis. Time should not be lost for radiological diagnosis since the false-negative rate is quite high and only moderately advanced lesions can be demonstrated by barium meal examination (Fig. 78.1).

Prompt surgical removal of the tumour early in the course of the disease offers the only chance of cure. Metastases have to be excluded by detailed investigation. If the lesion is resected at a very early stage the 5-year survival exceeds 90%. If the lesion does not involve the serosa or lymph nodes, the 5-year survival rate is around 50%. If the nodes are affected, survival falls to 10% or less. In advanced cases, chemotherapy using 5-fluorouracil in combination with methyl CCNU and adriamycin may

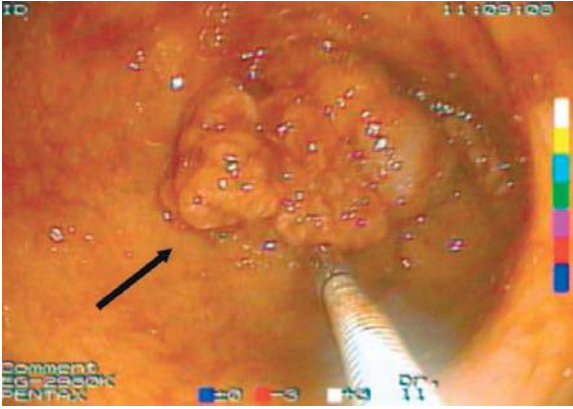


Fig. 78.1: Carcinoma stomach.
Note: the cauliflower growth (arrow)

induce temporary remission. Chemotherapy is generally used as an adjunct to surgery in such cases.

Gastric Outlet Obstruction

Syn: Pyloric obstruction

This is a common condition seen in clinical practice. Cicatrization due to peptic ulcers, antral carcinoma, pancreatic carcinoma, foreign bodies, and lymphomas may lead to pyloric obstruction. Rare causes are postsurgical stenosis, pyloric and duodenal diaphragm, adult hypertrophic pyloric stenosis, annular pancreas and acute pancreatitis.

Gastric outlet obstruction produces colicky pain, visible peristalsis and vomiting of stale food. The general condition of the patient rapidly deteriorates. Gastric peristalsis has to be distinguished from small-intestinal peristalsis. Gastric peristalsis is always from left to right, while intestinal peristalsis follows a stepladder pattern without any fixed direction. Another physical sign is succussion splash which is elicitable from the stomach even after several hours of ingesting food or fluids. Normally, the stomach is emptied within three hours after food. On gastric aspiration, a residue greater than 300 mL four hours after a meal, or overnight fasting gastric residue greater than 200 mL is suggestive of gastric outlet obstruction. Barium meal studies and endoscopy with biopsy or cytology can confirm the diagnosis.

Conservative treatment consists of fluid and electrolyte replacement, gastric aspiration, stomach wash, antacids and anticholinergics. The definitive treatment is surgical.

A common cause of gastric outlet obstruction in babies is *congenital pyloric stenosis* which is a familial disorder affecting more often males. In them the circular muscle coat of the pylorus is hypertrophied and this may become palpable. Pyloromyotomy relieves the obstruction.

Hematemesis

Hematemesis or vomiting of blood occurs when bleeding arises from the gastrointestinal tract proximal to the duodeno jejunal flexure (ligament of Treitz). The concentration of hydrochloric acid in the stomach and the amount of food present, determine the colour of the vomited blood. Action of the acid makes the blood brownish so that if vomiting occurs briskly after extravasation, the vomitus is bright blood, otherwise it is dark brown. A bout of hematemesis is often followed by melaena which may last for up to 5 days. The common causes of hematemesis are peptic ulcer, erosive gastritis, rupture of esophageal varices and carcinoma. Drugs such as aspirin, corticosteroids, anti-rheumatics especially NSAIDs and anticoagulants may produce hematemesis in susceptible subjects. Gastric erosions may complicate cerebral and subarachnoid hemorrhage, burns, renal failure, hepatic failure, viper bites and shock and hematemesis may develop in them. Rare causes include Mallory-Weiss syndrome (mucosal laceration of the cardia due to vomiting), gastric polyps, leiomyomas, lymphoma and blood dyscrasias such as purpuras and coagulopathies.

If bleeding from the upper gastrointestinal tract is small, it leads only to melaena. Hematemesis results from more massive bleeding. Hemorrhage leads to hypovolemic shock which depends on the extent and rate of hemorrhage and presence of other diseases. Loss of 20% of the blood volume results in postural hypotension and tachycardia. Shock supervenes if the bleeding continues or recurs.

Management

Emergency management consists of proper assessment, general measures to combat shock and replacement of lost blood.

In many cases the initial bout of bleeding may subside but soon fierce bleeding recurs, and leads to hypovolemic shock. Due to this possibility it is essential to hospitalize all patients with genuine hematemesis, even though the initial episode may be apparently mild. The patient should be monitored in an acute care ward.

1. The patient is sedated with IV diazepam in doses of 5-10 mg given slowly over a period of 3-5 minutes.
2. The pulse, respiration, and blood pressure are charted at 5-min. intervals to assess the condition and detect internal bleeding. The amount of blood lost from the stomach and in feces should be recorded.
3. An intravenous line using a wide-bore needle is established and compatible fresh blood is administered at the same rate as the blood is lost. Blood transfusion has to be continued till the bleeding stops. In an ordinary case, several units of blood may have to be given over the initial few days till the bleeding stops.

Central venous pressure record is a good indicator for monitoring proper volume replacement.

4. Prompt and adequate replacement of blood is the most effective single measure to tide over the crisis, save life and arrest the bleeding. If blood is not readily available normal saline or a plasma volume expander like 6% W/V dextran can be started as intravenous drip till blood is procured.
5. The stomach contents are aspirated at regular intervals through a nasogastric tube which is kept in position. This helps to detect intragastric bleeding promptly and also to administer foods and medications. Through the nasogastric tube ice-cold saline lavage can be instituted. It is beneficial in some cases. Iced milk can be introduced in small quantities at regular intervals when brisk hemorrhage subsides.
6. **Drug therapy:** H_2 receptor antagonists such as cimetidine and ranitidine are effective in controlling bleeding. Dose of cimetidine 200 mg IV 6 h. Dose of ranitidine is 50 mg IV 6 h. Antacids in large doses (aluminium hydroxide gel (30-60 mL every 4 h) is effective in stopping the bleeding in peptic ulcer. Proton pump inhibitor such as pantoprazole is available for slow IV injection in a dose of 40 mg daily.

Elective Endoscopic Management

Attempts must be made to establish the diagnosis. Emergency gastroduodenal endoscopy is indicated if the bleeding does not stop or recurs frequently. The bleeding spot can be visualized and cauterized by modern techniques. These include the use of bipolar electrodes, heater probes, neodymium yttrium-aluminum-garnet lasers, and local injection of vasoconstrictor agents like adrenaline. Esophageal varices can be occluded by injecting sclerosing solutions or banding. In the case of esophageal varices, compression with Sengstaken tube is an effective temporary measure in trained hands.

Indications for Emergency Surgery

1. Recurrent and profuse bleeding not amenable to conservative measures even after 12 h of admission. This period may be extended if modern facilities for intervention and adequate supply of blood are available.
2. In elderly subjects due to arteriosclerosis and hypertension the bleeding tends to persist. Moreover, bleeding is poorly tolerated by such subjects. They go into metabolic complications like uremia and vascular complications like shock and disseminated intravascular coagulation. Hence surgery should be

considered early. Large ulcers and posterior ulcers in the duodenum may require early surgery.

3. Presence of other medical conditions which are aggravated by blood loss.

Surgical techniques consist of ligation of bleeding vessels, undersewing the ulcer bed, or excision of the bleeding area in intractable cases.

MELENA

This term denotes the visible presence of altered blood in feces. Bleeding from any part of the gastrointestinal tract proximal to the middle of the colon can give rise to melena, if the bleeding is gradual and the blood gets partially digested during its downward passage. After a single isolated episode of bleeding the blood may be detectable in feces for upto five days. At least 60 mL of blood should be present to produce this symptom. The black colour and tarry consistency are caused by partial digestion of the blood. When bleeding in the upper gastrointestinal tract is brisk, the blood may pass down rapidly without allowing time for digestion and in this condition the stools may contain fresh blood. Melena occurring in a patient with obstructive jaundice imparts a silvery colour to the feces.

FRESH BLOOD IN STOOLS

Syn: Hematochezia

Bleeding lesions of the large intestine or rectum generally give rise to fresh blood in stools. Conditions which produce serious bleeding per rectum are ulcerative colitis, diverticulitis, typhoid ulceration, carcinomas, polyps, Henoch-Schonlein purpura, fulminant bacterial dysentery, and ischemic colitis. Bleeding from diverticulitis, ulcerative colitis, typhoid ulceration, fulminant bacterial dysentery, Henoch-Schonlein purpura and ischemic colitis can be massive. Polyps, carcinomas and other lesions such as angiodysplasia give rise to bleeding of variable severity. They are usually recurrent.

Hemorrhoids is probably the most frequent cause for the presence of fresh blood in stools, in all parts of the world. The blood is passed either along with the passage of stools or in drops after defecation. When the whole stool is collected in a pan, the blood will be seen on the surface of the stool or apart from the main stool mass. Proctoscopy reveals the lesion.

Presence of fresh blood in stools is an urgent indication for full investigation. The investigation should include the following.

1. Examination of the whole stools passed at one time, collected in a bed pan, while defecating. This will help to settle whether the bleeding is from hemorrhoids or from higher up in the colon.

- Digital examination of the rectum, proctoscopy and sigmoidoscopy.
- Colonoscopy if the lesions are beyond the reach of the sigmoidoscope.
- Contrast studies—barium enema.
- Isotope studies and selective angiography.
- Investigations to diagnose hemorrhagic disorders.

Management of Lower Gastrointestinal Tract Bleeding

This depends upon the cause. General measures include blood transfusion and attention to the primary cause.

If the lesions can be visualized by endoscopy, procedures to arrest bleeding such as cauterization, or ligation may be undertaken. Systemic diseases such as typhoid and Henoch-Schonlein purpura have to be managed on their own merits.

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Diseases of the Small Intestine

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8

Chapter Summary

Malabsorption States

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Malabsorption States

GENERAL CONSIDERATIONS

This term includes several conditions where intraluminal digestion of food and/or its subsequent absorption are defective. The processes that are impaired may be: (i) intraluminal digestion, (ii) transfer across the mucosal

lining, or (iii) transport from the mucosa to the circulation and to the target organs. In some cases the pathological mechanism is well-defined and evident, e.g. lactase deficiency. In others several mechanisms may be involved, e.g. blind loop syndrome in which there is bacterial overgrowth, short circuiting of intestinal contents and also mucosal abnormality.

Malabsorption state is quite common in India and this may result from a number of different conditions. The clinical picture is the total outcome of: (i) nonabsorption of ingested materials resulting in steatorrhea and creatorrhea, (ii) malnutrition manifesting as loss of weight and specific deficiencies, and (iii) symptoms of the underlying disease such as tropical sprue, tuberculous enterocolitis or chronic pancreatitis.

Causes of Malabsorption

- Abnormalities of the stomach:* These are (i) partial or total gastrectomy, (ii) gastrocolic fistula, (iii) hypertrophic gastritis (this leads to excessive protein loss in feces), and (iv) Zollinger-Ellison syndrome.
- Pancreatic disorders:* These include chronic pancreatitis, cystic fibrosis and carcinoma.
- Biliary disorders*
 - Long-standing obstructive jaundice leads to defective digestion and absorption of fat and fat soluble vitamins.
 - Deficiency of bile acids which may occur in two groups of conditions.

Interruption of the enterohepatic circulation of bile acids: Bile acids, which are normally absorbed from the distal ileum, cannot be absorbed if the distal ileum is diseased or removed. Bile acids pass into the colon and are lost in the feces. They stimulate secretion of water and electrolytes in the colon. Since the bile salts are not secreted in the bile through the enterohepatic circulation, they are not available in the proximal jejunum and, therefore, fat digestion and absorption become defective, leading to diarrhea.

When the upper small intestine is colonized by bacteria, the bile salts are deconjugated, micelle formation is inadequate, fat absorption is impaired, and steatorrhea results.

4. **Intestinal diseases:** These lead to defective transport across the gut mucosa. The mucosa may show gross pathological lesions or may be histologically normal. Mucosal damage occurs in intestinal tuberculosis, tropical sprue, celiac disease, Crohn's disease, Whipple's disease and intestinal lymphoma.

Parasitic infections like giardiasis, strongyloidiasis, schistosomiasis, trichuriasis, ascariasis, coccidiosis and cryptosporidiosis and intestinal capillariasis may interfere with absorption. The tape worm *Diphyllobothrium latum* uses up vitamin B₁₂ from the small intestine and deprives its host of this nutrient. Soil transmitted helminths such as *Ascaris lumbricoides* may lead to lactose intolerance in some cases. Heavy infestation by *Trichuris trichura* can lead on to inflammatory and motility changes and result in malabsorption.

The mucosa is histologically normal in specific enzyme defects like lactase deficiency. In pernicious anemia where absence of intrinsic factor results in the malabsorption of vitamin B₁₂ the intestine is normal histologically.

5. **Impairment of transport from the small intestine:** Blockage of lymphatics draining the small intestine prevents the discharge of absorbed chylomicrons into the systemic circulation. This occurs in intestinal lymphomas, intestinal and mesenteric tuberculosis and primary lymphangiectasia of the mesenteric lymphatics.

Though diarrhea is the prominent symptom in the vast majority of cases, rarely selective malabsorption (e.g. vitamin B₁₂) may be encountered even in the presence of constipation. Since different nutrients are processed at different regions of the gastrointestinal tract, the severity and type of malabsorption vary with the site of lesion. Absorption of fat and fat soluble vitamins is affected much earlier than that of the water-soluble vitamins. Loss of blood and exudates from the ulcerated mucosa further aggravates the condition in disorders like tuberculous enterocolitis and Crohn's disease.



Fig. 79.1: Malabsorption state—male 40—intestinal resection. Note: loss of weight and glossitis

The onset may be insidious as in sprue and intestinal tuberculosis and many patients seek medical help only several months after the onset. The onset can be explosive in conditions like giardiasis.

Clinical Features

Gastrointestinal: In most of the cases gastrointestinal symptoms predominate. Common presentations are diarrhea, especially steatorrhea, distension of the abdomen, abdominal discomfort and increased amounts of flatus which may be very foul-smelling, especially when digestion is impaired.

Diarrhea is more prominent during the early part of the day, with relief in the later part. Nutritional inadequacy results from general malabsorption. It manifests as weight loss, fatigue, lethargy, and failure of growth and development in children. Anemia occurs due to deficiency of iron, folate and/or B₁₂. Rickets, osteomalacia and tetany may develop due to defective absorption of vitamin D and calcium. Nutritional edema develops due to impairment of protein absorption. Glossitis, angulostomatitis, peripheral neuropathy and pellagra develop due to malabsorption of B complex factors (Fig. 79.1). Bleeding tendency results from vitamin K deficiency. Vitamin A deficiency leads to night blindness and other ocular manifestations.

Psychiatric symptoms such as anxiety, loss of confidence, irritability and depression are very common, especially when diarrhea is the prominent symptom.

Investigations

Examination of feces: The stools are large, bulky, greasy, and pale. There is a tendency to froth and stick to the toilet. In normal persons the stool fat is below 6-7 g per day on a diet which contains up to 100 g of fat. In malabsorption states the fat content is increased and this is referred to as steatorrhea. If the pancreatic digestion is

unaffected, the fat is present as fatty acids. If the pancreatic function is defective, the fat is present as neutral fat. Microscopic examination reveals fat globules.

Fecal nitrogen should be less than 2.5 g per day in normal subjects. Values above this level suggest malabsorption. Presence of intact muscle fibres in stools, demonstrable microscopically is called *creatorrhea*.

Blood examination: Serum albumin may be reduced in severe cases and they may show dependent edema. Serum iron, folate, vitamin B₁₂, carotene and cholesterol are lowered depending on the severity and duration of the malabsorption state. Vitamin K-dependent coagulation factors are deficient and this results in prolongation of the prothrombin time. Blood picture may be microcytic or macrocytic depending on the predominant deficiency.

Studies of Intestinal Absorption

Xylose absorption test: In this study, 5 g of xylose is given orally and the urinary excretion over the next 5 h and the serum levels are determined. Normal persons excrete at least 1 g in urine in 5 hours and the blood levels reach 25 mg/dL 2 h after the oral dose. In malabsorption due to mucosal disease affecting the upper small intestine, urinary elimination is lowered. This test is not foolproof since delayed gastric emptying, renal disease and sequestration of D-xylose in muscles and edema fluid reduce the urinary excretion.

Lactose absorption: This will be defective in lactase deficiency. Normal subjects absorb lactose and the blood level of glucose should increase 20-30 mg/dL 2 h after oral administration of 50-100 g of lactose. The blood levels will be deficient in subjects with lactase deficiency. The specific test for lactase deficiency is demonstration of diminished amount of the enzyme by biochemical estimation in biopsy specimens of intestinal mucosa.

Vitamin B₁₂ absorption (Schilling test): Radioactive vitamin B₁₂ is administered orally and the fecal loss and urinary elimination are estimated. Normally, more than 7% of administered vitamin B₁₂ is eliminated in urine in 12 hours. Vitamin B₁₂ absorption is impaired in lesions affecting the distal ileum.

Fecal fat estimation: Generally feces is collected for three days for the estimation of fat. Absorption studies employing radiolabeled fat (¹⁴C-triolein test) reveals excessive loss of ingested fat which appears in feces.

Fecal protein loss: Fecal nitrogen is grossly increased in protein-losing enteropathy. This is diagnosed by labeling serum protein with radioactive chromium and detecting its appearance in feces.

Radiology: Radiological study of the gastrointestinal tract after ingestion of barium-meal reveals reduction in transit

time of the intestinal contents and segmentation and flocculation of barium in the small intestine. Anatomical abnormalities such as ulceration, strictures, tumours, fistulae, and blind loops are demonstrated.

Sampling of the intestinal contents: Using special tubes which can be passed under fluoroscopic control, the intestinal contents can be sampled from different levels. Endoscopic aspiration can be performed from sites accessible to the endoscope. Aliquots obtained by aspiration are examined for enzyme content and nutrients, and also microbiologically. The effect of secretory stimulants like secretin, and pancreozymin can also be studied.

Biopsy studies: Using the Crosby capsule, peroral biopsies used to be obtained from various sites. This is seldom used to at present. Endoscopic biopsies can be obtained when facilities are available. The mucosa can be examined under the dissecting microscope to assess the villus pattern. Further histopathological and histochemical studies can be undertaken. In malabsorption, intestinal villi show blunting, confluence, atrophy, and varying degrees of round cell infiltration.

Since minor degrees of villus atrophy and cellular infiltration may be found in normal individuals, mucosal biopsy alone cannot be considered pathognomonic, especially if the abnormalities are mild. It gives valuable information when considered in the light of other investigations. Biopsy is the mainstay of diagnosis in conditions like tuberculosis, Crohn's disease and Whipple's disease.

Breath tests: They are useful in the diagnosis of steatorrhea, bacterial overgrowth of the intestines, lactase deficiency, and ileal disease. ¹⁴C-labeled triolein is given with a lipid meal and breath ¹⁴CO₂ is estimated. Level of ¹⁴CO₂ in breath correlates with the capacity for fat absorption. ¹⁴C-cholyglycine breath test is a screening test for bacterial overgrowth in the intestine and impaired ileal absorption of conjugated bile salts.

Estimation of breath hydrogen levels after an oral dose of 12.5-25 g of lactose gives an indication of the capacity to absorb lactose. In malabsorption states the unabsorbed lactose is acted upon by bacteria in the colon to produce excess hydrogen which appears in blood and is eliminated in the breath. Increased levels of breath hydrogen indicate bacterial overgrowth in the intestine. Lactulose can be given instead of lactose for the same purpose.

Treatment

Dietary management: The diet has to be modified depending upon the type and severity of malabsorption. Since fats, and to a lesser extent carbohydrates cause diarrhea, these have to be restricted. Proteins do not cause diarrhea and they should be given in the usual form or as

predigested proteins to avoid negative nitrogen balance. All vitamins have to be supplemented. Parenteral supplementation of nutrients has to be resorted to if oral feeding is not tolerated or is ineffective. Vitamins and minerals have to be given parenterally regularly.

Specific management: This depends upon the cause. Several diseases leading to malabsorption are curable, e.g. giardiasis, lactase deficiency, tuberculous enteritis. Many conditions which may not be curable ultimately, can be treated symptomatically and normal health restored, e.g. pernicious anemia. Such conditions should be looked for and treated appropriately.

CELIAC DISEASE

Syn: Gluten-induced enteropathy

This disease is produced by immunologically mediated or direct inflammatory response initiated by gliadin which is present in gluten which is a component of wheat, rye, barley and oats. Pathological changes are seen in the mucosa from the duodenojejunal junction to variable lengths distally. Circulating antibodies to gluten are demonstrable in many cases. The disease is less common in India compared to the West. In the west the prevalence of celiac disease in the general population is 1/266. HLA associations include HLA-DQ₂ (DOA 1-*05/DOB₁*0₂) or HLA DQ₈ (DOA1* 0301/DQBI*0302).

Gluten triggers the production of certain IgA class antibodies called R1 type reticulins and endomysial antibodies. These include IgA anti-endomysial AB, anti-tissue transglutaminase AB (tTG), and IgA anti-gliadin AB. Their presence is pathognomonic. The reticulins and endomysial antibodies are directed against fibroblast derived extracellular matrix-proteins known as celiac diseases autoantigen proteins. The disease is self perpetuating unless the trigger gliadin is removed.

CLINICAL FEATURES

The disease is more prevalent in young persons. Symptoms start between the ages of 1 and 3 when cereals are introduced into the diet. The child fails to thrive, becomes irritable and develops characteristic steatorrhea. The symptoms show periodic remissions and exacerbations over the years. There is increased incidence of intestinal lymphoma in these subjects.

Adult celiac disease may occur at any age. It is characterized by anemia, loss of weight, diarrhea and varying degrees of malabsorption.

Dermatitis herpetiformis: This is a frequent association of celiac disease. Skin shows blistering subepidermal eruptions. This is a classic nongastrointestinal manifestation of celiac disease. Histology shows granular IgA

deposit in the affected sites. Withdrawal of gliadin clears the skin lesion also.

Avoidance of gluten in the diet relieves the skin lesions as well. In intractable cases dapsone given orally in a dose of 50-200 mg/day helps to clear the lesions.

Diagnosis

It is made from the history, demonstration of malabsorption, and characteristic histology. Improvement on withdrawal of wheat or rye and aggravation on reintroduction suggest the diagnosis. Histologically the mucosal atrophy during the active stages of the disease and its clearance during abstinence from gluten containing diet can be demonstrated.

Serologic Diagnosis of Celiac Disease

The serologic tests available are IgA EMA (endomysial antibodies), IgA tTG (tissue transglutaminase), IgA AGA (anti-gliadin antibodies) and IgGAGA. AGA has lower sensitivity. EMA are directed against the connective tissue surrounding the smooth muscles. It is sensitive and specific, but expensive. The epitope against which EMA is directed is identified as tTG. IgA tTG is more specific and sensitive. It is also cheaper. In low-prevalence areas a negative tTG test virtually rules out celiac disease.

Treatment

Avoidance of wheat, barley, rye and oats in all forms brings about dramatic relief within weeks. Full recovery takes a few months to years. Apparent failure of therapy is due to inadvertent inclusion of the offending cereals in the diet.

TROPICAL SPRUE

This is a syndrome which occurs exclusively in the tropics. It is characterized by morphological abnormalities of the small intestine associated with malabsorption of two or more unrelated substances without any detectable cause. This disease has been reported from various parts of Asia, Africa and South America. In India the disease is present sporadically in all regions, but maximum number of cases have been reported from Vellore, Tamilnadu. Foreigners who have resided for varying periods in India and other neighbouring countries may be affected. In the indigenous population sprue is more common among poor malnourished young adults. Folate deficiency precipitated by pregnancy and severe malnutrition can aggravate the disease. More cases are seen during the hot humid months. The disease occurs sporadically though several small outbreaks have also been recorded.

The *etiology* of tropical sprue is not clearly understood. The prevalence of the disease in residents of certain localities, occurrence of several cases in the same household (sprue houses), seasonal prevalence, and the favorable response to antibiotics suggest an infective etiology. The onset is insidious. The clinical features are mainly steatorrhea and the sequelae of generalized malabsorption.

The jejunal histology is variable. The changes seen are epithelial cell damage, lengthening of the crypts, broadening and shortening of the villi, and varying degrees of chronic inflammatory cell infiltration. A normal jejunal mucosal biopsy rules out tropical sprue.

Treatment

Many patients improve with hospitalization and correction of malnutrition. In addition to general treatment, administration of tetracycline 1 g daily in divided doses for 3–4 weeks results in clinical improvement, reduction of jejunal bacterial counts, and correction of the histological abnormality. Folic acid 10 mg orally four times daily is given for 6 months. In cases of severe malabsorption, folic acid in intramuscular dose of 10 mg may have to be given for the initial few days. The condition is likely to recur in many cases if proper dietary care is not followed.

Carbohydrate Intolerance

Disaccharidase Deficiency

This is a common condition which is often missed. Carbohydrate intolerance may result from: 1. Deficiency of specific disaccharidase, 2. Impairment of transport of monosaccharides in the intestine or 3. Diffuse mucosal disease resulting in deficiency of disaccharidases and impairment of monosaccharide transport.

The *symptoms* are vague and they consist of bloated feeling, gaseous distension, belching, colicky pain, borborygmi, and diarrhea following ingestion of lactose or other carbohydrates. Diarrhea results from the osmotic effect caused by unabsorbed low molecular weight carbohydrates. Flatulence is produced by fermentation of carbohydrate in the intestines.

Most widespread enzyme deficiency is that of lactase. This may be acquired or congenital. The former manifests in later years whereas the latter is present from birth. Causes of acquired deficiency include diarrheal states, intestinal parasitism, and primary intestinal diseases. These tend to be transient and are relieved when the underlying condition is corrected.

Diagnosis is suggested by lactose absorption tests and breath tests showing excessive hydrogen after oral lactose challenge.

Treatment

Many patients learn to avoid symptoms by omitting the offending articles of diet. Exclusion of lactose (milk and dairy products and baked foods containing dairy products) from the diet gives relief.

Intraluminal Bacterial Proliferation in the Intestines

Normally the jejunal contents show only less than 10^5 bacteria per mL. Most of these are derived from swallowed bacteria. Gastric acidity and intestinal motility help to keep down the bacterial counts. Impairment of these functions results in bacterial overgrowth. The bacteria hydrolyze conjugated bile salts in the jejunum and this leads to defective micelle formation and absorption of fat. Deconjugated bile salts also damage the mucosa directly. In addition, proliferating bacteria use up essential vitamins like vitamin B₁₂ from the proximal small intestine before they reach the ileum and thus deprive the host of these vitamins. Paradoxically folate levels may be high since the bacteria produce folate.

1. **Structural lesions:** Diverticula, blind loops, fistulae, strictures occurring in intestinal tuberculosis, vascular lesions, radiation enteritis and Crohn's disease, post-operative or traumatic adhesions, and afferent loop stasis after gastric operations.
2. **Fistulae:** Gastrocolic, jejunocolic, jejunoileal and others.
3. **Hypochlorhydria and achlorhydria:** Post gastric-surgery mucosal atrophy, total gastrectomy, vagotomy, atrophic gastritis, pernicious anemia and severe malnutrition including iron deficiency anemia.
4. **Abnormalities of intestinal motility:** Systemic sclerosis, amyloidosis, diabetic and other autonomic neuropathies, paralytic ileus, pseudo-obstruction, and post-vagotomy ileus.
5. **Hypo- or agammaglobulinemia.**

Symptoms of the primary disease may be present. In addition, those due to malabsorption may also be present.

The condition is diagnosed by quantitative culture of the intestinal contents. Breath tests using lactulose or ¹⁴C-labelled cholyglycine are helpful. Appropriate investigations are indicated to detect the underlying cause and plan definitive therapy.

Treatment

Administration of tetracycline in a dose of 1 g/day in divided dosage for 3–4 weeks relieves the symptoms temporarily. Surgical treatment for the anatomical abnormality should be advised if the lesion is correctable.

PARENTERAL NUTRITION

Parenteral alimentation is necessary when ingestion and absorption of nutrients are inadequate, impossible over long periods of time or contraindicated. In several situations such as organ transplantation, postoperative states, post-traumatic states, burns and others where ingestion of food is not possible or excess have to be given to overcome hypercatabolic states, parenteral alimentation becomes mandatory. If excess of calories are administered this is called hyperalimentation. When the process has to be continued over several days or weeks, a central venous line is necessary. Proprietary preparations are available. These are highly expensive. It is preferable to use an infusion pump and monitor the rate of nutrient delivery.

Nutrient Solutions

Carbohydrates and fats form the two main sources of calories. Supply of 200-250 g of glucose daily is adequate to prevent starvation ketosis. Adequate calorie supply can be achieved by the administration of 600-700 g glucose given as a 20-30% solution through a central venous catheter. Administration of glucose in this concentration into peripheral veins causes damage to the venous walls and leads to thrombophlebitis.

Lipids can be given as a 10% emulsion intravenously. Fat emulsions being isotonic, can be infused into peripheral veins. Addition of amino acids and glucose to the fat emulsion provides all the proximate principles. The source of fat is soyabean or cottonseed oil and the fatty acid is oleic or linoleic acid. The common source of nitrogen is crystalline amino acids and the equivalent of 8-16 g is to be supplied daily. Amino acids are supplied as mixture of essential and nonessential amino acids in the ratio of 1:1.5. Amino acids will be used for anabolic activity only if 150-250 carbohydrate calories are also supplied simultaneously for each gram of nitrogen.

Vitamins, minerals and other electrolytes have to be supplied, their quantity is to be determined by biochemical estimations. Optimal quantities of electrolytes have to be supplied to ensure complete metabolic utilization of the nutrients in solution.

In general, for every 1000 Cal, NaCl 10 mmol; K⁺ 20 mmol; PO₄ 30 mmol; Mg²⁺ 8 mmol and Ca²⁺ 5 mmol are to be supplied in addition to daily losses. Several solutions are available commercially for parenteral nutrition.

When nutrients are administered into a peripheral vein without recourse to a central venous catheter, it is referred to as peripheral parenteral nutrition.

In the commercially available parenteral solutions energy is provided by glucose and long chain triglycerides in almost equal proportions. 150-250 cals should be provided with 1g of nitrogen which is provided mainly

as amino acids. For providing nutritional balance, energy supply should be 25-40 Cal/kg bw/hour. Nitrogen should be provided at the rate of 0.2-0.3 g/kg bw/hour. Complications include sepsis, blockage of the catheter and other mechanical problems. After initial hospitalization to set up parenteral nutrition, subsequent treatment can be continued at home. The solutions are prohibitively expensive for routine use.

Irritable Bowel Syndrome (IBS)

This condition has been known by several synonyms such as mucous colitis, spastic colon, irritable colon and colonic neurosis. In the west 20-30% of gastrointestinal disorders is constituted by IBS. In India this is very common and many cases used to be diagnosed as chronic amebiasis in the past. Irritable bowel syndrome is a functional disorder to the intestine characterized by alteration of the bowel habits and abdominal pain in the absence of any detectable organic pathology.

There is no morphologic, histologic, microbiologic or biochemical abnormality in IBS. Changes in gut motility are observed in several studies though they poorly correlate with the symptoms. In the constipated variety the frequency of high altitude peristaltic contractions is less whereas nonpropulsive segmentation contractions are more. Moreover food induced hypermotility of the colon occurring normally about one hour after the meal is reduced in many patients. This may account for their postprandial symptoms. Emotional stress is seen to aggravate the motility disorder.

Normally gut has two types of myoelectrical activity—the basic electric rhythm (BER) and spike activity (SA). The BER is in the continuous wave form at the rate of 6 cycles per minute. The SA is the form of electrical bursts superimposed on BER and this is responsible for the mechanical contraction of the gut. IBS patients have a slow BER at the rate of 3 cycles per minute. In normal people, feeding induces SA immediately which peaks in 30 minutes and lasts for about 50 minutes. But in IBS patients the feeding induced SA is dampened in the first 50 minutes, but it becomes stronger later on.

Clinical Features

In India the female to male ratio is 1:3, though in the West, females suffer more. The clinical spectrum is wide. The presentations include (i) painless functional diarrhea, (ii) painless simple constipation, (iii) alternating diarrhea and constipation, (iv) bloating of abdomen, and (v) pain due to spasm of colon and small intestine. The common age group is 20-40 years. Symptoms are vague and these include abnormal bowel habits ranging from constipation to diarrhea (often alternating irregularly), pellet like stools, increased gastrocolic reflex, vague abdominal pain

ranging from dull ache to severe colic, flatulence relieved by belching, capricious appetite, and insomnia. Around 20% of subjects complain of weight loss. All patients are emotionally tense and they tend to exaggerate the disability.

Examination does not reveal any abnormality except for vague tenderness over the abdomen, palpable cecum and sigmoid, increased bowel sounds, and signs of anxiety. The majority of these patients go from doctor to doctor getting repeated prescriptions such as amebicides, antibiotics, sedatives, tranquilisers, and massive doses of vitamins. Most of them are wrongly diagnosed as amebiasis, neurosis or other colonic disorders.

Clinical examination should always be followed by macroscopic examination of a total stool, passed in a clean container. The feces is large in volume, the consistency may vary from hard to semisolid, it may froth, and mucus may be present, but, there is no blood. Microscopy helps to exclude dysentery, amebiasis and other intestinal parasites. IBS seriously reduces the quality of life of the affected individuals and is an important medical cause of reduced work output. Investigations such as colonoscopy and tests for malabsorption need be done only in those patients with alarm symptoms.

Diagnosis

This condition (IBS) should be diagnosed clinically and other similar conditions should be excluded by investigations. Amebiasis, giardiasis, malabsorption states, tuberculous enterocolitis, ulcerative colitis, diverticulitis, purgative abuse and heavy helminthic infestations should be excluded. Till recently IBS remained a diagnosis arrived at by exclusion of similar conditions. At present diagnostic criteria have been laid down. These include:

1. Continuous or recurrent symptoms for at least three months.
2. Abdominal pain relieved by defecation or associated with a change in frequency and consistency of stool.
3. Disturbance in defecation on at least 25% of times with any three of the following features.
 - a. Altered stool frequency,
 - b. Altered stool form—hard, loose or watery,
 - c. Altered stool passage—straining, urgency, tenesmus,
 - d. Passage of mucus, and
 - e. Abdominal distension.

A slightly modified Rome II criteria is also in vogue at present.

Investigations

The blood picture in IBS is usually normal. Stool examination repeated thrice including one concentration smear helps to exclude amebiasis and other intestinal

parasites. All IBS patients do not require extensive investigation. Routine investigations may be done in all patients. Investigations such as colonoscopy, small bowel barium studies and tests for malabsorption are required only in a limited number in whom the diagnosis is not clear. Presence of blood in stools at any time, loss of weight, presence of constitutional symptoms and family history of colonic neoplasms are indications for full systematic investigation.

Sigmoidoscopy and colonoscopy reveal only hyperemia and normal nonfriable mucosa with excess of mucus. This helps to differentiate IBS from ulcerative colitis and amebiasis. Intestinal biopsy is normal. Barium enema is not diagnostic and may show only non-specific changes. It is ideal to reassure the patient only after excluding more serious underlying disease.

Management

Reassurance and psychological support is most important in allaying anxiety and this is very effective in the majority of cases. Even if the diagnosis of IBS seems to be the most likely one, it is advisable to follow up the patient at frequent intervals for at least one year to detect weight loss, development of anemia, presence of blood in stools and other systemic disturbances, which all should raise the possibility of more serious colonic diseases.

Diet

All offending articles of diet which aggravate symptoms should be avoided. In general, a moderate-roughage diet is advisable. The use of high fiber diets has been advocated in spastic colon but the results are not uniformly encouraging.

Substances that increase stool bulk like methylcellulose (*Isogel*, *ispagula husk*) or bran generally improve stool consistency and give relief. **Several drugs are in vogue for management of IBS. In practice, the ideal drug regimen has to be determined by trial and error since no drug may act predictably.** As a rule of the thumb, the following drugs may be tried first depending on the symptoms.

1. **Diarrhea—predominant**—Loperamide 4 mg, diphenoxylate 5 mg, anticholinergics, codeine phosphate 30 mg.
The 5-hydroxytryptamine (5HT₃) antagonists such as alosetran have proved effective in preventing urgency for defecation. Alosetran taken prophylactically helps to avoid embarrassment during travel and social functions.
2. **Constipation predominant**—Dietary fiber, osmotic laxatives, stool softeners like liquid paraffin, cisapride and enemata.
Tegaserod which is a 5 HT₄ antagonist helps to relieve constipation.

3. Pain, gas, bloating, etc. Anticholinergics, anti-gas preparations such as methyl siloxylene or activated charcoal, and antidepressant drugs.

Tranquilizers are indicated if there is severe anxiety. Psychiatric counseling helps in the majority of cases. Amitriptyline 10-25 mg given at night may benefit a few who have depression and despair.

CROHN'S DISEASE

Syn: Regional enteritis, Granulomatous colitis

This rare disorder is mainly characterized by localized areas of granulomatous inflammation of the small intestine. Rarely all other parts of the gastrointestinal tract may be affected. The etiology is unknown. It is more common in west especially among Jews, and it is rare in India. There is evidence that the incidence is increasing in India.

Etiology

Though the exact cause is not known, factors such as genetic predisposition, infective agents and autoimmune phenomena have been implicated.

Pathology

The role of disturbances in gut flora is being investigated. Viable *Mycobacterium avium paratuberculosis* has been detected in a substantial proportion of cases. Specific genes related to the development of Crohn's disease include CARD 15/NO D₂. This gene is expressed in monocytes, macrophages, dendrite cells and also intestinal epithelial cells including Paneth cells. Lesions are maximal in the terminal ileum. The bowel is edematous, swollen, and narrowed. Later the mucosa appears nodular and ulcerated. Classically normal and abnormal segments alternate and this is referred to as *skip lesions*. The mesentery and lymph nodes are involved. Histologically lesions are characterized by chronic granulomatous inflammation containing lymphocytes and plasma cells extending through all the layers of the intestinal wall. In 50% cases there are well-defined noncaseating granulomas containing multinucleate giant cells.

Clinical Features

The disease affects persons aged 15-35 years more, and it is characterized by remissions and relapses. Presenting symptoms include fatigue, weight loss, right lower quadrant pain, and diarrhea. The pain is continuous and localized but may be colicky. Moderate diarrhea follows. The feces is not visibly mixed with blood.

Physical Examination

Physical examination reveals a tender mass in the right lower quadrant made up of inflamed loops of bowel. Acute ileitis may resemble acute appendicitis and

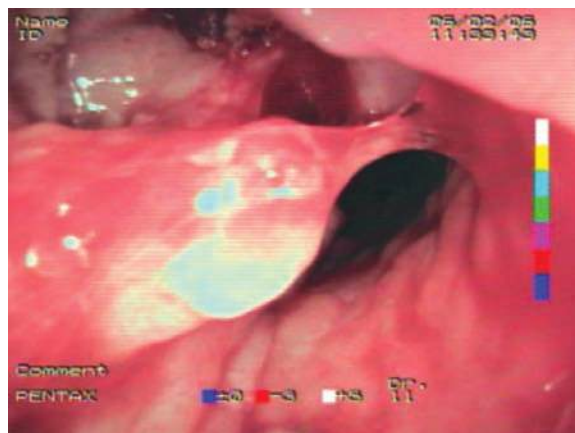


Fig. 79.2: Crohn's disease—Fistulous track endoscopic view

sometimes the diagnosis is made on laparotomy. Rarely the disease may present as prolonged pyrexia, intestinal obstruction, fistulization, and malabsorption syndrome. Enteropathic arthritis is a frequent complication.

Diagnosis

Diagnosis should be suspected clinically. Laboratory investigations are non-specific and are of little value. The ESR may be moderately raised. There may be leukocytosis, anemia, and presence of occult blood in stools.

A barium examination of the small bowel reveals loss of mucosal pattern, rigidity and narrowing of the affected segments, and a "cobble stone" appearance. The characteristic radiological feature is the "string sign" which is produced by the narrowing of the diseased segment with dilatation of the normal intestine on either side. Fistulous tracts, strictures, and fibrosis may be demonstrable in advanced cases. Stomach and duodenum may be involved and the picture may resemble an infiltrative tumour. Barium enema reveals colonic lesions. Endoscopy reveals the lesions, strictures, fistulae and other complications. Endoscopic biopsy is also confirmatory (Fig. 79.2).

Differential Diagnosis

Crohn's disease may be mistaken for tuberculosis of the ileocecal region, lymphoma, appendicular abscess, amebiasis, carcinoma cecum and ulcerative colitis.

Prognosis

In acute regional enteritis the prognosis is good since in two-third of the cases the condition subsides without recurrence. In chronic regional enteritis the disease tends to be recurrent and chronic.

Principles of Treatment

Low residue diet containing adequate calories and protein should be instituted. Diarrhea is relieved by drugs like diphenoxylate (Lomotil) 2-5 mg/day or codeine 30-60 mg orally 2 to 3 times a day.

Sulfasalazine 2-6 g/day is moderately effective. This drug is less effective in this condition than in ulcerative colitis. Corticosteroids are given if active disease persists. Prednisolone 40-60 mg/day is started and reduced over a few months. Budesonide which is a topically active glucocorticoid is effective in relieving symptoms, when given orally in a dose of 8 mg/day. Methotrexate, azothioprine, ciprofloxacin in combination with metronidazole have all been tried with benefit.

Acute exacerbation of Crohn's disease is difficult to treat. Remission can be induced with parenteral steroids, parenteral alimentation and intravenous antibiotics such as metronidazole and ciprofloxacin. *Infliximab* which is a monoclonal antibody to TNF- α may be useful in resistant cases and in complications such as fistulae. It can also be used as a primary modality in severe and complicated cases. *Sargramostim* which is a recombinant human GM-CSF has been found to be beneficial in reducing inflammation and improving the quality of life.

Surgery is reserved for complications like obstruction, fistulae or abscesses.

ABDOMINAL TUBERCULOSIS

Abdominal tuberculosis may be divided into: (i) *intestinal tuberculosis*, (ii) *tuberculosis of mesenteric lymph nodes*, and (iii) *tuberculous peritonitis*.

Intestinal Tuberculosis

This is the most common granulomatous disease of the bowel in India. The lesions may be secondary to a focus in the lung or they may develop primarily within the intestinal tract. The latter is fairly common. Highest incidence is in young adults in their second and third decades and women are more affected than men.

Pathogenesis and Pathology

Human and bovine strains of *Mycobacterium tuberculosis* produce intestinal lesions but human strain is more common. The infection may reach the intestine by four different routes—enterogenous, hematogenous, through the lymph channels, and by direct extension from tuberculous lesions in the female genital tract.

The most common site is the ileocecal region (85% cases). Stasis of the intestinal contents and the close contact of tubercle bacilli with the mucosal surface in this region make this part vulnerable. Ileum, cecum, colon, jejunum, and duodenum may be involved in that order of frequency. The lesion may be ulcerative, hypertrophic or ulcerohypertrophic. Pathological picture depends on the reaction of the host and virulence of the invading bacilli.

The bacilli infiltrate through the lymphatics into the submucosa. Tubercles are formed and intense inflamma-

tion with caseous necrosis occurs around the lymphatic channels. Enderteritis and lymphangitis lead to the formation of shallow mucosal ulceration. The ulcers are typically triangular running circumferentially (napkin ulcers). They heal by fibrosis leading to short segment strictures. Mesenteric lymph nodes are enlarged initially, later they may caseate and calcify.

Recurrent localized infection leads to the hypertrophic form. In this form there is increased fibrosis and fat. Ulcerohypertrophic type shows large stellate ulcers with necrosis. The abdominal mass is made up of adherent mesenteric lymph nodes, fat and fibrous tissue.

Clinical Features

The clinical manifestation may be classified into five following groups.

1. *Constitutional symptoms*, e.g. fever, weakness, anorexia, night sweats, and weight loss.
2. *Ulceration of the intestine* leading to abdominal discomfort, diarrhea, malabsorption, perforation, and rarely hemorrhage.
3. *Hypertrophic and ulcerohypertrophic forms* present with features of subacute intestinal obstruction, e.g. postprandial distress and distension, nausea, vomiting, constipation, colicky pain, borborygmi, and visible peristalsis. A tender lump may be palpable in the right iliac fossa.
4. *Involvement of adjacent tissues like peritoneum and lymph nodes* lead to the formation of localized or free ascites. Single or multiple masses in the abdomen, enlarged lymph nodes, and matted intestinal loops may be present. Extension of the disease to the pelvic adnexa gives rise to the formation of tubo-ovarian masses.
5. *Symptoms produced by tuberculosis in other parts of the body.*

Complications

Intestinal tuberculosis leads to complications such as intestinal obstruction, perforation, malabsorption state, and rarely massive hemorrhage. Malabsorption is the result of reduction in the absorptive surface, blind loop syndrome, and obstruction to lymphatics. Abdominal pain, weight loss and diarrhea form the symptom-triad of intestinal tuberculosis.

Diagnosis

Clinically abdominal tuberculosis should be suspected in all cases of vague dyspepsia associated with malabsorption. Presence of obstructive symptoms, ascites, and palpable masses strengthen the clinical suspicion. Evidence of tuberculosis elsewhere in the body strengthens the possibility further. Increased erythrocyte sedimentation rate and anemia occur in the majority.

A plain film of the abdomen may reveal dilated small bowel loops with fluid levels. Calcified lymph nodes may be seen.

In the barium meal study small intestinal loops show irregular widening of mucosal folds and irregularity and upward displacement of the cecum. Constricted segments with proximal dilatation may give rise to the “string sign” as in the case of Crohn’s disease. The ascending colon may be shortened.

Other investigations like ascitic fluid analysis, peritoneal biopsy, and peritoneoscopy may be helpful in arriving at a diagnosis. Endoscopic biopsy of the lesion is confirmatory. Adenosine diaminase (ADA) test in ascitic fluid is specific for tuberculosis and it is a useful and reliable test. PCR is useful to detect tubercle bacilli in peritoneal fluid and in endoscopic biopsy materials. The test is very sensitive, but too expensive for routine clinical use at present.

Treatment

General chemotherapy is given on the same lines as for the pulmonary tuberculosis. A low residue diet is advocated when there are obstructive symptoms. Most of the cases respond fully to antituberculosis treatment. Surgery may be very rarely required under the following conditions:

1. Intestinal obstruction
2. Perforation and hemorrhage
3. If there is doubt of malignancy and
4. When the diagnosis is uncertain, laparoscopy or laparotomy may be required.

Tuberculosis of the Mesenteric Lymph Nodes Syn: *Tabes mesenterica*

In most cases it is secondary to intestinal tuberculosis, single or multiple lymph nodes may be affected. Caseation is followed by calcification and the nodes are visible in X-rays. The presentation is variable. Some patients present with general symptoms like anorexia, loss of weight, and irregular pyrexia. Central abdominal pain with palpable abdominal lymph nodes should raise the possibility of mesenteric tuberculous adenitis.

Intestinal Polyposis

Polyps arise from the mucosal surface and project into the lumen. They may be benign or malignant.

Adenomatous Polyps

These are the most common. They may be sessile or pedunculated, solitary or multiple. The rectum and sigmoid colon are the most common sites accounting for more than 80% of the total. Majority of the polyps are silent, but at times they produce bleeding and intermittent

obstruction due to intussusception. Some polyps become malignant, especially if the diameter exceeds 1 cm, the smaller ones are benign. Polyps can be visualized by barium studies and endoscopy. Endoscopic removal of polyps within reach is feasible. Since recurrence occurs in 50% cases, all subjects must be followed up regularly.

Villous Adenoma

This occurs usually in the rectum or sigmoid. This is sessile, soft and friable, and it tends to bleed on mild trauma. Around 40-60% turn malignant in due course. Watery diarrhea and hypokalemia may develop rarely. Management consists of surgical excision and prolonged follow-up.

Familial Colonic Polyposis

This is a rare, autosomal dominant disorder characterized by the presence of numerous adenomatous polyps in the entire colon, especially the rectum and sigmoid, starting to appear from childhood and adolescence. These patients may present with lower abdominal pain, weight loss, diarrhea, tenesmus, and presence of blood and mucus in stools. There is almost a complete tendency to develop malignancy and hence prophylactic colectomy is indicated. Systematic follow-up of the patient and his family members is necessary (Fig. 79.3).

Juvenile Polyposis

This condition occurs in infants and children and is familial. Polyps are seen mainly in the colon and only sometimes in the small bowel. It presents with rectal bleeding and growth retardation. Histologically, inflammatory changes are seen in addition to columnar epithelium and mucus cysts. Therefore, these are also known as inflammatory polyps. There is no risk of malignancy and only symptomatic polyps should be removed. Prophylactic colectomy is not advised.

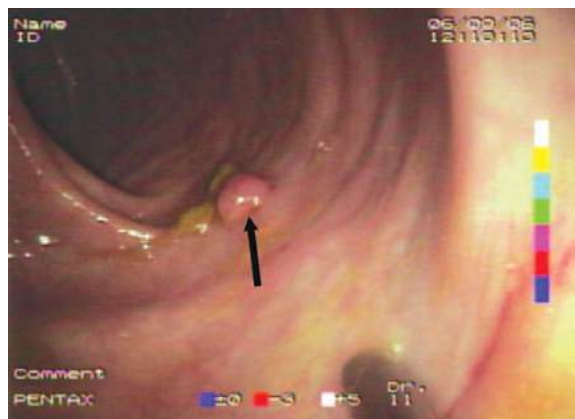


Fig. 79.3: Polyp colon: endoscopic view often polyps are precancerous

Peutz-Jeghers' syndrome: In this condition multiple hamartomatous polyps occur in the small intestine and colon along with spotted melanin pigmentation in the buccal mucosa, lips, and skin around the mouth, palms, and soles. Malignant change is less common. Treatment is required only if the polyps become symptomatic.

Vascular Disorders Affecting the Small Intestine

Arterial supply to the small intestine is derived from the celiac and superior mesenteric which are extensively connected to provide adequate collateral circulation. The distal transverse colon, the splenic flexure, and the junction of the superior and middle portions of the rectum are vulnerable to ischemia.

The causes of ischemic bowel disease are given in the Table 79.1.

TABLE 79.1
Causes of ischemic bowel disease
1. <i>Arterial occlusion</i> i. Atherosclerosis ii. Thrombosis iii. Embolism iv. Aorto-arteritis v. External compression (e.g. median arcuate ligament of the diaphragm) vi. Trauma
2. <i>Small vessel disease</i> i. Vasculitis ii. Connective tissue disorders iii. Anaphylactoid purpura iv. Radiation enteritis
3. <i>Venous occlusion</i> i. Primary ii. Secondary iii. Thrombophiliac states
4. <i>Non-occlusive mesenteric infarction</i>
5. <i>Steal syndromes</i>

The clinical features of arterial insufficiency depend on the site and degree of obstruction and the rapidity of onset. Clinical presentation ranges from transient malabsorption to frank infarction of extensive areas of the gut (Table 79.2).

Infarction of the Bowel

This may occur acutely or subacutely. It presents with severe colicky pain around the umbilicus which later leads to peritonitis, gastrointestinal bleeding, toxemia and hypovolemic shock. Fever indicates definite infarction. Stools contain frank or altered blood. Management is surgical if infarction has occurred. Gangrenous bowel is resected and vascular reconstruction is attempted.

TABLE 79.2
Clinical manifestations of ischemic bowel disease
1. <i>Acute intestinal ischemic syndromes</i> i. Infarction of the bowel ii. Ischemic colitis and enteritis
2. <i>Chronic intestinal ischemic syndromes</i> i. Intestinal angina ii. Stricture iii. Local ulcer iv. Celiac axis obstruction (median arcuate ligament syndrome) v. Intramucosal or intramural bleeding ("thumb printing" on X-ray) vi. Malabsorption syndrome

Intestinal angina occurs in partial obstruction of the superior mesenteric artery, especially when the other blood vessels are also diseased. The blood supply is inadequate to meet the demands of intestinal muscles after intake of food.

Twenty to thirty minutes after a heavy meal the patient develops severe crampy or colicky abdominal pain around the umbilicus lasting for 2-4 hours. The patient is afraid of taking food and, therefore, he loses weight. Often intestinal angina is a forerunner to intestinal infarction. Auscultation may reveal arterial bruit in the abdomen. Abdominal aortography or selective mesenteric angiography helps in locating the obstruction.

Treatment

The diet should consist of small quantities of easily digestible or predigested food given at short intervals. Surgical measures to revascularize the ischemic segments should be considered. Thrombophiliac states should be excluded by investigations and managed appropriately.

Carcinoid Tumours and the Carcinoid Syndrome

Carcinoid tumours arise from the endocrine argentaffin cells in the small intestinal mucosa. Argentaffin cells are most abundant in the cecum and appendix and these are the most common sites for carcinoid tumours. Carcinoid tumours may be associated with multiple endocrine adenomas. The tumours may arise singly or multifocally in 20% of cases. They vary in size from a few millimeters to a few centimeters. Those larger than 2 cm in diameter are malignant and they may spread to the liver, lungs, bones and local lymph nodes. The degree of malignancy is low and even with metastases about one-third of cases survive for more than 5 years. Atypical sites for carcinoids are the stomach and the bronchi. Extensive lesions produce metabolic abnormalities due to the production of large amounts of serotonin (5-hydroxytryptamine, 5 HT)

by the tumours and their secondaries. Several other substances like kallikrein, bradykinin, other kinin peptides, prostaglandins, and histamine have also been identified. The substrate for the production of 5-HT is tryptophan; 5-HT is deaminated by amine oxidase to 5-hydroxy-indole acetic acid (5-HIAA) which is excreted in urine in excess, i.e. more than 30 mg in 24 h.

Carcinoid Syndrome

This is produced by excessive production of 5-HT.

Clinical Features

Carcinoid syndrome is characterized by frequent episodes of flushing and watery diarrhea. Repeated flushing may give rise to facial edema and the development of telangiectasia. Asthmatic symptoms are prominent due to bronchospasm. Severe abdominal colic associated with borborygmi may occur. These attacks are precipitated by emotional upset, alcohol, and excessive foods. Right-sided heart lesions like pulmonary and tricuspid stenosis, tricuspid incompetence and right-sided heart failure may develop in long-standing cases. Death is due to intractable right-sided cardiac failure. Since tryptophan, which is the precursor of niacin, is used up for the formation of 5-HT, conditioned deficiency of niacin (pellagra) may develop. Carcinoid tumours arising from the intestines are late to produce symptoms. In gut carcinoid tumours the 5-HT

and other vasoactive molecules are released into portal system. They are metabolised in the liver first pass and hence such tumours will have no systemic symptoms early in the diseases. Later when hepatic metastases develop the vasoactive substance are released into systemic circulation. Thus typical carcinoid symptoms are late and often indicate hepatic metastases.

Diagnosis

Clinically carcinoid syndrome should be suspected in all cases of severe abdominal colic associated with hypermotility of the bowel, flushing, and palpable mass in the ileocecal region. Demonstration of excessive urinary 5-HIAA and raised serum levels of 5-HT will confirm the diagnosis. Foods like pineapples, bananas and walnuts, and drugs like phenothiazines, mandelamine, and glyceryl guaiacolate which increase urinary levels of 5-HIAA should be avoided for 3 days before undertaking the tests.

Treatment

Surgical excision of the primary tumour and the metastases, is undertaken. The results are dramatic in most cases. Another method is to perfuse the tumour with cytotoxic drugs through the hepatic artery. The diarrhea is controlled by methysergide 4 mg given four times daily. The flush is resistant to medical treatment. Treatment is given on usual lines when cardiac failure occurs.

Diseases of the Colon

K.R. Vinaya Kumar, K.V. Krishna Das

Chapter Summary

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Idiopathic Ulcerative Colitis

Ulcerative colitis is the idiopathic inflammation affecting the mucosa of the large intestine. Some patients have extra intestinal manifestations also.

This disease is present in all parts of the world and it is not uncommon in India. It is characterized by repeated bouts of diarrhea with blood and mucus, produced by inflammation and ulceration of the colon.

Many authors consider ulcerative colitis and Crohn's disease together under the term inflammatory bowel disease. The former affects only the large intestine, whereas the latter can affect all parts of the alimentary tract, though the predominant and most frequent involvement is in the distal part of the small intestine. Clinically and histologically the two conditions show overlap.

Ulcerative colitis results from environmental factors triggering loss of tolerance for normal intestinal flora in genetically susceptible individuals. Cigarette smoking confers a protective effect against this disease. The role of alteration in the normal protective gut flora in the causation of inflammatory bowel disease is established.

Etiology

The etiology is unknown. Psychological factors such as emotional stress, anxiety, or bereavement are evident in many cases. Since ulcerative colitis may be associated with diseases like arthritis, uveitis, erythema nodosum, hepatitis, and autoimmune hemolytic anemia, an autoimmune basis has been suggested. Other postulations include transmissible viruses, bacteria, allergy to milk proteins and genetic factors.

Pathogenesis

The disease usually starts from the rectum which is involved in 95% of cases. Whole of the colon up to the cecum may be affected with extension to the terminal ileum. In the ordinary case the inflammation is confined to the mucosa and submucosa. Initially the mucosa is hyperemic, swollen, roughened, and easily bleeding on contact. Superficial ulcers are seen which show diffuse infiltration of lamina propria and submucosa by chronic inflammatory cells. Crypt abscesses (cryptitis) may develop in 40% of the cases. The damage to mucosal epithelium is compensated by hyperplasia of regenerating mucosa which appears as pseudopolyps. Extension of the inflammatory process deeper into the muscularis and other structures causes strictures and shortening of the bowel in chronic cases.

Clinical Features

Moderately Severe Form

Majority of cases occur between 20 and 40 years. In the west, males and females are equally affected, but in India, the male to female ratio is 2 : 1. The disease starts with looseness of the bowel with blood and mucus, abdominal pain, weight loss and fever. The severity varies. The condition tends to be prolonged, unlike bacterial dysentery. In the majority of cases the condition is mild with less than 4 stools per day and the patient is afebrile. In the moderately severe form, there are disabling constitutional symptoms and the number of stools varies from 6-12/day.

In a few cases the disease takes a fulminant form and may be mistaken for severe bacterial dysentery. It is characterized by fever, bloody diarrhea, dehydration and electrolyte disturbances. Toxic megacolon occurs in a few cases in whom the inflammatory process affects all the layers of the bowel and mortality is high in such cases.

Diagnosis

The diagnosis should be suspected in all patients with a history suggestive of dysentery, but not relieved by the usual antiamebic and antibacterial drugs. Examination of the feces, colonoscopy and barium enema help in establishing the diagnosis. The feces is mixed with blood and mucus. Microscopy shows erythrocytes, neutrophils, and macrophages. These findings are similar to those found in bacillary dysentery.

Sigmoidoscopy/Colonoscopy

The mucosa is friable, granular, and it is covered with a thick inflammatory exudate consisting of pus, mucus, and blood. Frank ulcerations, pseudopolyps, and strictures may be seen in advanced cases. A rectal biopsy confirms the diagnosis. Microscopic examination of the fresh exudate helps in excluding amebiasis.

Colonoscopic Grading of Severity

1. Normal mucosa
2. Loss of vascular pattern
3. Granular non-friable mucosa
4. Friability of mucosa
5. Spontaneous bleeding with ulceration.

Barium Enema

This investigation helps to assess the extent and severity of the disease and its complications. Barium enema should not be done during the acute phase. In early cases no abnormality may be detectable or may show only loss of haustrations. Later, the mucosal surface is serrated or spiculated due to shallow ulceration. The picture reveals pseudopolyps and strictures in advanced stages of the disease. The presacral space is widened in the lateral view.

Colonoscopy

This should be done to assess the state of the disease and its extent. During follow-up, repetition of colonoscopy at 2-yearly intervals helps to detect the development of cancer early, in cases with duration above 10 years (Fig. 80.1).

Differential Diagnosis

Acute bacillary dysentery: This forms the most important differential diagnosis. The diagnosis is made on stool culture, since microscopic examination of the feces and sigmoidoscopic appearance are indistinguishable.

Amebiasis is to be differentiated by examination of the feces, sigmoidoscopy, and biopsy.

Other conditions such as inflamed hemorrhoids, ulcerating growths of the colon, tuberculosis of the colon,

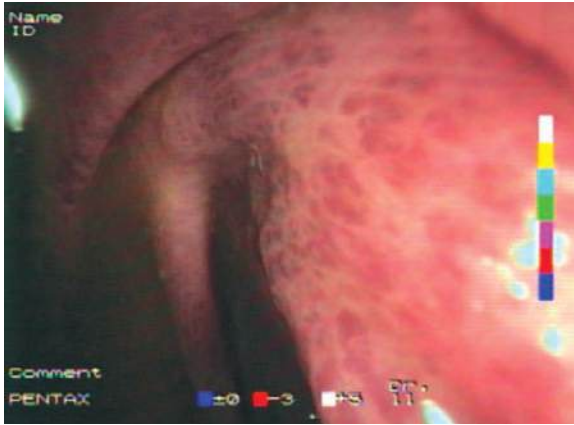


Fig. 80.1: Ulcerative colitis: endoscopy
Early stage: Note hyperemia and bleeding tendency

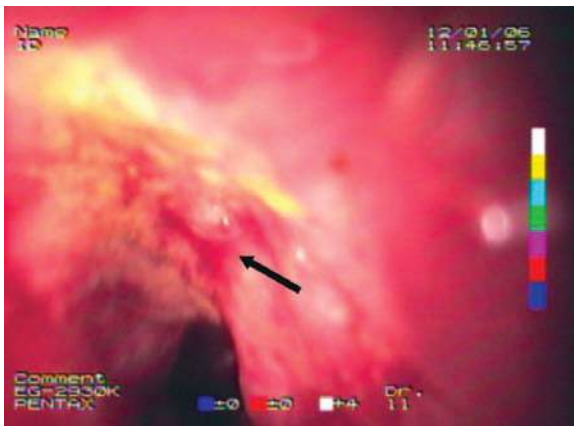


Fig. 80.2: Ischemic colitis: endoscopy. Note: mucosal ulceration and bleeding (arrow)

ischemic colitis, irritable bowel syndrome, and Crohn's disease have to be differentiated by appropriate investigations. Gonococcal proctitis and AIDS-related bowel disease have to be excluded in susceptible individuals (Fig. 80.2).

Complications

These may be local or systemic.

The local complications are:

1. **Toxic megacolon:** It is seen in 1-1.5% of cases, especially in fulminant colitis. This is characterized by acute dilatation of the whole or part of the colon to a diameter greater than 6 cm, usually measured at the midtransverse level. The symptoms include fever, tachycardia, prostration, and abdominal distension with diminished or absent bowel sounds. Plain X-ray of abdomen reveals dilated transverse colon. Perforation is identified by the presence of air under the diaphragm. In toxic megacolon the mortality is 12-30%.
2. **Colonic stricture.**
3. **Carcinoma of the colon** is 7-11 times more frequent if subjects with ulcerative colitis than in controls, and

more so in the chronic continuous form with extensive involvement. Risk of cancer is associated with the extent and duration of the disease. It is 1.7% for those with disease localized to the rectum, 2.8% for those with disease extending beyond the rectum to the hepatic flexure and 14.8% for those with disease extending proximal to the hepatic flexure.

The extraintestinal complications are:

1. **Liver disease:** Liver involvement occurs in the form of fatty liver, pericholangitis, sclerosing cholangitis, chronic hepatitis, and cirrhosis.
2. **Arthritis:** Sacroilits and seronegative monoarticular or polyarticular arthritis may develop.
3. **Ocular lesions:** Iritis (uveitis), episcleritis, superficial keratitis with blepharitis, retinitis, and retrobulbar neuritis occur rarely.
4. **The complications involving skin** are pyoderma gangrenosum and erythema nodosum which may occur in 1-3% of cases. Several other systemic complications have been described. Secondary amyloidosis may develop in a few.

Course and Prognosis

The course and severity of ulcerative colitis are variable. In the majority of cases symptoms are recurrent with complete symptomatic remission between attacks. In 5-10% of cases there are no recurrences after the initial attack; 5-15% follow a chronic continuous course without any remission.

Factors that determine the prognosis are: (i) severity of initial attack, (ii) extent of colitis, (iii) duration of illness prior to hospitalization, and (iv) age of the patient at the onset. Total involvement of the colon, severe disease, short fulminant course and elderly age are adverse prognostic factors. About 4-6% of patients will be dead within one year of the onset of illness and 13-20% within 5 years. Complications like toxic megacolon, associated liver disease, hypokalemia, and hypoalbuminemia also worsen the prognosis.

Management

Management of ulcerative colitis depends upon its severity and extent of the involvement. Patients with mild disease confined to the rectum and sigmoid respond to treatment satisfactorily. In moderate and extensive disease, relapses occur in 75% of cases.

Treatment of Moderately Ill Patients

The diet should be bland, low residue type, and with a high protein content. In patients with mild or moderately severe disease, initial therapy consists of sulfasalazine or analgesics. Salazopyrine has a sulfa moiety and an aminosalicilate moiety. The colonic bacteria split it into

5-amino salicylate (5ASA) which enters the mucosa to exert its antiinflammatory action. The beneficial action is due to the amino salicylate whereas the side effects are mainly due to sulfa moiety. The newer drugs which also deliver 5ASA are mesalazine and olsalazine. They do not contain the sulfa moiety and hence side effects are considerably less. Sulfasalazine (*salazopyrin*) is started in a dose of 500 mg thrice daily after food and then increased to 1 g three to four times daily, depending on the tolerance. Side effects include headache, malaise, skin rashes, hemolytic anemia, and very rarely, agranulocytosis. Mesalazine is effective in doses of 400-1200 mg thrice a day. Olsalazine is another drug with similar action. It is not freely available in India.

Corticosteroids form the mainstay of therapy in acute exacerbations of severe ulcerative colitis. They may be given intravenously, orally or as retention enemas depending on the condition. Prednisolone is given in the dose of 1-1.5 mg/kg bw daily (40-60 mg) for a week and then tapered off in 4-8 weeks. Steroids can be administered through rectal route as retention enema containing hydrocortisone 100 mg in 200 mL normal saline or as rectal suppositories which produce a foam inside. Beclomethasone, budesonide and prednisolone, metasulfobenzoate are topical steroids which produce good results. They are especially useful for severe ulcerative proctitis.

In some patients prednisolone may be ineffective and corticotrophin gel given in a single daily intramuscular dose of 60-120 units is effective.

Antibiotics are not normally indicated for the colonic lesions, unless systemic symptoms like fever or toxemia develop. Diarrhea may be partially allayed by drugs like codeine phosphate. General management includes reassurance by the physician, anxiolytic drugs such as chlordiazapoxide 10 mg, attention to nutrition especially supplements of proteins, iron and vitamins, and regular follow-up.

Treatment of Seriously Ill Patients

Features which indicate severity include:

1. Bowel movement > 9/day
2. Pulse > 100 minute
3. Body temperature > 38°C
4. Serum albumin < 3 g/dL
5. Plain X-ray abdomen showing intestinal dilation
6. Profuse hemorrhage with systemic effects.

Note: These patients may require surgery.

Such cases should be managed by the physician and surgeon jointly. At the outset an intensive regimen is started and continued for five days.

Only sips of water should be allowed by mouth. Hydrocortisone hemisuccinate is given intravenously in

a dose of 300 mg in 24 h. As an alternative, corticotrophin gel is given in a dose of 60-120 units administered intramuscularly or intravenously. Hydrocortisone retention enemas are given twice a day. Proper maintenance of fluid and electrolyte balance and replacement of blood form the essential supportive measures. In successful cases the temperature falls rapidly with return of the appetite and feeling of well-being. It takes a few days for the bowel frequency to return to normal. Surgical treatment has to be considered if the condition of the patient does not improve with conservative treatment in three to four days.

The onset of toxic megacolon is indicated by the presence of air filled colon with abnormal haustral pattern and irregular margins in plain X-ray of the abdomen. Since late surgery is associated with high mortality and morbidity, decision for undertaking surgery should not be unduly delayed. Surgical measures include total colectomy and ileostomy. Other indications for emergency surgery are colonic perforation and uncontrollable bleeding.

Surgery may also be required electively for the management of complications such as carcinoma, strictures, rectovaginal fistulae and frequent and severe relapses.

Long-term Management

Once the acute attack is controlled, the next step is to prevent relapses. Sulfasalazine given orally in doses of 2-4 g daily, continuously over a prolonged period exerts a suppressive effect to prevent relapse and maintain a symptom-free state. This drug is widely used. Small doses of corticosteroids orally or as topical applications have been used to prevent relapses but their value is still not firmly established.

Immunosuppressants like azathioprine can be used singly or together with corticosteroids for maintenance treatment in severe cases.

Cancer Prophylaxis

Since the risk of colon cancer is high in ulcerative colitis of long duration, there should be periodic evaluation for cancer detection. This is best achieved by colonoscopy every 1-3 years. Starting 10 years after the initial diagnosis, suspicious areas in the mucosa are biopsied to detect even dysplastic changes. Prophylactic total colectomy is indicated in high grade dysplasias.

Diverticulitis

The colonic mucosa may herniate through the muscularis mucosa to form diverticula. These small hernial sacs follow the course of the blood vessels on the mesenteric side and their wall consists of only mucosa and serosa. Many asymptomatic persons have colonic diverticula demonstrable by barium enema. This condition is referred

to as diverticulosis. The most common site is the sigmoid colon. Only rarely is the proximal colon affected. Inflammation of these diverticula leads to diverticulitis. Diverticula are reported in 20-50% of the western population over the age of 50. In India, though large population surveys are not available, the condition seems to be distinctly less common.

Pathogenesis

Diverticula are more common in people consuming low residue diets, which tend to lower the bulk of feces. Rise in intraluminal pressure required to move the colonic contents is probably responsible for diverticula formation in such persons. Inflammation sets in when fecoliths get impacted in the diverticula and cause reduction in blood supply and secondary infection. Intramural or pericolic abscesses may develop. It is, however, rare to produce generalized peritonitis. Sometimes the inflamed mucosa may bleed.

Clinical Features

8

The disease may present in several ways and clinical severity varies widely. The pain of acute diverticulitis may resemble that of acute appendicitis, but it is left-sided and worsened by defecation. Signs of peritoneal inflammation may be present. The subacute form presents with alteration in bowel habits or as discomfort and tenderness in the left iliac fossa. Though in 25% of cases occult blood can be detected in feces, gross bleeding is rare. Rarely dysenteric symptoms may occur. In chronic cases narrowing of the colon may lead to subacute obstruction. Physical examination may reveal palpable and tender sigmoid colon.

Diagnosis

Diverticulitis should be considered when an elderly person presents with subacute or chronic colonic pain associated with alteration in bowel habits. Diagnosis is confirmed by barium enema examination. The diverticula are seen as outpouchings of the colon. They are brought out better in films made with air insufflation into the rectum after voiding the barium. Rigidity, narrowing, and loss of haustrations of the affected segment should suggest the presence of inflammation. Sometimes differentiation from carcinoma is difficult. Contrast radiography should not be undertaken in the acute stage since it may lead to rupture of an inflamed sac.

Differential Diagnosis

Diarrhea and pain have to be differentiated from other forms of colitis. Severe hemorrhage may resemble that occurring in carcinoma, polyps, angiodysplasia or hemorrhoids. The subacute form with obstruction may resemble carcinoma.

Complications

These include free perforation, fistula formation, fibrosis, strictures and massive hemorrhage.

Treatment

In mild cases conservative management consisting of bed rest, stool softeners, and broad-spectrum oral antibiotics like tetracycline or ampicillin serve to tide over the acute phase. Introduction of high residue diet helps to regularise the bowel movements. Antispasmodics have to be given to relieve pain. Administration of ispaggol husk in a dose of 5-10 g after the evening meal helps to produce satisfactory bowel movement and relieve symptoms.

Complications like intestinal obstruction, perforation, abscess formation or massive hemorrhage are indications for surgical intervention. Surgery consists of a diverting colostomy and resection of the involved colon with subsequent reanastomosis.

Carcinoma of Colon

Carcinoma of the colon is common in India. The etiology is unknown. Villus adenoma, familial polyposis of the colon, chronic ulcerative colitis, and rarely adenomatous polyps may develop into malignant lesions. The peak incidence is between the fifth and the seventh decades.

Colorectal cancer is the third leading cause of death among malignancies all over the world. The incidence begins to increase after the age of 50 years and it doubles with each decade. Incidence is higher in the western world. In India this form of malignancy is quite common.

Genetics of Colon Cancer

Genetics of colon cancer has been extensively studied. Changes can be generally classified into three classes.

- Changes in proto-oncogenes:** They play a role normally in signal transduction in cell proliferation. Abnormal activation of these genes lead to tumour formation. Three human genes (ras genes) are identified in this category K-ras, N-ras and H-ras.
- Loss of tumour suppressor activity:** APC gene is a classic example. It is a tumour suppressor gene which is detected in familial adenomatous polyposis (FAP).
- Abnormalities in genes involved in DNA mismatch repair:** Classic example is gene mutation in hereditary non-polyposis colon cancer (HNPCC).

Amsterdam criteria for diagnosis of HNPCC

- At least three relations with colon cancer, one must be the first degree relative of the other two.
- Colorectal cancer involving at least two generations.
- At least one colon cancer occurring before the age of 50 years.

TABLE 80.1

Common inherited polyposis syndromes and the risk of developing cancer

Syndromes	Inheritance	Cancer risk	Distribution of polyps
1. Familial adenomatous polyposis	Autosomal dominant	Near 100%	Colon 100% Stomach 30-50% Duodenum over 90% Small bowel about 50%
2. Gardner's syndrome	Autosomal dominant	Near 100%	Colon 100%
3. Peutz-Jeghers syndrome	Autosomal dominant	About 50%	Small bowel > 90%

Note: In 1 and 2 polyps are adenomatous. In 3, they are hamartomas. Gardner's syndrome is also associated with other abnormalities such as osteomas, epidermoid cysts, fibromas, dental abnormalities, desmoid tumours and retinal lesions.

Germ line mutations in the mismatch repair genes MLH₁, MSH₂, MSH₆ and PMS₂ lead to the development of the Lynch syndromes which are strongly associated with the risk of colon cancer. Demonstration of this genetic abnormality in relatives of patients with colon cancer is an indication for prophylactic measures.

Genetics play a major role in colorectal cancer. Several forms of intestinal polyposis lead to cancer. Hereditary nonpolyposis colorectal cancer syndromes are also described. These include site specific colorectal cancer (Lynch syndrome I) and cancer family syndrome (Lynch syndrome II). Both these show autosomal dominant inheritance. In the latter condition other extraintestinal malignancies are also present, particularly in the ovaries, endometrium, stomach, small intestine, pancreas, urinary tract and larynx.

Risk of developing colorectal cancer is higher in persons who have first-degree relatives with colon cancer.

Number of first-degree relative with colon cancer	Risk of developing colon cancer in a lifetime
1	18%
2	33%
3	50%

In adenomatous polyps the cancer risk increases with the size of the polyp. Histological pattern also influences the cancer risk (Table 80.1).

Pathology

These tumours grow from the epithelial cells of crypts of Lieberkuhn. The lesion may be annular, tubular, ulcerative, or papilliferous. The annular type produces obstructive symptoms early. About 75% of tumours are seen in the descending colon, rectosigmoid, and rectum. Cecum and ascending colon are affected in 15% and the transverse colon is affected in 10% cases. Rectal examination and sigmoidoscopy are able to detect 50% of colonic cancers. Metastases occur initially by lymphatic spread to the

lymph nodes, and later through the bloodstream to the liver.

Clinical Features

Symptoms vary depending on the site of the growth. Growths in the cecum or ascending colon are usually flat or polypoid and they remain silent for long periods. Nonspecific symptoms like anemia, weight loss, anorexia or malaise may be the presenting features in some cases. Blood stained stool is the presenting complaint in 25% of right-sided lesions.

Left-sided lesions cause obstruction early since the contents are solid. Common symptoms are recent changes in the bowel habits and diarrhea alternating with constipation. Growths of the sigmoid colon may present with tenesmus. Colicky pain is often present. Rectal bleeding occurs in 70% of left-sided growths.

Diagnosis

The diagnosis is difficult when the symptoms are nonspecific. Digital examination of the rectum and sigmoidoscopy can pick up more than 50% of cases. Presence of occult blood in feces is suggestive of ulcerated growths.

Barium enema brings out the lesions in many cases. A growth may be seen as a filling defect or distortion of the colonic mucosa or as an ulcer. Post-evacuation air insufflated film is very useful for outlining colonic mucosal lesions.

In lesions beyond the reach of the sigmoidoscope, colonoscopy is diagnostic. Even when the barium enema is not definite, colonoscopic examination and biopsy serve to establish the diagnosis. Wherever possible histological diagnosis by endoscopic biopsy should be made before radical surgery since granulomas and ameboma may clinically resemble neoplasm (Fig. 80.3).

When secondaries occur in the liver, serum alkaline phosphatase, and 5-nucleotidase are elevated. Carcino-



Fig. 80.3: Carcinoma colon advanced: endoscopy
Note: cauliflower growth

embryonic antigen (CEA) is elevated in colonic cancer. Though this is not specific for colonic carcinoma, its use is mainly in following up patients who have undergone surgery. Rise in the level of CEA indicates recurrence of the growth or development of metastases.

8

Differential Diagnosis

Carcinoma of the colon should be differentiated from all other conditions which cause dysenteric symptoms and recent change in bowel habits, such as ulcerative colitis, polyps, diverticulitis and intestinal tuberculosis. In chronic amebiasis, granulomatous masses (ameboma) may develop and these have to be differentiated. Lymphoma, lymphogranuloma venereum, and endometriosis may also cause difficulty in diagnosis. It should be remembered that carcinoma may coexist with other lesions.

Complications

These include metastases, obstruction, intussusception, volvulus, bowel perforation, local peritonitis, massive

hemorrhage and spread to neighbouring organs like the ureters, bladder and uterus.

Treatment

In early cases colonic resection with colostomy is the treatment of choice. Preoperative radiation is advocated in rectal cancer. Even when the tumour is not removable, palliative surgery to overcome the obstruction may be required. Adjuvant chemotherapy with 5-fluorouracil and levamisole has good survival advantage. Even a few metastases in the liver are not a contraindication for surgery, since the liver metastases can also be removed.

Prognosis

Surgery offers almost cure, if colon cancer is detected early. Since most cases are detected late either when the growth is fixed or has metastasized, the prognosis is poor. In large series, overall five-year survival for patients undergoing radical surgery is about 50%. When the tumour is confined to the bowel wall, the five-year survival is 75-80%, whereas in those with lymph node metastases the survival is only 25%.

Prophylaxis

Carcinoma of the colon is largely preventable if premalignant conditions such as ulcerative colitis and colonic polyposis are regularly followed up with annual endoscopic examination. Colectomy should be undertaken early if malignancy supervenes.

It has been observed that regular use of statins have shown reduction of colon cancer. Regular use of NSAIDs such as sulindac and celecoxib has been shown to be associated with suppression of adenomatous polyps and regression of familial adenomatous polyposis and reduction of colon cancers. The therapeutic role of these observations is not fully evaluated.

81

Diseases of the Peritoneum

K.R. Vinaya Kumar, K.V. Krishna Das

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ASCITES

Collection of excess of free fluid in the peritoneal cavity is called ascites. A small quantity of fluid resembling lymph is normally present in the peritoneum. Increase in the hydrostatic pressure in the portal capillaries and the colloid osmotic pressure of the ascitic fluid favour further transudation into the peritoneum. Return of the ascitic fluid into the capillaries is brought about by the osmotic pressure of the plasma and the hydrostatic pressure in the peritoneum. The rate of formation and amount of fluid collecting in the peritoneum are determined by these two opposing forces. The peritoneal fluid is in dynamic equilibrium with blood and about 50% of the fluid enters and leaves the peritoneal cavity every hour. The extensive visceral peritoneum and its subjacent capillaries account for this free exchange. In all conditions where the ascitic fluid is a transudate, several factors operate simultaneously.

Cirrhosis of the liver accounts for the majority of cases of ascites in India. In cirrhosis of the liver, in addition to rise of portal venous pressure other factors also operate which help the accumulation of fluid in the peritoneum. These are hypoalbuminemia, secondary hyperaldosteronism which results in the retention of sodium, and increased secretion of antidiuretic hormone which favours the retention of water. Splanchnic arterial vasodilation caused by nitric oxide produced locally acts as a major factor in the development of ascites. Portal hypertension leads to the production of nitric oxide locally. Combination of portal hypertension and splanchnic arterial vasodilatation increases intestinal capillary pressure and

permeability resulting in the accumulation of fluid within the peritoneal cavity. As the disease progresses marked impairment of renal excretion of free water and renal vasoconstriction develop. The former leads to dilutional hyponatremia and the latter to hepato-renal syndrome respectively.

On the other hand, ascites in peritonitis is mainly the result of local inflammation and exudation. Table 81.1 lists the main causes of ascites.

Hemorrhagic fluid occurs in malignancy, acute pancreatitis or infarction of organs like the spleen or gut. The fluid is milky due to presence of fat (chylous fluid) in lymphatic obstruction and rarely in nephrotic syndrome. Meig's syndrome is a rare condition in which a fibroma of the ovary is associated with ascites and pleural effusion. It is a clinical curiosity often mentioned, but seldom encountered. Mucinous fluid accumulates in pseudomyxoma peritonei and in colloid carcinoma of the stomach. Pancreatic ascites develops as a complication of pancreatitis when a fistulous communication develops between the pancreatic duct and the peritoneal cavity. In this condition the ascitic fluid shows high levels of amylase and proteins.

Clinical Features

The onset may be acute as in the case of inflammatory exudates or insidious as in cirrhosis liver. The common symptom is progressive distension of the abdomen. The abdomen is uniformly distended and the flanks are full. In the early stages fluid may be detectable only in the flanks, later as accumulation proceeds the whole of the abdomen is filled. Due to rise in intra-abdominal pressure, the umbilicus becomes everted as a result of the development of an umbilical hernia. Inguinal, femoral or incisional hernias may develop. Striae develop due to stretching of the abdominal wall. **Free fluid in the peritoneum can be demonstrated by eliciting shifting dullness on percussion with changing positions of the patient.** For this sign to manifest, the fluid should be free so as to shift in the peritoneal cavity and the mesentery

TABLE 81.1

Causes of ascites	
<i>Transudate</i> Peritoneum is not actively involved	1. Due to combination of hypoalbuminemia and rise in portal venous pressure, e.g. cirrhosis 2. Hypoalbuminemia, e.g. protein malnutrition, nephrotic syndrome. 3. Increased flow of lymph from the hepatic surface. In hepatic venous obstruction, superficial hepatic veins distend and lymph transudes into the peritoneum, thus adding to the ascites and rise of portal pressure, e.g. Budd-Chiari syndrome. In this condition protein content of the fluid is high. 4. As part of generalized edema, e.g. congestive heart failure, myxedema.
<i>Exudate</i> Peritoneum is actively involved	1. Inflammations a. Infections-chronic peritonitis, e.g. tuberculosis and acute peritonitis. b. Dyscollagenosis, e.g. systemic lupus, polyarteritis nodosa. c. Acute pancreatitis, splenic infarct. 2. Malignancies a. Secondary carcinomatosis from liver, stomach, breast, colon, etc. b. Primary mesotheliomas of the peritoneum. c. Pseudomyxoma peritonei due to rupture of mucocoele of appendix or ovarian cyst.
<i>Miscellaneous</i> Peritoneum may or may not be involved	a. Perforation of hollow viscus, e.g. stomach, appendix, small intestine. b. Fibroma of the ovary (Meig's syndrome). c. Lymphatic obstruction-filariasis, secondary carcinoma, lymphoma.

should be free so as to allow the intestines to float up and give the hyper-resonant note. When the fluid is very tense or when the intestines are fixed due to involvement of the mesentery, shifting dullness may not be elicitable.

When the quantity of fluid is less than 200 mL, it can be detected only by eliciting dullness to percussion around the umbilicus, the patient being examined in the knee elbow position—"puddle sign". Fluid thrill can be elicited over the abdomen when the fluid is large in amount and under tension. In obese individuals the abdominal fat transmits "thrill" in the transverse direction and this should not be mistaken for fluid thrill.

Associated Findings

Ascites and pleural effusion may coexist. Fluid from the peritoneum may pass into the pleural cavities through defects in the diaphragm or lymphatic channels. The raised intra-abdominal pressure pushes up the diaphragm, resulting in the diminution of the respiratory excursions of the lower portion of the chest. The cardiac apex may be displaced upwards. Elevation of the diaphragm also leads to secondary rise in intrapleural and right atrial pressure. The jugular vein may be full due to this reason.

Differential Diagnosis

Free fluid in the peritoneum has to be differentiated from localized fluid collections such as abscesses, cysts, hydramnios and large hydronephrosis. Rarely a very much distended bladder may give rise to doubt. Localized fluid does not give rise to shifting dullness. Solid organs like

enlarged uterus and ovarian tumours do not produce fullness of the flanks.

Diagnosis

Presence of fluid is readily detectable by ultrasonography and this is the investigation of choice. In addition to fluid, solid masses and metastases can also be detected. The diagnosis should be confirmed by paracentesis, which is necessary to determine the etiology. Even when a major cause such as cirrhosis liver is evident, it is still advisable to do a diagnostic paracentesis to exclude other coexisting lesions like tuberculous peritonitis or hepatoma. The ascitic fluid is examined microscopically, biochemically and microbiologically.

Microscopic Examination

A fresh specimen of uncentrifuged fluid should be examined after adding one drop of methylene blue. This brings out the cells clearly. Further identification of cells can be done by examining the stained deposit or by Papanicolaou's technique. When parasites such as micro-filaria are suspected, the deposit should be examined after centrifugation. Presence of inflammatory cells is characteristic of exudates. Lymphocytes predominate in tuberculosis, malignancy and pancreatic ascites. In pyogenic infections like acute peritonitis, neutrophils predominate. Malignant cells are identifiable in wet stained preparations but they are better identified by Papanicolaou's technique. Bacterial organisms can be identified by Gram stain and Ziehl-Neelsen's stain.

Biochemical Tests

Protein content of the ascitic fluid is high in exudates. In transudates, the protein level seldom exceeds 2.5 g/dL. Higher values suggest infection, malignancy or infarction. Determination of serum albumin/ascitic fluid gradient (SAAG) is helpful in deciding upon the cause of ascites. Increase in alpha-fetoprotein suggests the presence of hepatoma. Rise in amylase levels above 100 units/L together with higher protein content suggests pancreatic ascites.

Laparoscopy

It helps to visualize the peritoneum and abdominal organs and also aids in the selection of suitable sites for biopsy.

Closed biopsy of the peritoneum can be performed using special (*Cope's or Abrams*) needles if facilities for laparoscopy are not available. This is helpful in the diagnosis of extensive diseases such as tuberculous peritonitis and disseminated malignancy.

Course and Prognosis of Ascites

These depend upon the cause. In hepatic cirrhosis the ultimate prognosis depends upon the state of liver function. If the liver function is considerably reduced, 40% cases die within 2 years of onset of ascites.

In peritonitis, the outcome depends on early diagnosis and prompt treatment. Ascites occurring in malignancy generally denotes advanced disease and this has a poor prognosis. Ascites secondary to hypoproteinemia, nephrotic syndrome, and cardiac failure clears up with improvement of the underlying condition.

Treatment

In all cases where the ascites is secondary to a treatable disease, cure of the primary disorder relieves the ascites as well. When the underlying cause is irreversible such as cirrhosis of liver, measures to relieve the ascites are undertaken.

PERITONITIS

The peritoneum is an extensive serous cavity lined by flattened epithelium. It is generally resistant to infection and in healthy subjects infection is promptly localized.

Peritonitis is inflammation of the peritoneum. It may be acute or chronic and localized or generalized. Acute peritonitis presents as a surgical emergency with severe pain, toxemia, and shock. Physical examination reveals extreme tenderness, board-like rigidity, and absence of peristaltic sounds because of intestinal paresis. If exudation develops into the peritoneal cavity, signs of ascites become evident. Chronic peritonitis presents with ascites.

Acute Peritonitis

Common causes of this condition include appendicitis, perforation of viscera occurring in peptic ulcer, typhoid fever, cholecystitis, Crohn's disease, ulcerative colitis, dysentery, diverticulitis, gangrene, strangulated internal hernias, and injury by foreign bodies. Gonococci and pneumococci may cause localized or generalized peritonitis as a primary infection or by spread from other foci.

Diagnosis

Examination of the ascitic fluid shows the presence of intestinal contents, organisms and large number of neutrophils. Plain X-ray of the abdomen may reveal dilated loops of intestines and subdiaphragmatic gas in the case of perforation. Ultrasonography is very helpful.

Acute peritonitis is a surgical emergency. Principles of management consist of correction of fluid and electrolytes, antibiotic therapy, measures to combat shock, and surgical measures. All cases should be managed under the combined care of the surgeon and physician without delay.

Chronic Peritonitis

This condition is commonly caused by tuberculosis, malignancy or chemical causes, e.g. peritoneal dialysis. It presents as progressive ascites or peritoneal adhesions with intermittent subacute intestinal obstruction. Diagnosis is established by examining the ascitic fluid which shows increase in protein and chronic inflammatory cells. Treatment for the underlying causes relieves the condition.

Malignant Lesions of the Peritoneum

Many neoplasms metastasize into the peritoneum early and, therefore, secondary tumours are much more common. The primary may be abdominal neoplasms from the stomach, liver, or ovaries or extra-abdominal sites like carcinoma of the breast and lungs. These patients present with rapidly developing ascites and cachexia and they run a downhill course. Examination may reveal nodular masses in the abdomen, presence of **Virchow's glands** and periumbilical subcutaneous tumour deposits (**Sister-Joseph's nodules**).

Sister Mary Joseph (1856-1939) surgical assistant to Dr. William Mayo, noted the association between para-umbilical nodules and metastatic intra-abdominal cancer. Ascitic fluid may be hemorrhagic in many cases and microscopy reveals tumour cells. Chemotherapy may be palliative in some cases.

Primary tumours are rare. Histologically these are mesotheliomas. In many cases there is association with exposure to asbestos.

RETROPERITONEAL FIBROSIS

Retroperitoneal fibrosis may develop as an adverse side effect of therapy with drugs like methysergide. Other recognized causes are retroperitoneal lymphoma, carcinomatous secondaries, and post-irradiation fibrosis.

The etiology is unknown in many cases. The disease is more common in middle-aged males. Progressive fibrosis of the peritoneum on the posterior abdominal wall leads to constriction of the ureters and bilateral obstructive uropathy. Surgical measures are required to relieve ureteric obstruction. Clinical features include malaise, back pain, normochromic anemia and raised ESR. Contrast urogram shows the obstruction at the level of the pelvic brim with distension proximally, often the distension is

asymmetrical. CT scan may show the fibrosis as a para-aortic mass.

Treatment is to relieve the obstruction surgically. Withdrawal of methysergide early during the course of the illness arrests further progress, and the fibrosis may even regress.

Pseudomyxoma Peritonei

It is a rare metastatic peritoneal disease the primary being in the ovary or the appendix. This is characterized by the accumulation of a jelly like material in the peritoneal cavity. The condition is very indolent and many patients survive more than five years after diagnosis. Surgical debulking of the tumour and local drugs administered intraperitoneally may be beneficial.

9

Hepatobiliary System and Pancreas

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Hepatobiliary System:
General Considerations

K.R. Vinaya Kumar, K.V. Krishna Das

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ANATOMY

The liver weighs 1.2 to 1.5 kg in the adult. It is comparatively bigger in infants, weighing around 6% of the birth weight. It is held in its place by the general intra-abdominal pressure and also by its peritoneal and vascular attachments.

Anatomically, falciform ligament divides the liver into a large right lobe, which is six times the size of the left, and the left lobe. The right lobe has two other lesser segments—the quadrate lobe in its inferior aspect and the caudate lobe located posteriorly. A portion of the left lobe is felt in the epigastrium in normal subjects. Based on its vascular supply and biliary drainage, the liver can be divided into physiological right and left lobes. The line of functional division lies to the right of the falciform ligament.

Structure of the Liver

The basic architecture of the liver is formed by the hepatic lobules which measure about 1 mm in diameter and are polyhedral in shape. Clearcut demarcation between lobules is not present in the human liver as is seen in the pig. Traditionally, the central hepatic vein was thought to be at the center of the lobule and portal triad at the periphery. The portal triad contains the radicles of the portal vein, hepatic artery and the bile duct, a few round cells and some connective tissue. A limiting plate of hepatic cells surrounds the portal tract.

Rappaport gave the acinar concept with the central vein at the periphery and the portal tracts at the center. An acinus is made up of a group of liver cells which is supplied by the terminal branches of the hepatic artery, portal vein, and bile duct. The acinus is the functional unit of the liver. A group of acini forms a complex acinus.

The liver cells are arranged in the form of sheets (hepatic laminae) which are connected by interlaminar bridges. In between the sheets of liver cells are vascular spaces—the sinusoids. The liver tissue is pervaded by two systems of tunnels formed by the portal tract and by the hepatic venous radicles. These two systems interlace in such a way that they do not come in contact. They are separated in the terminal portions only by a few liver cells that extend from the central vein to the portal triad.

The sinusoids are lined by a layer of endothelial cells. In between the hepatocyte and the endothelial cells is a narrow space—the *space of Disse*—which contains lymph. The hepatocytes account for 60% of the weight of the organ. They are polygonal, 30μ in size and show a central nucleus 8-10μ in diameter. Life span of the hepatocyte is 150 days. The bile canaliculi are found between adjoining liver cells. The hepatocyte has several complex metabolic functions to perform.

The phagocytic cells in the liver are the *Kupffer's cells* which belong to the reticuloendothelial system. They are situated in the walls of the sinusoids. In addition to Kupffer's cells, the sinusoidal walls contain endothelial cells, fat storing cells known as lipocytes or *Ito cells* and *pit cells* which have probably an endocrine function.

Under the electron microscope, hepatocytes reveal desmosomes which are anchoring pegs on the sides of contact of the cells. Microvilli project into the bile canaliculi. In the sinusoidal border, microvilli project into the perisinusoidal tissue space of Disse. The mitochondria contain several enzymes concerned with various metabolic activities including beta-oxidation of fatty acids. The rough endoplasmic reticulum (RER) synthesizes several proteins, including albumin, clotting factors and enzymes, and the smooth endoplasmic reticulum (SER) is the site of bilirubin conjugation, detoxification of many drugs and steroid synthesis. Adjacent to the bile canaliculi dense pericanalicular bodies are seen and these lysosomes contain many hydrolytic enzymes. Some of the pericanalicular dense bodies are termed microbodies. Golgi apparatus lies near the bile canaliculi. Lysosomes, microbodies, and Golgi apparatus are concerned with the

sequestration and elimination of ingested materials and this system is deranged in cholestasis. The hyaloplasm contains granules of glycogen, lipids, and fine fibrils. The cytoskeleton is formed by microtubules and micro-filaments.

Blood Supply

The liver receives a dual blood supply; 1500 mL of blood perfuses the liver every minute. The arterial blood supply is from hepatic artery which supplies 20% of blood. The remaining 70-80% of blood (1000 to 1200 mL) come from the portal vein. More than 70% of the oxygen supply to the liver is derived from the portal vein. When the portal venous oxygen tension is low during digestion, the major source of oxygen supply is the hepatic artery. The portal blood also contains some hepatotrophic factors which are essential for hepatic regeneration. The normal portal pressure is 7 mm Hg (90-120 mm water). The blood is drained into the inferior vena cava by three or more hepatic veins which are formed by radicles which commence in the intralobular veins which drain the sinusoids. The intralobular veins join to form sublobular veins and then the hepatic veins. Lymphatic channels from the liver drain into groups of nodes in the porta hepatis and thence into the nodes around the celiac axis. The mediastinal lymph nodes and those around the thoracic portion of the inferior vena cava also receive some lymphatics from the liver.

Bile secreted into the bile canaliculi by the hepatocytes drains into the intralobular cholangioles which join to form the larger interlobular bile ducts in the portal tracts. From each physiological lobe the interlobular bile ducts join to form the right and left hepatic ducts which join to form the common hepatic duct. The common bile duct is formed by the union of the cystic duct from the gallbladder with the common hepatic duct. It travels behind the head of the pancreas to open into the second part of the duodenum at the ampulla of Vater. Bile is secreted continuously and stored in the gallbladder which is a pear-shaped sac with a capacity of 50 mL. Normally this organ is not palpable, but when it enlarges it becomes palpable under the edge of the liver. The neck of the gallbladder shows a sacculation (*Hartmann's pouch*) which is a common site for lodgement of gall stones. The gallbladder contracts to release bile into the duodenum and this is related to the passage of food. The bile contains secretory and excretory products. The normal composition of bile is given in Table 82.1

PHYSIOLOGICAL CONSIDERATIONS

The liver plays a key role in the metabolism of carbohydrates, proteins, lipids, hormones, bilirubin,

TABLE 82.1

Normal composition of bile	
	(%)
Water	97.62
Total solids	2.38
Bile salts	0.90
Mucin and pigments	0.50
Lipids	0.25
Inorganic salts	0.73

porphyrin, bile salts and many drugs. It is only natural, therefore, that liver diseases lead to a wide variety of systemic manifestations. Because the liver has tremendous reserve capacity, the manifestations of disease occur only when the liver disease is advanced. Regardless of the etiology, the systemic features of liver disease are fairly similar.

Glucose Metabolism

One of the major functions of the liver is to maintain normal blood glucose level. Even though man is an intermittent feeder, the liver acts to dampen the effects of absorption and prevents surges in the blood glucose level and maintains blood glucose levels in the normal range. A fairly steady blood sugar level is maintained by the processes of glycolysis, glycogenolysis, glycogenesis and gluconeogenesis. Liver disease can lead to hypo- or hyperglycemia. Fulminant hepatitis and hepatomas can induce even fatal hypoglycemia due to reduction of gluconeogenesis and reduction of glycogen stores. Hyperglycemia may occur in chronic liver disease, especially cirrhosis. Reduced glucose uptake and glyco-genesis by the liver, coupled with hepatic resistance to insulin, are responsible for this feature.

Protein Metabolism

The liver is the major site of amino acid metabolism. The enzymes responsible for transamination and oxidative deamination are found in very high quantities in hepatocytes. Except for branched chain amino acids, the majority of amino acids entering the liver are catabolized. Levels of aromatic amino acids normally metabolized in the liver are increased and branched chain amino acids metabolized by the skeletal muscle are depressed in liver disease. The alteration of the ratio between the two types of amino acids has been incriminated in the pathogenesis of hepatic encephalopathy.

The liver synthesizes not only the protein it needs but also many export proteins (all plasma proteins except immunoglobulins), the most important of which is albumin. Albumin contributes significantly to the plasma oncotic pressure.

Coagulation Factors

Many of the blood clotting factors such as I, II, V, VII, VIII, IX and X are synthesized in the liver. The vitamin K dependent factors are synthesized in the liver and are made functionally active by the vitamin (See also Ch. 30). In addition to coagulation factors, intrinsic antithrombotic proteins such as protein C and proteins S are also synthesized in the liver. The capacity of the liver to produce coagulation factors is limited. Therefore, in hepatic failure coagulation function is deranged early.

Lipid Metabolism

Fatty acids produced by lipolysis of adipose tissue and those absorbed from the intestine reach the liver. Some fatty acids may be esterified with cholesterol, conjugated to phospholipids or converted to triglycerides. The triglycerides are cleared from the liver as lipoproteins by combination with apoproteins. Disturbances in these — either increased entry of fatty acids into the liver or decreased clearance — can lead to fatty liver.

Alterations in cholesterol and lipoprotein metabolism are seen in patients with cholestatic liver disease. The liver contains an enzyme lecithin-cholesterol acyltransferase (LCAT). A decrease in the production of LCAT is responsible for the increase in free cholesterol in serum. The reduced level of LCAT is also correlated with the appearance of lipoprotein-X (LP-X) in patients with cholestasis. Lipoprotein-X has a high concentration of free cholesterol and triglycerides.

Hormonal Metabolism

The metabolism of various hormones is affected in liver disease, e.g. insulin, glucagon, thyroxine, steroids, and sex hormones. Abnormalities of sex hormone metabolism account for spider angioma, loss of axillary and pubic hair, testicular atrophy and gynecomastia seen in patients with chronic liver disease. In addition to the hepatic dysfunction, the factors which lead to liver injury also directly impair gonadal function, e.g. alcohol, hemochromatosis.

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Chapter Summary

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Definition

Jaundice is yellow discoloration of skin, sclera, mucous membranes, and other tissues due to excess of bilirubin in the blood. The normal level is 0.5-1.0 mg/dL. Clinically, jaundice is manifest when serum bilirubin rises above 3 mg/dL (50 μ mol/liter). The term 'latent jaundice' is used when the level is between 1-2 mg/dL. Examination in bright daylight is absolutely essential to detect mild jaundice (Fig. 83.1).

Biochemical Abnormalities in Jaundice and Classification

Approximately 30 mg of bilirubin is formed in the body every day of which 80% is derived from senescent erythrocytes and 20% from other sources. Bilirubin combines with albumin and this product being insoluble in water does not appear in urine. In hemolytic jaundice in which most of the bilirubin is unconjugated, urine does not contain bilirubin. Three main phases are recognized in the metabolism of bilirubin. These are: (i) entry into the liver cell, (ii) conjugation, and (iii) excretion into the bile. After uptake, bilirubin is conjugated with glucuronic acid in the endoplasmic reticulum of hepatocytes with the help of glucuronyl transferase. Reduced levels of this enzyme are responsible for certain forms of congenital hyperbilirubinemias like *Crigler-Najjar syndrome*. Conjugated



Fig. 83.1: Obstructive jaundice male aged 55: Carcinoma head of pancreas. Note: dark yellow pigmentation of sclera and skin

bilirubin is water-soluble and it freely passes into urine. *Bilirubin* diglucuronide in the gut is acted upon by bacteria present in the distal small intestine and the colon and is converted into urobilinogen. Urobilinogen is reabsorbed mainly from the small intestine and to a small extent from the large intestine into the portal blood. It is subjected to enterohepatic circulation. The portion that is present in stool without being absorbed is called *stercobilinogen*.

Both unconjugated and conjugated bilirubin stain tissues. Collagenous and elastic tissues have the maximum

affinity for bilirubin and, therefore, tissues rich in these are stained early and most deeply.

In adults, bilirubin does not cross the blood-brain barrier and the brain is not stained. In neonates the blood-brain barrier is not well developed and it is disturbed in inflammations (e.g. Weil’s disease). In such situations the brain and CSF are also stained. Presence of bilirubin in ocular fluids may lead to yellow vision-xanthopsia which is extremely rare. Sweat, milk, semen, and synovial fluid may contain bilirubin in most cases, but tears, saliva and pancreatic juice are discolored only if the jaundice is severe. In long-standing jaundice the skin shows a greenish tinge due to the formation of biliverdin, an oxidation product of bilirubin.

Jaundice can be classified in different ways (Table 83.1).

Classification based on pathophysiological mechanism:

- 1. *Overproduction of bilirubin*—hemolytic.
- 2. *Decreased hepatic uptake* — hepatocellular dysfunction.
- 3. *Decreased hepatic conjugation* and release into biliary canaliculi—hepatocellular dysfunction.
- 4. *Obstruction to the biliary passages*—cholestasis with regurgitation of bile into blood.

TABLE 83.1	
Classification of jaundice based on the type of pigment	
I. Predominantly unconjugated hyperbilirubinemia	
A. Overproduction of bilirubin	
1. Hemolysis—intra- or extracorpuscular causes	
2. Ineffective erythropoiesis	
B. Impaired hepatic uptake	
1. Drugs-rifampicin, cholecystographic dye	
2. Familial-Gilbert’s syndrome	
C. Impaired bilirubin conjugation (decreased glycoronyl transferase activity)	
1. Hereditary absence or deficiency of transferase—Crigler-Najjar syndrome—Type I and Type II	
2. Immaturity of transferase (neonatal jaundice)	
3. Acquired transferase deficiency	
a. Drug effect-chloramphenicol, novobiocin	
b. Hepatocellular disease—hepatitis and cirrhosis	
II. Predominantly conjugated hyperbilirubinemia	
A. Impaired hepatic excretion (intrahepatic defects)	
1. Acquired disorders of the liver cells—Viral hepatitis, leprospirosis, drug-induced hepatitis, e.g. INH, methyl dopa, alcohol	
2. Hereditary disorders—Dubin-Johnson syndrome, Rotor’s syndrome	
B. Intrahepatic cholestasis	
1. Viral hepatitis	
2. Drug induced cholestasis, e.g. oral contraceptives, anabolic steroids methyl testosterone, sulfadiazine, chlorpromazine, thiouracil, PAS	
3. Primary biliary cirrhosis	
4. Extensive involvement of liver by malignant secondaries, Hodgkin’s diseases, etc.	
5. Intrahepatic biliary atresia	
C. Extrahepatic causes for cholestasis (surgical jaundice): Gall stones, carcinoma head of the pancreas, biliary stricture, carcinoma of the ampulla of Vater, obstruction of masses in the porta hepatis	

Based on the pathology, jaundice may be classified into *hemolytic*, *hepatocellular* or *obstructive*. Though in the majority of cases the jaundice runs true to type, in many instances more than one factor may be operative and this tends to make the biochemical picture more complex. For example in long-standing hemolytic jaundice, biliary calculi may develop and produce obstructive jaundice as well.

Differentiation of the types of jaundice: Differentiation between *medical*, i.e. *prehepatic* and *hepatic* types or *surgical*, i.e. *extrahepatic cholestasis*, is crucial in deciding upon the management. The investigations have to be planned suitably. Medical jaundice is to be treated mainly with drugs whereas surgical jaundice demands invasive investigations and surgery.

Diagnosis

Majority of cases can be diagnosed by the history, physical examination and simple biochemical tests. Preliminary tests include urinalysis, examination of feces and biochemical and immunological tests of the serum. More definitive diagnostic tests to delineate the anatomy of the biliary tree are ultrasonography, radiological studies, liver biopsy, isotopic investigations, endoscopic investigations, CT scan, MRI and laparotomy.

Table 83.2 gives the clinical differentiation of the types of jaundice.

Biochemical Tests

Preliminary investigations: Laboratory investigations are necessary to determine the type of jaundice and its etiology.

Detection of Bile Pigments and Urobilinogen in Urine

	Hemolytic	Hepatocellular	Obstructive
Bile pigment	Absent	Present	Excessive
Urobilinogen	Excess	Present, may be in excess	Absent

Examination of feces: The stools are dark coloured in hemolytic jaundice due to excessive bile pigment, whereas it is pale and chalky white (clay coloured) in obstructive jaundice due to absence of bile. Ulcerating malignant lesions give rise to occult blood in stools. Silvery colour of feces occurring in obstructive jaundice indicates the presence of altered blood.

Serum bilirubin: The total, conjugated and unconjugated fractions can be estimated. This helps in assessing the severity of jaundice and also in identifying the type. *Van den Bergh reaction* is a qualitative test used in detecting the type of bile pigment in the serum. Direct positive test is given by conjugated bilirubin, unconjugated bilirubin gives rise to the indirect reaction. When both pigments are present the reaction is biphasic.

Enzyme Determination

- a. **Increased levels of SGOT** (serum glutamic oxaloacetic transaminase, aspartate transaminase, AST), and **SGPT** (serum glutamic pyruvic transaminase, alanine transaminase — ALT): Liver cells are rich in transaminases SGPT and SGOT. In the normal state these enzymes are present in serum (10-40 U/L), but when hepatic cells undergo necrosis large amounts are released into circulation. The serum levels of these enzymes are raised in all forms of hepatocellular necrosis, irrespective of the etiology. Though these enzymes are not specific to the liver, when taken in conjunction with other tests of hepatic function, raised levels give a semiquantitative idea of the extent of liver cell necrosis in most cases. In fulminant hepatic failure where most of the liver cells have been lost the amount of enzyme released falls and so transaminase levels may fall despite very severe hepatic necrosis. In such a situation the enzyme levels may be misleadingly low.
- b. **Serum alkaline phosphatase** levels above 30 KA units/dL (210 IU/L) indicate cholestasis, if bone disease can be excluded. In extrahepatic biliary

TABLE 83.2				
Clinical differentiation of the types of jaundice				
Clinical features	Hemolytic	Hepatocellular	Obstructive (Cholestatic)	
*1. Depth of jaundice	Usually mild	Variable	Usually deep	
2. Pruritus	Absent	Variable	Present	
3. Bradycardia	Absent	Absent	Present	
4. Anemia	Present	Absent	Absent	
5. Splenomegaly	Present	Variable	Absent	
6. Palpable gallbladder	Absent	Absent	May be present	
7. Bleeding tendency	Absent	Present	Present in the late stages	
8. Features of hepatocellular failure	Absent	Present early in the disease	Present often late	
* Not a reliable sign.				
Note: The depth of jaundice is not a reliable parameter to differentiate the types				

obstruction, it is disproportionately increased compared to plasma bilirubin. The raised levels are brought about by overproduction of hepatic alkaline phosphatase. Rise in serum alkaline phosphatase is even a more reliable parameter of biliary obstruction than serum bilirubin levels.

- c. **Other enzymes such as gammaglutamyl transpeptidase and 5'-nucleotidase** are helpful in some cases when alkaline phosphatase levels are equivocal.

Serum cholesterol: It is markedly elevated in obstructive jaundice, especially primary biliary cirrhosis. Several other disorders lead to elevation of serum cholesterol and, therefore, this test is not specific.

Serum albumin: It is lowered in hepatocellular failure. In hepatocellular disease gammaglobulin is elevated whereas in chronic biliary obstruction alpha-2 and betaglobulins are elevated.

Prothrombin time: In obstructive and hepatocellular jaundice prothrombin time is prolonged. Shortening of the prothrombin time with parenteral administration of vitamin K₁ suggests that the jaundice is mainly obstructive. Total lack of response indicates gross liver cell damage.

Immunological Tests

Many hepatocellular disorders are immunologically mediated and so several antibodies can be demonstrated. Among them the most useful is the *antimitochondrial antibody* which is present in primary biliary cirrhosis. High titers of *antinuclear and smooth-muscle antibodies* suggest chronic active hepatitis. The different *serological markers of hepatitis B infection* such as HBsAg, HBeAg and their respective antibodies are most helpful in making specific diagnosis. Other viruses producing hepatitis give rise to specific diagnostic immunological markers (See Chapter 55).

Ultrasonography

It is perhaps the most useful noninvasive method to delineate dilated bile ducts, dilated portal vein, pancreatic cysts and tumours, the gallbladder, and the liver. This should be done as the initial imaging procedure to visualize the liver, gallbladder, biliary passage and the venous systems since this can confirm the diagnosis in many cases and further expensive and invasive tests can be avoided.

Liver biopsy: This may be necessary in long-standing jaundice when noninvasive investigations are unrewarding. In the presence of bleeding tendency, as revealed by prolonged prothrombin time, liver biopsy has to be undertaken with care. Percutaneous liver biopsies are now done with Trucut needles or biopsy guns. In liver

failure with severe coagulation disturbances, only transjugular biopsy can be done. In focal lesions of the liver, guided biopsies are required, either ultrasound or CT guided biopsies.

Radiological Studies

Plain X-ray of the abdomen may reveal radiopaque biliary calculi in a minority of cases. Plain radiograph of the abdomen may show gall stones as a chance finding. Contrast radiography such as oral cholecystography, intravenous cholangiography and percutaneous transhepatic cholangiography (PTC) are seldom done now. But selective hepatic arteriography is useful for the diagnosis of focal lesions in the liver, planning hepatic resections and interventions such as embolization and local chemotherapy. For these, more elegant and non-invasive procedures employing ultrasound, CT and MRI principles are adopted at present.

Computed Tomography

CT scan is a very reliable method to demonstrate hepatic lesions. This should be employed when ultrasonography is not fully diagnostic. Structural lesions in the liver such as tumours, abscesses, vascular malformations, parasites, cirrhosis and others can be demonstrated by CT. When ultrasonography and CT scan are used in conjunction the diagnostic yield is much higher. Both these modalities can be employed for guided biopsies and aspirations.

Magnetic Resonance Imaging (MRI)

This gives more information than CT in the following conditions:

1. Infiltrative disorders, especially fatty liver.
2. Accumulation of heavy metals such as copper and iron.
3. When hemangioma and metastatic deposits are suspected, and
4. To determine the patency of blood vessels in the abdomen.

CT cholangiopancreatogram (CTCP) and MR cholangiopancreatogram (MRCP) are useful non-invasive imaging modalities to delineate biliary and pancreatic ductular systems. They are equally informative compared to ERCP.

Isotopic Liver Scan

⁹⁹Tc labelled biliary analogues such as disopropylimino-diacetate (HIDA) and para-isopropyl iminodiacetic acid (Pipida) when given IV are taken up by liver cells and excreted into bile. In obstructive jaundice this is delayed. These tests help to detect the cause of obstructive jaundice due to mechanical cholestasis (Table 83.3).

TABLE 83.3

Differential diagnosis of jaundice

	Hepatocellular jaundice	Intrahepatic cholestasis	Extrahepatic obstruction
Common causes	Viral hepatitis spirochetal jaundice	Viral hepatitis, drugs biliary cirrhosis	Biliary stones, carcinoma of pancreas, carcinoma bile duct
Age	More in the young	Any age	Above 40 years
Duration of jaundice	Less than 3 months	Usually less than 3 months	Often more than 3 months
Itching	May be present	Common	Common
Color of feces	Slightly pale	Pale	Very pale (clay-coloured)
Jaundice	Mild to moderate	Mild to moderate or deep	Very deep in the later stages
Pain	Mild discomfort	Nil	characteristic pain in gall stones; constant radiating pain in pancreatic carcinoma
Liver	Tender and slightly enlarged	Variable	Enlarged and firm in long-standing jaundice
Gallbladder	Not palpable	Not palpable	Palpable in many cases of carcinoma head of pancreas and in some cases of bile duct obstruction
Bilirubin	Total and direct high	Total and direct high	Total and direct very high
Serum cholesterol	Normal	Raised	Markedly raised
Cephalin cholesterol flocculation	2 to 4+	1 to 2+	1+ in the early stages
Alkaline phosphatase (KA units)	10 to 15/dL	Over 15/dL	Over 30/dL
Transaminases	Markedly increases	Moderately increased	Only slightly increased in early stages
Obstruction to major bile ducts	Nil	Nil	Present

Note: Alkaline phosphatase—Normal value 3 to 13 KA unit/dL or 21 to 91 IU/L

Endoscopy

Esophago-gastroscopy: This gives indirect evidence of portal hypertension. Presence of varices in the esophagus and stomach is due to rise in portal pressure, persisting over long periods.

Presence of spider nevi in the oesophagus and/or stomach is suggestive of hepatic failure.

Endoscopic retrograde cholangiopancreatography (ERCP): This procedure helps in visualizing the biliary and pancreatic duct systems. In addition to diagnosis, the same method may be employed to dislodge obstructing stones or relieve a stricture (Fig. 83.2).

Peritoneoscopy: (Syn : Laparoscopy) Direct inspection of the liver and gallbladder through the laparoscope and biopsies under vision from suspicious areas improve diagnostic accuracy considerably.

Surgery

If the diagnosis is not clear by all these tests, laparotomy may have to be performed for initiating the treatment without further delay. Moreover, even in incurable malignant obstruction, drainage of bile through a cholecystojejunostomy helps to relieve symptoms and



Fig. 83.2: Hemobilia. Note: The presence of blood in the opening of the bile duct ERCP

allay misery for considerable periods. At present less traumatic procedures such as laparoscopic surgery are adopted.

Complications due to Jaundice

Jaundice may give rise to further complications, apart from those caused by the primary disease.

a. Obstructive Jaundice

Skin: Skin changes include melanotic pigmentation, chronic pruritus, thickening, and excoriation. Xanthomas develop due to hypercholesterolemia. Bleeding tendency manifests as purpura and bruises.

Malabsorption: Since bile does not reach the intestine, absorption of fat and fat soluble vitamins is defective. This leads to steatorrhea and deficiencies of vitamins A, D, E and K and calcium.

Accumulation of copper: Copper is normally excreted in bile. In chronic obstructive jaundice copper accumulates in the liver and may reach high values. Unlike as in Wilson's disease in which copper is deposited in the lysosomes, in biliary cirrhosis the copper is present in the cytosol.

Hepatocellular failure: Back pressure of bile and prolonged obstruction leads to hepatocellular necrosis, secondary biliary cirrhosis, and hepatic failure. Elderly subjects are more prone to develop these complications.

Renal failure: This may develop during the icteric stage or after surgical relief of the obstruction.

b. Hemolytic Jaundice

Damage to nervous system: In the newborn the blood-brain barrier for unconjugated bile pigment is not developed. The bilirubin is bound to albumin, but when the level exceeds 20 mg/dL, the binding capacity. The binding capacity of albumin is exceeded. Bilirubin passes into the nervous tissues and gets fixed to the mitochondria whose function is impaired resulting in neuronal death. The basal ganglia are affected most but no part of the CNS is totally free. This used to be dreaded complication of hemolytic diseases of the newborn. The CNS of the newborn is most susceptible to this damage.

Pigment gall stones: Presence of excess of bilirubin in bile results in its precipitation and formation of pigment gall stones. Though asymptomatic in many cases, rarely they may become symptomatic and lead to obstructive jaundice.

MANAGEMENT OF JAUNDICE

Definitive management depends upon the cause, but symptomatic treatment is necessary when the cause cannot be corrected.

Hemolytic jaundice: Treatment of the underlying disorder relieves the jaundice in most cases. In severe hemolytic disease of the newborn, measures such as exchange transfusion are necessary to lower serum bilirubin urgently and prevent neurological damage. Phototherapy (exposure to UV rays) benefits mild cases. Early detection of blood group incompatibility of the pregnant women with her husband and appropriate therapy helps to avoid severe hemolytic disease in the newborn.

Obstructive jaundice: Troublesome pruritus may be relieved by antihistamines like diphenhydramine in a dose of 50 mg twice daily. External application of calamine lotion gives relief. In intractable cases, the anion binding resin cholestyramine has to be given in a dose of 4-16 g/day orally in divided doses to lower the bile acid levels in the body. It binds the bile acids in the intestine, prevents their absorption, and facilitate their elimination. The main dose (4-8 g) is mixed in water or fruit juice and given in the morning with breakfast, since this is the time when bile salt concentration in the duodenum is the highest. Since cholestyramine also binds other ingested drugs, such drugs should be given at least one hour before administering cholestyramine. Cholestyramine is of no avail if bile does not reach the intestine as in complete obstruction. In such cases analogues of sex hormones may be effective. Methyltestosterone 25 mg is given sublingually for men and norethandrolone 10 mg is given orally for women. The antipruritic effect of these drugs will be manifested within a week of starting the drug.

Ursodexychoic acid (UDCA) promotes biliary flow and is useful in intrahepatic cholestasis.

Steatorrhea occurs in obstructive jaundice and this can be troublesome. This can be minimised by reducing the fat intake below 40 g/day. Since medium chain triglycerides are absorbed even without the help of bile acids, administration of such fats helps to avoid steatorrhea. Parenteral injection of vitamin K (10 mg) and vitamin D (2.5 mg) should be given monthly. Calcium gluconate given in a dose of 2-4 g orally helps to prevent negative calcium balance.

Endoscopic Management

Interventional endoscopic procedures such as endoscopic cholangiopancreatography are the methods of choice for relieving biliary obstruction and these have eliminated the need for surgery to a great extent. Endoscopic interventions can be done by special instruments during the procedure. These include extraction of stones, division of strictures, and stenting of the pancreatic and bile ducts. Stones can be extracted from the common bile duct, hepatic duct or even from intrahepatic portions of the smaller biliary ducts using baskets or balloons. Benign and malignant strictures can be dilated and stents deployed to restore the lumen (Fig. 83.2).

Surgical treatment: This should be undertaken immediately in cases of extrahepatic obstruction not amenable to endoscopic methods. Even in incurable lesions, palliative surgical procedures to overcome the biliary obstruction such as cholecystojejunostomy, help in relieving the symptoms, especially the intractable pruritus and steatorrhea. Surgical decompression of the biliary tree also helps in arresting the progress of hepatocellular damage. Many years of symptom-free life can be achieved and hence such procedures should be considered in suitable cases without delay.

84

Cirrhosis

K.R. Vinaya Kumar, K.V. Krishna Das

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9

Cirrhosis: General Considerations

Among the chronic parenchymal liver diseases seen in India, cirrhosis is most common. It is characterized by diffuse fibrosis and conversion of normal architecture into structurally abnormal nodules. At all times during the pathological process, there is evidence of liver cell necrosis, fibrosis, and the development of regenerative nodules which do not conform to normal anatomical pattern. The diffuse lesion involves the major portion of the liver. In many cases hepatocellular necrosis resulting from different pathological lesions initiate the process. In India the common identifiable causes are hepatitis B and C virus infections, alcoholism and chronic ingestion of toxic substances contaminating diet, or as drugs. Protein deficiency may act as an aggravating factor in the presence of other causes.

PATHOGENESIS

When liver cells undergo necrosis, the hepatic lobules collapse and this leads to the formation of diffuse fibrous septa. As a compensatory mechanism nodular regeneration of hepatocytes occurs. When the necrosis is associated with collapse of the reticulin framework cirrhosis results. If the reticulin framework is not collapsed but preserved, hepatocytes regrow and reproduce the normal histological pattern. Damage to the reticulin framework results in the

formation of abnormal nodules which derive nourishment from the hepatic artery, but without portal and biliary connections. The nodules vary in size from a few millimeters to several centimeters. The liver surface becomes nodular. Hepatic vascular bed is distorted, truncated and obstructed, the obstruction being maximal at the level of sinusoids.

Several vascular abnormalities develop. These include:

1. Generalized arterialisation of the liver.
2. Formation of shunts between the branches of the hepatic artery, portal vein and hepatic vein.
3. Formation of arteriovenous shunts also in the pulmonary circulation.
4. Development of a hyperdynamic circulatory state with increased cardiac output and reduced peripheral vascular resistance.

Obstruction to portal venous flow results in the development of portal hypertension. As the nodules grow, their centers are rendered ischemic. Once the disease process is initiated, other factors such as autoimmunity, continuing necrosis, and chronic effect of toxins lead to the progression of the pathological lesions.

Basement membrane forms in the Disse's space and this interferes with the metabolic functions of the liver. The necrotic foci stimulate the proliferation of fibroblasts and collagen and fibrous septae develop in the portal zones and hepatic lobules. Hepatic fibrosis is a common sequel to chronic liver injury from various causes such as alcoholism.

Etiological classification: Cirrhosis may be the end result of several unrelated conditions persistent viral and helminthic infections and hereditary copper or iron overload. In all these conditions the mechanism of fibrosis is similar, but the location varies. In chronic alcohol injury the fibrosis is pericentral whereas in viral hepatitis it is periportal. The perisinusoidal *Ito cells* may also transform into fibroblasts and produce intralobular collagen. Though these cells produce at least five types of collagen, only types I and III are found in the final scar tissue.

Etiological Factors in Cirrhosis

1. Infections	: Hepatitis B, C, D, <i>Schistosomiasis mansoni</i> , congenital syphilis
2. Drugs and toxins	: Alcoholism, methotrexate, arsenic, methyldopa, isoniazid, and several others
3. Metabolic causes	: Galactosemia, glycogen storage disease type IV, alpha-1-antitrypsin deficiency, hemochromatosis, Wilson's disease, urea cycle enzyme defects, tyrosinosis
4. Primary immunological disorders	: Autoimmune hepatitis (lupoid) and primary biliary cirrhosis
5. Vascular causes	: Hepatic venous obstruction, chronic congestive cardiac failure, constrictive pericarditis, veno-occlusive disease
6. Miscellaneous	: Indian childhood cirrhosis
7. Biliary obstruction	: Gall stones, biliary atresia, biliary strictures, mucoviscidosis and non-alcoholic steatohepatitis
8. Cryptogenic	: No cause is detectable even after full investigations. The majority of cases are cryptogenic.

Fibronectin, which is a soluble glycoprotein present in plasma, is rendered insoluble and deposited on the surface of the liver cells. Fibronectin binds collagen to form the extracellular matrix which replaces areas of liver cell necrosis. The matrix consists of proteoglycans, fibronectin and hyaluronic acid.

Cytokines initiate and perpetuate fibrogenesis. Among them platelet derived growth factor (PDGF) is most important. In the early stages fibrogenesis is reversible, but once established, it is not so.

Morphological Classification

The morphological types are:

- micronodular*,
- macronodular*, and
- mixed*.

In micronodular cirrhosis, the nodules are less than 3 mm in diameter, uniform, and these are seen involving the whole liver. The fibrous bands are indistinct and fine. In macronodular cirrhosis the nodules are coarse, irregular, and may grow up to several centimeters. The liver surface is grossly distorted. The mixed type is a combination of the two. In some cases at least the morphology may suggest the cause, though to a large extent this is decided by the extent of necrosis and other aggravating factors as well. In all types of cirrhosis in the later stages when fibrosis predominates the organ shrinks.

CLINICAL FEATURES

Early stages of the disease are asymptomatic. Vague illhealth, anorexia, loss of weight, loss of libido, impotence, abdominal distention, and dependent edema may bring the patient to the doctor. Night blindness is a common symptom in many and this results from the impairment of metabolism of vitamin A. Ascites is probably the most prominent feature which draws attention to the hepatic problem (Fig. 84.1).



Fig. 84.1: Male 60 years—cirrhosis liver with gross ascites and edema. Note: The pale nails and shiny abdomen

The major clinical features depend on the two main pathological processes, **hepatocellular failure and portal hypertension**. These processes often develop simultaneously in the majority of cases but independent of each other. The liver is enlarged in the early stage due to infiltration but in the later stage it shrinks and becomes harder in consistency. The spleen enlarges in size due to portal hypertension and reticuloendothelial hyperplasia. **Clubbing of fingers** may develop in a few. **Dupuytren's contracture** has been found to be associated with cirrhosis, but this association is not strong in Indian subjects (Figs 84.2 and 84.3).

Diagnosis

Cirrhosis has to be suspected clinically by the firm nodular feel of the liver, splenomegaly, signs of portal hypertension and hepatocellular insufficiency. The biochemical tests reflect parenchymal cell damage. Serum albumin is



Fig. 84.2: Male 50 years alcoholic cirrhosis, hepatic failure
Note: Spider nevi on the chest arrows



Fig. 84.3: Cirrhosis liver abdomen showing caput medusae
Note: The prominent veins on the abdominal wall, arrows point to the direction a blood flow

lowered with rise in gammaglobulin. *Bromsulphthalein (BSP) retention* is high. Transaminase levels are elevated if active necrosis is present. In all cases of doubt liver biopsy should be performed for establishing the diagnosis and identifying the morphological pattern, since the diagnosis is based on hepatic morphology.

Since removal of the underlying cause is necessary to arrest progression of the disease, etiological diagnosis should be attempted. In conditions like Wilson's disease, hemochromatosis and autoimmune chronic hepatitis, specific measures can be employed for reversing the lesions.

MANAGEMENT OF HEPATIC CIRRHOSIS

All cases of cirrhosis should be carefully managed. Considerable symptomatic and functional improvement can be achieved and useful life prolonged.

Uncomplicated Cases

Removal of the primary cause: If treatment is started early, the lesions can be reversed, as in alcoholism, HBV and HCV infection, drug toxicity, biliary obstruction and schistosomiasis.

Diet: The diet should contain 2500-2800 Cal/day. Protein intake of 1.25-1.5 g/kg of body weight should be attempted, if possible. The limiting factor is the development of hepatic encephalopathy. Vitamin and mineral supplements are indicated if there are overt or latent deficiencies.

Avoidance of precipitating factors: Factors that precipitate upper gastrointestinal bleeding and hepatic failure should be strictly avoided. Drugs should be administered to cirrhotics only after taking into consideration these potential complications.

Management of Ascites

General Measures

1. Bed rest helps the functional recovery of the liver and prevents deterioration of ascites. Low sodium diet-60-90 mmol/day of sodium (1500-2000 mg of sodium chloride) is ideal. If the serum sodium is < 130 mmol/L in the presence of ascites or edema, it suggests dilutional hyponatremia, due to impairment of water elimination by kidney, caused by syndrome of inappropriate secretion of antidiuretic hormone (SIADH).
2. In many advanced cases of cirrhosis the urinary loss of sodium is generally less than 2 g/day. Therefore, dietary sodium has to be drastically restricted. Apart from added salt at table, several articles of diet contain considerable amounts of sodium. These include pickles, bread, biscuits, salted canned food, milk (if more than 300 mL/day), and salted butter. The diet should contain moderate protein (50-70 g) and adequate calories. Since vegetable proteins are better tolerated than animal protein by patients with hepatic failure, these should be preferred. Failure to conform to a low salt diet is the most important cause of therapeutic failure. Fluid intake should be restricted to one liter a day.
3. **Diuretics** are indicated if salt-restricted diet alone is not effective in clearing the edema and ascites. Loss of weight of at least 1 kg in 4 days is ideal. The diuretic has to be chosen depending on the severity and response to therapy. Powerful diuretics like furosemide, thiazides, ethacrynic acid, and bumetanide cause loss of sodium and potassium. Potassium should be supplemented in a dose of 2 g/8h. Combination of potassium sparing diuretics like spironolactone, triamterine or amiloride, and the powerful diuretics enhances effectiveness and reduces the need for potassium replacement. An effective combination is furosemide with spironolactone or amiloride. Excessive diuresis may lead to hepatic failure, hypotension and uremia in 30-40% of cases and this should be avoided.

When potassium sparing diuretics are given, potassium intake should not exceed 50 mmol/day (3.75 g of KCl). Diuretic therapy may have to be continued over prolonged periods to get sustained benefits.

A convenient and popular regimen is to give spironolactone 25-100 mg thrice a day with frusemide 20-40 mg once a day. This can be continued for several months under supervision.

Frequent determination of serum levels of sodium, potassium and bicarbonate is necessary to avoid electrolyte disturbances.

Some of the resistant cases in whom the serum albumin level is below 2 g/dL respond to intravenous infusion of salt-free human albumin, dextran or ascitic fluid itself. This temporarily raises the colloid osmotic pressure.

As the hepatic function improves and the ascites clears up, dietary intake of salt can be increased and diuretics can be withdrawn in stages. 5-10% of patients with ascites become resistant to treatment. They do not respond even to high doses of diuretics (100-200 mg of spiranolactone and 40-160 mg of frusemide/day). In some others complications such as hepatic encephalopathy, hyponatremia, hyperkalemia or azotemia preclude further increase in diuretic dosage. Risk of hepatorenal syndrome (HRS) occurs in 10% of cases of hepatic failure with ascites.

Resistant Ascites

If the ascites tends to persist despite intensive general measures, fluid should be removed by paracentesis.

Paracentesis: This is a short-term measure and the fluid reaccumulates rapidly. The loss of protein and electrolytes from the body may worsen hepatic function further. Paracentesis is indicated when the ascites increases rapidly despite adequate general measures and causes severe embarrassment and pain. Only the minimum amount of fluid should be removed to relieve these symptoms. If the abdominal distention is severe and accompanied by dyspnea, removal of 4-5 liters of fluid in 12-16 hours brings about temporary relief. Complications of paracentesis include shock, bleeding into the peritoneum, infection and precipitation of hepatic coma. Recently interest in this procedure has increased and controlled paracentesis is being employed more frequently. Regular removal of fluid by paracentesis helps to reduce the dose of diuretic. It is advisable to give albumin infusion to prevent hemodynamic alterations when the paracentesis exceeds 5L of fluid (large volume paracentesis).

It is possible to maintain patients for long periods in reasonable comfort with judicious abdominal tapping repeated at regular intervals.

Spontaneous Bacterial Peritonitis (SBP)

In advanced liver cirrhosis bacterial translocation of the gut microbes into the ascitic fluid occurs. This condition is called spontaneous bacterial peritonitis which is seen in about 50% of patients with cirrhosis and ascites. The ascitic fluid protein is typically low but more than 250 polymorphs/cmm occur. Culture is positive for gram negative enterobacteriaceae, usually a single type. The presentation is with mild fever or abdominal pain. Sometimes rapid worsening of cirrhosis may be the presenting feature. Untreated, the mortality is high with worsening of ascites, hepatorenal syndrome and encephalopathy. Treatment is with cefotaxime 2g tid for 5 days. These patients also require secondary prophylaxis with norfloxacin.

Other forms of peritonitis in cirrhosis are

1. **Culture negative-neutrocytic ascites** where the polymorph count is > 250/cmm; but culture is negative.
2. **Monomicrobial non-neutrocytic ascites.** In this the culture is positive for single type of microbial species; but polymorphonuclear count is less than 250/cmm
3. **Polymicrobial bacterial ascites.** In this condition culture is positive for multiple species of microbes. This usually results from needle puncture of the bowel while attempting paracentesis.
4. **Secondary peritonitis.** In this condition polymorph count is very high, usually > 10000/cmm. This is a serious condition resulting from lesions such as bowel perforation, cholecystitis, appendicitis, diverticulitis, duodenal ulcer and others. Often surgical management is required.

Ascitic fluid ultrafiltration and re-infusion: Using an automated ultrafiltration apparatus (Rhodiascit) proteins of the ascitic fluid can be concentrated and infused intravenously. The equipment is expensive and the procedure demands special skills.

Le veen peritoneovenous shunt: This surgical procedure establishes intermittent drainage of the peritoneal fluid into the superior vena cava through a valve. The respiratory movements of the diaphragm and the reciprocal pressure changes within the abdomen and thorax serve to operate the valve. Limited success has been reported in some cases.

The treatment of complications like hematemesis and hepatic failure is described in Chapters 85 and 86 respectively.

Intercurrent infections: These are common and early treatment is essential to prevent hepatic failure. Ampicillin and amoxycillin are safe. Tuberculosis occurs more frequently in cirrhotics (4-6%). The lesions include pulmonary, lymph nodular or peritoneal tuberculosis. Such patients require standard chemotherapy.

Development of primary carcinoma: Cirrhosis predisposes to the development of primary carcinoma (hepatoma). Rapid enlargement of the liver, fever, pain, rapid loss of weight, development of massive hemorrhagic ascites or sudden hepatic or portal vein obstruction should suggest this possibility.

Prevention: Prevention of viral hepatitis, abstinence from alcohol, enforcement of laws on food adulteration, and proper food hygiene to avoid contamination by toxins, serve to reduce the incidence of cirrhosis on a long-term basis. Widespread vaccination against hepatitis B has brought down the incidence of cirrhosis and carcinoma in many South East Asian countries.

Special forms of Cirrhosis

ALCOHOLIC CIRRHOSIS

The final phase of alcoholic liver disease is alcoholic or Laennec's cirrhosis. This may result from repeated bouts of acute alcoholic hepatitis which is the more likely mechanism in most cases (50%). Presence of hepatic encephalopathy, deep jaundice with bilirubin above 20 mg/dL, prolongation of prothrombin time more than 5 sec. above normal, azotemia and severe hypoalbuminemia are associated with a higher risk of developing cirrhosis. The cirrhosis is micronodular and the liver is moderately enlarged, except in a few cases in whom it is shrunken.

Ascites, esophageal varices, muscle wasting and renal failure are common complications in alcoholic cirrhosis. Continued intake of alcohol leads to persistence of alcoholic hepatitis, progressive deterioration of liver function and death. Withdrawal of alcohol may arrest progress of the disease and in many cases even lead to regression. The inactive stage is compatible with prolonged survival.

NON-ALCOHOLIC FATTY LIVER DISEASE

This was initially recognized in women with diabetes with insulin resistance. Histology shows cytolytic changes in hepatocytes such as ballooning degeneration, Mallory hyaline, and lobular inflammation. Variable degrees of fibrosis may be present. This condition is not caused by alcoholism. This condition may be mistaken for alcoholic liver disease. Increase in liver enzymes may occur. Diet control and exercise to reduce weight and improve insulin sensitivity brings about relief. Drugs like ursodeoxycholic acid, metformin, vitamin E and others are tried with varying degrees of success.

BILIARY CIRRHOSIS

This results from prolonged obstruction to the biliary passages anywhere between the canaliculi and the ampulla of Vater. This may be primary or more commonly secondary.

Secondary Biliary Cirrhosis

Obstruction to the larger bile passages by stones, strictures, growths or extrinsic pressure, is the primary mechanism. Cirrhosis develops after a prolonged latent period. Biliary cirrhosis should be looked for if recurrent fever, chills, tender hepatomegaly, leukocytosis, and features of obstructive jaundice develop.

Treatment

Early removal of the primary cause leads to regression. Secondary biliary cirrhosis is prevented by prompt relief of biliary obstruction. Elderly subjects are more prone to develop cirrhosis as a result of biliary obstruction and therefore in them, procedures to relieve obstruction should be undertaken without undue delay.

PRIMARY BILIARY CIRRHOSIS (PBC)

Recent reports from the west suggest that this disease is quite frequent in middle-aged and elderly women. The disease is still considered to be rare in India accounting for 0.6 to 2% of all cirrhosis. Primary biliary cirrhosis is characterized by chronic cholestasis, pigmentation, xanthomatous eruptions, and histological features of chronic nonsuppurative, destructive cholangiohepatitis. The disease is immunologically mediated. There is a familial tendency, the incidence among close relatives is 1000 times more than in the general population.

Pathology

The liver is enlarged in the early stages, later it shrinks, portal hypertension develops late, and the spleen enlarges. 40% show stones in the gallbladder. The pathology is one of lymphocytic cholangitis involving small intralobular bile ducts within the liver. The first step in pathogenesis is immunological attack on biliary radicles, the next step is hepatotoxicity caused by retention of toxic bile acids secondary to cholestasis and loss of bile ducts.

Histologically the smaller bile ducts show epithelial damage and necrosis surrounded by granulomas consisting of histiocytes, CD8 + lymphocytes, plasma cells, eosinophils and giant cells. Fibrosis of the portal tracts progress (stage III) and give rise to frank cirrhosis (stage IV). The larger bile passages are normal. Antimitochondrial antibodies directed against a family of enzymes, especially pyruvate dehydrogenase complex which are inhibited *in vitro* are characteristic and are present in over 95% of cases.

Clinical Features

Classically, the disease affects middle-aged women and starts with fatigue, pruritus and jaundice. Male to female ratio is 1:9. Complications include malabsorption of fat-

soluble vitamins, especially vitamin D, osteoporosis, progressive hepatic failure, and portal hypertension. Copper accumulates in the liver. Unlike Wilson's disease in which copper accumulates in the lysosomes, in primary biliary cirrhosis it is in the cytosol. The disease progresses to end fatally within 5-7 years because of complications like hepatic failure or portal hypertension.

Diagnosis

Clinical suspicion is important in making a diagnosis. Conditions like chronic biliary tract disease, viral hepatitis, other causes of intra and extrahepatic biliary obstruction, toxic damage to the liver, systemic lupus erythematosus and other forms of cirrhosis have to be excluded. Some cases are associated with other autoimmune disorders such as CREST syndrome (calcinosis, Raynaud's phenomena, sclerodactyly, and telangiectasia), Sjögren's syndrome, thyroid diseases and esophageal dysmotility.

In some cases anti-mitochondrial antibodies may not be present; but all other clinical features resemble PBC. In prognosis and response to ursodeoxy cholic acid (UDCA) it is similar to that in classic PBC. Such cases are known as autoimmune cholangitis. It may lead to metabolic bone disease and hepatocellular carcinoma.

Laboratory Diagnosis

Features of obstructive jaundice such as raised alkaline phosphatase and increased serum bilirubin may be obvious. Alanine transaminase (SGPT) may be elevated to different levels, sometimes it may be normal. Serum cholesterol is elevated. Since the HDL fraction is also considerably elevated, the risk of atherosclerosis is relatively less.

Specific test is the demonstration of **antimitochondrial antibodies** in the serum in titers above 1080 in over 95% of the cases. Titers above 1/40 are suggestive.

Other immunological phenomena such as presence of immune complexes (raised levels of IgG and IgM) and abnormalities of complement may be present, but are nonspecific. Around 70% of cases of primary biliary cirrhosis have raised levels of IgM.

Liver biopsy is confirmatory. Serum cholesterol may be high and xanthomas may develop. Median survival after diagnosis varies from 10-16 years.

Treatment

General measures include relief of pruritus by antihistaminics such as diphenhydramine 50 mg given twice daily or cholestyramine 4-8 g/day with breakfast. The diet is adjusted to contain less than 40 g fat per day, supplied as medium chain fatty acids, e.g. coconut. Monthly injection of vitamin D 2.5 mg and vitamin K 10 mg and oral supplementation of calcium gluconate 2-4 g/day serve to

compensate for the malabsorption state. Rifampicin in doses of 150-600 mg/day helps to allay pruritus.

Specific measures are directed:

1. Towards the primary disease, and
2. Towards the complications.

Attempts to treat the liver lesion with corticosteroids have given equivocal results and in many centers this drug is no longer given due to its tendency to worsen osteoporosis. D-penicillamine has shown promise in recent years. In addition to its copper chelating effect, it relieves inflammation in the liver. Dose ranges from 250-900 mg/day. An alternate drug is colchicine given in a dose of 0.6 mg twice daily. Cyclosporine has been employed with partial success. Ursodeoxycholic acid, given in a daily dose of 12-15 mg/kg bw has been reported to arrest progress and bring about relief. Methotrexate given in a dose of 0.25 mg/kg twice a week orally produces resolution of lesions over a period of 6-12 months. The drug is toxic. Interstitial pneumonitis is one of the serious ill-effects. Portal hypertension, if already established, does not respond to medical therapy. This has to be treated on its own merits—if necessary by shunt surgery. If the condition is advanced, hepatic transplantation is indicated.

PRIMARY SCLEROSING CHOLANGITIS

Definition

Primary sclerosing cholangitis (PSC) is an idiopathic inflammatory disorder affecting the intra and extrahepatic biliary system resulting in fibrosis and stricture formation. 80% of cases are associated with inflammatory bowel disease, especially ulcerative colitis. Despite the association between inflammatory bowel disease and PSC, the latter appears to progress independent of each other.

Etiopathogenesis

The etiology and pathogenesis of PSC are unknown. A variety of causative mechanisms have been proposed, including toxins, infectious processes, ischemia, and genetic and autoimmune factors.

Clinical Features

The median age of diagnosis of PSC is 39, males are affected more. The most common symptoms at the time of diagnosis are jaundice, pruritis, and abdominal pain. The onset and progression of symptoms are usually insidious; rarely the disease can present as acute hepatitis like- illness. Loss of weight can occur at an alarming rate. Patients often experience chronic fatigue. Febrile episodes can occur, usually a manifestation of acute cholangitis. Symptoms and signs such as jaundice, pruritis, abdominal pain and fever may remit spontaneously and for prolonged periods. Rarely the initial presentation may be with

complications such as cirrhosis and portal hypertension. About 20-40% of patients are asymptomatic. Jaundice and hepatomegaly are the most common abnormal physical findings, and the spleen is enlarged in about one-third of patients.

Investigations

Typically, the serum alkaline phosphatase (SAP) level is increased three- to five-folds in PSC. Elevation in the SAP level is usually matched by increase in *serum gamma glutamyl transpeptidase* and *5'-nucleotidase levels*. Serum aminotransferases levels are usually elevated. Levels of conjugated bilirubin are increased in jaundiced patients. In others it may be normal. Serum albumin may be low and prothrombin time may be prolonged. Levels of immunoglobulin in the serum are often elevated. About 97% of patients with PSC have at least one autoantibody. The most common antibody is antineutrophil cytoplasmic antibody (ANCA). Other antibodies include anticardiolipin antibodies and antinuclear antibodies. Non-specific markers of cholestasis such as increased serum cholesterol and lipoprotein X may also develop.

The most common characteristic histopathologic changes is “onion skin” fibrosis, which describes the appearance of periductal concentric fibrosis around the interlobular and septal bile ducts. Ludwig has developed a histologic classification for PSC.

1. In stage I: portal hepatitis with or without bile duct abnormalities and cholangitis
2. In stage II: periportal fibrosis or hepatitis may develop.
3. Stage III : characterized by septal fibrosis or bridging necrosis and stage
4. Stage IV: biliary cirrhosis.

Non-invasive abdominal imaging can be suggestive but not diagnostic of PSC. Ultrasonography and CT may detect extrahepatic and intrahepatic ductal dilation, lymphadenopathy and evidence of cirrhosis or mass lesion. MRI cholangiopancreatography is a useful investigation for PSC. ERCP is considered the gold standard for diagnosis. ERCP not only confirms the diagnosis of sclerosing cholangitis, but also provides information about the distribution of the disease and the presence of dominant strictures that may be amenable to interventional therapy.

Complications

The chronic cholestasis of PSC leads to malabsorption of fat and fat-soluble vitamins and secondary biliary cirrhosis, biliary tract calculi, pancreatic disease, and possibly, cholangiocarcinoma.

MANAGEMENT

There is no definite medical, endoscopic, or surgical therapy, except for liver transplantation, which improves

the general health and well being. Though several drugs including antibiotics, glucocorticoids and immunosuppressants have been used from time to time, none showed any survival benefit. Results with ursodeoxycholic acid (UDCA) are encouraging. Intervention such as balloon dilatation and stent placement for strictures are palliative and safe. This can allay acute exacerbations of jaundice, pruritis and cholangitis and improve the quality of life.

Liver transplantation is indicated for patients with the complications of portal hypertension, hepatic failure, worsening cholestasis with cirrhosis, and recurrent cholangitis, refractory to medical or interventional therapy.

The median survival from diagnosis to death or liver transplantation has been estimated to be 12 years. A number of mathematical models have been developed to predict survival and optimal timing of liver transplantation. These are CTP score, Modified Mayo natural history model, Cox regression model and Swedish prognostic index, which may be referred to as further reading.

Liver Transplantation

First performed in 1963, this has become a standard therapeutic modality in several developed countries. In India this facility is available in a few centres only.

Indications

As a curative therapy it is employed in cirrhosis, hepatobiliary neoplasms, biliary atresia, metabolic disorders such as glycogen storage disease (type II), Wilson's disease, alpha-1 antitrypsin deficiency, homozygous familial hypercholesterolemia, sclerosing cholangitis, hepatic vein occlusion and fulminant hepatic failure. In advanced centers the one-year survival is about 70% and around 45% at 2 years. The perioperative mortality (within 30 days) is 30%. Best results are obtained in subjects with primary biliary cirrhosis, sclerosing cholangitis and cryptogenic cirrhosis.

Contraindications include the presence of extrahepatic malignant disease, active replication of HBV despite treatment, presence of irreversible disease in other organs and age above 55 years. The cost of hepatic transplantation is above \$ 70,000.

Liver in Wilson's Disease

Syn: Hepatolenticular degeneration

(see also Chapter 93 pp 591).

Wilson's disease (WD) is named after the British neurologist Samuel Kinnier Wilson who described the familial syndrome of cirrhosis liver with lenticular degeneration in the brain. WD is an autosomal recessive

disorder and a gene for WD has been mapped to chromosome 13 (13q 14). About 200 mutations in the WD gene have been identified.

The fundamental abnormality is impairment of biliary excretion of copper which is the main mechanism to regulate body content of copper. Accumulation of copper in cells leads to cellular damage by free radicals, oxidative stress and depletion of glutathione. Though the metabolic defect is congenital, symptoms occur only after 5 years of age.

Pathology

Hepatic cirrhosis predominates in young subjects, while in older subjects neurological lesions predominate. The liver shows a variety of pathological changes such as periportal fibrosis, submassive necrosis, and macronodular cirrhosis. Liver cells show fatty change, glycogen vacuolation, and multinuclearity. Copper is deposited in the periportal regions in a patchy manner and this is demonstrable by staining with rubianic acid or rhodamine. Wilson's disease is not rare among many communities in India and, therefore, all young subjects presenting with chronic parenchymal liver disease should be screened for this disorder.

Clinical features resemble those of cirrhosis, chronic active hepatitis, fulminant hepatitis, or chronic hepatic failure. Presence of *Kayser-Fleischer ring* is diagnostic.

Serum ceruloplasmin is low (< 20 mg/dL), urinary excretion of copper exceeds $100 \mu\text{g/day}$. Liver biopsy and estimation of hepatic copper are diagnostic. Hepatic

copper $> 250 \mu\text{g/g}$ of dry weight of liver tissue (normal $< 35 \mu\text{g/g}$ liver tissue) is diagnostic.

Course of the disease is steadily downhill ending with cirrhosis, portal hypertension and hepatic failure. Early treatment arrests the progress and prolongs survival. Dietary articles rich in copper such as nuts, liver, shell fish and chocolates should be avoided. Severe cases may require liver transplantation.

Note: Management is described in Chapter 93 pp 592.

Hemochromatosis

(see also Chapter 93 pp 590).

This results from iron overload and the deposition of iron in several organs. The liver is enlarged, firm and tender. Histologically, deposits of iron can be demonstrated in the periportal liver cells. Fibrosis of the portal zone develops. Kupffer's cells are filled with iron. Macronodular cirrhosis develops if the condition proceeds. There is a high risk of developing primary carcinoma. Removal of iron can be achieved by repeated venesection and use of iron chelating agents such as desferrioxamine.

Indian Childhood Cirrhosis

This term was used to describe symptoms of peevishness, anorexia, abdominal distension, failure to thrive, ascites, hepatosplenomegaly and jaundice occurring in children aged 1 to 4 years. With adequate nutritional supplementation most of them recovered without sequelae. At present this entity is not considered as a primary liver disease.

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Hepatic Failure

K.R. Vinaya Kumar, K.V. Krishna Das

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Hepatic failure is a syndrome characterised by functional failure of hepatic parenchymal cells. It can result from

various liver diseases with different pathological processes. Hepatic failure may be acute and fulminant or subacute and chronic.

CHRONIC HEPATIC FAILURE

This may result from liver cirrhosis, carcinoma, drug toxicity, cholestatic jaundice and surgical obstruction of

the biliary tree. Factors like high protein diet, hypotension, gastrointestinal bleeding, infections, and overdose of sedatives like morphine precipitate the onset of symptoms. Portal-systemic collateral circulation contributes to the development of encephalopathy. The clinical features differ in the acute and chronic forms.

Biochemical Disturbances in Hepatic Failure

In general, the biochemical abnormalities are more marked in acute fulminant hepatic failure than in the chronic form.

The failing liver is unable to convert ammonia into urea and hence ammonia accumulates. Glutamine is synthesized from ammonia and this is the major detoxification pathway to dispose ammonia. Glutamine is synthesized in astrocytes and this causes brain swelling. The degree of brain swelling correlates with the neuropsychiatric abnormalities. Since amino acids are not further metabolized, aminoaciduria occurs. Synthesis of albumin is impaired. Hypoalbuminemia leads to ascites and dependent edema in chronic liver disease. Vitamin K-dependent coagulation factors (especially prothrombin) are reduced or not made functional, and this leads to generalized bleeding tendency.

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Causes of Chronic Hepatocellular Failure

- 1. *Predisposing factors*
 - a. Cirrhosis—all types.
 - b. Cholestatic jaundice.
 - c. Drug toxicity.
 - d. Surgical obstruction of biliary tract.
 - e. Carcinoma—primary and metastatic.
- 2. *Precipitating factors*
 - a. High protein diet.
 - b. Gastrointestinal bleeding, hypotension.
 - c. Hepatotoxic drugs or alcohol.
 - d. Intense diuretic regimen leading to hypokalemia and hyponatremia.
 - e. Infections.
 - f. Surgical intervention and trauma.

Hepatic Encephalopathy

This is a neuropsychiatric syndrome that occurs in the presence of significant hepatocellular dysfunction and which has a full potential for reversal. The condition may be full-fledged or mild or even subclinical, occurring in 30-40% of cirrhotic patients.

This is associated with portal systemic shunting of blood. The blood is diverted through preformed collateral channels in portal hypertension. In acute hepatic failure, the liver cells do not metabolize the contents of the portal blood and hence these pass unaltered into the hepatic veins and further to the systemic circulation, thereby in effect producing a functional shunt. The nitrogenous products absorbed from the colon which reach the brain unaltered by hepatic metabolism lead to neurological dysfunction. The toxic products include ammonia and

several pharmacologically active amines produced in the intestines by bacterial action and other products of protein digestion. Several of them have been implicated. The blood brain barrier is deranged. As a consequence these products reach the brain.

GABA and Endogenous Benzodiazepines

Gamma amino benzoic acid (GABA) and endogenous benzodiazepines probably play their roles in the pathogenesis of this disorder. GABA and benzodiazepines are synthesized by the gut bacteria. The former has no major role in hepatic encephalopathy. It is possible that endogenous benzodiazepines which accumulate in hepatic encephalopathy play a major role in neuroinhibition.

The ill-effects of ammonia and other amines are further aggravated by alkalosis, hypoxia, hypokalemia, hypoglycemia and increase in the concentration of fatty acids in serum. Even though several biochemical abnormalities have been identified, the exact pathogenesis is still not clearly known. The blood levels of ammonia or other possible toxic metabolites do not correlate with the mental state, but serial estimations of blood ammonia can be used to monitor the effect of treatment. These metabolites do not cause neurological dysfunction in normal subjects. This fact suggests that an abnormal susceptibility of the brain to toxic metabolites is an important factor in leading to the clinical picture. The CSF is initially normal, but late in the disease, protein, glutamic acid, and glutamine may be increased.

CLINICAL FEATURES

The onset is insidious with general loss of health, fatigue and weight loss. Jaundice may occur, but this is not constant. The early stage may be missed if clinical suspicion is not high.

Hyperkinetic circulation occurs which manifests as high volume pulse, warm extremities, tachycardia, and ejection systolic murmur over the pulmonary area. It is likely that the circulatory disturbances are due to opening up of arteriovenous shunts and the effect of circulating vasodilator substances.

Neurological Manifestations Predominate

- 1. **Alteration of consciousness** ranging from confusion to coma may develop. Sleep rhythm is altered early, with sleep during day and insomnia at night. Personality changes may be marked and these could be mistaken for primary psychiatric disorders.
- 2. **Parkinsonian features**, especially akinesia may develop. Constructional apraxia develops which can be demonstrated by making the patient to draw along the Reitan number chart (Fig. 85.1).
- 3. **A diagnostic physical sign is flapping tremor (asterixis)** elicited by holding the hands outstretched

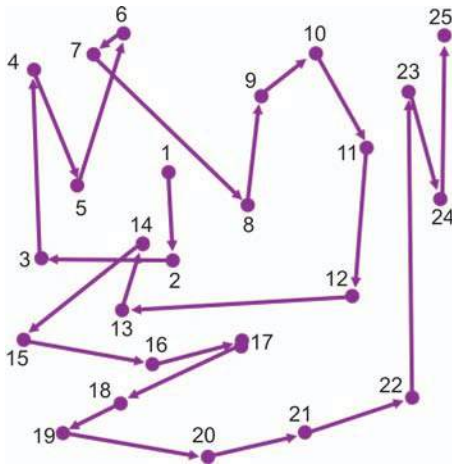


Fig. 85.1: Reitan number chart for trail making test

with extension of the wrist. The fingers and wrist show coarse tremors comparable to the flap of a bird's wing. In early cases the tremor (flap) is confined to the extremities but later on it extends to the proximal joints of the limbs, trunk, jaw, neck, and tongue. Flapping tremors are bilateral, asynchronous on both sides and absent at rest. The tremors fluctuate in severity with changes in hepatic function.

3. **Electroencephalogram:** The EEG mainly shows slowing of rhythm from alpha (8-13 cps) to the delta (4 cps) range. Other abnormalities may also occur. Diffuse bilateral high voltage slow waves occur.

The EEG changes closely reflect hepatic functional impairment. The EEG abnormalities can be precipitated by giving a high protein diet. As hepatic function deteriorates, coma sets in.

MRI show hyperintensity of globus pallidus on T₁ weighted imaging.

Vascular phenomena Cyanosis occurs in one-third of patients due to hypoxia. Intrapulmonary arteriovenous shunts develop. The diffusing capacity of the lung is also impaired.

Finger clubbing, palmar erythema and spider nevi are common. Erythematous patches may occur over several parts of the body, especially the chest wall and supraclavicular regions. Arterial spiders are quite suggestive of chronic hepatic failure, though they can occur less commonly in other conditions such as pregnancy and estrogen therapy. A few may occur even in normal subjects. The upper limbs, and the mucous membranes of the nose, mouth and gastrointestinal tract are the sites of predilection. An arteriole comes to the surface and breaks up into capillaries which radiate like the legs of a spider. The central arteriole may pulsate in large nevi. Pressure over this vessel blanches the whole spider and on releasing the pressure blood fills from the center to the periphery. Liver disease should be suspected



Fig. 85.2: Male 50 years alcoholic cirrhosis, hepatic failure
Note spider nevi on the chest arrows

when they are numerous, and fresh spiders are appearing. The vascular phenomena of liver failure have been attributed to hyperestrogenism (Fig. 85.2).

Other features: Fotor hepaticus develops in some patients with severe hepatic failure. It is a slightly fecal odor attributed to the presence of methyl mercaptan and dimethyl sulfoxide in breath. This is present more often in acute hepatic failure. However, this sign is not prominent in Indian subjects when compared to those from the west.

Low grade fever attributable primarily to the liver disease may be present. Gram-negative bacteremia and low grade septicemia are common due to shunting of the blood through collateral channels. Spontaneous bacterial peritonitis and endocarditis may occur with atypical presentations.

Skin changes occur in long-standing cases. They include the appearance of white spots, white nails (leuconychia), loss of hair and pigmentation.

Endocrine disturbances: Males develop hypogonadism which presents as loss of libido and impotence and feminization manifested by gynecomastia and loss of facial hair. In females endocrine symptoms are less pronounced. The cause of feminization is still not fully understood.

Ascites: In chronic hepatic failure due to cirrhosis, when hypoalbuminemia and portal hypertension develop, ascites invariably occurs. The kidney plays a part in the development of ascites. Cirrhosis leads to a spectrum of renal abnormalities ranging from retention of sodium to full fledged hepatorenal syndrome.

Drug metabolism: The detoxification function of the liver is impaired and elimination of drugs becomes defective. Even small doses of morphine produce profound sedation and tip the patient into hepatic coma. Several other drugs such as tetracycline may reach toxic levels in these patients. As the coma deepens, signs of upper motor

neurone lesion, such as exaggeration of deep reflexes, patellar and ankle clonus and Babinaski's sign develop.

Hepatic encephalopathy has been graded into four grades.

Grade	Characteristics
1.	Altered sleep patterns, altered mood, irritability, inability to maintain attention
2.	Lethargy, altered speech, increased memory loss, dysarthria
3.	Progressive stupor, decreased level of consciousness but responsive to stimuli
4.	Coma, unresponsive to painful stimuli

Prognosis

The prognosis depends upon the underlying condition, the presence of precipitating factors, and the management of the case.

Precipitating factors: Following are the precipitating factors:

1. High protein diet.
2. Gastrointestinal or other hemorrhage, extravasated blood in the gastrointestinal tract acts as a source of nitrogenous products and is more harmful in this regard than other proteins on a weight for weight basis.
3. Hepatotoxic drugs like morphine, ammonium salts and alcohol.
4. Intense diuretic regimen which produces hypokalemia and hyponatremia.
5. Infections.
6. Minor or major surgery including liver biopsy and abdominal paracentesis, and
7. Progressive deterioration of hepatic function.

If the precipitating factors are avoided and the patient is properly managed, satisfactory physical and mental state can be maintained for prolonged periods. Cases with a removable precipitating factor do better than those in whom the hepatic failure is the result of advanced liver disease.

MANAGEMENT

The aim of treatment is to improve hepatic function, relieve symptoms, and prolong useful life.

Symptomatic treatment: The patient should be put to bed rest in the acute and subacute stages.

Diet: The total dietary intake should be 2000-2500 Cal. and the amount of protein has to be adjusted so as to give the maximum possible nourishment without precipitating portal systemic encephalopathy. This has to be determined by trial and error. Vegetable proteins are tolerated better than animal proteins and they may be preferred. On an average, many patients tolerate about 40 g proteins daily.

Considerable persuasion may be necessary to make the patient eat despite the anorexia. Adequate intake of food definitely brings about improvement. Hematinics such as iron, folate, and other vitamins should be given. The hemoglobin level has to be maintained above 10 g/dL, if necessary by transfusion.

Sedatives like morphine and paraldehyde precipitate coma and these should be avoided. While long-acting barbiturates like phenobarbitone which are mainly excreted by the kidney are tolerated, the short-acting ones like pentobarbitone and thiobarbitone which are mainly metabolized by the liver should be avoided. Oxazepam and diazepam may be used.

Treatment of Hepatic Precoma and Coma

Diet: Proteins should be totally withdrawn. Carbohydrates are given orally or parenterally to supply 1500-1600 CAL in 24 h. As the condition improves proteins are added to the diet.

Antibiotics: Broad spectrum antibiotics which sterilize the intestinal flora prevent bacterial breakdown of the products of protein digestion and the formation of toxic products. The ideal drug is neomycin 4-6 g/day given in divided doses. Being nonabsorbable, it reaches the colon in adequate concentrations to exert its effect. Ampicillin in a dose of 2 g/day in four divided doses is a suitable alternative.

Lactulose: This unabsorbable disaccharide is broken down by bacterial flora into lactic acid and small amounts of acetic acid when it reaches the ileum and cecum. The pH value of the colonic contents is lowered. At this low pH the lactose splitting organisms overgrow, suppressing the protein splitting organisms like *bacteroides* which produce ammonia. At a dose of 10-30 mL given thrice daily, lactulose is very effective in relieving chronic portal systemic encephalopathy. *Lactitol*, which is a derivative of lactulose, has a better taste and is more acceptable.

Purgatives: Proper evacuation of bowels helps in improving the mental state whereas constipation tends to worsen it. Purgation is achieved by the administration of magnesium sulfate 15-30 g orally. Lactulose itself acts as purgative. Enemas are employed to clear the bowels when purgation is contraindicated. The enemas should be at mildly acidic or neutral pH to prevent the absorption of ammonia. Bowel wash with saline or 1% dextran solution twice a day helps to clear the colon and this measure is effective in improving the mental state.

Attention to Precipitating Factors

1. *Intestinal blood loss* should be treated by quantitative replacement of fresh blood. Blood should be removed from the intestines by aspiration and purgation. Oral broad spectrum antibiotics should be given to prevent the formation of ammoniacal products.

- If the coma has been precipitated by the use of sedatives, the *appropriate antidote* should be used, e.g. nalorphine in the case of morphine.
- Electrolyte imbalance* should be corrected. Potassium deficiency can be prevented and mild cases treated by the use of copious administration of fruit juices, and oral potassium chloride 2 g every 6 h. Intravenous administration of potassium is done if serum potassium is below 3.5 mmol/L.

Dopamine agonists: In some patients levodopa given in a dose of 0.5 g 6 h brings about benefit. Similar effect has been seen with bromocriptine in a dose of 15 mg/day.

Flumazenil

Flumazenil is a GABA benzodiazepine receptor antagonist. In controlled trials it is found to improve hepatic encephalopathy significantly.

Follow-up: Improvement should be monitored clinically and by objective evaluation with EEG, trail-making test and blood ammonia levels. Irreversible hepatic failure is an indication for hepatic transplantation.

Subclinical Hepatic Encephalopathy

Clinically there is no change in the level of consciousness; but abnormality is detected during psychomotor testing such as trail making test. The reaction time is prolonged and visual evoked potentials may be delayed. Such patients are unfit for handling fast mechanisms and for jobs such as driving vehicles and piloting aircraft.

ACUTE HEPATIC FAILURE (AHF)

Syn: Fulminant hepatic failure

Definition

Altered mental status with coagulopathy occurring in the setting of acute liver disease unaccountable by other obvious causes should suggest the possibility of acute hepatic failure (AHF). Encephalopathy is an essential feature for diagnosis. The term fulminant liver failure denotes the occurrence of hepatic encephalopathy developing within eight weeks of onset of liver disease. If the condition develops later on in the illness (even up to 26 weeks) it is called sub-fulminant or late onset hepatic failure. AHF is a serious clinical state with mortality reaching upto 80%.

Pathology

Massive necrosis of liver cells leads to sudden impairment of liver function. Cerebral symptoms are caused by hepatic encephalopathy as well as development of cerebral edema which occurs in upto 80% of cases. Coning of brainstem may occur.

Causes of Acute Hepatic Failure

- Viral hepatitis**—B, D, E and A and other viruses can cause AHF. Over 70% of cases of AHF are caused by viral infections. Overall incidence of AHF in viral hepatitis is around 1%. Frequency of AHF in different types of viral hepatitis is given below:

HAV	0.35%. AHF is more common in the elderly and drug users. Prognosis is relatively better with survival over 60%.
HBV	1%.
HCV	By itself, it is rare to produce AHF. In combination with HBV, it predisposes to AHF.
HDV	In combination with HBV it increases the frequency and severity of AHF.
HEV	This is likely to cause AHF, especially in pregnant women

 Other viruses such as CMV, EBV and herpes viruses 1, 2 and 6 cause AHF especially in immunocompromised subjects.
- Drugs**—halothane, monoamine oxidase-inhibitors such as iproniazid and phenelzin, isoniazid.
- Poisoning**—paracetamol, mushrooms, weedicides, copper sulfate, alcohol, organic solvents.
- Shock**—surgical shock or gram-negative toxic shock.
- Occlusion of major hepatic veins** (Budd-Chiari syndrome)
- Acute fulminant biliary tract infection with obstruction.
- Other Causes**
 - Disseminated malignant deposits obstructing sinusoidal blood flow, e.g., Cancer of stomach and breast, oat cell tumour of lung, myeloblastic leukemia, and carcinoids.
 - Miscellaneous causes: Acute veno-occlusive disease, bone marrow transplantation, Wilson's disease, acute fatty liver of pregnancy.

Clinical Features

Neurological manifestations predominate in this disorder. They are much more varied than in chronic hepatic failure. Flapping tremors, headache, change of personality and behavior, delirium, decerebrate rigidity, convulsions, abnormalities of ocular movements and coma occur in varying combinations. Finally the majority of cases go into coma. For clinical purposes the coma is graded from I to V.

Grading of Coma (Sherlock S)

Grades

I	Confused, altered mood or behaviour, psychometric defects
II	Drowsy, inappropriate behaviour
III	Stuporous, but able to speak and obey simple commands, inarticulate speech, marked confusion
IV	Coma
V	Deep coma and no response to painful stimuli

The light reflex and the plantar response are unaffected till late in the disease.

The patient is often jaundiced. Brainstem function is impaired and this manifests as irregularity of respiration, **515**

circulatory disturbances and hypotension. Generalized bleeding tendency occurs in most cases. This manifests as bleeding from the mucous membranes, gastrointestinal tract, skin and injection sites. Prothrombin time is prolonged. Factors II, V, VIII, IX, and X are reduced. Thrombocytopenia may develop in some. Other complications include pancreatitis, shock and circulatory failure.

Renal symptoms: Oliguric renal failure occurs as a result of hepatorenal syndrome in upto 50% cases.

Other general symptoms: Due to the increasing intracranial pressure there is reflex hypertension and bradycardia (Cushing's reflex). Hypoglycemia is a common accompaniment. Superadded infections develop if the coma persists for a few days or more.

Depending on the duration, AHF can be subdivided into hyperacute, acute and subacute (Table 85.1).

TABLE 85.1

Clinical feature	Hyperacute AHF	Acute AHF	Subacute AHF
Encephalopathy	+	+	+
Duration of acute disease	0-7 days	8-28 days	29-72 days
Cerebral edema	Common	Common	Infrequent
Prolongation of prothrombin time	+++	++	+
Rise in serum bilirubin	++	+±	+
Prognosis for recovery with treatment	moderate	poor	poor

Biochemical changes: Urine may show bile pigments, increased urobilinogen and amino acid crystals such as leucine and tyrosine.

The blood sugar is lowered. Serum bilirubin is increased. Serum albumin may be lowered as the disease progresses. Elevation of aspartate and alanine transaminases occurs in the early phase. As hepatic necrosis advances, the levels of these enzymes may even fall. Prothrombin time is prolonged. Blood ammonia level may be raised.

Complications

These include cerebral edema, renal failure, bacterial infections, circulatory failure, hemorrhage and hypoglycemia.

Course and Prognosis

If the coma is of grade IV or V, mortality is 75-80%. The prognosis is worse in females, older subjects and those with longer duration of coma. In those that recover, cirrhosis liver does not usually develop. It is essential to

TABLE 85.2

Adverse prognostic factors in AHF

Prothrombin time exceeding 100 secs, irrespective of the grade of encephalopathy or any three of the following:

1. Age below 10 and above 40 years.
2. AHF caused by non-A non-B hepatitis, halothane or allergic drug reactions.
3. Duration of jaundice before onset of encephalopathy, more than 7 days.
4. Prothrombin time over 50 secs and
5. Serum bilirubin level over 17.5 mg/dL.

Death is usually due to shock, respiratory failure, bleeding, renal failure, cerebral edema or infection.

assess the prognosis early in the disease, in order to decide the need for liver transplantation (Table 85.2).

MANAGEMENT

1. The precipitating causes should be looked for and eliminated. Proteins are totally withdrawn from the diet. Neomycin, lactulose, magnesium sulfate and bowel washes should be started.
2. The patient should be nursed as a case in deep coma. Nutrition is supplied parenterally. Continuous infusion of 10% glucose or intermittent administration of 50% glucose is necessary to prevent hypoglycemia. Sedation must be avoided, if possible. If the patient becomes restless, a sedative antihistaminic like diphenhydramine or buclizine may be used. Barbitone sodium has to be given parenterally if a patient becomes violent and unmanageable. Measures to avoid rise in intracranial tension include artificial hyperventilation, infusion of intravenous mannitol 0.5 g/kg bw as a 20% solution within 10-15 minutes, hemodialysis and hemoperfusion.
3. Infection has to be diagnosed early and treated with broad spectrum antibiotics like third generation cephalosporins such as cephalexime, ceftriaxone, ceftazidime and others.
4. **Electrolytes:** Generally serum sodium and potassium are low. Hyponatremia may become severe as a preterminal phenomenon. Excess sodium should not be supplemented unless there is evidence of sodium loss, but potassium should be supplemented orally or parenterally. Serum calcium tends to be low and this is attributable to coexistent hypoalbuminemia and pancreatitis. Intravenous calcium gluconate (10%) is administered to make up the serum calcium levels to normal.
5. Renal failure may require dialysis.
6. Bleeding due to vitamin K deficiency may be allayed by the intramuscular administration of vitamin K 10 mg daily, but if the bleeding is due to hepatic functional impairment vitamin K is not beneficial. Such cases have a poor outcome. Fresh blood, coagulation factor concentrates or fresh plasma may be required at times.

7. The principles employed in the management of chronic hepatic failure have to be followed as the condition improves and the patient's chances of survival become brighter.

Artificial Liver Support

The principle is similar to hemodialysis in renal failure. The aim is to maintain or support liver function artificially till the patient's liver recovers or a donor liver is available for transplantation. The most effective bioartificial liver (BAL) model is based on the principle that viable hepatocytes are maintained in a chamber through which blood is passed through permeable artificial capillaries (to favour exchange of plasma components). Several of such extracorporeal devices are under trial with encouraging results.

Charcoal hemoperfusion (charcoal removes water soluble toxic metabolites) and Rhone-Poulenc hemodialysis system using special polyacrylonitrile membrane which removes middle molecules up to a molecular weight of 5000 KD.

Hepatocyte Transplantation

This is another procedure under trial with favourable results. Unlike liver transplantation, donor hepatocytes can be obtained more readily and the procedure is technically easier.

In experienced hands and advanced centres all these have shown temporary benefit but none has been accepted universally. At present these are of value in tiding over a crisis in a patient with reversible hepatic disease and also for the preoperative preparation before hepatic transplantation. *Hepatic transplantation* should be considered as an emergency procedure if a donor organ and facilities for surgery are available.

Prognostication in cirrhosis liver which helps to determine the priority for liver transplantation.

Conventionally Child Pugh Turcotte classification is used where 1-3 scores are given to five parameters-serum bilirubin, serum albumin, ascites, encephalopathy and

prothrombin time. A score of 5 and 6 is classified as child's A, 7,8 and 9 as child's B and 10 or more as child C. The prognosis for survival worsens as the class moves from A to C. It has the disadvantage of lack of proper discrimination in later stages of liver disease for which another scoring system has been recently introduced. The modified end stage liver disease, (MELD) score is based on serum bilirubin, prothrombin time (INR) and serum creatinine for which different weightages are given. The system is currently under validation.

In the case of hepatic cancer, additional points are given to facilitate early transplantation. Over the previous decade liver transplantation is being done in India with successful results. Upto the end of 2003, 37 liver transplants were done; in Delhi, Chennai, Vellore, Hyderabad and Bangalore. At present this surgery is being done with greater success. Liver transplantation can be done with liver obtained from cadavers or living donors. In the latter case part of the donor's liver from the right lobe is removed for transplantation. Postoperatively the donor's liver re-grows and makes up the volume of the organ.

Major Indications for Liver Transplantation

1. End stage liver disease
2. Acute fulminant liver failure
3. Hepatocellular carcinoma
4. Large benign tumours such as hemangioma
5. Biliary cirrhosis with intractable pruritus, and
6. Metabolic disorders

HLA haplotyping and detailed immunological testing are not required. Blood group compatibility and physical factors such as size of the transplant are of importance in cross matching. Post transplantation immunosuppressant regimen consists of tacrolimus, cyclosporine, azathioprine or mycophenolate mofetil with or without corticosteroids. Operative mortality is around 5% and one year survival exceeds 80% in most centers. In the presence of renal failure concomitant renal transplantation is also needed. The long term survival depends also upon the primary condition for which transplantation was done.

Portal Hypertension

K.R. Vinaya Kumar, K.V. Krishna Das

Chapter Summary

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 Noncirrhotic Portal Fibrosis 522

General Considerations

9

The superior mesenteric and splenic veins join to form the portal vein which divides initially into the left and right branches and thereafter, in a dichotomous fashion. The portal blood is drained into the hepatic sinusoids. Major branches of the portal vein do not have valves. The abdominal parts of the alimentary tract, spleen, pancreas, and gallbladder drain into the portal system. The portal venous flow is 1000-1200 mL of blood/minute. In the normal liver the whole of the portal blood passes through the sinusoids and is drained by the hepatic veins into the inferior vena cava. When onward flow of blood is obstructed, portal vein radicles develop extensive collaterals with systemic veins so that even more than 80% of its blood can be drained into the systemic circulation without passing through the liver. Normal pressure in the portal vein is 7 mm Hg. Portal hypertension results from obstruction to onward flow of portal blood. The term “portal hypertension” is applied when the portal venous pressure exceeds 12 mm Hg.

Classification

Portal hypertension can be classified in different ways. Depending on the site of obstruction in relation to the hepatic sinusoids, it may be divided into two types—*presinusoidal* and *postsinusoidal*.

Presinusoidal Extrahepatic: Portal venous obstruction due to any cause or splenic vein occlusion. Intrahepatic: All types of cirrhosis, noncirrhotic portal fibrosis, schistosomiasis, myelofibrosis.

Postsinusoidal Major hepatic vein obstruction (Budd-Chiari syndrome).

Obstruction to small radicles of hepatic vein—veno-occlusive disease.

Generalized rise in inferior vena caval pressure, e.g. right-sided heart failure, constrictive pericarditis and pericardial effusion.

The two most common causes of portal hypertension are mechanical obstruction to venous outflow in the liver by nodules developing in hepatic cirrhosis and extrahepatic occlusion of the portal vein. In many cases portal hypertension remains silent till complications become visible. The portal blood normally carries oxygen and hepatotrophic factors into the liver. When portal blood is shunted away, the liver depends more and more on hepatic arterial blood for oxygen supply and it undergoes functional impairment and atrophy. Bacteremias develop since the portal blood passes into the systemic circulation without being filtered by the hepatic macrophage barrier. Entry of the products of digestion directly into the systemic circulation without being metabolized by the liver hastens the onset of portal systemic encephalopathy.

Rise in portal pressure tends to favour ascites when other factors like hypoproteinemia and sodium retention also develop.

PORTAL HYPERTENSION IN CIRRHOSIS

In cirrhosis the development of portal hypertension is the result of different complex mechanisms. The regenerating nodules of cirrhosis distort, obstruct and reduce the vascular bed. Obstruction occurs at all levels from the portal zones through the sinusoids to the hepatic venous outflow. The regenerating nodules derive their nourishment from the hepatic artery since they have no portal blood supply. Direct communications between the hepatic artery and portal radicles develop in cirrhosis and these serve to transmit arterial pressure to the portal venous system.

Clinical Features

Signs of portal hypertension include asymptomatic splenomegaly, gradual development of portal systemic



Fig. 86.1: Portal hypertension—barium swallow X-ray showing esophageal varices. Note the longitudinal filling defects caused by the dilated veins

collateral veins and bouts of hematemesis or melena. In some cases chronic blood loss due to oozing of blood leads to iron deficiency anemia.

The Common Sites for Portal-systemic Collaterals

- In the lower end of esophagus and gastric fundus, left gastric and short gastric veins communicate with esophageal veins. These form esophageal and gastric varices and are responsible for fatal hematemesis.
- The veins of the abdominal wall become prominent and they radiate from the umbilicus. Rarely they may form a “*caput medusae*” around the umbilicus. The direction of blood flow is the same as in the normal veins of the abdominal wall, but the flow is considerably increased. Blood from the portal vein is brought to the abdominal wall through the paraumbilical veins and other veins in the falciform ligament and these are drained by the abdominal veins (see Fig. 84.3 on pp 506).
- Communication between the inferior mesenteric veins and the hemorrhoidal veins results in the formation of varices in the rectum. These varices are distinct from hemorrhoids. The former may regress when the portal hypertension is relieved.
- Hepatic veins communicate with diaphragmatic veins, veins in the leinorenal ligament and omentum, and venous collaterals developing in the scars of previous laparotomies.
- Portal blood may be drained to the left renal vein from the splenic vein directly or through collaterals in the diaphragm, pancreas, stomach, or left adrenal. This blood passes mainly into the superior vena cava through the azygos and hemiazygos systems. A small

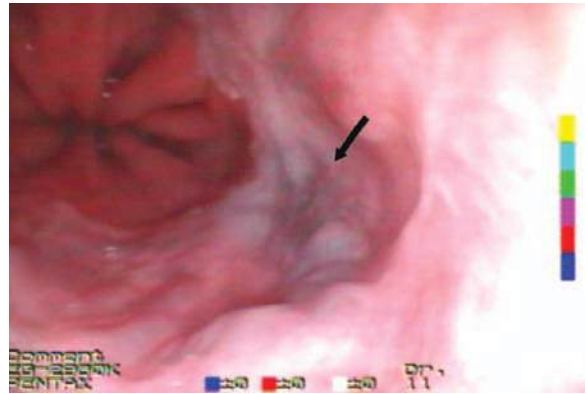


Fig. 86.2: Esophageal varix endoscopic view. Note: dilated veins in the esophagus (arrow)

quantity of blood enters the inferior vena cava and even into the pulmonary veins.

In addition to the classic sites, other venous collaterals may also develop in extrahepatic portal obstruction.

The severity of portal hypertension and its cause have to be determined by investigations.

The portal pressure can be measured by the following methods:

- Intrasplenic pressure* can be directly measured by a needle introduced percutaneously or during surgery into the spleen.
- By *umbilical vein catheterization*.
- By *transhepatic portal vein puncture*.
- Wegged hepatic venous pressure* can be measured by a catheter introduced through a hepatic venous radicle until it gets arrested. This pressure represents the sinusoidal venous pressure. Normal wedged hepatic pressure is 5-6 mm Hg which may go up to 20 mm Hg in portal hypertension.

The portal systemic blood flow can be estimated by radio-isotopic methods.

Demonstration of the Collaterals

- Esophageal varices:** These stand out prominently in a properly made barium swallow picture. These can be seen directly by endoscopy. Rectal varices can be visualized by proctoscopy (Figs 86.1 and 86.2).
- Percutaneous trans-splenic portal venography:** Radio-opaque dye is injected into the splenic pulp. This visualizes splenic and portal veins and their collaterals. The dye can be traced up by proper timing of the pictures. Deep jaundice and prolongation of the prothrombin time are contraindications for this procedure since the risk of bleeding is high.
- Scinti-photo splenoportography:** This is an isotopic method by which serial scans are made using a gamma camera after injection of ^{133}Xe (Xenon) or $^{99\text{m}}\text{TcO}_4$ (technetium) into the spleen. The venous flow pattern can be traced.

4. **Selective visceral angiography:** The celiac axis is catheterized and dye injected. The contrast material flowing into the splenic artery returns through the portal vein which is visualized. Similarly superior mesenteric artery can be catheterized.
5. **Selective venous catheterization:** Umbilical vein catheterization and injection of contrast material visualizes the portal venous system.
6. **Transhepatic portography:** The portal vein is visualized by injecting dye through a cannula introduced through the liver.
7. **Ultrasound study, Doppler and CT scan:** These are elegant methods which delineate the portal vein and its major branches. Dilatation, occlusion and deformity can be made out but the results are poorer in comparison to direct visualization by phlebography. In the ordinary case all these advanced procedures are not necessary for diagnosis, but proper evaluation is essential when surgery is contemplated.

BLEEDING ESOPHAGEAL VARICES

Causes which precipitate bleeding are not clearly known but in some cases ingestion of aspirin or similar drugs and upper respiratory infections are responsible. The bleeding may be dramatic and fatal if left untreated, or more often, it may be a continuous ooze. This is followed by ascites, hepatic coma, and hepatocellular failure. Immediate effects of blood loss are shock and rapid deterioration of liver function. Reduction in hepatic arterial flow results in necrosis of liver cells which depend upon the hepatic arterial supply. Blood in the gastrointestinal tract acts as a source of toxic nitrogenous products and this precipitates hepatic coma. The common site for rupture of the varices is within 7 cm of the lower end of the esophagus. Rupture is mostly caused by rise in the intravariceal pressure and disruption of the venous walls. Even in patients with esophageal varices, in about a third, bleeding may be from other sites such as peptic ulcers, gastric erosions and esophageal tears (**Mallory-Weiss syndrome**). These have to be identified in order to institute effective therapy.

Portal hypertensive gastropathy: This is a change brought about in the gastric mucosa as a result of ectasia of submucous capillaries and veins, without any inflammatory change. Relief of portal hypertension leads to regression of this condition as well (Fig. 86.3).

Management of Variceal Bleeding

Variceal bleeding is a medical emergency and carries a mortality of about 35%. It is best managed in the intensive care units of a tertiary level hospital. Oxygen inhalation through an airway is started. The patient should be given first aid as for any major upper gastrointestinal bleed in order to stabilize his condition. This consists of IV



Fig. 86.3: Stomach bleeding portal gastropathy

fluids and fresh blood replacement, sedatives to allay anxiety and IV injection of H_2 receptor antagonist such as ranitidine 50 mg, or a proton pump inhibitor such as pantoprazole 40 mg, over a period of 2-5 minutes. Large doses of oral antacids such as aluminium hydroxide and magnesium trisilicate 1-2g initially and repeated hourly to reduce bleeding from co-existing ulcers, in the esophagus and stomach. The patient should be transported to a medical centre with facilities for specialized care, as soon as possible, preferably with the blood transfusion in place.

Principles of Management

1. To stabilize the patient's vital functions
2. To diagnose the site of bleeding
3. To arrest the bleeding
4. To prevent re-bleeding and
5. Secondary prevention

Stabilizing the Patient

The patient requires rapid intravenous fluids, blood transfusion and oxygen inhalation to stabilize the vital functions. CVP monitoring is essential. A moderate or severe bleed usually requires three units of fresh blood transfusion. Over-transfusion increases the risk of bleeding further. Systemic diseases such as diabetes, infections, electrolyte abnormalities and abnormalities of coagulation also require attention.

Identifying the Site of Bleeding

After stabilizing, the patient should be taken up for emergency esophagogastrosocopy. This is technically difficult during the emergency and should be done by a skilled endoscopist in a well equipped center with therapeutic facilities. The bleeding sites may be single, multiple or diffuse.

Arrest of Bleeding

Methods include

1. Pharmacotherapy
2. Balloon tamponade

3. Endoscopic interventions and
4. Surgery.

Pharmacotherapy

Somatostatin: It is given as an initial intravenous infusion for 3-5 days at the rate of 250 mcg/hr. It controls bleeding in 80-85% of patients and prevents the re-bleeding also.

Octreotide, which is the analogue of somatostatin is equally effective. The initial bolus dose is 50 mcg followed by continuous infusion at the rate of 50 mcg/hr. Vasopressin given in an IV bolus dose of 20 units over a period of 10-15 minutes at 4 hour intervals used to be the drug of choice prior to the use of somatostatin, which is more effective. Vasopressin also reduces portal pressure but troublesome side effects such as angina, bowel ischemia and gangrene of the toes may develop at times. **Terlipressin** (Triglycyl lysine vasopressin) is a vasopressin analogue which is more effective and has less of side effects.

Vapreotide and **lanreotide** are newer analogues of somatostatin which have also been introduced. The dose is 250 µg as bolus followed by 250 µg hourly as continuous infusion for upto five days.

Balloon Tamponade

Sengstaken Blackmore or Linton Nechlon tube may be useful for temporary tamponade while the patient is being transported to a higher centre. It is not as effective as somatostatin or endoscopic interventions. It is not used unless there are exceptional circumstances.

Endoscopic Interventions

Endoscopic sclerotherapy (EST) can arrest 85 to 90% of active bleeding. The common sclerosants used for esophageal varices are sodium tetradecyl sulfate (STD), polydocenol and alcohol. The gastric varices require cyanoacrylate for injection. Endoscopic variceal ligation (EVL) is a better procedure than EST to prevent variceal bleeding (Figs 86.4 and 86.5).

In this procedure the varices are sucked into a hood attached to the distal end of the endoscope and a rubber band applied at its base. Transjugular intrahepatic portal systemic shunt is a catheter intervention procedure that may be undertaken to reduce portal venous pressure as an emergency measure.

Surgery

The emergency surgical procedures to stop variceal bleeding carry high mortality. The same result can be achieved with endoscopic procedures. Hence the role of surgery is limited.

Long-term Prophylaxis

Large varices and varices which have bleed previously require obliteration with EVL or EST. Drug therapy can lower portal pressure on a long-term basis. The drugs useful for prophylaxis are nonselective beta-blockers such

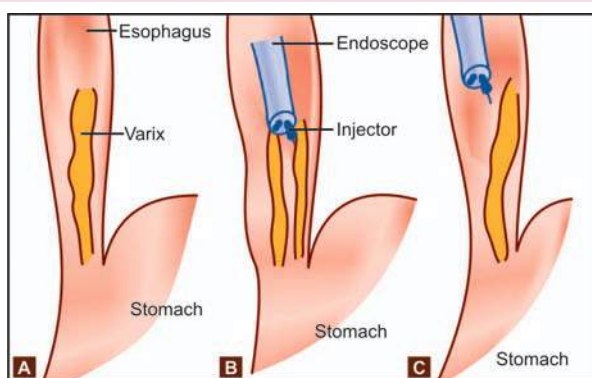


Fig. 86.4: Technique of sclerotherapy for esophageal varices A—Esophageal varix, B—Intra-variceal injection, C—Para-variceal injection

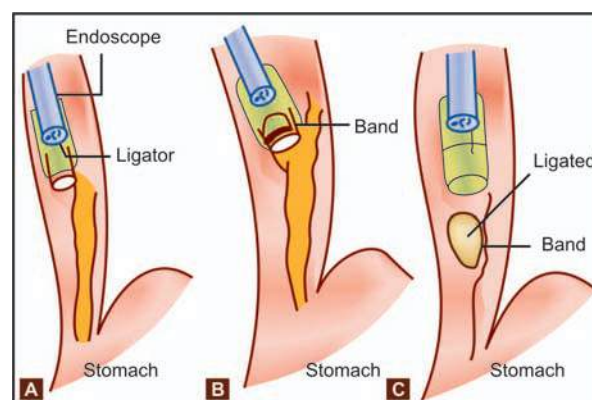


Fig. 86.5: Technique of variceal ligation of esophageal varices. B—varix sucked into the housing cylinder

as propranolol 80 to 160 mg/oral daily or nadolol 80 mg oral daily and long acting nitrates such as isosorbide mononitrate 20-40 mg/day. Portacaval shunt surgery may be useful in selected cases of extrahepatic portal hypertension and noncirrhotic portal fibrosis. This surgery is not done as a first line procedure at present.

Indications for Portacaval Anastomosis

1. At least one episode of severe hemorrhage in subjects in whom esophageal varices have been demonstrated endoscopically and portal hypertension, recorded.
2. Preferably below 40 years of age, since survival rates are lower in cases above 50 years.
3. Adequate hepatocellular function indicated by serum bilirubin below 2.5 mg/dL, serum albumin above 3 g/ dL, and absence of established ascites and even transient encephalopathy.
4. Presence of stable and nonprogressive hepatic lesion.

In ideal cases over 50% survive in reasonable health at the end of 5 years. Relative contraindications include moderate or advanced hepatic failure and congenital or other acquired abnormalities of the portal vein. Portacaval shunting should not be undertaken if future liver transplantation is to be undertaken.

Long-term complications of portacaval anastomosis include deterioration of hepatic function, portal systemic encephalopathy, occlusion of the shunt, shunt myelopathy (paraplegia due to demyelination of the pyramidal tracts), chronic extrapyramidal and cerebellar syndromes and hemosiderosis.

Porto-pulmonic Syndrome

Significant pulmonary hypertension is seen in about 4-6% of cirrhosis patients with portal hypertension. Pulmonic vasculature shows medial hypertrophy, endothelial hyperplasia and luminal thrombosis. The changes may be due to the vasoconstrictors escaping hepatic metabolism in cirrhosis with porta-systemic anastomosis. Thromboembolism from the dilated and tortuous paraesophageal and mediastinal varices to the pulmonic vascular bed may be another mechanism.

Development of PPS seriously shortens the life span in cirrhosis patients. There is no effective treatment. Epoprostanol (prostacyclin) and nitric oxide inhalations show some clinical benefit. Portosystemic shunts are also tried. Severe PPS is a contraindication for liver transplantation.

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Portal hypertensive enteropathy is a recently identified manifestation of portal hypertensive intestinal vasculopathy. Endoscopic findings include bleeding vascular ectasias, ulceration and small bowel varices. The stomach, small intestine and colon can be affected (Fig. 86.6). Cirrhosis liver is the most frequent cause and the lesion is mainly related to the level of portal hypertension. The patients present with continuous gastrointestinal blood loss, requiring repeated blood transfusions. Wireless capsule endoscopy is the investigative modality of choice to detect the bleeding lesions all along the GI tract. Treatment consists of trans jugular intrahepatic porto-systemic shunting which promptly reduces the portal hypertension and arrests the bleeding (Fig. 86.7).

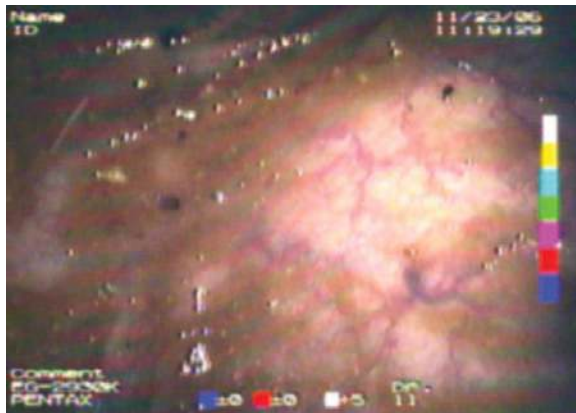


Fig. 86.6: Portal colopathy. Note: The dilated submucosal blood vessels. These may bleed colonoscopy

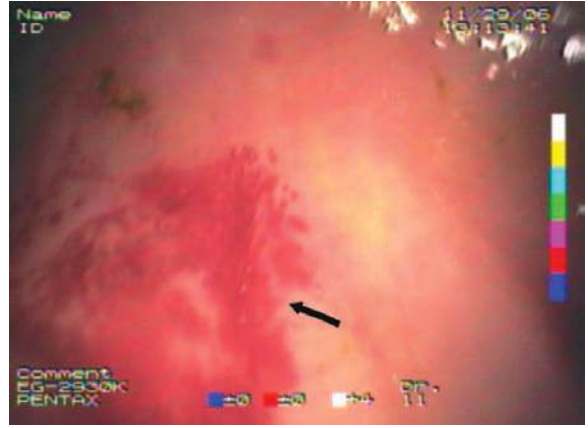


Fig. 86.7: Portal colopathy colonoscopy. Note: Active bleeding (arrow)

Extrahepatic Portal Hypertension (EHPH)

Extrahepatic portal hypertension is caused by portal or splenic vein thrombosis. This is a common cause of portal hypertension in India. The liver is normal. The disease starts in childhood and present for the first time between 11-25 years but sometimes symptoms may manifest even as early as 3 to 4 years.

Etiology

1. Portal vein thrombosis secondary to neonatal umbilical sepsis.
 2. Intra-abdominal infections like acute appendicitis and peritonitis.
 3. Abdominal trauma.
 4. Malignant tumours of the pancreas, stomach, colon or periportal lymph nodes.
 5. Acute pancreatitis and pancreatic cysts.
 6. Hematological disorders like polycythemia, thrombocythemia and thrombophilic conditions such as deficiency of protein C and S and antithrombin may be present in a third of these cases.
 7. Congenital anomalies of the portal veins.
 8. Vascular lesions such as arteriovenous fistulae in the spleen or hepatic artery-portal vein fistula in the liver.
- Hematemesis is the presenting symptom in the majority.

Management: It consists of emergency medical treatment of variceal bleeding followed by appropriate shunt surgery depending on the availability of suitable veins. Since the liver function is good, long-term prognosis is bright.

Noncirrhotic Portal Fibrosis

Syn: Idiopathic portal hypertension

This disorder is frequently seen in India and the neighbouring countries. It is characterized by gross splenomegaly and portal hypertension with patent extrahepatic

portal veins. Hepatic function is normal. Histological and clinical features do not suggest cirrhosis. Liver biopsy may be normal or varying degrees of portal fibrosis and cellular infiltration may occur. Studies from Punjab suggest chronic arsenic intoxication as a probable cause.

The condition is most common in the third and fourth decades. Many patients complain of several attacks of

hematemesis which are better tolerated by these patients than those with hepatic cirrhosis. Ascites and jaundice are uncommon.

Management: Since this condition may present with severe hematemesis, the treatment is that of bleeding esophageal varices.

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Other Hepatic Disorders

K.R. Vinaya Kumar, K.V. Krishna Das

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HEPATORENAL SYNDROME

Syn: Syndrome of functional failure

Definition

Hepatorenal syndrome (HRS) is defined as functional renal failure occurring in the setting of advanced liver disease but in the absence of intrinsic renal disease. The HRS is characterized by intense constriction of renal cortical vasculature with resultant diversion of blood flow from the renal cortex. As a result GFR comes down, plasma renin level increases, urine output decreases and sodium is avidly reabsorbed in the distal nephron. Histologically, the kidneys are normal. Such kidneys can perform normally when transplanted into subjects without portal hypertension. In the same individual correction of

portal hypertension and liver failure by transplantation restores renal function too.

Functional renal failure occurs in 18% of decompensated cirrhosis and portal hypertension within 1 year. The three most important risk factors of HRS are low sodium concentration, high plasma renin activity and absence of hepatomegaly. Other risk factors include ascites, poor nutritional status, and esophageal varices.

Pathogenesis

HRS is characterized by sodium retention, water retention, and renal vasoconstriction. It is associated with decrease in renal blood flow, glomerular filtration rate and urine output. These lead to azotemia. However the pathophysiological mechanisms are not fully defined, though several propositions are made.

Diagnostic criteria

HRS should be suspected in any patient with acute or chronic liver disease and portal hypertension, when there is a rise in serum creatinine to above 1.5 mg/dL. The criteria are divided into major criteria, which must be present in all patients for diagnosis, and minor criteria, which provide support for diagnosis.

Major criteria:

1. Chronic or acute liver disease with advanced hepatic failure and portal hypertension.
2. Low glomerular filtration rate, with creatinine clearance < 40 mL/min and blood serum creatinine > 1.5mg/dL
3. No history of treatment with nephrotoxic drugs, shock, infection, or significant recent fluid losses.

4. Absence of sustained improvement in renal function following diuretic withdrawal and volume expansion with 1.5 L isotonic saline.
5. Proteinuria < 500 mg/dL, and absence of ultrasonographic evidence of urinary obstruction or parenchymal renal disease.

Minor criteria:

1. Urine volume < 500 mL/day
2. Urine sodium < 10 mmol/L
3. Urine osmolality greater than plasma osmolality.
4. Urine red blood cells < 50 per high power field.
5. Serum sodium concentration < 130 mmol/L.

Clinical Types

HRS is divided into 2 types. *Type 1 HRS* is rapid in onset and rapid and progressive in course. Impairment of renal function, defined as a doubling of the initial serum creatinine to a level higher than 2.5 mg/dL, or a 50% reduction of the initial 24-hour creatinine clearance to a level lower than 20 mL/min occurs in less than 2 weeks. Patients with type 1 HRS are usually very sick, with signs of advanced liver failure.

Type 2 HRS is defined as the impairment in renal function evidenced by S creatinine level more than 1.5 mg/dL, which does not meet the criteria for type 1 HRS. Commonly it manifests as refractory ascites.

Untreated, the median survival time for patients with type 1 HRS is less than 2 weeks.

Management of HRS

Currently liver transplantation remains the definitive treatment of choice for hepatorenal syndrome. According to the *Model of End stage Liver Disease scoring system*, (MELD) which is a new scoring system which sets priorities for liver transplantation, patients with impaired renal function get priority for transplantation. Other measures can only be used as a bridge to transplantation.

Hemodialysis is frequently used to control azotemia and maintain electrolyte balance before liver transplantation. Continuous veno-venous hemofiltration causes less hypotension but requires the continuous services of a dialysis nurse. Usefulness of combination of various vasoconstrictors such as octreotide and midodine, epinephrine, terlipressin and albumin is under current investigation. Transjugular intrahepatic portal systemic shunt (TIPS) may also be beneficial and life saving during the waiting period before transplantation.

Alcoholic Liver Disease

Alcohol-related liver injury is common in places where alcohol consumption is high. Severe forms of injury usually occur when the intake is above 150 g ethanol per day for a few years. The three recognizable syndromes are *fatty liver*, *alcoholic hepatitis* and *Laennec's cirrhosis*.

Alcoholic fatty liver is the most benign one. Infiltration of the liver with triglyceride is extremely common in men consuming alcohol regularly. The most frequent physical finding in such patients is hepatomegaly without any evidence of cirrhosis. Abstinence from alcohol at this stage leads to rapid regression within weeks.

Alcoholic Hepatitis

Approximately 25% of chronic alcoholics develop histological evidence of alcoholic hepatitis. This is characterized by hepatocellular necrosis affecting mainly the centrilobular zone. Remaining hepatocytes are often distorted and enlarged. In addition, inflammatory exudate consisting of polymorphs and perisinusoidal and perivenular fibrosis is usually present. Cytoplasmic inclusions known as alcoholic hyaline or *Mallory bodies* are seen. These changes may occur alone, but are usually accompanied by significant fatty infiltration and often by cirrhosis.

Clinically, alcoholic hepatitis tends to be more serious than fatty liver, although a few are asymptomatic. Anorexia, nausea, upper abdominal pain, weakness, vomiting, fever, jaundice, and diarrhea may occur in various combinations. The pain may be in the right upper quadrant and closely resembles cholecystitis.

Biochemical abnormalities include elevation of transaminases, hyperbilirubinemia, hypoalbuminemia, and prolongation of prothrombin time. The ratio of SGOT/SGPT is usually >2/1 in alcoholic liver disease. Ratios >3/1 is more suggestive and significant. Alkaline phosphatase is elevated in approximately 30% of such patients. Neutrophil leukocytosis is common (12000-20000 cmm).

These are non-specific changes, but in an alcoholic, these strongly suggest hepatitis. The diagnosis can be confirmed only by liver biopsy. It is to be remembered that the entire histological picture of alcoholic hepatitis may appear in conditions other than alcoholism, such as obesity, diabetes, short bowel syndrome, Indian childhood cirrhosis, and drug toxicity. The outcome in patients with alcoholic hepatitis is not nearly as benign as in those with alcoholic fatty liver alone. The reported overall acute mortality is 15-20% and approximately 50% cases develop alcoholic (Laennec's) cirrhosis.

Management: There is no specific therapy. Abstinence from alcohol is essential. Nutritional support, corticosteroids, propylthiouracil, glucagon, insulin, intravenous amino acids, pentoxifylline and colchicine have been tried with inconclusive results. Some of these agents seem promising but none has yet been established as an effective therapy.

Course: The healing of alcoholic hepatitis in survivors is slow, despite good nutrition, rest, and abstinence from alcohol. Most patients show activity of the disease even

after 3 to 4 months. The final phase of alcoholic liver disease is alcoholic cirrhosis. Alcoholic cirrhosis is described in Chapter 84 pp 508.

Chronic Hepatitis

Definition

It is defined as chronic inflammatory activity in the liver continuing without improvement for more than six months. In asymptomatic patients estimation of the duration may be difficult. Features such as spider angioma, firm irregular hepatomegaly and splenomegaly suggest a chronic process. Fibrosis seen in liver biopsy also would suggest chronicity. The terms chronic persistent hepatitis and chronic active hepatitis are replaced by the term 'chronic hepatitis' at present.

Etiology

1. Hepatitis B and C are the most common
2. HDV +ve in 5-10% of HBV + cases
3. Autoimmune hepatitis
4. Wilson's disease
5. Drug toxicity—several drugs
6. Chronic alcoholic hepatitis
7. A third of the cases are idiopathic, since no causative factor can be identified. They form a heterogenous group.

Natural History

It depends on various factors such as the degree of necro-inflammatory activity, stage of the disease, etiology and the host response to treatment. Most of patients are asymptomatic and progress towards cirrhosis liver. The risk of hepatocellular carcinoma (HCC) is increased in HBV and HCV related chronic hepatitis. Some patients with high inflammatory activity present with jaundice and even liver failure.

CHRONIC HBV HEPATITIS

Clinical Features

Most of the patients are asymptomatic and present with elevation of aspartate transaminase (AST) and alanine transaminase (ALT) or viral markers detected during routine check-up especially during blood donation. Sometimes asymptomatic hepatomegaly is detected clinically or on ultrasonography for some other purposes. Rarely they may present with acute hepatitis and the jaundice fails to clear within six months. In some cases the presentation is with acute onset of jaundice, but symptoms persist and the ALT and AST may remain high. Liver biopsy may reveal chronic hepatitis.

Pathogenesis

After an acute attack of hepatitis B more than 95% of adults clear the virus completely. If the host immune response is inadequate, the virus tends to persist. Causes of poor immune defence response include (i) poor expression of HLA class I antigens on the hepatocyte membrane, (ii) increased suppressor T-cell function (iii) defective cytotoxic (K) lymphocyte function and (iv) presence of blocking antibodies on the liver cell membrane.

Pathology

The entire disease activity spectrum caused by HBV has to be labeled as 'chronic hepatitis B infection' and further classification should be based on histology. Necroinflammatory activity and fibrosis form the basis of histological classification.

Modified Knodell's classification scores the necro-inflammatory activity which is the histologic activity index scored on a scale 0 to 18 and this forms the basis of Knodell's classification. Presence of fibrosis is scored on a scale of 0 to 4 and this forms the basis of grading (see box).

Diagnosis

The viral etiology is established by viral markers—HBsAg, HBeAg, HBcAg and their antibodies. HBV virus can exist in the liver in a replicating stage or integrated stage. In the replicating stage, the virus multiplies actively. It is present in blood and the disease can spread. The Histologic Activity Index is high and the patients require antiviral treatment.

<i>Knodell's Histologic Activity Index (HAI)</i>		
Component		Score
Periportal necrosis with or without bridging necrosis		0-10
Intralobular necrosis		0-4
Portal Inflammation		0-4
<i>Staging (Fibrosis)</i>		
		Score
Fibrosis	none	0
Portal expansion	+	1
Portal to portal tract fibrosis	+	2
Bridging fibrosis	+	3
Cirrhosis	+	4

The viral genome integrates with host hepatocyte DNA and there is no independent viral replication or viremia in the integrated phase. Hepatic necrosis is minimal at this stage and the benefit of antiviral treatment is probably only slight.

Clinical feature	Replicating stage	Integrated stage
Infectivity	High	Low
HBsAg	Positive	Positive
HBeAg	Positive	Negative
Anti-HBe	Negative	Positive
HBV DNA	Positive	Negative

Treatment

Interferon alpha (IFN- α) is the preferred drug which is given in the dose of 5-10 million units thrice a week for 4-6 months. HBeAg clears and HBV DNA disappears in 40-60% of cases. IFN therapy should be closely supervised. It is costly (Rs. 1500/dose) and side effects are seen in up to 30% of cases. The common side effects are flu like syndrome myalgia, anorexia and alopecia. Bone marrow suppression, thyroiditis and depressive state with suicidal tendency may occur. A flare up of inflammatory activity is usually seen with conversion (i.e.) HBeAg +ve to Anti-HBe + ve status. Newer drugs such as lamivudine, adefovir and thymosin- α are also effective.

CHRONIC HEPATITIS C

60-90% hepatitis caused by HCV tend to become chronic. It is the most common cause of post-transfusion chronic hepatitis and cirrhosis. There is increased incidence of hepatocellular carcinoma.

CLINICAL FEATURES

Most of the patients are asymptomatic or have only mild symptoms like anorexia and fatigue. The ALT and AST levels are often elevated. Periods of normal transaminase levels are characteristic of HCV infection. They may also present with extrahepatic manifestations such as lichen planus, thyroiditis or membranous glomerulonephritis. Mixed cryoglobulinemia may develop and lead to symptoms see chapter 55.

The course of the illness is slower compared to chronic HBV infection. Cirrhosis liver and liver failure develop only after 10 years or more.

Diagnosis

Third generation anti-HCV test (ELIZA) is useful for screening. Radioimmunoassay (RIBA) is confirmatory. HCV-RNA can be detected by PCR and can be quantified. Tests are available for genotyping also. Genotyping is helpful in predicting treatment response. PCR test done in reliable laboratories only should be accepted since several factors vitiate the test results.

Liver biopsy helps to assess the activity and the results are expressed according to Metavir scoring system. Lymphoid aggregation, fatty changes and bile duct injury are features of HCV infection.

Treatment

For HCV also IFN- α is the mainstay of therapy. Pegylated interferon with ribavirin is the treatment of choice. Interferon is given in doses of 3 million units thrice weekly for six months. HCV-RNA disappears and transaminases return to normal in more than 50% of patients. Reappearance HCV-RNA occurs in half of the responders. Response rate, (i.e.) HCV-RNA negative and transaminases returning to normal levels after one year of therapy can be enhanced by increasing the dose of IFN and duration of therapy. Adjuvants such as ribavirin and ursodeoxycholic acid also enhance the response. In chronic liver disease there is a general tendency to accumulate iron in the liver. Increased hepatic iron content is associated with poorer outcome. In such cases phlebotomy and regular removal of blood improves the outcome if done along with IFN treatment.

Factors which predict a favourable therapeutic outcome in chronic HCV hepatitis	
Young age Females Non-obese Short duration of infection Hepatic iron content not raised	Non-alcoholics Low viral load Less fibrosis Elevated transaminases Virus genotype II or III

AUTOIMMUNE HEPATITIS

The definite diagnosis of autoimmune hepatitis requires not only periportal hepatitis, hypergammaglobulinemia and auto-antibodies, but also the absence of viral markers, chronic alcoholism, exposure to blood products, hepatotoxic drugs and biliary lesions. The serum gammaglobulin levels are usually more than twice the normal.

Pathogenesis

Hepatitis results from cell mediated cytotoxicity in an susceptible host. There is an aberrant display of class II HLA antigens on the hepatocyte surface which initiates cytotoxic response. The aberrant display may be due to viral infection or exposure to drugs or other environmental factors.

Classification

There are three types of autoimmune hepatitis based on immunoserological markers (Table 87.1).

Treatment

There is good response to steroids. Prednisolone is given initially in the dose of 30 mg which is tapered to 5-15 mg after about 4 weeks. The exact duration of treatment is not clear. Azathioprine can be given in cases where steroids cannot be tapered.

TABLE 87.1

Classification of autoimmune hepatitis			
Features	Type I	Type II	Type III
Diagnostic antibodies	Smooth muscles Antinuclear— actin	Liver/kidney microsome Type I P 450 II D 6	Soluble liver antigen Liver/pancreas
Age	Bimodal	Pediatric	Adults
Female %	78	89	90
Concurrent organ specific antibodies	4%	30%	No data
Gamma globulin elevation	+++	+	++
HLA	B8 DR3 DR4	B14 DR3 C4A-Q8	Uncertain
Steroid response	+++	++	+++
Progression to cirrhosis	45%	82%	75%

DRUG TOXICITY ON THE LIVER

Liver is one of the main organs concerned with drug metabolism. Most of the drugs are converted into more water soluble, inactive, and nontoxic compounds for elimination by the kidneys or through bile. The enzymes required for drug metabolism are present in the microsomes of the endoplasmic reticulum. The enzymatic reactions occur in two steps. The first step includes oxidation, reduction or hydrolysis. The second step reactions are conjugation and excretion. Some drugs are directly conjugated. Though majority of the metabolites are harmless, some are toxic, e.g. acetaminophen and INH. Some drugs induce enzymes which accelerate the metabolism of the same drug as well as others, e.g., barbiturates, alcohol, anesthetics, oral hypoglycemic drugs, anticonvulsants, griseofulvin, rifampicin, phenylbutazone, meprobamate and warfarin. Protein deficiency and pregnancy make the liver more vulnerable to toxic damage.

Drug injury to the liver is of two types: The injury is predictable and dose-dependent in one; the other type, which is due to idiosyncrasy to the drug, is unpredictable and independent of the dose. Hypersensitivity reaction is triggered off by the drug or its metabolites which act as complete antigens or haptens. The patterns of adverse reactions of the liver to drugs are limited. The general pattern of injury to the liver caused by some of the common drugs is listed in Table 87.2.

Peliosis hepatis is a rare ill-defined lesion, the cause of which is unknown. The liver appears mottled blue and the section shows numerous small blood filled lacunar spaces which may arise from sinusoids or portal or hepatic veins. Sometimes this may be a chance finding at autopsy in patients dying of tuberculosis (Table 87.2).

HEPATIC VENO-OCCLUSIVE DISEASE (VOD)

Though originally described from West Indies, it is reported from several parts of the world. In India small outbreaks have occurred in Punjab, Rajasthan, and Madhya Pradesh. Though the exact etiology is unknown, it is most likely caused by toxic phlebitis produced by *pyrrolizidine alkaloids* found in plants like *senecio*, *heliotropium* and *crotolaria*, consumed as local herbal remedies or accidentally in contaminated cereals. Pathological changes lead to occlusion and fibrosis of the central and sublobular veins. Cirrhosis may develop in the subacute and chronic forms.

The presentation may be acute, subacute or chronic. In children, it tends to be acute with sudden development of hepatomegaly and ascites. Hepatic failure develops in them and mortality is higher. Those who recover may pass into the subacute or chronic phase. In the subacute variety, ascites and hepatosplenomegaly tend to persist. The chronic form leads to cirrhosis of liver with portal hypertension.

Treatment

In the acute phase general nutritional support, maintenance of fluid and electrolyte balance, and symptomatic measures help in tiding over the crisis. There is no specific treatment (see also Section 4, Chapter 24).

BUDD-CHIARI SYNDROME

Budd-Chiari syndrome (BCS) is caused by thrombotic obstruction of the hepatic venous outflow, usually at the level of inferior vena cava or the major hepatic veins. Most of the cases are idiopathic. A membrane is seen in the IVC in some cases. This may be congenital or acquired.

TABLE 87.2

Liver injury caused by drugs	
Types of reactions	Causative drugs
1. Chronic hepatitis	Acetaminophen, tetracycline, acetylsalicylic acid, INH, alpha methyl dopa, sulfonamides, nitrofurans, phenylbutazone aspirin
2. Cholestasis	INH, methyltestosterone, chlorpromazine, thiouracil, para-aminosalicylic acid
3. Granuloma formation	Phenylbutazone, long-acting sulfonamides, allopurinol, dilantin, diazepam, (granulomatous hepatitis) chlorpropamide, hydralazine, halothane, methyl dopa, procainamide
4. Fulminant hepatitis	Acetaminophen, combination of INH and rifampicin
5. Hepatic vein thrombosis (Budd-Chiari syndrome)	Oral contraceptives
6. Peliosis hepatitis	Anabolic steroids, oral contraceptives
7. Acute intermittent porphyria	Barbiturates
8. Cholelithiasis	Clofibrate
9. Cirrhosis	Oral antidiabetic drugs, alcohol
10. Tumour formation	Oral contraceptives, anabolic steroids
Several types of hepatic tumours have been associated with drug administration	
a. Hepatocellular adenoma	Oral contraceptives, anabolic steroids
b. Focal nodular hyperplasia	Oral contraceptives
c. Hepatocellular carcinoma	Oral contraceptives, anabolic steroids, methotrexate, androgens
d. Angiosarcoma	Diethyl stilbesterol, vinyl chloride
e. Peliosis hepatitis	Azathioprine, corticosteroids, diethyl stilbesterol, fluoxymesterone, methyl testosterone, oxymetholone

In 75% of cases there is a pro-thrombotic state. Myeloproliferative diseases, especially polycythemia vera and essential thrombocythemia account for over 50% of cases. Thrombophilic states predispose to this syndrome (Table 87.3) (see also Chapter 160).

CLINICAL FEATURES

Budd-Chiari syndrome may present in three forms

1. **Acute form:** This constitutes 20%. The onset is acute with sudden onset presenting with occlusion of all the hepatic veins, characterized by abdominal pain, ascites and even fulminant hepatic failure.
2. **Subacute form** occurs in 40%. The onset is slow and the signs and symptoms persist for over 6 months. Ascites is mild. Hepatic necrosis is minimal due to the development of collateral circulation.
3. **Chronic form** This constitutes 40%. Duration exceeds 6 months. Cirrhosis may be associated. Compression to inferior vena cava by enlarged caudate lobe leads to BCS.

The hepatojugular reflux is abolished and this should raise the possibility of obstruction to hepatic veins.

Diagnosis

Budd-Chiari syndrome has to be distinguished from occlusion of the portal vein and inferior vena cava. In

portal vein thrombosis, ascites is rare and there is no tender hepatomegaly. Inferior vena caval occlusion leads to edema of lower limbs and distention of abdominal veins without ascites. Often hepatic veins and the inferior vena cava may both be occluded by the same process. Doppler studies, CT and MRI demonstrate the lesion. Direct venography using transjugular techniques can confirm the diagnosis. The transaminases may show moderate elevation upto 4-5 times the normal levels. Ascitic fluid

TABLE 87.3

Pro-thrombotic conditions pre-disposing to BCS
1. Factor V. Leyden mutation
2. Prothrombin mutation G20210A
3. Antiphospholipid antibody syndrome
4. Paroxysmal nocturnal hemoglobinuria
5. Deficiency of protein C,S and AT.111
6. Cancers such as hepatocellular carcinoma, adrenal and renal cancer, retroperitoneal sarcoma and thrombophlebitis migrans complicating distant neoplasms.
7. Oral contraceptives, Behcet's syndrome
8. Local conditions such as liver abscess and echinococcal cysts.
9. 20% seem to be idiopathic, but many of them prove to be occult myeloproliferative diseases, on follow-up.
Latent myeloproliferative diseases can be identified by demonstrating mutations in the Janus Kinase 2 (JK2) gene.

in BCS shows high serum/ascitic fluid albumin gradient with high ascitic fluid protein, often $< 2.5\text{g/dL}$.

Prognosis is generally poor and to a great extent it depends on the primary condition. Acute cases terminate in hepatic coma. Only a few patients survive more than a year. Survivors may develop portal hypertension later.

Treatment

This consists of removing local causes if any, fibrinolytics and long term anticoagulation. Stenting the hepatic veins and insertion of transjugular porto-systemic shunts (TPS) help to prevent further occlusion. In severe cases liver transplantation may be required.

LIVER DYSFUNCTION IN CIRCULATORY IMPAIRMENT

Acute circulatory failure: Hepatic cells are very susceptible to anoxia caused by cardiac failure or fall in hepatic artery perfusing pressure as in shock. These reflect as functional derangement. The left lobe is more affected than the right. Microscopically, central veins and central zones show congestion. These zones show hemorrhage, focal necrosis, hydropic changes, and polymorphonuclear infiltration. The reticulin network is usually preserved.

Chronic congestive heart failure: The liver is enlarged, congested, and dark purplish in colour with rounded edges. The central vein is dilated and congested and the sinusoids are distended. Liver cell necrosis occurs, but there is no marked cellular infiltration. The degenerating cells may show pigmentary disturbance. Fibrous bridges form between central veins, leaving the portal zones relatively unaffected. The ill effects of hypoxia and back pressure are felt maximally in the central zones. A complex micronodular cirrhotic picture develops (**cardiac cirrhosis**).

Jaundice may occur in chronic congestive heart failure, due to hepatic necrosis and release of bilirubin from multiple foci of infarction such as the lungs. Ascites may develop. The ascitic fluid is highly proteinaceous. Mild grades of hepatic dysfunction develop. Mild portal hypertension occurs in many. Though mild splenomegaly may occur, other features like esophageal varices are uncommon. Treatment of cardiac failure in long-standing cases partially reverses the functional derangement but the structural abnormalities persist.

PYOGENIC ABSCESS OF THE LIVER

Liver is a common site for pyemic abscesses. In gram-negative septicemia microscopic abscesses are common and tender hepatomegaly is a common event. However, liver may be the seat of focal collection of pus which may be more often multiple. Bacteria can reach the liver

through the portal vein, hepatic artery and bile ducts, or by direct extension from contiguous organs and through penetrating injuries. Secondary infection of an amebic abscess or hydatid cyst converts it into pyogenic abscesses.

The organismal flora is mixed, containing *E. coli*, *Staph. aureus*, *Str. fecalis*, *Pr. vulgaris*, *Pseudomonas*, *Bacteroides* and anaerobic streptococci. Continuous pain, high fever, chills, jaundice, toxemia, neutrophil leukocytosis, and tender hepatomegaly should draw attention to the possibility of pyemic abscess. Aspiration of the pus and microbiological examination confirm the diagnosis. Treatment consists of appropriate antibiotic therapy and supportive care. Needle aspiration and rarely surgical drainage is required. Surgical drainage of the pus is required if medical measures alone are inadequate. The source of infection should be removed to prevent recurrence.

Carcinoma of the Liver

PRIMARY CARCINOMA

Syn: Hepatoma

Primary carcinoma of the liver is a common neoplasm seen in India, South Africa, Malaysia and China. It is less common in Caucasians. Hepatocellular carcinomas form 75% of the primary tumours while cholangiocarcinomas form 20%.

Etiology

The etiological factors vary in different geographical regions. Carcinoma supervening on cirrhosis accounts for 20% of the total. The regenerating nodules in macronodular cirrhosis may become malignant. Hepatitis B and C and aflatoxins from *Aspergillus flavus*, alcoholism, hemochromatosis, and clonorchiasis predispose to carcinoma. In many cases the tumour arises *de novo*.

Though the majority are unicentric, some are multiple. The right lobe is more affected. The hepatocytes show hyperchromatic nuclei and mitotic figures with only scanty stroma. The tumour spreads throughout the liver, involves the peritoneal surface and spreads to the peritoneum. It spreads locally through the portal vein, inferior vena cava and bile ducts causing obstruction to these channels. Distant metastasis is rare. Nodes in the porta hepatis, mediastinum, and cervical chains may also be affected.

Clinical Features

In India younger subjects (second and third decades) suffer more, though any age group can be affected. Vertical transmission of hepatitis B from mother to offspring and development of B hepatitis early in life accounts for this phenomenon. Males are four to five times

more affected than females. The presenting complaints are pain, fullness in the right hypochondrium, feeling of a mass, fever or jaundice. Auscultation may reveal arterial bruit and venous hum along the porta hepatis. This venous hum is referred to as **Cruveilhier-Baumgarten syndrome**. This may occur in cirrhosis liver with portal hypertension also. Portal hypertension and intraperitoneal hemorrhage are late features. Left supraclavicular nodes may be enlarged due to metastases. Liver function is maintained till late in the disease. Pleural effusion and atelectasis of the right lower lobe can occur. Occlusion of the portal vein or hepatic vein may present with acute symptoms of portal hypertension.

Diagnosis

Carcinoma should be suspected if massive enlargement of the liver occurs with fever, cachexia and hemorrhagic ascites. Jaundice is usually a late manifestation in hepatoma whereas it occurs early in cholangioma. Rarely secondary polycythemia may develop.

Diagnosis of Hepatocellular Carcinoma (HCC)

Imaging techniques such as ultrasonography (USS), CT and MRI are very useful. A lesion more than 2cms has high sensitivity and specificity for diagnosing HCC. Triple phasic helical CT is diagnostic. The unenhanced phase, enhanced phase and arterial and portal venous phases can be studied. *Alfa fetoprotein* (AFP) values above 200 ng/mL (normal 0-8.5ng/mL) are also diagnostic. If the diagnosis is not possible by imaging and AFP levels USS guided FNAC is useful. Complications include hemoperitoneum, dissemination of the lesion and needle track seeding.

Liver biopsy confirms the diagnosis, if the selection of the site is proper. Celiac axis angiography reveals the abnormal branches of the hepatic artery feeding the tumour. Angiography is necessary if surgical excision is planned.

MANAGEMENT

It may be curative or palliative. Curative modalities may be surgical or interventional. Surgical resection and liver transplantation are the surgical procedures. Unfortunately only around 15% of HCC are rescetable at the time of diagnosis. Local resection has the advantage that transplantation is not needed. Liver transplantation is the surgical procedure of choice in the western world. It is especially useful for HCC with cirrhosis and hepatic failure.

Interventions

Trans arterial chemoembolization (TACE): The hepatic artery is selectively catheterized and the chemotherapeutic

agent is directly delivered into the tumour followed by gel occlusion. Occlusion of the artery will lead to necrosis of the tumour which is mainly dependent on arterial blood supply, whereas the normal liver parenchyma is supplied by the portal vein.

Radiofrequency ablation (RFA) and alcohol injection into the tumour are the other interventions which are effective.

Operability

To be operable single lesions should be less than 5cms in diameter and multiple lesions should be less than 3 in number and less than 3 cms in diameter. The rest of the liver parenchyma should be normal.

Surveillance for HCC in cirrhosis: Cirrhotic patients are at higher risk for developing HCC and hence they have to be followed up. The current practice is to screen them with USS and AFP at 6 month intervals. Operability is high in HCC detected by surveillance.

SECONDARY CARCINOMA OF THE LIVER

Liver is a very common site for metastasis. These are thirty times more common than primary carcinoma. The usual primary sites are stomach, esophagus, other parts of the gastrointestinal tract, bronchus, breast, thyroid, kidney, adrenal, or melanoma of the skin. Biopsy from the secondaries may give clue regarding the primary.

Clinical examination reveals the irregular enlargement of the liver (**hob-nail liver**). The nodules show umbilication due to necrosis in the center. Jaundice occurs early if any of the major biliary passage is obstructed. The secondaries are generally less vascular than primary tumours and, therefore, arterial bruit is not heard. Splenomegaly may be present. Secondaries may lead to hypoglycemia. Ascites develops in due course. Ascitic fluid shows increase in proteins. Carcinoembryonic antigen may be detectable in the fluid. Lactic dehydrogenase is elevated to thrice the normal value. Cytology of the fluid shows malignant cells. Liver biopsy confirms the diagnosis. The progress is rapidly downhill and death occurs within weeks or months. Causes of death include malignant cachexia, hepatic failure and bleeding esophageal varices.

Therapy is at best only palliative. 5-fluorouracil given singly or as a combination regimen given either systemically or by local infusion into the hepatic artery is beneficial in some cases.

Benign tumours, which are rare, include adenoma and hemangioma.

Hepatic Adenoma

This may be associated with the administration of sex hormones and oral contraceptives. This may present as

local tumours or with peritoneal hemorrhage. Treatment is surgical resection.

Hemangioma Liver

It is the most common benign tumour. Two types are seen— cavernomas and the true hemangiomas. Some of them are associated with regular use of oral contraceptives. These tumours may sequester platelets and lead to consumption coagulopathy especially disseminated intravascular coagulation (**Kasabach-Merritt syndrome**). X-ray may show calcification. The ultrasound scan appearance is characteristic and in doubtful cases contrast CT may be diagnostic.

Treatment is largely aimed to reassure the patient and prevent injuries and bleeding. Definitive management includes surgery or angiographic embolization. Very large lesions which lead to consumption coagulopathy may have to be resected with liver transplantation, if needed.

Reye's Syndrome

During the course of viral infections like influenza A and B, varicella and probably others, toxic damage to the liver occurs. The condition is more common in children, especially if given aspirin. The liver shows fatty infiltration. Clinically it presents with hepatic failure, encephalopathy and rise in intracranial tension. Jaundice is usually absent. The mortality is high, if untreated (see chapter 52).

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Diseases of the Gallbladder and the Major Bile Ducts

9

K.R. Vinaya Kumar, K.V. Krishna Das

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General Considerations

The right and left hepatic ducts join to form the common hepatic duct. It joins the cystic duct to form the common bile duct which ranges in length from 2-9 cm. It passes behind the duodenum through the head of the pancreas to join the pancreatic duct and opens into the second part of the duodenum at the ampulla of Vater.

The gallbladder, situated below and in close contact with the liver, is pear-shaped, and has a capacity of 50 mL. Its fundus lies beneath the tip of the right ninth costal cartilage. In 10% of people the gallbladder has a mesentery (floating gallbladder) and it is freely movable.

The liver secretes 600 to 700 mL of bile in 24 hours at a pressure of 15-25 cm of water. The gallbladder concentrates the bile ten-fold by absorption of water and electrolytes. Bile secretion is inhibited when the pressure in the common bile duct exceeds 30 cm water. Vagus, which is the motor nerve, probably maintains the tone of the gallbladder. Gallbladder contracts in response to cholecystikinin (CCK) secreted by the duodenal mucosa. Cholecystikinin also causes relaxation of the sphincter. Drugs like morphine and pethidine cause spasm of the sphincter of Oddi and glyceryl trinitrate relaxes it.

Symptomatology of Biliary Tract Disease

The most obvious sign is jaundice which may be constant and progressive or fluctuating. This may or may not be associated with pain. Acute inflammatory lesions cause severe pain in the right hypochondrium, referred to the right shoulder. Obstruction to the cystic duct or common bile duct causes colicky pain with periodic waxing and waning. Unlike as in renal colic, mild constant pain persists between spasms. Persistence of continuous pain

for more than five hours should suggest complications such as infection or perforation of the gallbladder.

The fundus of an enlarged gallbladder can be palpated at the lateral border of the right rectus abdominis as a globular firm mass. Sometimes an elongated or floating gallbladder may reach as low as the right iliac fossa. Obstruction of the common bile duct due to external pressure as in carcinoma of the head of the pancreas causes enlargement of the gallbladder (*Courvoisier's law*). Since the gallbladder may enlarge only intermittently, repeated examinations may be necessary to detect it. Gall stones lead to chronic infection and thickening of the gallbladder, and this restricts enlargement. Tenderness over the gallbladder is elicited over the right hypochondrium. *Murphy's sign* is sudden catching pain felt on inspiration when the palpating finger exerts gentle pressure below the liver edge at the right border of the right rectus abdominis. The *Boas's sign* is tenderness, sometimes elicited over the region of the right scapula. Gallbladder pain may occasionally radiate to the chest and this may be mistaken for anginal pain. Gallbladder disease and ischemic heart disease coexist in many instances.

Investigation of the Gallbladder and Bile Ducts

Radiographs: Plain radiograph taken in the antero-posterior and right lateral positions may reveal radiopaque calculi. Only 10% of biliary calculi are radiopaque. Opacities due to renal calculi, calcified lymph nodes and fecoliths have to be differentiated from gall stones. An enlarged gallbladder may throw a soft tissue shadow. Gas in the biliary tree and pancreatic calculi are also seen at times.

Ultrasonography: It is the most useful noninvasive method to detect dilated biliary passages, gallbladder and calculi. This is the investigations of first choice.

CT scan: It demonstrates dilated biliary passages, intra and extrahepatic lesions and the gallbladder. The neighboring organs can also be well-visualized.

Contrast radiography: With the advent of noninvasive procedures such as ultrasound, CT scan and MRI which are much more effective in bringing out the abnormalities, the cumbersome and less precise investigations such as oral cholecystogram, intravenous cholangiography and blind percutaneous transhepatic cholangiography are seldom performed at present. Still in particular situations, USS guided or CT guided needling procedures and biopsies are done.

Endoscopic retrograde cholangiopancreatography (ERCP): This is an elegant method for visualizing the biliary and pancreatic duct systems. It utilizes endoscopy and radiography simultaneously. The ampulla of Vater is

cannulated through a side-viewing duodenoscope and the contrast is injected. The pancreatic duct, bile duct, and their tributaries are visualized in over 80% of cases. The ERCP also facilitates the collection of specimens for biopsy, cytology, and analysis of the juices. Therapeutically, ERCP has been employed to remove stones from the ducts and relieve strictures and even malignant obstructions. Endoscopic ultrasound scan (EUS) is a very sensitive imaging modality for terminal CBD lesions.

Operative cholangiography: The bile duct can be opacified during surgery by injecting contrast medium and its progress is followed.

Choledochoscopy: Visualization of the intra- and extrahepatic biliary system intraoperatively is possible by the choledochoscope which is introduced into the common bile duct. Stones and lesions missed by other investigations can be detected.

Barium meal: A properly conducted barium meal examination may give valuable clues in hepatobiliary disease. Distortion of the stomach and duodenum, abnormalities of the duodenum produced by ampullary carcinoma or pancreatic tumours, presence of fistulae, and regurgitation of the barium through the incompetent biliary sphincter are all useful diagnostic findings. This is seldom done at present since direct visualization is possible by endoscopy.

Radionuclide imaging: Scintiscans using ^{131}I rose-bengal or $^{99\text{m}}\text{Tc}$ -pyridoxylidene iminodiacetic acid derivative (HIDA) when given intravenously is taken up by the liver and excreted in bile. The biliary tree can be visualized.

Duodenal biliary drainage: Bile can be collected for examination through a duodenal tube after injecting cholecystokinin.

CHOLECYSTITIS

This may be acute or chronic.

ACUTE CHOLECYSTITIS

Obstruction to the gallbladder neck or cystic duct by gall stones, mucus plugs, neoplasms or other foreign bodies leads to stasis and infection. Initially the lesion is sterile but soon infection by *E. coli* and *Streptococcus fecalis* supervenes. Anaerobes such as *fusobacteria* and *Bacteroides* are also common. Inflammation may be mild or fulminant. The gallbladder may become filled with pus (**empyema of the gallbladder**) and the organ may burst after perforation, leading to severe biliary peritonitis and shock. Invasion by gas-forming organisms leads to the presence of gas in the wall of the gallbladder (emphysematous gallbladder) or in its cavity.

CLINICAL FEATURES

The disease is more common in middle-aged women. Sudden severe pain in the epigastrium and right hypochondrium referred to right shoulder, fever, vomiting and restlessness should suggest acute cholecystitis. Deep jaundice is rare unless the biliary tree is diffusely involved or the common bile duct is blocked. Heavy fatty meals at night, violent exercise, travel or even abdominal palpation in some cases may precipitate the attack. Pain may be colicky or continuous. The abdomen may be rigid. In some cases the gallbladder may be enlarged and palpable but local tenderness and rigidity preclude proper palpation. **Murphy's sign** and **Boas's sign** may be positive. General features of infection like fever, rigor, and neutrophil leukocytosis accompany these attacks. The condition subsides with treatment but recurs after varying intervals. Perforation of the gallbladder, ascending cholangitis, and shock occur in severe cases.

Differential diagnosis of acute cholecystitis includes hepatitis, cholangitis, gastric perforation, pancreatitis, appendicitis, acute intermittent porphyria and peritonitis. Pain may radiate to the chest, which could be mistaken for angina pectoris.

Diagnosis

The condition should be suspected clinically. Polymorphonuclear leukocytosis with a shift to the left is usually seen. The ultrasound scan may demonstrate stones in more than 90% of cases. Radionuclide scan (HIDA) is typical. It may demonstrate the bile ducts without visualizing the gallbladder.

Treatment

Conservative treatment consists of bed rest, analgesics and intravenous fluids to give symptomatic relief. Antibiotics like penicillin, cephalosporins and cotrimoxazole reach the bile in adequate amounts and these have to be employed judiciously. Metronidazole is to be given if anaerobic infection is suspected. In more than 90% of cases the condition subsides with conservative treatment within 3-4 days.

Surgical Management

Elective cholecystectomy can be done within three months after the acute phase subsides. The surgical mortality is about 0.5 to 1%. With the advent of laparoscopic cholecystectomy the operation has become more simple and less traumatizing.

Acute gangrenous cholecystitis is seen in the elderly and immunosuppressed individuals. The gallbladder may rupture at the fundus giving rise to local peritonitis, adhesions with other viscera or formation of internal biliary fistula. Acute gangrenous cholecystitis should be

suspected in any individual if the pain and toxemia increase despite treatment, and shock supervenes. The mortality is 15-20%. Initial treatment consists of massive antibiotic therapy and supportive measures. Emergency cholecystectomy or cholecystostomy and drainage of abscesses are indicated if the condition deteriorates in spite of adequate conservative measures.

CHRONIC CHOLECYSTITIS

This is the most common medical lesion affecting the gallbladder, and it is invariably due to cholelithiasis. The gallbladder is thickened and fibrotic and the mucosa may be destroyed by scarring.

CLINICAL FEATURES

Vague upper abdominal pain, colic, gaseous distension after fatty meal or recurrent episodes of acute cholecystitis should suggest the possibility of chronic cholecystitis. Peptic ulcer, hiatus hernia, and chronic pancreatitis have to be excluded by investigations. Murphy's sign may be positive and in the absence of hepatic disease it is very suggestive of cholecystitis. Calculi may be seen in plain radiographs of the abdomen. Oral cholecystogram, cholangiogram, ultrasonography and ERCP help to localize the lesion.

Course and Prognosis

The condition persists for several years with exacerbations and remissions. There is increased risk of malignancy.

Treatment

Medical treatment consists of dietary adjustment, reduction of weight, antispasmodics, antacids, and antibiotics. Early cases may subside completely. Drugs which dissolve cholesterol gall stones are worth a trial. *Chenodeoxycholic acid* in a dose of 13-15 mg per kg body weight given orally at bed time is effective in dissolving these stones in a period of 6-24 months. Recurrence may occur on stopping therapy. Side effects include mild diarrhea and elevation of serum cholesterol. *Ursodeoxycholic acid* is a better drug in this class and in a dose of 10 mg/kg given twice daily, it acts faster. Troublesome diarrhea does not occur. Rowachol is a mixture of essential fatty acids capable of dissolving gall stones. Medical treatment is generally not preferred on long term basis.

Shock wave lithotripsy disintegrates the stones. This helps in quicker resolution. Surgical removal of the gallbladder is indicated if medical treatment fails. With the availability of laparoscopic cholecystectomy in many centers in India at reasonable cost, this has become more popular as the definitive long-term treatment.

Typhoid cholecystitis: The biliary tract may be colonized by *Salmonella typhi*. More commonly chronic cholecystitis may occur in typhoid carriers.

Typhoid bacilli form a nidus around which calculi may form. The gallbladder becomes chronically infected with *Salmonella* and this perpetuates the fecal carrier state. Cholecystectomy helps in clearing the focus of infection and the carrier state.

Carcinoma of the Gallbladder

It is a rare condition in South India, but is more common in the Gangetic belt of India. It is seen more in people

above the age of 50 years. Around 90% cases are adenocarcinomas. It presents with progressive biliary obstruction. Chronic calculous cholecystitis predisposes to malignancy.

Cholangiocarcinoma

This is a rare slow-growing adenocarcinoma arising from any part of the biliary tree from the bile canaliculi to the sphincter of Oddi. Progressive jaundice occurs depending on the site of obstruction.

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Diseases of the Pancreas

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General Considerations

Applied Anatomy

Pancreas is situated posteriorly in the upper abdomen. It contains both exocrine and endocrine cells. Since the head of the pancreas lies within the duodenal loop in close approximation, enlarging lesions of the head of the pancreas produce radiologically demonstrable changes in the inner margin of the duodenum. The common bile duct passes through the head of the pancreas and tumours of this region compress the common bile duct to produce obstructive jaundice. Being deeply placed, lesions of the pancreas may remain without producing clinically demonstrable local physical signs for long periods.

The pancreas is made up of large lobules, each made up of smaller lobules containing acini. Each acinus

contains two types of cells. The zymogen-containing cells secrete the digestive enzymes and these predominate. Cells situated near the center of the acini secrete water and bicarbonate. The main pancreatic duct is formed by the confluence of smaller ducts. It opens into the second part of the duodenum along with the common bile duct at the ampulla of Vater. The islets of Langerhans which are made up of four types of cells known as alpha, beta, gamma and delta, are scattered throughout the organ. These cells secrete glucagon, insulin, and other peptide hormones. Endocrine tumours may arise from them.

Applied Physiology

The pancreas secretes 1.5-3 liters of juice daily. It is alkaline with the pH 8-8.3. Trypsin, chymotrypsin, amylase and lipase form the main enzymes. Sodium bicarbonate, which is the major electrolyte, renders alkalinity to the secretion. Potassium, calcium, zinc, chloride, phosphate, and sulfate are also present in smaller amounts. The secretion is under hormonal and neural control, the former being more important. When acidic gastric contents enter the duodenum and the pH goes down to 4.5, the duodenal and jejunal mucosa release secretin. Cholecystokinin (pancreozymin) is also secreted from the duodenal and jejunal mucosa when long-chain

fatty acids, amino acids (especially tryptophan, phenylalanine, valine and methionine) and acidic gastric contents enter. Copious amounts of alkaline juice are produced in response to secretin. Cholecystokinin stimulates the production of thick juice which is rich in enzymes. Gastrin is also a weak stimulus for pancreatic secretion. Vasoactive intestinal peptide (VIP) antagonizes the effect of secretin. Bile acids in the intestinal lumen also stimulate pancreatic secretion.

Neural control is through the vagus which exerts direct effect on the acinar cells. Indirectly, it influences pancreatic secretion through the mechanism of gastrin.

Actions of pancreatic juice: Amylase secreted in the active form digests starches into oligosaccharides and to the disaccharide maltose. The lipolytic enzymes (*lipase* and *co-lipase*) breakdown fat into glycerol and fatty acids.

The proteolytic enzymes are *trypsin*, *chymotrypsin*, *carboxypeptidases*, *aminopeptidases*, *elastase*, *ribonuclease*, and *deoxyribonuclease*. They are secreted as inactive precursors (zymogens) which are activated later. *Trypsinogen* is activated by *enterokinase* found in the intestinal mucosa to *trypsin*. Trypsin further activates the other proteolytic enzymes sequentially.

Pancreatic Function Tests

Enzyme levels in blood and urine: Amylase, *trypsin*, and *lipase* are present in normal serum in small amounts. In acute pancreatitis, within a short interval, the amylase reaches very high levels and this rise is suggestive of the diagnosis. Normal value of amylase is about 60-180 Somogyi units/dL (or 150-340 IU/L). The serum levels come down within a few days.

Since serum amylase levels are not specific for pancreatic disease, measurement of renal clearance of amylase from blood has been suggested as a more reliable test for diagnosis of acute pancreatitis. The clearance ratio is calculated by simultaneous estimation of amylase and creatinine in serum and urine. Normal amylase/creatinine clearance ratio is around 3.1. Value of more than 5 suggests the diagnosis of acute pancreatitis. The value of this test is also doubtful.

Analysis of feces: Steatorrhea and creatorrhea are seen commonly in pancreatic disease. Fecal fat estimation done on feces collected for 3 days on a high fat diet (about 75 g/day) helps in confirming the presence of steatorrhea. Normal subjects do not lose more than 6 g of fat in feces daily. Higher values suggest pancreatitis or malabsorption. In pancreatitis, feces contains neutral fat, whereas in malabsorption states it contains mainly fatty acids.

Estimation of fecal trypsin and chymotrypsin is useful in the diagnosis of chronic pancreatic insufficiency, particularly cystic fibrosis.

Tests for exocrine function: Pancreatic juice can be collected by duodenal aspiration or by endoscopy. Exocrine function may be tested directly (secretin pancreozymin test) or indirectly (Lundh test). The ability to produce enzymes and bicarbonate is tested after giving secretin 1 unit/kg I.V and pancreozymin 4 units/kg. This test is the gold standard for exocrine pancreatic function.

Normal Values

1. Volume output should be more than 2 mL/min and amylase more than 6 units/kg.
2. Bicarbonate concentration should be more than 80 mmol/L.
3. Bicarbonate output should be more than 10 mmol in 30 min.

Enzymes are also estimated and compared with the norms for the population studied.

Lundh test: This test is based on the effect of fatty acids and amino acids on the endogenous release of cholecystokinin which in turn stimulates secretion of pancreatic enzymes. This is an indirect test of pancreatic function since it depends on the endogenous release of pancreozymin from duodenal mucosa. The test may be misleading in the presence of duodenal mucosal disease. Normal value of tryptic activity by this test is 19.6 ± 3.5 mEq/mL per min.

Tubeless pancreatic function tests: The principle is to estimate the urinary elimination of digestion products of substances given orally. This indirectly estimates the digestive function. The two tests in this group are the 'benteromide test' and pancrealauryl test.

Benteromide test: N Benzyl-L-tyrosyl P-aminobenzoic acid is administered orally and its urinary elimination product para-amino benzoic acid is estimated. Chymotrypsin is the enzyme concerned. In the pancrealauryl test fluorescein laurate is given and the fluorescein eliminated in urine is estimated. Pancreatic esterases are the enzymes responsible.

Cytology of duodenal aspirate: Cytological examination may reveal the presence of neoplastic cells.

Isotopic scanning of pancreas: The isotopic scanning of pancreas can be done by using radioactive selenomethionine using ^{75}Se which is taken up by the pancreas.

Assessment of endocrine function: Studies of glucose homeostasis and determination of serum levels of insulin, glucagon, cholecystokinin and other peptide hormones help to assess the hormonal activity of the pancreas.

Radiography: Pancreatic calculi and calcification can be demonstrated in plain radiographs. In acute pancreatitis indirect evidences like dilatation of small bowel loops due to ileus may be present.

Ultrasound and CT scan: These are very helpful non-invasive methods for demonstrating deep-seated lesions. Ordinary method of ultrasonography is less reliable since the pancreas does not lend itself to proper imaging and, therefore, small lesions may be missed.

Endoscopic ultrasonography is a more reliable method to detect lesions even as small as 1 cm or less. It is helpful in staging pancreatic cancers, differentiating benign from malignant cystic lesions, obtaining FNAC from pancreatic mass lesions and guiding endoscopic drainage of pseudocysts.

Hypotonic duodenography and barium meal reveal the changes produced in duodenum and intestines by pancreatic lesions.

Endoscopic retrograde cholangiopancreatography (ERCP) is a very valuable tool in investigating the pancreas directly. ERCP shows ductal abnormalities such as dilation, obstruction and stones. It is the gold standard for the diagnosis and staging of chronic pancreatitis, with sensitivity of 75-95% and specificity of over 90%. Morbidity caused by ERCP is 3-4% and mortality 0.1 to 1%.

MRI cholangiopancreatography is a recently developed imaging modality with about 96-100% sensitivity to detect ductal stages in the pancreatic duct.

Pancreatitis

Pancreatitis may be acute or chronic. The incidence varies in different ethnic groups. Acute pancreatitis is seen infrequently as a medical or surgical emergency in India. Chronic pancreatitis accounts for a significant proportion of malabsorption syndrome. Chronic calcific pancreatitis with secondary diabetes is seen in some endemic areas, especially in Kerala. Pancreatitis is closely associated with alcoholism and biliary tract disease.

ACUTE PANCREATITIS

Pathogenesis: Acute pancreatitis results from auto-digestion of the pancreas by its own enzymes. The inactive precursors of proteolytic enzymes are activated by regurgitated bile, viral infections, ischemia, anoxia, trauma or toxins, within the pancreas. Digestion of the tissues results in edema, hemorrhage, vascular damage, coagulation necrosis, and fat necrosis. Secondary factors like liberation of activated enzymes, bradykinin and histamine-like substances into the pancreas result in vasodilation, exudation, and disseminated intravascular coagulation. These factors lead to further damage.

Acute pancreatitis has been defined as an acute inflammatory process of the pancreas with variable involvement of other regional tissues or remote organ

systems. In mild disease when organ dysfunction is minimal prognosis for recovery is good. In severe disease there are local lesions such as necrosis, abscess or pseudocyst formation and systemic complications such as respiratory distress, shock, gastrointestinal bleeding, renal failure and others. The extent of severity has been semiquantified by using clinicopathological criteria such as Ranson's criteria or Apache II scores (see Chapter 36).

Causes

1. *Alcoholic bouts.*
2. *Biliary tract disease*, especially cholelithiasis in the common bile duct.
3. *Trauma*—blunt abdominal injuries, surgical trauma, post-ERCP reaction.
4. *Metabolic causes*—hyperlipidemia, diabetes, renal failure, hypothermia.
5. *Endocrine causes*—hyperparathyroidism, corticosteroid therapy, oral contraceptives.
6. *Infections*—mumps, viral hepatitis, coxsackie and echo-viruses, mycoplasma.
7. *Pancreatic ductal obstruction* due to migration of *Ascaris lumbricoides* and other causes.
8. *Inflammation spreading from neighboring tissues*, e.g. penetrating peptic ulcer.
9. *Connective tissue diseases*, e.g. systemic lupus erythematosus.
10. *Drug-induced pancreatitis* caused by diuretics, anti-inflammatory drugs, azathioprine, 6-mercaptopurine, L-asparaginase, isoniazid, rifampicin, tetracycline, phenformin.

In many cases there may not be any identifiable cause.

Clinical features: Onset is sudden with acute upper abdominal pain which may radiate to the chest, precordium, back or lower abdomen. An alcoholic bout or heavy eating may precipitate the attack. The patient adopts a stooping posture with pressure on the abdomen to get relief. Nausea, vomiting, dehydration, and signs of shock occur in severe cases. Mild jaundice may be present in a few cases. Erythematous skin nodules may form due to fat necrosis. Secondary pleural effusion may develop on the left side.

Examination of the abdomen shows rigidity, marked tenderness, mild distension due to ileus of the intestines, and absence of peristaltic sounds. A bluish discoloration may be seen in the flanks (**Turner's sign**) or around the umbilicus (**Cullen's sign**) due to extravasation of blood into the abdominal wall. When present, these signs strongly suggest acute necrotising pancreatitis. Ascites may develop as a complication (*pancreatic ascites*).

Course and Prognosis: The acute phase subsides within a week but recurrence may occur. In general the mortality

is 10-20%. In hemorrhagic pancreatitis with profound shock the mortality is high. Adverse factors include elderly age, severe shock, respiratory failure, fall of serum calcium below 8 mg/dL, azotemia and high fluid requirements.

Laboratory features: Serum amylase is increased early during the stage of acinar necrosis and it comes down in 3-4 days. Amylase levels may reach even 2000 Somogyi units/dL. Urinary amylase is raised initially during the illness and it remains so for 4-7 days. In acute pancreatitis the renal clearance of amylase is higher than that of creatinine. The amylase/creatinine clearance ratio (Cam/Ccr) is increased in acute pancreatitis and this is a diagnostic feature. Serum amylase levels are elevated in other conditions such as cholecystitis, intestinal infarction, perforation and obstruction, and mumps. Amylase level is increased in the ascitic fluid of pancreatic ascites.

Moderate neutrophil leukocytosis is common. Blood glucose is increased and calcium is lowered. Serum bilirubin may be transiently elevated, up to 4 mg/dL in a few cases. Electrocardiogram abnormalities such as ST-T-wave changes may develop in some cases and this may resemble myocardial ischemia.

DIAGNOSIS

Radiology: Calculi in the biliary and pancreatic duct systems may be seen in the plain radiograph of the abdomen. Loops of duodenum and jejunum are distended (**sentinel loop**) due to ileus. The inner wall of the duodenal loop may show pressure effects and widening on barium meal and hypotonic duodenography.

Ultrasonography and CT scan help to assess the morphological abnormality in the pancreato-biliary system. Endoscopic retrograde cholangiopancreatography performed after subsidence of the acute phase helps to demonstrate the underlying abnormality.

Contrast enhanced CT is a very good imaging modality to reveal morphological changes in the pancreas. MRI scan gives additional information.

Differential diagnosis: Acute emergencies like gastric or duodenal ulcer perforation, acute cholecystitis, renal colic, hepatitis, peritonitis, acute myocardial infarction and pleurisy have to be considered in the differential diagnosis.

General complications: These include shock, hyperglycemia, hypertriglyceridemia, hypocalcemia, and disseminated intravascular coagulation. Infection generally supervenes on the necrotic tissue in 40-60% of cases. 10-15% of patients develop systemic inflammatory response syndrome (SIRS) leading to a fulminant course and multi-organ failure. SIRS is the result of activation of the inflammatory cascade mediated by cytokines, immunocytes and the complement system.

Local Complications

1. **Pancreatic phlegmon:** A solid mass composed of inflammatory tissue and fat necrosis develops and this may persist for 1-2 weeks.
2. **Pancreatic abscess.**
3. **Pancreatic pseudocyst:** Fluid and tissue debris collect in the lesser sac of peritoneum over a period of 1-4 weeks after the acute attack. Pseudocysts, in contrast to true cysts, lack epithelial lining on their walls. Wall of the pseudocyst is made up of necrotic material, granulation, and fibrous tissue around. Pseudocysts present like mass lesions, giving rise to local pressure effects.
Treatment consists of endoscopic or surgical drainage into the stomach or the small intestine.
4. **Pancreatic ascites** develops due to the rupture of pancreatic duct into the peritoneum. Massive intraperitoneal hemorrhage may develop.
5. **Intestinal infarction.**
6. **Obstructive jaundice.**

The terms hemorrhagic pancreatitis, phlegmon and pseudocyst which were in vogue, are seldom used at present.

Systemic Complications

Respiratory system: Atelectasis, left-sided pleural effusion, mediastinal abscess, adult respiratory distress syndrome.

Cardiovascular system: Myocarditis, pericardial effusion, sudden death.

Renal failure

Central nervous system: Fat embolism, psychosis.

Fat necrosis in several organs: This may involve skin, central nervous system, bones, and other organs.

TREATMENT

Mild cases require only symptomatic measures.

Medical management: Analgesics like methadone 10 mg or pethidine 100 mg are used to relieve pain. In severe cases, morphine 10-20 mg may be required. Since morphine causes spasm of the sphincter of Oddi, it may be combined with atropine 0.5 mg or propantheline bromide 15-30 mg. Oral feeding is avoided in the acute stages. Food is gradually introduced when the condition subsides.

Shock: It is managed on general lines by replacing fluids and electrolytes and the use of pressor agents when required. Intravenous administration of glucose and electrolytes has to be continued till the ileus disappears. Hypocalcemia is corrected by the administration of calcium gluconate intravenously. If diabetic state

develops, insulin has to be administered. Broad spectrum antibiotics are indicated to treat secondary infection.

If there is troublesome abdominal distension, continuous nasogastric aspiration may help. Necrotic lesions and local fluid collections should be evacuated by guided needle aspiration.

Surgery may be indicated at times in acute pancreatitis.

Indications

1. Excision of necrotic tissue (necrosectomy) is needed if there is extensive necrosis as demonstrated by helical CT with pancreatic protocol.
2. Drainage of pus is required if there is evidence of infection and abscess formation. Gram staining of FNAC specimen may reveal organisms.
3. Pancreatic ascites may have to be drained at times.
4. Relief of biliary obstruction if medical treatment by itself is not successful.

In the presence of biliary stones or other obstructive lesions, surgery is undertaken electively to prevent relapse of pancreatitis. Necrotic lesions and local fluid collections should be evaluated by guided needle aspiration. The material should be submitted for microbiological tests. Surgical debridement is indicated if there is infection and also in sterile abscesses which fail to improve with medical therapy.

Sometimes biliary obstruction may have to be relieved in the acute phase of pancreatitis itself if conservative measures fail to resolve the condition.

CHRONIC PANCREATITIS

Chronic pancreatitis is of two types—**relapsing** and **non-relapsing**. In this condition the pancreatic tissue is progressively destroyed and replaced by fibrosis.

Pathology: The pancreas is firm to hard, fibrotic, and distorted. Calculi may develop inside the distorted ductal system. Acinar tissue may also become calcified. Exocrine pancreatic function suffers when 80-90% of the acini are destroyed. Though the islets are relatively spared, they are also affected finally, resulting in diabetes. In chronic relapsing pancreatitis seen in India, diabetes mellitus is a prominent feature.

CLINICAL FEATURES

Chronic pancreatitis is more common in the fourth and fifth decades. It presents with recurrent upper abdominal pain following alcoholic bouts or dietary excesses. The pain may be referred to the back between T₁₀ and T₁₂ segments. These patients adopt a characteristic squatting posture with pressure applied to the abdomen. When present, this feature may suggest the diagnosis. Overt diabetes develops in one-fifth of the cases. Except for vague tenderness over the epigastrium, physical

examination may not reveal much. Less commonly, enlarged pancreas, pseudocyst or pancreatic abscess may be palpable.

Course and prognosis: Chronic pancreatitis tends to be persistent or recurrent, especially if accompanied by biliary tract disease. Complications include malabsorption state, malnutrition, obstructive jaundice, diabetes mellitus and higher risk of malignancy. Chronic pancreatitis carries a mortality of 50% in 20-25 years. Malabsorption develops when the exocrine function falls by 80%.

Diagnosis: Chronic pancreatitis should be suspected clinically in any alcoholic patient complaining of epigastric pain referred to the back.

Investigations: Plain X-ray of the abdomen may reveal pancreatic calculi and calcification of the substance of the gland in 30-40% of cases. Ultrasonography reveals enlargement, cysts, abscesses, and ductal abnormalities. Functional impairment can be assessed by undertaking exocrine function tests. The ERCP helps to delineate the biliary and pancreatic duct system and also in obtaining biopsies and to carry out procedures to relieve obstruction. Glucose tolerance test brings out the diabetic state. Serum amylase is not constantly elevated in chronic pancreatitis but its level may increase during acute exacerbations. Stool fat is increased (above 7 g in 24 h), this is made up of neutral fat. This helps to distinguish the condition from intestinal malabsorption in which the lipids are in the form of fatty acids. Vitamin B₁₂ malabsorption occurs since the vitamin is bound in the gut by proteins other than intrinsic factor and thus, rendered unabsorbable.

Treatment: Abstinence from alcohol and smoking and reduction of weight help to reduce exacerbations. Analgesics and antispasmodics may be necessary to relieve pain. Reduction of dietary fat to 20-30 g/day helps to reduce the abdominal discomfort and relieve steatorrhea in mild cases. Fat soluble vitamins have to be supplemented orally or parenterally as required.

Digestion can be aided by the administration of pancreatic enzymes or enzymes derived from fungal or other plant sources given orally after food. Pancreatic extract (Pankreon, Pancreatin) is available commercially. Four to six tablets (2-3 g) have to be given with meals or more frequently. This measure helps in digestion, corrects the steatorrhea, and also ameliorates pain. Vitamin B₁₂ malabsorption is also corrected. Though this is generally safe, excessive use of pancreatic extracts leads to hyperuricemia. In moderate and severe cases H₂ receptor blocker drugs such as ranitidine 150 mg bd or a proton pump inhibitor such as omeprazole 20 mg bd are given orally to reduce gastric acidity and thereby limit the inactivation of pancreatic enzymes in the intestine.

Medium chain triglycerides are useful to reduce diarrhea. They require only small amounts of pancreatic

enzymes for digestion. Moreover bile salts are not required for their absorption. Medium chain triglycerides are contained in oils such as coconut oil. Diabetes has to be treated on its own merits.

Surgery: Intractable pain, pancreatic cysts, pseudocysts and neoplasms are indications for surgery. In many cases, relief of obstruction and withdrawal of alcohol results in improvement of pancreatic function. In some cases removal of the affected portion of the pancreas may be required.

AUTOIMMUNE PANCREATITIS (AIP)

Syn: Autoimmune related pancreatitis

This was first described in 1955 by Yoshida et al to describe the form of pancreatitis that is associated with autoimmune manifestations revealed by clinical and laboratory parameters. AIP is a form of chronic pancreatitis caused by autoimmune inflammation. This leads to lymphocytic infiltration with associated fibrosis of the pancreas leading to organ dysfunction. AIP forms 5-11% of the total cases of chronic pancreatitis. Male to female ratio is 2:1 the disease is present in India and formed 1% of a serious from Vellore.

Ref: Etiology and clinical profile of chronic pancreatitis the CMC Vellore experience. Ashok Chacko and Shajan Peter in chronic pancreatitis and pancreatic diabetes in India. Edited by V. Balakrishnan and others published by The Indian Pancreatitis Study Group 2006.

Some cases show association with other autoimmune diseases such as rheumatoid arthritis, Sjögren's syndrome and inflammatory bowel disease.

Clinical features: A wide variety of symptoms may occur. Jaundice and mild to moderate abdominal pain are frequent. Imaging studies shows biliary duct strictures which may resemble those of primary sclerosing cholangitis. Histology helps to confirm the diagnosis.

Diagnosis: The CT scan image is characteristic. Endoscopic ultrasonography is an important tool to diagnose AIP. AIP has to be differentiated from alcohol induced pancreatitis and pancreatic cancer.

Treatment: Corticosteroids form the mainstay of treatment. Prednisolone in a dose of 40 mg/day/should be started orally and continued for a week, before tapering the dose.

TROPICAL PANCREATITIS

This is described under Section 10 chapter 92.

CYSTIC FIBROSIS OF THE PANCREAS

Syn: Fibrocystic disease of pancreas, Mucoviscidosis

Cystic fibrosis (CF) of the pancreas which was thought to be rare in India, is now reported to be present, though

infrequently. The incidence in orientals is 1/90000 of population, compared to 1/20000 in caucasians and 1/17000 in negroid races. CF is an autosomal recessive disease. The defective gene is located in the long arm of chromosome 7. Normally this gene encodes for a 1480-amino acid protein called cystic fibrosis transmembrane regulator (CFTR). The CFTR is a protein that regulates and participates in the transport of electrolytes across epithelial cell membranes and probably across intracellular membranes as well. At least more than 1000 mutations in the CFTR has been identified. Several molecular abnormalities in the gene give rise to a wide spectrum of clinical features.

CFTR mutations can be classified into six groups

1. CFTR is not synthesized
2. The processing is defective
3. Defective regulation
4. Defective conductance.
5. Partially defective production and processing and
6. Defective regulation of other channels

The primary defect in CF is one of disordered ion-transport in epithelial cells. This abnormality is manifested in almost all secretory glands particularly the sweat glands and mucus secreting organs such as pancreas, liver, lungs, intestines, salivary glands, prostate, testes and others.

Normally sweat is formed in the secretory coil of the sweat glands as an ultrafiltrate of plasma containing 135 and 100 mmol/L of sodium and chloride respectively. These ions are reabsorbed by the ductal epithelium and normal sweat contains only less than 50 mmol/L of Na^+ and Cl^+ , when the flow rate is 10 nanoliter/gland/minute. One of the main abnormality which is highly diagnostic, is the increase in chloride in the sweat to levels above 60 mmol/L.

Bicarbonate content of pancreatic juice is less than normal. The mucus secreted by mucous glands in all organs is abnormally viscid. This is responsible for blocking the smaller duct system and impairing ciliary activity.

Pathology: Pancreatic ducts are occluded and dilated to form cysts. Acini undergo atrophy. There is interstitial fibrosis. Islets of Langerhans are relatively unaffected. Intrahepatic bile ducts may show obstruction in 10% of cases. Cirrhosis with portal hypertension may develop. Lungs which are normal at birth, soon develop purulent bronchitis, bronchiectasis, and cystic changes. Other glands which develop ductal obstructions are the sublingual salivary glands, prostate, and testes.

Non-classic forms of CF occur in which milder mutation of the CFTR gene occurs, with partial preservation of pancreatic function. In this form malabsorption is rare.

Clinical Features

Earliest manifestation in the newborn is meconium ileus in which the meconium which is abnormally thick leads to intestinal obstruction. As the child grows the intestinal symptoms take the form of recurrent subacute or acute intestinal obstruction, ileocolic intussusception and rectal prolapse.

Pancreatic lesion leads to varying degrees of pancreatitis and malabsorption. Glucose tolerance may be impaired, frank diabetes is less common. If diabetes occurs, it shows features of both types 1 and 2.

In comparison to the respiratory morbidity, pancreatic dysfunction is milder.

Respiratory Infection

Occurrence of respiratory infection and sinusitis is also genetically related. The age of onset and severity of the lesions vary, depending on the genetic abnormality. Respiratory tract lesions include chronic sinusitis, nasal polyps, chronic otitis media and conductive deafness. Deafness is due to blockage of eustachian tubes. Respiratory findings include bronchiectasis, recurrent purulent infection, hemoptysis and pneumothorax. Main infective agents are *Staph. aureus* and *Ps. aeruginosa*. The latter is more serious and often drug resistant. Infection by *Ps. aeruginosa* marks the onset of a progressive downhill course. Death is normally due to respiratory failure. CF is one of the causes of chronic obstructive pulmonary disease and pancreatic insufficiency occurring before the age of 30 years. Congenital absence of vas deferens is almost universal.

Azoospermia occurs in 80-90% of males, and almost all males are infertile. Women can bear children. The degree of sub fertility is also related to the genetic mutation.

Diagnosis

This is established by determining sweat electrolytes. Sweat is collected by stimulating diaphoresis with pilocarpine iontophoresis. Major and minor diagnostic criteria are given below. Normal sweat chloride level is <40 mmol/L. In the non-classic form it may be 40-59 mmol/L.

Sweat chloride may rarely be increased in heavy tobacco smoking, chronic bronchitis, malnutrition, hereditary nephrogenic diabetes insipidus, adrenal insufficiency and ectodermal dysplasia. When sweat tests are inconclusive estimation of electrical potential difference between the nasal mucosa and forearm skin is helpful. Genotyping the CFTR gene helps to make more precise diagnosis.

Course and prognosis: If untreated, 80% of cases die in the first year of life. With treatment, median survival has

Criteria for diagnosis of cystic fibrosis

Major criteria

1. Sweat chloride exceeding 60 mmol/L in children and 80 mmol/L in adults.
2. Evidence of pulmonary involvement.
3. Obstructive azoospermia.

Minor criteria

1. Sweat chloride 40 mmol/L in children and 60 mmol/L in adults.
2. Family history of cystic fibrosis or azoospermia.

Definite diagnosis is made if two major criteria, or a combination of one major and one minor criterion from two different organ systems are present.

gone up to about 30 years. Death is due to respiratory complications.

MANAGEMENT

Digestive enzyme replacement therapy and nutritional support help to reduce the ill-effects of chronic pancreatitis.

Respiratory problems are treated with antibiotics, respiratory physiotherapy, bronchodilators and expectorants. Attempts are being made to deliver the aminoglycoside tobramycin, as aerosol, with partial success. Advances in therapy include the use of inhaled glucocorticoids in selected cases, NSAIDs like ibuprofen and the interleukin r.IL₁₀.

Intractable cases have to undergo lung-transplantation. Attempts to institute gene therapy are in progress. Relatives of CF patients should undergo genetic tests and sweat tests to enable diagnosis early.

PANCREATIC ASCITES

Pancreatic ascites is due to leakage of pancreatic juice into the peritoneum from a ruptured duct or pseudocyst. The fluid is rich in proteins and enzymes. The fluid may leak into the pleura causing a pancreaticopleural fistula. 50% of these cases can be managed nonsurgically by paracentesis, diuretics, carbonic anhydrase inhibitors or octreotide, and parenteral nutrition. If these fail, surgical measures aimed at diversion of the pancreatic juice to jejunum or using stents in the pancreatic duct may be needed.

CARCINOMA OF THE PANCREAS

This neoplasm is seen in all parts of India not uncommonly. It is more common in women of the age group 55-70 years, but both sexes may be affected. Histologically, they are adenocarcinomas arising from the ductal epithelium and occasionally from the acini. In some cases ductal carcinomas arise multicentrically.

Genetic analysis has revealed that several germline mutations of P16, BRCA1, BRCA2, Rb and APC genes are associated with increased incidence of pancreatic cancer. Cigarette smoking, hereditary pancreatitis and hereditary non-polyposis colorectal cancers are associated with higher risk of cancer pancreas.

Clinical features: Pancreatic carcinomas may remain asymptomatic for long periods. The lesion is generally advanced by the time it becomes symptomatic. Early symptoms are vague such as nonspecific dyspepsia, epigastric pain, and vomiting. Thrombophlebitis migrans (recurrent venous thrombosis occurring in different parts) may develop in carcinomas of the body and tail of the pancreas.

Many cases may be misdiagnosed as hysteria or other neurotic disorders, before the actual diagnosis reveals itself.

Growths arising from the head of the pancreas cause painless progressive obstructive jaundice because of pressure on the common bile duct. The gallbladder enlarges and becomes palpable. The tumour may become palpable in the epigastrium on rare occasions. Lesions affecting the body and tail do not produce jaundice but diabetes may develop when the lesion is extensive. Cachexia sets in late. Severe boring pain referred to the back develops when the nerves are affected. Death follows within 6 months of the onset of obstructive jaundice in untreated cases. Only 10% survive one year.

In carcinoma of the ampulla of Vater, obstructive jaundice is an early symptom. Ulceration and bleeding from the growth give rise to melena or a silvery colour to feces.

Investigations: Carcinoma of the pancreas should be suspected when elderly persons complain of vague upper abdominal symptoms, painless progressive obstructive jaundice with a palpable gallbladder, migrating thrombophlebitis or progressive cachexia. Ultrasonography, CT scan, and ERCP give diagnostic information. Pancreatic juice collected endoscopically may reveal malignant cells. Angiography helps to visualize the mass and its blood supply.

Spiral CT, MRI, cholangiopancreatography, and endoscopic ultrasonography help to bring out even small tumours better.

Treatment: Operable tumours of the ampulla of Vater are treated by excision of the duodenum and head of the pancreas. In inoperable cases biliary obstruction is relieved by cholecystojejunostomy or choledochojejunostomy. This drainage procedure gives immense symptomatic

relief. Effective palliation of jaundice can be achieved with endoscopic stenting of bile duct.

Endocrine Tumours of the Pancreas

These are rare, but characteristic clinical features develop when they occur.

Islet cell tumours: Benign adenomas are rare. They secrete insulin and give rise to spontaneous hypoglycemia, which develops in the morning on a fasting stomach or after heavy exercise. This condition is relieved by food.

Zollinger-Ellison syndrome: This is due to gastrin-secreting tumours arising from the islets of Langerhans.

They are more common in the body and tail of the pancreas. Sometimes they may be multicentric. They may form part of multiple endocrine adenomatosis (MEN type I-Werner's syndrome), the other lesion being parathyroid adenoma. Excessive gastrin leads to the secretion of large amounts of gastric acid and aggressive gastric ulceration. (Refer section 8, Chapter 78, pp 470).

Other Non-beta Cell Pancreatic Tumours

Glucagonoma: This arises from the alpha cells which grow to form adenomas or carcinomas and secrete excessive glucagon. These patients present with diabetes mellitus, severe weight loss and a skin rash termed as necrolytic migratory erythema seen particularly over the face, buttocks, abdomen, perineum, and distal parts of the limbs. Treatment involves surgical removal of the tumour.

Watery diarrhea, hypokalemia achlorhydria (WDHA) syndrome, Verner-Morrison syndrome, Pancreatic cholera: This condition is caused by a non-beta cell pancreatic islet neoplasm which produces excessive quantities of vasoactive intestinal peptide (VIP). In comparison to the other endocrine tumours, these are larger. The severe watery diarrhea gives rise to shock, renal shut down, fatal hypokalemia, and metabolic acidosis. The VIP also causes hyperglycemia and hypercalcemia. When located, treatment is surgical removal.

Somatostatinoma: Tumours producing somatostatin have been described in a few cases. Somatostatinomas are associated with hyperglycemia, loss of weight, hypochlorhydria, steatorrhea, and gallbladder disease.

Tumours secreting adrenocorticotrophic hormone: These may arise from pancreatic islets. Cushing's syndrome produced by these tumours is milder than the classical types. In many of the cases several hormones may be produced, e.g., insulin, gastrin, serotonin, etc.

Diabetes Mellitus, Other Metabolic Disorders and Inherited Disorders of Connective Tissue

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Diabetes Mellitus

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General Considerations

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia with or without glycosuria, resulting from an absolute or relative deficiency of insulin. This is brought about by an impairment of insulin production or its release by the beta cells of the islets of Langerhans. More often it is due to a resistance to the action of insulin either due to a receptor/post receptor defect or an imbalance between insulin and its counter regulatory hormones. Clinically diabetes is characterized by a wide spectrum of disorders ranging from asymptomatic hyperglycemia to abnormalities in the various organs.

PANCREAS

The endocrine component of the pancreas consists of different types of cells: α -cells, β -cells, δ -cells and PP cells contained in the islets of Langerhans which constitute 1% of its weight. There are 100,000 islets in the pancreas, and each islet contains 1000-3000 cells. Thus altogether there are 100-300 million β -cells in the pancreas.

Pancreatic beta cells can store 200 units of insulin and can release 30-50 units of insulin per day.

95% of cells of the pancreas have exocrine function and 5% have endocrine function. The beta cells produce insulin, alpha cells produce glucagon, delta cells produce somatostatin and the PP cells produce pancreatic polypeptide.

Epidemiology

Diabetes is a major public health problem all over the world. Its prevalence varies in different populations, being very high to the extent of 40% of all those above the age of 15 years in Pima Indians, 34% in Micronesians particularly of Naura, and in migrant Indians in S. Africa, Fiji, UK and USA. It is low in Eskimos, tribes in India and primitive populations of Africa. The prevalence of diabetes is likely to double itself during the next few years. By the year 2025, the number of people suffering from diabetes in the world is estimated to be 350 million, of which 70 million will be in India (Table 90.1). *The previously used terms insulin dependent diabetes mellitus (IDDM) and non-insulin dependent diabetes mellitus (NIDDM) are now termed as type 1 and type 2 diabetes mellitus.*

The Multicenter ICMR study done in 1972 reported prevalence rates 2.3% in urban and 1.5% in rural populations. More recent studies have shown that the prevalence is increasing with rates of 10-13% in urban and 2.4% in rural areas.

TABLE 90.1

Top five countries for estimated number of adults with diabetes (in million)

Country	1995	2025
1. India	19.4	70
2. China	16.0	37.6
3. United States	13.9	21.9
4. Russian Federation	8.9	12.2
5. Japan	6.3	8.5

TABLE 90.2

Age of onset of type 2 diabetes	
	%
Below 30 years	4
31-40	25
41-50	37
51-60	20
61-70	9
Above 70	5

TABLE 90.3

Ethnic variation in type 2 diabetes— prevalence in individuals aged 30-64 years (WHO)	
	Prevalence (%)
1. Pima Indians	50
2. Nauruans (South Pacific)	40
3. Native Australians	25
4. South Asians	20
5. West Africans	12

Type 2 diabetes is by far the most common type of diabetes encountered in India, accounting for more than 95% of the total. It generally starts between the age 30-40 years. The incidence increases with age, males are more commonly affected and 58% of the Indian diabetics have a positive family history of diabetes. The incidence of type 1 DM in India is very low (Tables 90.2 and 90.3).

Type 1 diabetes or IDDM is more common among the Caucasian populations of Finland, Sweden, USA and the UK accounting for 25-150 per 100,000 populations. Its prevalence in India is less than 1% of all diabetics.

A survey conducted in Neyyatinkara taluk of Trivandrum district under the auspices of Health Action by People on 83,00 persons revealed the overall prevalence of type 2 diabetes mellitus in persons aged 20 and above was 6.7% with higher prevalence in males. When adjusted to an internationally comparable population, the prevalence in those aged 30-64 worked out to be 8.2%. The demographic pattern of type 2 diabetes is also changing with a shift to start in younger persons. In the USA, where the overall prevalence increased by 33% between 1990 and 1998, the prevalence in the age group 30-39 years rose by 70%.

CLASSIFICATION

The Classification suggested by American Diabetes Association (ADA) is called as the etiological classification of diabetes and has the two main types of diabetes labeled as type 1 and type 2, along with gestational diabetes mellitus and the other specific types where a precise etiological factor is identified.

The revised diagnostic criteria give equal importance to the fasting and 2 hours post glucose load plasma

Break up of types of diabetes mellitus seen in a tertiary care hospital in Trivandrum 2005-2007

Type 2 DM	96%
Type 1 DM	0.8%
Gestation DM	1.2%
DM secondary to drugs, pancreatic disease and viral infections	± 2%
(Personal communication K.P. Poulouse Total no. of cases 8206)	

glucose (2h PG) for the diagnosis of diabetes, thereby eliminating the need for a routine oral glucose tolerance test (OGTT) for the diagnosis of diabetes. The cut-off level of fasting plasma glucose (FPG) for diagnosis of diabetes has been fixed as 126 mg/dl, since this reflects the same degree of hyperglycemia as a 2hr-PG of 200 mg/dl in terms of susceptibility for the development of micro-vascular and macrovascular complications. These criteria are expected to rationalize and simplify the diagnosis of diabetes and a larger number of people could be screened due to the simplification of the procedure of doing only fasting plasma glucose rather than an OGTT.

An intermediate group of subjects are recognized whose glucose levels, although not meeting the criteria for diabetes, are nevertheless too high to be considered altogether normal. This group is defined as having FPG levels above 100 mg/dL (6.1mmol/L) but below 126 mg/dL (7.0 mmol/L) and/or 2-hour values in the OGTT of 140 mg/dL (7.8 mmol/L or above, but below 200 mg/dL (11.1 mmol/L) (Table 90.4).

TABLE 90.4

Criteria for diagnosis of prediabetes		
Category	Fasting plasma glucose	2-hr post-prandial
1. Normal	< 100 mg/dL	< 140 mg/dL
2. Impaired fasting glucose (IFG)	100-125 mg/dL	<140 mg/dL
3. Impaired glucose tolerance (IGT)	<100 mg/dL	140-200 mg/dL

Etiopathogenesis

Type 1Diabetes: Type-1 diabetes mellitus has been classified into type-1A in which cell-mediated autoimmune attack on the beta cells is more prominent and type-1B in which the mechanism is less clear. Type1B is less frequent of the two. In Asians and Africans type-1B is seen more frequently than in the whites. HLADR / DQ confer 50% susceptibility whereas other genes confer 15%.

Classification of type-1 diabetes mellitus

- 1. Preclinical
 - a. Autoantibodies + / OGTT normal.

- b. Autoantibodies + / OGTT abnormal.
- c. Autoantibodies + / fasting hyperglycemia
- 2. Clinical – with diabetes
 - 1a. Autoantibodies present (autoimmune)
 - 1b. Autoantibodies absent (idiopathic)
- 3. Explosive onset / fulminant onset
- 4. Rapid onset
- 5. Late onset (LADA).

HLA Associations

Type 1 diabetes is a heterogeneous disorder in which several factors may play a role. These are the HLA system, viral infections, and autoimmune processes. Type 1 tends to be a familial disorder and there is a 25-fold increase in the risk amongst the siblings than the general population. Its inheritance is related to HLA loci on chromosome 6. It is seen that HLA B8, B15, B6, B21, BW3, DR3 and DR4 are associated with a higher risk of diabetes mellitus. On the other hand, a negative association has also been noted with HLA B7. In Asian Indians and Japanese, Type 2 appears to be associated more with HLA BW21 and BW 54 than with B8. HLA DR 4 is associated with two alleles of the DQB1 locus— DQW8 and DQW7 and five alleles of DRB1 locus. 96% of type 2 diabetes are homozygous for the amino acid aspartate at position 57 of the DQB chain, compared with only 19% of the general population. Both DQW8 (DR 3 associated) and DQW2 (DR4 associated) have a neutral amino acid at position 57 rather than aspartate. DR3 and DR4 (DQW 8 and DQW2) heterozygous individuals in the general population can now be identified who have an 8% risk of developing type 1 diabetes. DR2 and DQPi afford strong protection. Among identical twins only 50% show concordance for type 1 diabetes as against 100% for type 2 diabetes.

Despite current emphasis on genes within the major histocompatibility complex it is likely that genetic susceptibility to type 1 DM in humans will be influenced by multiple genes. Genetic heterogeneity will not only influence the probability of autoimmune-beta cell destruction but also the rate of damage and age of onset of type 1 DM. The DQB 1 allele is associated with high levels of anti-GAD (glutamic acid decarboxylase) antibodies and the DR4 alleles are associated with elevated levels of anti-insulin antibodies. For the development of type 1 DM, 50% susceptibility is conferred by HLA. Other genetic factors confer 15%. In the west, only 50-60% of type 1 diabetes are below the age of 18 years. The situation in India is not very clearly known.

The immunological and metabolic changes occur long before the development of symptoms of hyperglycemia. This period preceding the development of diabetes, is known as prediabetes during which there is increase in the levels of pancreatic islets cell antibodies (PICA) and impaired first phase insulin release (FPIR) and this is the stage where preventive strategies are being aimed at in interventional trials (Tables 90.5 to 90.7).

TABLE 90.5

Etiological classification of diabetes mellitus (ADA)

1. Type 1 diabetes (cell destruction, usually leading to absolute insulin deficiency)
 - Immune mediated
 - Idiopathic
2. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)
3. Other specific types
 - A. Genetic defects of cell function
 - Chromosome 12, HNF-1 (MODY 3)
 - Chromosome 7, glucokinase (MODY 2)
 - Chromosome 20, HNF-4 (MODY 1)
 - Mitochondrial DNA
 - Others.
 - B. Genetic defects in insulin action
 - Type A insulin resistance
 - Leprechaunism
 - Rabson-Mendenhall syndrome
 - Lipotrophic diabetes
 - Other
 - C. Diseases of the exocrine pancreas
 - Pancreatitis, Trauma, Pancreatectomy
 - Neoplasia
 - Cystic-Fibrosis, Hemochromatosis
 - Fibrocalculous pancreatopathy
 - Others
 - D. Endocrinopathy
 - Acromegaly/Cushing's syndrome
 - Glucagonoma, pheochromocytoma
 - Hyperthyroidism, somatostatinoma
 - Aldosteronoma
 - Others
 - E. Drug or chemical induced
 - Pentamidine
 - Nicotinic acid
 - Glucocorticoids
 - Thyroid hormone, diazoxide
 - Adrenergic agonists
 - Thiazides, phenytoin
 - Interferons
 - Others. Immunosuppressive drugs, steroids, tacrolimus, cyclosporin
 - F. Infections
 - Congenital rubella
 - Cytomegalovirus
 - Others
 - G. Uncommon forms of immune mediated diabetes
 - Stiff man syndrome
 - Anti-insulin receptor antibodies
 - Others
 - H. Genetic syndromes associated with diabetes
 - Down's syndrome, Turner's syndrome
 - Klinefelter's syndrome
 - Wolfram's syndrome, Friedreich's ataxia
 - Huntington's chorea
 - Laurence-Moon-Biedl syndrome
 - Myotonic dystrophy, porphyria
 - Prader-Willi syndrome
 - Others
4. Gestational diabetes mellitus

TABLE 90.6

Criteria for diagnosis of diabetes mellitus (ADA 1997) – accepted all the world over

- 1. Symptoms of diabetes plus casual plasma glucose 200 mg/dl (Casual is defined as any part of the day without regard to time since the last meal. The classic symptoms of diabetes include polyuria, polydipsia and unexplained weight loss)
OR
- 2. Fasting plasma glucose (FPG) 126 mg/dl (fasting is defined as no caloric intake for 8 hours)
OR
- 3. A 2-hour post-glucose-load plasma glucose (2 hr PGBS) 200 mg/dL during oral glucose tolerance test (OGTT).

Note: The test should be performed as described by the WHO using a glucose load containing the equivalent of 75g of anhydrous glucose dissolved in water. In the absence of unequivocal hyperglycemia with acute metabolic decompensation, these criteria should be confirmed by repeat testing on a different day.

The expert committee on the diagnosis and classification of diabetes mellitus (American Medical Association) has defined normal plasma glucose as 100mg/dL. Values between 100 and 126 are classified as impaired fasting plasma glucose (FPG).

Infections

Coxsackie B4 has been incriminated to play a causal role in the pathogenesis of type 1 DM. The other viruses known to play a role are mumps, CMV, EBV, varicella and the viruses causing infective hepatitis. An autoimmune etiology is suggested by its association with other autoimmune disorders such as Hashimoto’s thyroiditis, pernicious anemia and Addison’s disease. Pancreatic islet cell antibodies (PICA) and cell surface antibodies are demonstrable in several patients with recent onset type 1 DM. It is possible that all the three factors namely HLA status, viral infections and autoimmunity interact to produce the disease. In type 1 DM there is progressive loss of beta cell and in severe forms they may be totally absent. Insulin secretion progressively decreases to almost nil when the disease is fully established.

Autoantibodies in Type 1 DM

These are the antibodies produced against certain antigens of the beta cells. They have not been found to have any etiological role in type 1 diabetes, but mainly serve as markers of type 1 diabetes. These antigens are glutamic acid decarboxylase (GAD), insulin, islet cells etc. Based on the pathogenesis, type 1 DM has been divided into type 1A and type 1B. In the former there is cell mediated autoimmune attack on beta cells. Type 1B is less frequent. The cause is not clearly known. Type 1B is more seen in Asians and Africans.

TABLE 90.7

HLA antigens and the effects they confer on Type 1 diabetes susceptibility

HLA antigen	Effect on diabetes susceptibility
DQ2	Predisposes
DQ8	Predisposes
DQ7	Neutral/protects
DQ6	Protects
DQ18	Protects

Latent Autoimmune Diabetes in the Adult (LADA)

A slow onset form of type 1 diabetes has been described. In this subtype, subjects are initially well controlled with oral drugs (mimicking type 2 diabetes) but have a rapid acceleration of beta cell failure, leading to a frank autoimmune beta cell failure and long-term dependence on insulin in later years.

Type 2 DM

Type 2 DM (previously known as NIDDM) is considered as a ‘multifactorial’ or ‘complex’ disease due to the complex interaction between various genetic and environmental factors in its pathogenesis. Multiple evidence suggests that genetic factors play a major role in this condition. A genetic predisposition running through families is evident. Identical twins invariably develop type 2 diabetes when exposed to the same environmental factors. In genetically predisposed individuals several environmental factors precipitate the onset of diabetes. Important among these are obesity, physical inactivity, repeated pregnancies, infections, physical or psychological stress and *diabetogenic* drugs. Birth of large babies weighing above 4 kg is a strong pointer to the subsequent development of diabetes in the mother.

Obesity

The current obesity epidemic due to the modern sedentary life and caloric abundance is a major factor that predisposes to type 2 diabetes. Hence it is invariably seen that type 2 diabetes is closely related to obesity. Obese subjects show a relative resistance to the action of insulin due to a reduction in the number of insulin receptors on the target cells. The full complement of receptors is restored on shedding the excess weight.

There is an association between low birth weight in infancy and occurrence of IGT or DM in young adulthood. Increase in the body mass index (BMI) after the age of 2 years is also associated with the chance to develop DM.

Physical Inactivity

It seems to act as a factor favoring the onset of type 2 diabetes. Many of the diabetics are physically inactive. Physical exercise improves their exercise tolerance.

Role of Insulin antagonists: Glucose metabolism is delicately balanced by the coordinated effects of insulin antagonist hormones like glucagon, cortisol, catecholamines and growth hormone. Several other hormones also take part in the metabolism of carbohydrates. Imbalance of this hormonal profile results in carbohydrate intolerance.

Other antagonists to insulin: Antibodies to insulin may develop in individuals who are on treatment with insulins especially the animal insulins. The antibodies inactivate endogenous as well as administered insulin. Such patients show progressive insulin resistance. Fatty acids which compete with carbohydrate for metabolism in muscle lead to insulin resistance. In hyperlipidemia insulin dependent carbohydrate metabolism suffers and a relative insulin resistance develops.

Thus it would seem that persons are predisposed to develop type 2 diabetes by genetically. However lifestyle factors will determine the onset, age of onset, severity of the metabolic defect and further course. The interplay of genetic and environmental factors is well brought out by the studies on migrant Indians who have settled in affluent countries. These studies show that although the prevalence of diabetes in India is about 6-7%, it increases sharply to 10- 12% in Indians who have migrated to the developed countries.

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Amylin

The role of amylin, a 37-amino acid protein in the pathogenesis of type 2 diabetes has been established. Amylin is normally produced by the beta cells and co-secreted with insulin. This amylin has favorable metabolic effects in normal healthy individuals. But due to several reasons it gets deposited as insoluble fibers in the islets of patients with type 2 diabetes. This islet amyloidosis which is the main pathological hallmark seen in 90% of patients with type 2 diabetes at autopsy studies is considered to be one of the factors responsible for beta cell failure in addition to glucotoxicity and lipotoxicity.

INSULIN

This is the hormone produced by the beta cells of the islets of Langerhans and is composed of two polypeptide chains A and B linked together by two disulfide bonds. The precursor of insulin is proinsulin (big insulin) from which C-Peptide is broken off to form insulin with a molecular weight of 6000 D. Insulin is stored in the granules of the beta cells to be discharged into the interstitial fluid under appropriate stimulus. The proinsulin cross-reacts with insulin antibodies but has none of the metabolic effects of insulin. Insulin secreted by the beta cells enters the portal circulation and the liver traps 50-60%. The remaining portion enters the peripheral circulation. This

can be estimated as immunoreactive insulin (IRI). Basal value of IRI in health is 2-20 μ U/ml. Since C-peptide is secreted in equimolar quantities with insulin its level can be estimated to assess the functioning beta cell reserve.

The main stimulus for insulin formation and release is hyperglycemia caused by ingestion of carbohydrates. Other stimuli include rise in amino acids produced by protein digestion, growth hormone, glucagons, gastrin, pancreozymin, secretin and several other gut hormones especially gastric inhibitory polypeptide (now called glucose dependent insulinotropic polypeptide - GIP and neurohormones such as enkephalin and endorphins. Glucagon like peptide (GLP-1) is a potent insulin-releasing hormone, which triggers insulin release in response to postprandial hyperglycemia. Substances having this property are listed as **incretins**. Insulin reaches its target cells through blood. Levels of circulating insulin vary during the different periods of the day, being lowest in the fasting state. Immunoreactive insulin level ranges from 5-50 IU/mL in fasting normal subjects. On the target cell insulin binds to specific surface receptors and then initiates further biochemical events within the cell. The insulin receptors are large molecular weight proteins (500,000 D), which mediate insulin action. The metabolic actions are together known as post-receptor effect. Sensitivity of insulin depends upon the number of unbound receptors. The number of receptors varies inversely with the levels of circulatory insulin. The sensitivity of the receptors to insulin has a major role to play in the causation of diabetes mellitus. The genetic locus for insulin is on chromosome 11 and that for the receptors is on chromosome 19. Alteration of the cell membrane by insulin favors the entry of glucose, potassium and amino acids into muscles, liver and fat cells. Insulin retards gluconeogenesis in the liver. Excess glucose entering the skeletal muscle is converted into glycogen. Insulin helps to build up adipose tissue by aiding the conversion of glucose into fat and blocks the escape of fatty acids from fat cells. In conjunction with growth hormone, insulin enhances the incorporation of amino acids into peptides in the liver and skeletal muscles.

Insulin activates a series of lipid and protein kinase enzymes linked to the translocation of glucose transporters to the cell surface, synthesis of glycogen, proteins, messenger RNAs (mRNAs) and nuclear DNA which affect cell survival and proliferation.

Pathological Changes

Pancreas: In **type 1** diabetes the beta cells of the islets of Langerhans show reduction in number, degranulation and hyalinization. In recent onset type 1 DM lymphocytic infiltration of the islets occurs and this may be caused by viral infection. Inflammation is seen particularly around the beta cells only and not around the other types of cells.

In type 2 DM during the early phase the beta cells are normal in number or only slightly reduced. The beta cells lose their sensitivity to the hyperglycemic stimulus for releasing insulin. As a result insulin secretion loses its smooth and fine relationship with glucose level. It tends to be erratic. In the early stages of evolution of type 2 DM—the reduction in the sensitivity of the receptors is compensated by overproduction of insulin and accompanying hyperinsulinemia. Frank diabetes results when beta cells starts failing and insulin production comes down.

Insulin resistance in muscle develops early in persons who would develop type 2 diabetes later. Beta cell function starts deteriorating about 10 years before the onset of DM, by which time the beta cell function has fallen to 30% or less.

Acanthosis nigricans is a cutaneous marker of hyperinsulinemia. Both impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) lead to type 2 diabetes in a variable proportion of patients.

Several factors account for the frequency and time of onset of complications in diabetes. These include the abnormalities of glucose levels, genetic factors, smoking, obesity, hypertension, hyperlipidemia and others.

Vascular Changes

Diabetics show a predisposition to develop vascular lesions affecting both small and large blood vessels. In microangiopathy, there is specific involvement of the small blood vessels. Venules, capillaries and arterioles are affected in this process. There is deposition of PAS (periodic acid Schiff) positive material in the capillary basement membrane. Glycosylation of several proteins in the vessel wall results in increased permeability. The basement membrane is thickened. Ultimately there is vascular occlusion.

Microangiopathy is most marked in type 1, developing early in life but also occurs in type 2. Various factors like endothelial damage, increased plasma viscosity, erythrocyte aggregation, reduced red cell deformability and increased platelet adhesion lead to microangiopathy. The problem is more complex and the entire process is still not fully understood. Microangiopathy affects several organ systems. The main lesions are seen in the retina; kidneys, peripheral nerves and heart giving rise to diabetic retinopathy, nephropathy, many forms of diabetic neuropathy and cardiomyopathy.

Macroangiopathy

The diabetic is prone to develop occlusive vascular disease in medium sized arteries such as the coronary, cerebral and peripheral limb vessels. The process is one of atheroma which sets in at younger ages and is more extensive than that occurring in non diabetics. These lesions lead to increased risk of ischemic heart disease, cerebrovascular accidents and ischemia to the limbs with

intermittent claudication and peripheral gangrene. Macroangiopathy largely accounts for the steep rise in mortality in middle-aged diabetics.

Retinopathy

Diabetes mellitus produces a classical retinopathy. A specific change occurs in the vessels leading to loss of mural cells (pericytes) and the formation of micro aneurysms. The occurrence of retinopathy is related more to the duration of the disease than to the severity. Once initiated the fundus changes are usually progressive. The early changes are venous dilation and the appearance of small dot like micro aneurysms in the perimacular area. Arterial blood is shunted and this leads to ischemia of the retina. Increased vascular permeability accounts for the formation of exudates. In the next stage dot and blot hemorrhages predominate. Large subhyaloid hemorrhages and vitreous hemorrhages may develop and vision is seriously impaired. Such hemorrhages are due to rupture of newly formed blood vessels. As these hemorrhages are absorbed, organization by fibrous tissue results and multiple bands of retinitis proliferans develop. These lead to permanent visual impairment. The fibrous bands may contract giving rise to retinal detachment. Leaking vessels in the retina can be demonstrated by fluorescein angiography. Retinopathy is usually associated with advanced nephropathy. Sometimes in diabetic ketoacidosis with severe hyperlipidemia the fat gives a milky white appearance to the retinal arteries called “lipemia retinalis”.

Renal Lesions

These are commonly seen in subjects who have had diabetes for over 15-20 years. Vascular changes include (i) arteriosclerosis of the renal artery, (ii) sclerosis of the arterioles and (iii) glomerulosclerosis. Glomerulosclerosis may be nodular (Kimmelstiel-wilson lesion) or diffuse. There is accumulation of PAS positive eosinophilic material within the mesangium. There is thickening of the glomerular capillary basement membrane. The establishment of glomerulosclerosis is indicated by the presence of proteinuria. Further damage to the glomeruli results in the development of chronic renal failure.

Distinct stages can be defined in the evolution of diabetic nephropathy. In the initial stages, asymptomatic microalbuminuria in which up to 200 mcg/minute of albumin may be lost in the urine. Normal subjects do not lose more than 20 mcg/min or 300 mg of protein in 24 hours. Microalbuminuria is not detectable by the ordinary laboratory tests. In type 1 DM there is elevation of systolic BP during sleep preceding micro albuminuria. This rise in BP is an important contributory factor in the development of structural changes in the kidneys. It is absolutely necessary to control blood pressure also along with blood sugar to prevent deterioration.

In the early stage the kidneys are enlarged, more vascular and the glomerular filtration rate (GFR) is

increased. *In the second stage*, there is microalbuminuria and in *third stage* the proteinuria is more pronounced and easily detectable by routine tests. Loss of 3.5g or more of protein in 24 hours may lead to the development of nephrotic syndrome. Hypertension develops during this stage. In the fourth stage further structural changes develop and the glomerular filtration rate comes down with gradual increase in the blood levels of metabolic waste products such as creatinine and urea. The fifth stage is one of gross reduction of glomerular filtration and overt renal failure with azotemia, severe hypertension and complications such as cardiac failure and end stage renal failure. Autonomic neuropathy may lead to functional obstruction of the bladder, retention with over flow, urinary infection and further deterioration of renal functions. Another system of classification is based on creatinine clearance.

The diabetic patient is predisposed to develop urinary infection and therefore acute and chronic pyelonephritis are very common. Fulminant urinary infection leads to ischemic necrosis of the renal papillae. This presents as acute anuric renal failure. Fleshy masses may be passed in the urine. These are the necrosed papillae and the condition is called papillitis necroticans ulcerans. Emphysematous pyelonephritis is another serious complication.

Peripheral Nerves

In the myelinated nerve fibers, axonal atrophy was considered to be the primary lesion, secondary to ineffective axonal transport. Axoglial dysfunction, and abnormalities of paranodal connections between the terminal myelin loops and the axonal membrane have also been described. This could explain the reduction in nerve conduction velocity. This improves with therapeutic inhibition of aldose reductase. More recent studies, however provide evidence for the presence of demyelination and hence Schwann's cell involvement is the primary lesion. As the myelinated fibers degenerate, there is an attempt to regenerate, which manifests in the form of regeneration clusters. With progress of the neuropathy the density of the regeneration clusters also comes down.

Structural abnormalities have also been found in the vessels supplying the nerve fibers. The epineural vessels show arteriolar attenuation, venous distension, arterio-venous shunting and new vessel formation along with intimal hyperplasia and hypertrophy, denervation and reduction in neuropeptide expression. The perineural vessels also demonstrate basement membrane thickening and endothelial cell hypertrophy and hyperplasia. There is also a reduction in capillary density and occurrence of pericyte loss with reduction of endoneural oxygen tension and blood flow to the nerves. In a large series from south India overall prevalence of diabetic neuropathy was 19.1% among a group of 1000 consecutive diabetic patients. Age and the duration of diabetes were important risk factors.

CLINICAL FEATURES

The clinical manifestations of diabetes are protean. Though the symptoms are similar in both types of diabetes, in type 1 they develop acutely whereas in the majority of the type 2 the onset is insidious. Type 1 patients are usually below the age of 30, thin and emaciated and unless promptly treated with insulin, they would develop ketoacidosis.

Clinical features	Type 1	Type 2
Usual age at onset (yrs)	5-30 years	35-65 years
Sex	M:F 1:1	F>M (in India)
Prevalence Among diabetes	15-18% in Caucasians 1% in Indians	95-98% of Indians
Genetic	Heredity+ Strong HLA association	Heredity +++ No HLA association
Nutrition	Lean	Often obese
Usual onset	Rapid with classic symptoms	Slow, insidious, often with only mild symptoms
Ketosis	Prone	Not prone
Islet cell antibodies	May be present within 1 year of onset	Absent
Treatment modality	Almost all require insulin for control of sugar	Majority can be controlled by oral hypoglycemic drugs (OHAs)

Due to the high prevalence of obesity, type 2 diabetes is occurring at earlier ages as a global phenomenon, especially in developed countries.

Type 2 patients are generally above the age of 30, obese, usually asymptomatic and may present directly with the vascular complications of diabetes. **Around 50% of the cases present with the classical symptoms of polyuria, polyphagia and weight loss.** These symptoms can be directly correlated with hyperglycemia and glycosuria. Other clinical presentations which warrant full investigation to exclude diabetes are (i) non-healing ulcers (ii) recurrent respiratory or urinary tract infections (iii) Rapid changes in refraction of the eyes (iv) steady and unexplained rapid weight loss (v) increased tendency for fungal infections like moniliasis, balanoposthitis and vulvitis; (vi) unexplained peripheral neuropathy (vii) premature onset of ischemic heart disease, stroke or vascular occlusions (viii) history of overweight babies and recurrent fetal loss in women (ix) premature cataract often below the age of 50 years and retinopathy

(x) impotence in males, and (xi) any vague ill-health. In some cases, diabetics may present to the doctor for the first time with any of the major emergencies, without any apparent illness previously.

Malnutrition Related Diabetes Mellitus (MRDM)

Syn: type 2 lean diabetes

The latest classification proposed by WHO has deleted the term MRDM and replaced it by the title “type 2 lean diabetics.” There patients may require insulin for control. A significant proportion of young people with diabetes in developing tropical countries present with certain characteristics symptoms and metabolic profile rendering their categorization into either type 1 or type 2 difficult. Previously this subset has been classified separately by the WHO study group as malnutrition related diabetes mellitus (MRDM). MRDM has been further subclassified into (a) fibrocalculous pancreatic diabetes (FCPD) and (b) protein deficient diabetes mellitus.

Clinical characteristics of MRDM are as follows: Age of onset between 10 and 30 years, body mass index <19, moderate to severe hyperglycemia, requirement of large doses of insulin for control, ketosis resistance and history of malnutrition in childhood. The subgroup of FCPD shows evidence of pancreatic calcification, often demonstrable in plain x-ray of the abdomen.

Maturity Onset Diabetes of the Young (MODY)

The incidence of type 2 DM is increasing in the younger age groups all over the world. In India there is 54% increase in the prevalence of type 2 DM in the 15-19 years old adolescents. Many risk factors are associated with this increase in prevalence during childhood. These include obesity which increases insulin resistance, racial factors, puberty and gender characteristics. In addition there is

decrease in physical activity, unhealthy food habits including excessive consumption of calories and trans-fatty acids, and faster ways of life.

The different types of diabetes that can be seen in the young are:

- 1. Type 1 DM
- 2. Type 2 DM
- 3. Malnutrition related DM (MRDM) and
- 4. Maturity onset diabetes of the young (MODY).

MODY accounts for about 2-3% of all type 2 DM and about 27% of all diabetes in the young below 30 years in India. The clinical picture of type 2 DM and MODY are almost similar. Both are insidious in onset and non-ketotic, but the latter develops at a much younger age. Family history is very prominent in MODY. BMI may be high in more than 40% of MODY cases. It may be low in 13%. Features of the metabolic syndrome such as acanthosis nigricans, hypertension and abdominal obesity are absent in MODY. Strong family history running into three generations with autosomal dominant inheritance is the most characteristic feature of MODY.

Although six different forms of MODY have been identified MODY-1 to MODY- 6, each involving mutation of a different gene located in a different chromosome, only three are considered more important. The first MODY gene to be recognized was a glucokinase gene (GCKI) followed by hepatocyte nuclear factors (HNF 1α, 4 α, 1β).

HNFs are transcription factors that regulate the expression of several genes in the liver and beta cells of pancreas.

In all types of MODY, there is defect in insulin secretion by the beta cells, but the clinical presentation may be different. Some may respond to OHAs, but others require insulin (Tables 90.8 and 90.9).

Prediabetes: Some patients show borderline values of glucose on oral glucose tolerance test (OGTT), not completely fulfilling the criteria for diagnosis of diabetes.

Genetic and clinical features of MODY			
Type	Gene defects	Prevalence	Signs
1. MODY 1	HNF 4 α Chromosome-20q12, 13 involved	5%	Severe hyperglycemia, microvascular complications, they may need insulin
2. MODY 2	Glucokinase chromosome 7p 15	10%	Mild, microvascular complications are mild. Diet control alone may be sufficient
3. MODY 3	HNF 1 α commonest type chromosome 12q.24	70%	Symptoms as in MODY 1
4. MODY 4	IPFI mutation (insulin promoter factor 1) chromosome 13q. 12	Rare	Like MODY 3
5. MODY 5	HNF 1B mutation chromosome 17q 12-21	Rare	Microvascular complications and renal failure are common
6. MODY 6	Chromosome 2q. 32	Very rare	

TABLE 90.9

Clinical differences between type 1 and type 2 DM

	Type 1 DM	Type 2 DM
Insulin deficiency	++++	+
Insulin resistance	Rare	+++ common
Insulin requirement	Low to moderate	Variable
Sulphonylurea drugs	Unresponsive	Responsive
Common cause of death	Nephropathy CHD, DKA	CHD, nephropathy, stroke and gangrene
CHD – coronary heart disease; DKA- diabetic ketoacidosis.		

This group has been delineated as a separate entity- prediabetes. This includes (1) impaired fasting glucose (IFG) and (2) impaired glucose tolerance (IGT) based on data from several epidemiological studies (Table 90.4). IGT progresses to diabetes in many subjects, usually at a rate of about 2% per year if not managed early. Some patients with IGT continue to remain in the same category or may revert to normal glucose tolerance. Treatment with oral hypoglycemic agents does not influence the subsequent outcome. There is increased frequency of morbidity and mortality from macroangiopathy and cardiovascular disease, while specific diabetic microangiopathy is rare. Hypertension and coronary artery disease (CAD) are also common in IGT patients as in classic type 2 DM patients. Prevalence of IGT is also increasing and a recent study from Chennai (MV diabetic centre) revealed that 16% of the adult population had IGT. Therefore it is obvious that the diagnosis of IGT warrants careful follow-up of the subjects, with appropriate advice in lifestyle modifications- diet, exercise and cessation of smoking.

DIAGNOSIS

Diabetics with classic symptoms can be diagnosed clinically, but since many cases may be asymptomatic, diabetes should be suspected even in the absence of symptoms. The clinical symptoms and the biochemical alterations do not go hand in hand in many cases. Diabetes being mainly a biochemical disease with several different but inter-related biochemical and molecular abnormalities, should always be diagnosed and managed with biochemical monitoring along with clinical examination. Fasting plasma glucose levels above 126 mg/dL (6.7 mmol/L) or postprandial plasma glucose levels above 200 mg/dL are diagnostic. It is always better to do both estimations to confirm the diagnosis.

Estimation of FBS and PPBS has become mandatory investigations in all health check up examinations.

Urine tests: These tests can be used for initial screening and follow-up of cases under treatment. Urinary glucose

does not always directly reflect the blood glucose level. The value of urine examination cannot be underestimated since proteinuria, ketonuria and the microscopic abnormalities can be detected only by examining the urine.

Glucose in urine is tested by the Benedict's test and Clinitest (Chemtab), which detect reducing substances non-specifically. While glucose is by far the most common reducing substance in urine, the possibility of other reducing substance should be kept in mind and the enzyme methods (employing glucose oxidase) which are specific for glucose (Clinistix, Diastix) should be employed.

If the Benedict's test is positive and the glucose oxidase is negative, the presence of other reducing substances such as ascorbic acid, aspirin and lactose should be suspected.

Blood glucose estimation: Various methods are employed to estimate the blood glucose. The methods using copper reduction (Folin-Wu or Nelson Somogyi) also detect the reducing substances like uric acid, creatinine and hence their values are 20-30 mg/dL higher than those obtained by the glucose oxidase method which gives the true glucose values. Highly accurate and rapid (1-2 min) devices are now available based on immobilized glucose oxidase electrodes. Hexokinase and glucose dehydrogenase methods are used for reference. Blood sugar estimations are mandatory for confirming the diagnosis of diabetes. Both fasting and postprandial values should be estimated. In mild diabetes the fasting blood sugar values may be below 126 mg /dL and therefore the diagnosis is likely to be missed if only the fasting blood sugar is estimated.

Glucose tolerance test (GTT): The oral glucose tolerance test (OGTT) is mainly used for diagnosis of diabetes when blood glucose levels are equivocal, during pregnancy, or in an epidemiological setting to screen for diabetes and impaired glucose tolerance.

The OGTT should be administered in the morning after at least 3 days of unrestricted diet (greater than 150 g of carbohydrate daily) and usual physical activity. The test should be preceded by an overnight fast of 8-14 h. during which period only water may be drunk. Smoking is not permitted during the test. The presence of factors such as medications, inactivity and infection that influence interpretation of the results of the test must be recorded.

After collection of the fasting blood sample, the subject should drink 75 g of anhydrous glucose dissolved in 250-300 mL of water over the course of 5 minutes. For children, the test load should be 1.75g of glucose per kg of body weight, up to a maximum of 75g of glucose. Blood samples should be once again collected 2 hr after the test load.

If there is delay in estimation of glucose the blood samples should be collected in a tube containing sodium fluoride (6 mg/mL of whole blood) and immediately

centrifuged to separate the plasma. In subjects having symptoms of diabetes, a single fasting value above 126 mg/dL or a 2-hour blood glucose value above 200 mg/dL after 75 g of glucose oral may be taken to be diagnostic. In asymptomatic subjects at least two abnormal blood glucose values should be insisted upon to confirm the clinical diagnosis.

The glucose tolerance test may be abnormal in conditions other than diabetes mellitus. These include cirrhosis of the liver, chronic renal failure, starvation and under nutrition, stressful situations, hypokalemia and use of diabetogenic drugs.

Glucometers: these are instruments which can be used at home for self monitoring of blood glucose and is freely available in India for prices ranging from Rs. 1500-3500. The blood glucose can be estimated within 5 seconds using a special paper strip and blood from finger prick. Usually the values are higher by 10-15 mg/dL as compared to laboratory values, since laboratory values denote venous blood glucose while glucometers use capillary blood.

Glycosylated hemoglobin: Glycosylation is an irreversible non-enzymic process. It depends directly on the blood levels of glucose. Once the hemoglobin is glycosylated it remains in circulation as such till the erythrocyte completes its life span. The percentage of glycosylated hemoglobin has been used as a guide to the presence and level of hyperglycemia during the past 3 months. Glycosylated hemoglobin is termed HbA1c. This particular fraction is measured and expressed as the percentage of the total hemoglobin content. A diabetic is considered to be well controlled if the HbA1c is below 6.5%. As the life of an RBC is about 120 days, HbA1c is an index of the average sugar levels over the previous 3 months.

Even at the time of first consultation, major complications may be present in the patient. Patients with hypertension, microalbuminuria, early sensory neuropathy and retinopathy may be completely asymptomatic, and hence these may be missed, if not looked for. Many patients go around with the disease without being diagnosed till they get major complications.

In addition, lipid profile, urine examination for microalbuminuria, ophthalmic examination, exercise ECG, neuropathy tests using biothesiometer and Doppler studies should be done routinely at the first examination in those with duration above 5 years.

Prognosis

Once diabetes is established, it tends to be life long. Proper management can achieve euglycemia during most part of the day and thereby confer clinical normalcy and prevent complications. Prognosis in the diabetic depends largely on the presence or absence of chronic vascular

complications. Present day treatment has served to prevent or successfully overcome acute complications like ketoacidosis, infections, hypoglycemia and lactic acidosis. The long-term complications affecting the kidneys, nerves and blood vessels also depend on a great deal on hyperglycemia. Other parameters such as lipid abnormalities, microalbuminuria and hypertension influence the prognosis adversely.

These complications can also be prevented to a great extent by rigid diet control, exercise and regular therapy. Once established the degenerative complications progress relentlessly and lead to damage of vital organs like the kidneys, heart and brain unless properly managed. Death is mainly due to complications like myocardial infarction, cerebrovascular accidents, end stage renal failure or acute diabetic complications such as diabetic coma, hypoglycemia and infections. Cumulative morbidity occurs due to blindness, peripheral vascular disease and peripheral neuropathy which cripple the long term survivors. Proper therapy also arrests the progression of established complications. Cardiovascular complications can be reduced further by elimination of other risk factors like hypertension, cigarette smoking, obesity and hyperlipidemia.

The Diabetes control and Complications Trial (DCCT) (1991-95) which was carried out at 14 different centers in the USA and Canada had enrolled 1441 patients with type 1 diabetes with the objective of assessing the role of intensive insulin therapy in the primary prevention of microangiopathic complications as well as in arresting the progression of these complications. The data has convincingly brought out the importance of tight metabolic control in preventing the development of microangiopathy and arresting its progression. The risk reduction of various measured outcomes ranged from 35-75%. A beneficial effect on the macroangiopathy was also demonstrated.

The United Kingdom Prospective Diabetes Study (UKPDS), a large study carried out in 23 centers all over the United Kingdom, followed 5102 patients with newly diagnosed type 2 diabetes over 5 years (1987-91) and reported a significant decline in the incidence of macrovascular disease with strict glycemic control. Additional benefits were also obtained with control of blood pressure. Strict control of blood pressure also brought down the incidence of stroke and heart failure. Both these trials and several other reports emphasize the role of strict biochemical control of all forms of diabetes mellitus in reducing the incidence of complications. Follow-up of patients included in the DCCT 1993 trial has shown that the benefits of strict control of the diabetic state continued even four years after the termination of the study. With proper motivation and education of the patient, considerable improvement in glycemic control can be achieved in almost all patients at relatively low cost.

TREATMENT

The aim of treatment is to achieve normal blood glucose levels throughout day and night, to alleviate symptoms and to prevent complications. The four pillars of diabetic management are diet, exercise, drugs and patient education, backed up by regular monitoring of glycemic control and early detection and treatment of complications.

Dietary Management
(Medical Nutrition Therapy)

Diet is the corner stone in the management of diabetes. The objective of dietary therapy is the optimization of glycemic control and to provide a nutritious and balanced diet. In type 1 DM patients the total energy input has to be relatively higher in order to regain ideal weight and growth. In type 2 patients the calories need to be restricted in order to avoid obesity. Dietary articles such as saturated fats, excess salt and cholesterol which promote vascular complications have to be avoided.

Goals of Medical Nutrition Therapy

1. To achieve and maintain near normal glycemia (euglycemia).
2. To achieve and maintain optimal lipid profile. (total cholesterol < 150, triglyceride $\pm$ 120, HDL>50 and LDL<100/mg/dL).
3. To achieve and maintain normal blood pressure levels around 120 to 130 / 80 to 85 mmHg.
4. To adjust the nutrient intake to restore and maintain ideal body weight to avoid dyslipidemia, cardiovascular disease, hypertension and nephropathy. During childhood and pregnancy adjustment for growth also should be provided.
5. For elderly patients, provision for proper nutrition and psychosocial needs.

In type 2 diabetic patients the first step would be dietary therapy alone along with exercise. They should be given a trial of dietary therapy for 4-8 weeks. About 50% of the patients come under control with diet alone. Proper patient education helps to improve adherence to treatment.

The following points have to be considered while prescribing a diet for a diabetic-

1. The type of diabetes- type 1 or type 2
2. The weight of the individual in comparison with his ideal body weight (BMI)
3. His occupation and activities and to assess his caloric requirements
4. The presence of any complications

An appropriate assessment of the caloric needs of each diabetic individual should be done.

TABLE 90.10

Optimum daily needs in calorie intake per kg of desirable body weight			
Body weight	Activity		
	Sedentary	Moderate	Heavy
Obese	20	25	30
Standard weight	30	35	40
Underweight	35	40	45
(Additional allowances are required in case of pregnancy, lactation and growing children.)			

Total Caloric Intake

This is the most important step while prescribing a diet. Total caloric intake depends on the patient's body weight, degree of physical activity and the presence of any other comorbid illnesses. Obesity is an important factor in terms of target cell resistance to insulin action.

The body mass index (BMI) will help to determine the total caloric requirement.

BMI = Weight (in Kg) / Height in m². It is desirable to keep the BMI between 22 and 25.

Ideal body weight can be readily calculated by the formula:

ideal body weight = height in cm – 100.

The recommended daily allowance is 30 Kcal/kg of desirable body weight to patients with average activity except in the case of obesity where appropriate changes have to be made as given in the Table 90.10.

Having calculated the number of calories required, they are distributed into at least three principal meals and one or two small snacks. These calories are derived from three principal sources—carbohydrates, protein and fats. Each fraction has its own importance and should provide 60% of the calories from carbohydrates and 20% each from proteins and fats.

When instructing on the diet regime the following points should be stressed.

1. ***It is not a reduction in the diet; on the other hand it is a modulation to suit the particular need of the individual.*** This concept will help to reduce the psychological resistance in accepting the diet.
2. The patient and his spouse should be counseled together, so that the latter will understand the principles and help to provide the diet appropriately.
3. Whenever possible, the dietary articles should be prescribed in terms of weight so that at least on a few occasions the actual quantities would be determined and adopted.
4. It is better to prescribe the diet in terms of the primary food articles such as rice, meat, fish and others so that the patient can determine the various items of the menu in relation to the allowed foodstuff.

5. Many patients are under the wrong impression that reducing the food further than what is prescribed may be beneficial and this should be avoided.
6. Both the quantity to diet and its timing are important since other aspects of management such as medication and exercise are timed in relation to the diet. As far as possible the diet should conform to the cultural habits and socioeconomic condition of the patient.
7. Vast majority of treatment failure can be avoided by proper dietary instructions.
8. At all follow-up visits enquiry on the diet should be made and the need for strict adherence stressed.
9. As far as possible the patient should be involved in the formulation of the diet and such a participatory instruction assures better compliance.

Carbohydrates

The amount of carbohydrates to be permitted in diet of diabetic patients has been an area of controversy. Till recently most people recommended restriction of carbohydrates in the diet to provide only 30-40% of the calories. Our diets in India are cereal based and have a high carbohydrate component (about 70%). Several studies in India have shown that good metabolic control can be achieved with high carbohydrate diets, provided the caloric intake is optimized. Such diets provided better patient compliance and had no adverse effect on the long-term complications.

The American Diabetic Association and the European Diabetic Association study groups have also altered their dietary recommendations. In an attempt to reduce cardiovascular morbidity and mortality, they now recommend a liberalized use of carbohydrates in the diet up to 50-60% of the calories. This also helps to reduce the intake of saturated fats. Modification in the type of carbohydrate can be achieved by increasing the intake of legumes and pulses, green leafy vegetables and other vegetables, which will increase the content of complex carbohydrates and fiber.

Fats

The fat content of diet should be 20-25% of the total calories. The distribution of the type of fat should be equal, i.e. saturated fats and mono and polyunsaturated fats should be equally distributed to make up the total fat intake. The dietary cholesterol should be less than 300 mg/day. Invisible fat is derived in a fair amount from cereals, legumes and seeds and contributes to 5-10% of the total energy intake. Milk and Milk products contribute approximately to 40-45% of the total fat content in vegetarian diets. Milk fat is a saturated fat.

Proteins

Protein intake has been recommended as 0.8 g/kg body weight and should contribute to 12–20% of the total caloric intake. Vegetable proteins derived from cereals and lentils, do not contain cholesterol. They have high fiber content. Animal protein is rich in saturated fats and tends to increase cholesterol and triglycerides. Lean meat and fish are to be preferred to fatty meat in order to minimize the risk. When renal failure occurs, strict-protein restriction is instituted.

The dietary salt should be less than 6 g/day. In the presence of hypertension or renal failure it should be reduced to around 3 g/day.

Alcohol should be avoided as far as possible. Alcohol intake will increase the risk of hypoglycemia by inhibiting gluconeogenesis. It may induce ketoacidosis, lactic acidosis and may contribute to peripheral neuropathy. Alcohol also induces hypertriglyceridemia and hyperuricemia. Alcohol is an additional source of calories, without any further nutritional values each mL providing 7 calories. If consumed it should be taken only in moderate quantities (1-2 drinks/day i.e. 20-40 mL/day).

Exercise

In type 2 diabetes, regular exercise forms an important component of therapy along with dietary regulation and oral hypoglycemic agents. However a careful assessment of the expected benefits and associated risks of exercise in individual patients should be made while incorporating an exercise program in the treatment. Appropriate monitoring should be done to avoid complications. Exercise should not be recommended indiscriminately in all type 1 diabetic patients but efforts should be made, to make it possible for those who want to exercise to do so as safely as possible.

Endocrine/Physiological Responses during Exercise

1. Suppression of insulin release – directly as well as through epinephrine.
2. Sympathetic system activation – which inhibits insulin release (by alpha-receptor stimulation) and stimulates lipolysis.
3. Non-insulin dependent glucose uptake in the periphery.

In both type 1 and type 2 diabetic patients who are under good control the response to exercise will be normal. In untreated type 1 patients there is an increased production of FFA from adipocyte lipolysis, which leads to decreased glucose uptake in the periphery. This can even precipitate diabetic ketoacidosis in some patients. In the well-controlled patients this does not occur (Tables 90.11 and 90.12).

TABLE 90.11

Exercise in diabetes: benefits exceed the risks

Benefits of Exercise:

1. It lowers blood glucose concentration.
2. It improves insulin sensitivity.
3. Decreases triglyceride, increases HDL cholesterol and decreases LDL cholesterol.
4. It lowers blood pressure in mild to moderate hypertension.
5. It causes weight reduction by metabolizing adipose tissue.
6. It helps in cardiovascular conditioning.
7. It improves sense of well-being and quality of life.

Risks of unsupervised exercise in uncontrolled diabetic

1. Hypoglycemia
2. Hyperglycemia after very strenuous exercise, particularly in poorly controlled diabetes.
3. Precipitation or exacerbation of cardiovascular disease and acute cardiac events like arrhythmias, sudden death and cardiac failure.
4. Worsening of long term diabetic complications – particularly proliferative retinopathy, nephropathy (increases proteinuria), peripheral neuropathy risk of soft tissue and joint injuries. Autonomic neuropathy (causes reduced exercise tolerance, impaired response to dehydration and postural hypotension).

While prescribing exercise, it should suit the social and economic condition of the patient and his work schedule. Regular exercise as part of the therapeutic intervention should be taken by all diabetics, irrespective of the physical activity entailed in their regular occupation. Maximum benefit is achieved by exercises such as brisk walking (4-5 km/hour), swimming, cycling and such other aerobic exercises. At least five sessions a week should be performed in order to achieve optimal benefit. While starting the exercise program in persons above the age of 35 years clinical assessment of their cardiovascular status should be done and introduction of the exercise regimen should be gradual, so as not to precipitate any acute cardiovascular events.

For the average middle-aged Indian diabetic the following exercise regimen is adequate.

- Walk 3 km on level ground over a period of 45 minutes
- Swim for 30 minutes at average speed without cardiovascular distress.
- Cycle on level ground at 8 km/hour for 30 minutes.

Regular sports and games activities can be undertaken and should be encouraged by those who desire to do them, with special provision made for the diet and medications. Since such sport activities are likely to be intermittent rather than regular, in practice walking or cycling is more regularly available.

Before an exercise program is initiated, a fair control of blood glucose is to be ensured and a thorough clinical evaluation of the patient should be made particularly in regard to complications of diabetes such as hypertension, coronary artery disease, peripheral vascular disease, retinopathy and nephropathy.

Yoga exercises Recently several well-planned studies have demonstrated the beneficial effects of yogic practices in diabetics. Patients with diabetes demonstrated a significant fall in fasting and postprandial blood glucose values and HbA1c, with reduction in the requirements of OHA and insulin. Type 1 diabetic patients with brittle diabetes showed marked improvement with the practice of yoga. There was a salutary effect on the lipid profile, with a fall in serum cholesterol, triglycerides and an increase in HDL- cholesterol fraction. Certain *Asanas* (specific postural manipulations which have to be learnt under supervision) have been identified as useful in the control of diabetes. Thus yogic practices have a useful role in the control of diabetes and prevention of its long-term complications.

ORAL HYPOGLYCEMIC AGENTS (OHAs)

The oral hypoglycemic agents are indicated in type 2 diabetes when diet and exercise fail to achieve euglycemia. The two major groups of drugs in use are a) Insulin

TABLE 90.12

Pre-exercise checklist for diabetic patients

1. Correct planning of exercise program (which includes duration and intensity of exercise).
2. Review diabetic medications (need to alter dosage, timing/site of insulin injection).
3. Perform necessary tests to rule out any long-standing, silent diabetic complications that may need a change in exercise pattern:
 - a. Treadmill test/Stress Echo – to rule out coronary artery disease and also to know the individual's exercise tolerance capacity.
 - b. Ophthalmic fundoscopy – to rule out proliferative retinopathy; if present, anaerobic exercise has to be avoided.
 - c. Biothesiometry. This is the method to determine any impairment of vibratory sensation in the extremities accurately in order to assess the extent and severity of sensory loss.
The patients should be advised on appropriate footwear which will ensure protection to the feet and avoid localized pressure and trauma.
4. The blood glucose should be checked before the exercise.

Plasma glucose levels:

- a. If < 100 mg/dL – advise pre-exercise snacks.
- b. If 100-250 mg/dL – can proceed with exercise.
- c. If > 250 mg/dl – check urinary ketones – if positive, insulin should be started. Resume exercise only after correction of ketosis.

secretagogues (sulfonyl urea compounds) and b) insulin sensitizers (glitazones).

Contraindications to the use of OHA

- 1. Type 1 diabetes
- 2. Type 2 diabetes patients during episodes of infections
- 3. Other stressful situations like myocardial infarction stroke
- 4. During pregnancy
- 5. On patients who have to undergo surgery and
- 6. In renal and hepatic insufficiency. Lean type 2 diabetes patients with a postprandial blood sugar of >400 mg/dl and MRDM patients will also require insulin therapy.

Sulphonylurea (SU) Compounds
(Tables 90.13 and 90.14)

Actions and Indications

The SU compounds stimulate the beta cells of the pancreas to release insulin, as evidenced by an increase in the plasma levels of both basal and postprandial insulin in Type-2 diabetes mellitus patients. A minimum of 30% of beta cells is required for their optimal action. They improve the sensitivity of beta cells to glucose and other secretagogues. They have a beta cytotropic action. They also have extra pancreatic actions and reduce neoglucogenesis and glycogenolysis. They improve the receptor binding of insulin and also act on the post receptor sites. Both these actions help in decreasing the peripheral insulin resistance – a key factor in the pathogenesis of type-2 DM. This action leads to improvement in the response to exogenous insulin as well. There is no evidence that SU cause beta cell exhaustion. However continuous exposure to maximum doses may result in desensitization of beta cells.

Therapy should be initiated with the smallest dose, taken 15-30 minutes before breakfast and small increments should be made at weekly intervals till the optimum dose is reached. The sulphonylureas are similar in effectiveness in equipotent doses and in the absence of any specific reason such as adverse side effects, cost or nonavailability, there is no need to change the medication in patients who are adequately controlled. So

TABLE 90.13 Classification of OHAs	
Mode of action	Drugs
1. Insulin secretagogues	a. Sulphonylureas b. Meglitinides c. GLP-1 agonists d. Amylin
2. Insulin sensitizers	a. Biguanides b. Thiazolidenidiones
3. Inhibitors of GI glucose absorption	a. Alpha-Glucosidase Inhibitors

also there is no advantage in combining two or more sulphonylurea drugs.

Choice of compound: Tolbutamide and chlorpropamide which were among the initial sulphonylurea drugs have been almost replaced by the newer derivatives which are easier to administer, safer and predictable in action. **Glibenclamide** has a better effect on fasting plasma glucose than glipizide as it causes greater suppression of hepatic glucose production. **Glipizide** and **gliclazide** induces greater insulin levels in the postprandial state.

Glimepiride is the recently developed sulphonylurea, which is referred to as the third generation sulphonylurea, because it differs from all other preceding members of its class in several important attributes. It has the *highest weight for weight potency*, and long duration of action requiring once daily dosage. Its onset of action is very rapid. It has no pharmacokinetic or pharmacodynamic interaction with beta-blockers, calcium channel blockers, H₂ receptor blockers, ACE inhibitors or anticoagulants. It does not require dose adjustment in hepatic or renal impairment. The effective dose is 1-8 mg/day.

On the pancreatic beta cells, glimepiride binds to a different receptor site as compared to the other sulphonylurea compounds. It also acts as an insulin sensitizer by promoting glucose utilization by peripheral tissues, by increasing the availability of the glucose transporters GLUT 1 and GLUT 4 in the cell membranes. It brings about a comparable reduction of blood glucose levels as other sulphonylureas, with lower insulin and C-peptide levels.

On long-term treatment about 40-50% of patients develop resistance to the action of the particular sulphonylurea-(secondary sulphonylurea failure). In this situation

TABLE 90.14 Dosage of sulphonylureas						
Drug	Relative potency	Dosage mg/day	Duration	Peak action hours	Half-life (hours)	Significant effect (hours)
Glibenclamide	150	2.5-30	Medium	3-4	10-16	Up to 24
Glipizide	100	2.5-20	Short	1	3-7	Up to 24
Gliclazide	80	80-320	Medium	4	10-12	Up to 24
Glimepiride	450	1-8	Long	1	12-16	Up to 24

other sulphonylureas may be tried. If found ineffective, biguanides or insulin may be needed.

Adverse effects of SU: The most common adverse side effect is the development of hypoglycemia coinciding with the peak action of the drugs. Some people are more susceptible to this type of reaction. Depending upon type of SU and the dose, the duration and severity of hypoglycemia varies. In otherwise well stabilized subjects, factors such as avoidance of meal, vomiting or increased physical activity may bring on hypoglycemia. If undiagnosed in time, SU induced hypoglycemia can be even fatal.

Non-specific gastrointestinal symptoms ranging from dyspepsia to diarrhea can occur with SUs in 3-5% of patients. Minor skin reactions occur which readily resolve on stopping the drugs. However occasionally severe reactions like exfoliative dermatitis or Stevens-Johnson syndrome may occur. Cholestatic type of jaundice and bone marrow depression are rare complications.

Occasionally water retention with dilutional hyponatremia may occur with sulfonylureas. Hypoglycemia occurs when there is an absolute or relative overdose.

Non-sulphonylurea Secretagogues: Meglitinides (Table 90.15)

This group includes repaglinide and nateglinide. These act through separate receptors on β -cell membrane, compared to SUs.

1. **Repaglinide:** It is a benzoic acid derivative. It was the first meglitinide analogue to become available. It initiates insulin secretion by closing the K^+ATP channels. It induces rapid postprandial insulin response. The drug's short half-life ensures that insulin concentrations peak at 1-2 hours, by 6 hours they are back at fasting concentrations. It does not have the risk of severe or prolonged hypoglycemia. It is given in doses of 0.5-4.0 mg/day in divided doses taken 15 minutes before meal.
2. **Nateglinide:** It is a d-phenylalanine derivative. This drug has a unique property of fast association and dissociation kinetics at the pancreatic beta cell. The other unique property of this drug is that it doesn't inhibit the KATP in the presence of low sugars. This glucose sensitizing property explains the low incidence of hypoglycemia associated with nateglinide. It is given in dose of 60-240 mg/day in three divided doses, 10-15 minutes before the meal.

Insulin Sensitizers

Biguanides: Actions and Indications

Mode of action: The biguanides lower the blood glucose levels in diabetics through their extra pancreatic effects, but do not reduce the blood glucose levels in

normal individuals, unless they are starved. They do not stimulate endogenous insulin secretion and do not cause hypoglycemia. The glucose lowering effect of these compounds has been shown to occur through three main mechanisms: i) inhibition of intestinal glucose absorption, ii) increase in utilization of glucose by peripheral tissues and iii) stimulation of anaerobic glycolysis in the liver, which inhibits hepatic gluconeogenesis and increases production of lactate. The biguanides are rapidly and almost completely absorbed from the GI tract. Occurrence of drug induced gastric side effects can be reduced by giving the drug after food.

Metformin

This biguanides is the most widely used since the longest duration. Metformin is neither metabolized by the liver nor bound to serum proteins. It is excreted unchanged by the kidneys. Its plasma half-life of 1.5-2.8 hours is much shorter than that of phenformin. Daily dosage of metformin is 500-2500 mg. Studies have shown that metformin can delay the onset diabetes in high risk groups. Effects of metformin are potentiated by other hypoglycemic agents, such as sulfonylureas and salicylates.

Insulin receptor effects: Metformin may help to improve insulin sensitivity in diabetic subjects by increasing insulin receptor binding in individuals with a reduced number of insulin receptors. The effects of metformin on the post receptor sites is of much greater importance for the potentiation of insulin action.

Lipid metabolism: Circulating triglyceride concentrations are decreased by metformin in both normal and type-2 diabetes patients. This is largely due to reduction in VLDL. A small increase in HDL has been observed in patients treated with metformin.

Other indications for metformin: This drug has been used for conditions other than diabetic mellitus. e.g. Polycystic ovarian syndrome (PCOS) in women, which is an insulin resistance state and metformin is the first line of drug to be used in such patients. Since metformin passes the placental barrier, it is not approved for use in pregnancy. Recent studies have shown that metformin reduces the risk of spontaneous abortion during the first trimester and reduce the incidence of fetal anomalies. It effectively reduces the development of gestational diabetes mellitus.

Phenformin: This was popular before the introduction of metformin. It is very effective. Adverse effects include severe lactic acidosis. Due to this adverse side effect phenformin is not generally used at present.

Biguanide and sulphonylurea combination: The addition of biguanide in cases where sulfonylurea alone cannot normalize blood sugar levels has allowed the continuation of oral therapy in many patients.

Sulfonylurea increase insulin release and cause greater suppression of hepatic glycolysis whereas metformin increases peripheral insulin mediated glucose disposal. Many diabetologists in India prefer to initiate treatment with combination of a sulfonylurea and metformin.

Metformin-insulin combination: Addition of metformin decreased the daily insulin requirement by 16% in a group of insulin requiring type 1 diabetes patients. Due to their insulin potentiating effects the biguanides have also been used as adjuvants of insulin therapy in both type 2 and type 1 diabetes patients. Metformin monotherapy is not effective in type 1 diabetes patients.

The adverse effects of biguanides: These are usually mild and limited to the gastrointestinal tract. Side effect includes a bitter or metallic taste in the mouth, anorexia, nausea, occasional vomiting and intermittent diarrhea. These are usually dose related and can be minimized by the use of timed disintegrating tablets or by very slowly increasing the dosage. Less frequent toxic effects include stress reactions and malabsorption of B12 and folic acid with resultant macrocytic anemia. Pancreatitis had been reported with the use of phenformin. Undoubtedly the most serious side effect associated with the use of biguanides is lactic acidosis. This is more commonly encountered with phenformin therapy and led to its ban in the USA. Metformin is a less lipophilic drug than phenformin and it is not metabolized in the body but excreted unchanged in the urine. On the other hand, phenformin is metabolized in the liver, so the chances of lactic acidosis increase with phenformin. The risk of developing lactic acidosis increases if the metformin level builds up in the blood. Since metformin is cleared primarily by the kidneys, patients with impaired kidney function (serum creatinine > 1.4 mg/dL in women and > 1.5 mg/dL in men) should not be treated with metformin.

Metformin is also employed as a primary mode of therapy in obese type 2 diabetic patients without complications.

Thiazolidinediones: The thiazolidinediones currently in use are **pioglitazone** and **rosiglitazone**. These drugs act by improving insulin sensitivity by binding to the peroxisome proliferator activated receptor gamma (PPAR γ), a molecule implicated in the transcription of numerous genes controlling carbohydrate and lipid metabolism. PPAR γ is the target for thiazolidinediones. They reduce insulin resistance thereby acting as hypoglycemic agents on their own, as well as insulin sparing agents. In addition they improve the lipid profile, lower blood pressure in hypertension and reduce cardiovascular risk factors. They promote fatty acid uptake and storage in adipose tissue, thereby increasing body fat and weight gain. They lead to fluid retention and cardiac failure in susceptible subjects, especially if combined with insulin.

These can also be used to treat PCOS like metformin, however they should be stopped if the women with PCOS becomes pregnant. These drugs are not approved for use in pregnancy because they pass the placental barrier and affect fetal growth and development. Unlike metformin, these drugs cause modest weight gain of approximately 1-3 kg. This is due to increased subcutaneous adipose tissue in the periphery and fluid retention.

Dose: Pioglitazone – 15-45 mg /day as a single daily dose.

Rosiglitazone – 2-8 mg/day in two divided doses.

Contraindications for the use of thiazolidinediones:

1. Congestive heart failure
2. Hepatic dysfunction with alanine transaminase (ALT) > 2 times the normal
3. Obesity.

Alpha-glucosidase inhibitors: **Acarbose** and **miglitol** belong to this group. They competitively inhibit the enzyme alpha-glucosidase, which is present in the brush border of small intestine. This enzyme breaks down complex carbohydrates into glucose and favours its absorption. Use of **acarbose** or **miglitol** as a supplement to sulfonylurea therapy reduces postprandial hyperglycemia. Use of acarbose permits slightly liberal use of complex carbohydrates in the diets without causing hyperglycemia.

Acarbose or miglitol is to be administered orally with the first bite of each meal. The currently recommended initial dose is 25 mg three times daily with the dose increased slowly, every 4 weeks to a maximum of 100 mg three times/day. Only 2% of the administered acarbose gets absorbed into systemic circulation. Acarbose is metabolized exclusively by the kidneys. Its use is contraindicated in the presence of hypersensitivity to the drug, severe renal failure, diabetic ketoacidosis, inflammatory bowel disease, colonic ulcers, partial bowel obstruction, chronic intestinal disease associated with impaired digestion or absorption and other disorders that may deteriorate with intestinal gas formation. These drugs are to be avoided in pregnancy.

Miglitol has less side effects than acarbose in doses of 25-50 mg tds. Another recently introduced drug is **voglibose** 0.2 to 0.3 mg at a time which is more potent in action with less of side effects (Tables 90.15 and 90.16).

INSULIN THERAPY

The discovery of insulin at the University of Toronto in 1921 by Sir Frederick Banting and Charles Herbert Best revolutionized the treatment of diabetes, extending the life expectancy of insulin dependent diabetics. The early commercial preparations of insulin were from bovine and porcine pancreas. They were impure and of variable quality, still they dramatically improved the prospects of

TABLE 90.15

Commonly used non-SUs oral hypoglycemic agents				
Class	Name	Duration of action hrs	Daily dose	Type of action
a. <i>Non-sulphonyl Urea secretagogues</i>	Nateglenide	8 hours	180-240 mg	(1)
	Repaglinide	8 hours	8-16 mg	(1)
b. <i>Biguanides</i>	Metformin	8 hours	500-2500 mg	(2 and 3)
c. <i>Thiazolidinediones</i>	Rosiglitazone	6-8 hours	6-12 mg	(2)
	Pioglitazone	18-24 hours	15-45 mg	(2)
d. <i>Alfa glucosidase inhibitors</i>	Acarbose	6-8 hours	50-100 mg with each meal	(4)
	Miglitol	6-8 hours	25-50 mg "	(4)
	Voglibose	6-8 hours	0.2-0.3 mg "	(4)

Key:
 (1) Insulin secretagogue (2) Insulin sensitizer (3) Diminishes hepatic glucose production (4) Inhibits alfa glucosidase and absorption of glucose.

TABLE 90.16

Approximate glucose lowering potential of type-2 diabetes therapies		
Drug	FPG reduction	HbA _{1c} reduction
1. Sulphonylurea	50-60 mg/dL	1-2%
2. Metformin	50-60 mg/dL	1-2%
3. Meglitinide	≤ 70 mg/dL	1-2%
4. Thiazolidinediones	50-60 mg/dL	1-2%
5. Alpha-glucosidase inhibitors	15-30 mg/dL	0.5-1%
6. Combination of 1 and 2	100-120 mg/dL	3-4%

TABLE 90.17

Differences between insulins from three species			
Species	A chain A ₈	A ₁₀	B chain B ₃₀
Bovine	Alanine	Valine	Alanine
Porcine	Threonine	Isoleucine	Alanine
Human	Threonine	Isoleucine	Threonine

Note: Bovine insulin is more different from human insulin, compared to the porcine variety.
 At present both bovine and porcine insulin are not manufactured, and all available insulin is of the human variety (Table 90.17).

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life in several thousand diabetics. Banting was awarded the Nobel Prize in 1923 along with Mcleod, professor of physiology in whose laboratory Banting and Best conducted their study.

During the past five decades several developments have taken place in insulin production, purification and formulation, aimed at improving metabolic control, safety and convenience of its use. Improvement in insulin purity was the first challenge and has been the goal ever since. This resulted in the production of chromatographically purified insulin and later, insulin with the chemical and molecular composition of human insulin referred to as **human insulin**. Similarly attempts to retard the subcutaneous absorption of insulin to spare diabetics the discomfort of multiple daily injections resulted in the development of intermediate and long-acting insulins. The preparations such as lente insulin, NPH (neutral protamine Hagedorn) insulin and protamine zinc insulin have longer duration of action.

Human insulin has a molecular weight of 5807 Daltons and contains 51 amino acids arranged in two polypeptide chains. The A chain contains 21 amino acids and is linked to the B chain by 2 disulfide bridges. Pre-pro-insulin and proinsulin are the precursors of insulin. Human insulin differs structurally from bovine and porcine insulin as shows below:

Insulin is relatively soluble at pH below 4 or above 7; the addition of Zinc broadens the pH in which precipitation occurs.

Like other proteins, insulin is also unstable and it is susceptible to chemical degradation and inter- and intra-molecular transformations. The presence of contaminants and immunogenicity of bovine and porcine insulins used to give rise to problems such as:-

- Immunogenic insulin resistance
- Insulin allergy
- Insulin-induced lipo-atrophy and lipo-hypertrophy and
- Insulin—insulin antibody complex mediated complications.

Human insulin is produced by recombinant DNA technology, the composition of the final product being identical to that of natural human insulin chemically and in molecular configuration. Being synthetic, the supply can be modified to meet the need, without shortage. It is more rapidly absorbed and has a somewhat shorter duration of action when compared with insulin of animal origin.

Therapeutics of Insulin

Insulin therapy aims at providing ideal physiological insulin profiles with peaks at meal times and maintenance

TABLE 90.18

Indications for insulin therapy

- 1. All type 1 diabetes patients.
- 2. In type 2 diabetes patients
 - a. During episodes of metabolic complications like diabetic ketoacidosis, hyperosmolar non ketotic coma and lactic acidosis.
 - b. During infections, myocardial infarction, stress, surgery, renal insufficiency or infective hepatitis.
 - c. During pregnancy
 - d. When diet, exercise and oral hypoglycemic agents fail to achieve euglycemia (primary and secondary sulfonylurea failure)
 - e. Lean type 2 diabetes patients with very high blood glucose levels at onset
 - f. Pancreatic calculi patients most of whom require insulin and
 - g. Even in non-diabetics, when the blood glucose level rises under stress such as myocardial infarction or septic shock, insulin is used to lower blood glucose.

of basal levels between meals and at night. This can be achieved by administering soluble insulin before each meal and adding a dose of intermediate acting insulin at bed time. The alternative regimes would be; (i) a split dose of soluble and intermediate acting insulin before breakfast and dinner, (ii). a single dose of soluble and intermediate acting insulin before breakfast, (iii) a single dose of intermediate acting insulin before breakfast. With the introduction of premixed insulin it is easier for the patients to adopt these regimes. As in the case of other hypoglycemic agents, diet control and exercise should be instituted along with insulin therapy (Table 90.18).

Dosage of Insulin

There are no hard and fast rules to assess the initial dose of insulin. It is ideal to start with a small dose and gradually increase at intervals of 2-3 days till the optimum dose is achieved as judged by the plasma glucose levels. The initial dose required can be calculated at the rate of 0.5 units/kg/day for type 1 and 0.2 units/kg/day for type 2 diabetes. If the patient is not symptomatic 50% of the calculated dose can be given initially and the dose can be gradually increased by 4 units every 4th day. If the patient is symptomatic, the calculated dose can be given in full at the start and adjusted subsequently.

Duration of action of insulin depends on the route of administration as well. There is no upper limit for insulin dose. The half-life of soluble insulin is 4-6 hours when given subcutaneously and 1-2 hours when given intramuscularly but it is only 5-10 minutes when the I V route. **For simplicity one can assume that the half-life of IV insulin, I M insulin and SC insulin are 4 minutes, 40 minutes and 4 hours respectively** (Table 90.19).

Site of Insulin Injection

Subcutaneous insulin can be given at one of the following sites: anterior abdominal wall, lateral aspect of the thighs and arms. Intramuscularly it can be administered over the deltoid or other regions. **The rate of absorption of insulin from the injected site varies.** More rapid absorption occurs from the abdominal wall compared to the deltoid region and the thighs when given SC. Intramuscular injections are more rapidly absorbed and duration of action is only for several minutes. Intravenous injections produce immediate effect, but only for a few minutes.

TABLE 90.19

Insulin preparations

Insulin preparation	Onset of action	Peak action	Total duration
Short acting (regular, or soluble)	0.5-1 hour	2-4 hour	4-6 hours
Intermediate acting			
NPH	2-4 hours	10-16 hours	20-24 hours
Lente	2-4 hours	10-16 hours	20-24 hours
Long acting			
Ultralente	6-8 hours	14-20 hours	24-32 hours
PZI	6-8 hours	14-20 hours	24-32 hours
Premixed insulins containing regular and NPH 30:70 and 50:50	0.5 hours	2-10 hours	12-18 hours
Note: Insulin manufacturers supply different-formulations of insulin separately or in the premixed form containing regular and longer-acting preparations.			
Newer insulins/insulin analogues			
Insulin Lispro	-	Short acting	
Insulin Aspart	-	Short acting, also long acting preparations combined with protamine.	
Insulin Detemir	-	Long acting, given twice a day	
Insulin Glargine	-	Long acting- 24 hours action	
Insulin glulisine	-	Short acting	

Storage

It should preferably be stored at 4-8°C. However it is stable at room temperature for 3-4 weeks.

Intensive Insulin Therapy

Awareness of the significance of tight metabolic control in the prevention of long-term complications of diabetes has led to the development of newer insulin delivery systems and different types of insulin therapy. Intensive insulin therapy of type 1 diabetes uses either 3-4 injections daily or a continuous subcutaneous insulin infusion from an insulin infusion pump. Blood glucose determinations done prior to each meal and at bedtime helps to determine the dose of soluble insulin to be administered based on an adjustment schedule algorithm.

Self Injection

This can be done using conventional disposable syringes specially calibrated for insulin. **Insulin pens using specially made insulin cartridges are available which are disposable or suitable for permanent use.** Availability of insulin pen facilitates the injection of insulin and also ensures the availability of the injection at the exact time, irrespective of the activity of the patient. The insulin pen with its insulin cartridge should be stored at room temperature. The cost of the insulin pen is around Rs. 700. Insulin available in cartridge is 25% more expensive than insulin available in multi-dose vials.

Insulin pump therapy or continuous subcutaneous insulin infusion (CSII), delivers insulin continuously into the subcutaneous tissue through a subcutaneous needle. The system is driven by a battery powered pump. By delivering insulin in the physiological basal-bolus pattern, it can mimic the body's insulin secretory pattern and is an excellent form of insulin delivery, provided patient selection is ideal. Artificial pancreas is a self-adjusting continuous infusion device which the patient can wear. The glucose sensor activates the pump and automatically adjusts the dosage to maintain euglycemia. This sensor-cum-delivery device is still not approved for commercial use (Table 90.20).

Insulin analogues: Insulin analogues are molecules which differ from insulin in their molecular structure, but produce the same biological response as insulin. Two types of insulin analogues are available, short-acting and long-acting analogues.

The short-acting insulin analogues start action within 5-10 minutes after administration, and the duration of action is only for 4 to 5 hours thereby, mimicking the normal physiological insulin response to meals. The rapid acting insulin analogues in use are *insulin Lispro*, *insulin aspart* and *Glulisine*. They are produced by recombinant DNA technology and they differ in structure from human

TABLE 90.20

Newer insulin delivery systems

- i. Insulin pump
- ii. Inhaled insulin
- iii. Intranasal insulin
- iv. Jet injectors (transdermal insulin)
- v. Oral insulin
- vi. Rectal insulin
- vii. Insulin administration via liposomes

insulin in the transposition of amino acids in the B chain. The sequence of amino acids at B 28 and 29 in human insulin is proline and lysine and in lispro it is lysine and proline. This transposition reduces the capacity for self-association of insulin, thereby keeping it in monomeric state and resulting in more rapid absorption after subcutaneous injection and shorter duration of action. Lispro insulin is used with advantage in the control of postprandial hyperglycemia. It is given by injection immediately before a meal.

Insulin aspart which is short acting has the proline in position B28 replaced by aspartic acid.

Glulisine is another new rapid-acting analogue which differs from human insulin by the replacement of asparagine by lysine at position B3 and lysine by glutamic acid at position B29. All these insulins can be given during pregnancy.

Among the *long-acting insulin analogues*, **glargine** is the widely used one. In glargine, there is addition of two arginine molecules at position B 30 and a substitution of glycine for asparagine at position A21. This analogue is widely used for basal supplementation. It does not produce peaking of insulin levels and therefore the risk of nocturnal hypoglycemia is negligible. Because of its long duration of action, once daily administration is sufficient. Since this insulin has acidic pH, it should not be mixed with any other insulin.

The other newer long-acting insulin analogue which is ideal for basal insulin supplementation is **Detemir**. In this, threonine at B30 is removed and lysine at position B 29 is acylated with myristic acid (C14 fatty acid chain). This allows insulin detemir to reversibly bind to the human albumin, which delays its absorption from the site of injection. This insulin is given twice daily.

Insulin analogues provide the therapeutic tools for finer adjustments of insulin dosage.

These are given by SC injection in doses of 0.1 to 0.2 unit/kg bw (Table 90.21).

INSULIN RESISTANCE

This may be due to genetic factor, development of antibodies to insulin or the receptor, and interaction of counter regulatory hormones. This can be managed by:

1. Increasing the dose of insulin and adjusting the frequency of injections

TABLE 90.21

Duration of action of insulin analogues			
Type	Onset of action	Peak action	Effective duration
Lispro	5-15 mts	30-90 mts	4-6 hours
Aspart	5-15 mts	30-90 mts	4-6 hours
Glargine	2-4 hours	None	20-24 hours

Note: Rapid acting analogues are available in premixed form with lispro and protamine crystalline aspart so that the action of insulin can be prolonged.

- 2. Changing the brand of insulin
- 3. Use of immunosuppressants such as cyclosporine and tacrolimus, or newer insulin analogues
- 4. Use of insulin- like growth factor, if available.

Emerging Therapies: Making Use of the Incretin Pathway

Several newer drugs are emerging in the therapy of diabetes. They mimic the actions of incretins like GLP-1 which are gut-derived peptides with beneficial effects on insulin action, insulin secretion, gut emptying and satiety.

Exenatide, a drug that is derived from the salivary secretion (venom) of a lizard called the Gila monster, and liraglutide, a synthetic molecule, are designed to mimic the actions of GLPI. This is given parenterally.

Dipeptidyl peptidase IV (DPPIV) inhibitors which inhibit the GLPI degrading enzyme (DPPIV) and enhance the action of GLPI are also available at present. They can be given orally.

Amylin agonists: Amylin, secreted by the beta cells, stomach and small intestine enhances insulin secretion. Inhibitors of gastric emptying are also emerging as antidiabetic drugs. Pramlintide is an amylin agonist which can be given parenterally.

Monitoring Control of Diabetes (Table 90.22)

Whole blood or plasma glucose estimation is the best available index of diabetic control. Blood glucose estimation should be done in the fasting and postprandial states. Usual diet and medication should be continued on the day of the tests.

Frequency of blood sugar studies varies with the type of diabetes and its severity. In type-1 DM patients it should be done as frequently as possible. If the patient is doing self-blood glucose-monitoring (SBG) the results have to be cross-checked at monthly intervals. In well controlled type-2 DM patients the blood glucose levels should be done once in 4-6 weeks. Those on insulin therapy and during periods of stress the patients need closer follow up as in type 1 DM. It is preferable to do both fasting and postprandial blood glucose.

TABLE 90.22

Targets for control of diabetes
Fasting blood glucose – 90-130 mg/dL
2-hr postprandial blood glucose — < 180 mg/dL
HbA ₁ C — < 6.5%.

Glycosylated hemoglobin: In normals hemoglobin is glycosylated (HbA1c) and the level is 6%. Levels above 8% indicate the existence of higher levels of plasma glucose. Once glycosylated, the level of HbA1c is maintained as such till the erythrocytes disintegrate. Glycosylated hemoglobin estimation gives the time-related measure of the prevailing average blood glucose concentrations to which RBC's are exposed. Since the RBC life span is 120 days, the levels of HbA1c indicate the glycemic state of the past 2-3 months. This is in contrast to the fasting and post-prandial blood glucose levels which are indicative of diabetic control on that particular day. HbA1c level can not be manipulated by the patient, unlike blood glucose levels.

Glycosylated fructosamine is a marker of medium term control of glycemia over the preceding 2-3 weeks. It is a useful test for monitoring during pregnancy.

Monitoring the progress of complications: Factors other than glycemic control also determine the complication rate. These include the genetic make-up, tobacco smoking, obesity, hypertension, hyperlipidemia and presence of other precipitating factors. All these should be taken into account while monitoring complications.

Renal function tests should be performed every 3-6 months. Lipid profile and estimation of urinary micro-albumin, ECG, X-ray chest, biothesiometry and ophthalmic examination should be carried out annually. Biothesiometry is based on the pattern of electrical response of different region of the feet to electric current. Typical abnormalities develop along with the development of neuropathy. Biothesiometry helps to quantify the severity, extent and progress of neuropathy.

Education of the Diabetic

In a chronic disorder like diabetes mellitus the patient's co-operation and participation are of utmost importance

TABLE 90.23

Components of diabetes education
i. Since diabetes lasts lifelong, it has to be kept under control with diet, exercise and drugs.
ii. The aim of therapy is to provide relief from symptoms, and prevent the long-term complications of diabetes.
iii. Recognition of hypoglycemia early and its prompt correction so as to prevent further consequences.
iv. The importance of foot care in preventing infections.

in the management. Education regarding the various aspects of diabetes helps to achieve better compliance from the patients (Table 90.23).

BRITTLE DIABETES

Syn: Unstable diabetes, labile diabetes

This term is used to denote patients who have wide swings in blood glucose levels after the institution of appropriate treatment. These patients undergo frequent disturbing episodes of hypo- and hyperglycemia. The severity and frequency varies.

Type A: Incapacitated by glucose excursion. This may be primarily hyperglycemia, hypoglycemia or mixed.

Type B: Incapacitated, but lifestyle disturbed by decompensation of glucose control more than thrice a week.

Causes

1. Disorders of glucose regulations.
2. Disturbances in other hormones, which influence glucose levels.
3. Disorders of insulin pharmacokinetics
 - a. Insulin antibodies
 - b. Insulin receptor antibodies
 - c. Renal insufficiency
 - d. Hepatic cirrhosis
 - e. Erratic absorption from subcutaneous injection of insulin
4. Gastrointestinal disorders
 - a. Gastro paresis diabeticorum
 - b. Malabsorption state
5. Coexistent systemic illnesses
6. Psychological problems
 - a. Self-induced therapeutic problem
 - b. Bulimia (eating disorder)
 - c. Depression
 - d. Alcohol abuse
 - e. Communication gap between the doctor and the patients.

Management

Empirical therapy: Frequent small doses of insulin or employing as insulin pump which will self-regulate its action.

Specific therapy aims at tracking the cause.

DIABETES DURING PREGNANCY

Diabetes mellitus encountered during pregnancy may be gestational or pregestational. It should be determined whether the woman had type 1 or type 2 diabetes even before the onset of pregnancy.

Diabetes mellitus leads to serious complications during pregnancy. Not only the complications of the disease may get worse in the mother, but the fetus and neonate are also placed at a risk, leading to increased perinatal morbidity and mortality. Gestational diabetes, defined as carbohydrate intolerance of variable severity with the onset or first recognition during the present pregnancy and which clears up spontaneously after delivery.

Tissue sensitivity to insulin is slightly increased between 12 and 14 weeks of pregnancy and thereafter it declines through out the rest of the pregnancy. It returns to normal immediately after delivery.

In normal pregnancy, development of insulin resistance is a mechanism to provide higher energy substrate to the baby. Blood glucose and free fatty acid levels increase. This, in turn leads to higher insulin secretion. In 2-4% of women the pancreatic insulin response is inadequate and gestational diabetes ensues.

If perinatal morbidity and mortality are to be reduced, gestational diabetes mellitus (GDM) must be detected as early as possible and treatment instituted promptly. Screening of all pregnant women for gestational diabetes between 24-28 weeks gestation with a 50 g oral glucose challenge is the most widely used method. Women showing whole blood glucose value more than 140 mg/dL at 1hour are given a 100 g OGTT. The criteria of O' Sullivan and Mahan remains the most commonly used standard for the diagnosis of GDM (Table 90.24). Diagnosis of GDM is made if any two values are above the normals.

Maternal complications: The most common obstetric complications include hydramnios, pre-eclamptic toxemia, urinary tract infections, vaginal moniliasis and premature labour. Hyperemesis gravidarum and infections are associated with higher risk of ketosis in diabetic women. Diabetic retinopathy may worsen during pregnancy.

Fetal Complications: These include intrauterine death, prematurity, congenital anomalies, respiratory distress syndrome, hypoglycemia, hypercalcemia and hyperbilirubinemia. Prenatal mortality is increased due to placental

TABLE 90.24

O' Sullivan and Mahan's criteria (ADA recommendation) for diagnosis of gestational diabetes mellitus after a 100 g glucose load

Plasma glucose (mg/dL)	
Fasting	95
1 hr	180
2 hr	155
3 hr	140

Note: 2 or more values must be abnormal to make a diagnosis of GDM

insufficiency, prematurity, or trauma during birth. The risk to fetus increases as the pregnancy advances and intrauterine death of fetus is more frequent towards the later stages. Incidence of intrauterine fetal death can be reduced by proper control of the diabetic state.

The management of diabetes during pregnancy is a demanding task and can be best achieved through a team work approach involving the obstetrician, diabetologist, pediatrician and dietician. The management of pregnancy complicated by diabetes should begin before pregnancy is contemplated. Information about the potential complications of pregnancy for the mother and offspring should be explained to the couple. The importance of good stable metabolic control before conception should be highlighted. The aim of therapy should be to maintain the post-prandial blood glucose levels below 120 mg/dL. The insulin requirements may fall during the first trimester, then there is a progressive increase in the requirements until about 34-36 weeks of pregnancy. The requirements come down soon after delivery. It is better to put on 3 doses of short acting human insulin or 2 split doses of soluble and intermediate acting insulin.

Dietary management: A meal plan is made to maintain euglycemia and to provide sufficient calories to sustain adequate nutrition for the mother and the fetus without excessive weight gain. Addition of 150 calories during the first trimester and 300 calories in the second and third trimesters above the basal requirements is adequate. Protein intake should be increased to 1.5-2 g/kg body weight. Exercise should be advised as is compatible with the obstetric condition.

Monitoring control of Diabetes: Preferably plasma glucose levels should be done by the patient before the main meals and also post-prandially at least twice a day. Present day glucometers (available at Rs.1500) enable self monitoring. The advent of glucometer and home blood glucose monitoring helps to achieve good glycemic control. Measurements of HbA1c at 4-6 week intervals help to confirm the status of long term glycemic control. Urine examination for glucose does not give proper assessment of control, since renal threshold for glucose is lowered during pregnancy.

Fetal monitoring techniques: Ultrasound examination for evaluating fetal growth, estimating fetal weight, detecting hydramnios and malformations should be repeated at 4-6 week intervals. Determination of maternal serum alphafetoprotein at 16 weeks along with ultrasound at 18 weeks helps to detect neural tube defects and other anomalies. Fetal echocardiography at 20-22 weeks reveals

cardiac defects. Amniocentesis is performed before elective delivery to document fetal pulmonary maturity.

Timing of delivery: Delivery should be timed when fetal maturation is achieved. Maternal diabetes should be controlled meticulously. The route of delivery for the diabetic patient has to be decided individually. Diabetes as such is not an indication for caesarean section. The decision for caesarian section should be based on the obstetric indications. Termination of pregnancy at the optimum time is a combined decision of the team of doctors based on the degree of control of diabetes, fetal growth, maturity and viability; general condition of the mother, outcome of previous pregnancies and the neonatal services available. In many instances induction of labour and delivery are done by about 36-38 weeks by which time the risk of hyaline membrane disease of the lung is low. On long-term follow-up more than 30% of gestational diabetes patients develop type 2 diabetes.

NEONATAL DIABETES MELLITUS (NDM)

This is defined as insulin-requiring hyperglycemia that is diagnosed within the first three months of life. It may be transient; subsiding by three months, or may continue for longer periods.

Neonatal diabetes mellitus (NDM) is different from other forms of diabetes. It is caused by activating mutations of genes KCNJ 11 which encodes kir 6, 2-a subunit of the ATP sensitive potassium channel (KATP) of the beta cell.

The disease is rare with an incidence of 1/50000 to 1/100000 live births. Such children show intrauterine growth retardation. The disease manifests in the first 3-6 months of life with glucosuria, polyuria, dehydration, failure to thrive and frank diabetic ketoacidosis.

Serum levels of insulin and insulin-like growth factor are low. Treatment with insulin results in dramatic catch up growth and improvement. In 50% of cases insulin can be discontinued, but DM may recur in the second to third decade of life. 50% of cases of NDM develop permanent DM. Interestingly these cases respond to oral hypoglycemic agents such as glyburide. These are the cases which have mutations in the SUR1 regulatory subunit of KATP or Kirb 2 genes. Identification of these genetic mutations can predict cases which will respond to oral sulfonylurea. This response may result from the closing of mutant KATP channels, thereby increasing insulin secretion in response to incretins and glucose metabolism.

Further Reading: Mack A.Sperling ATP- sensitive Neonatal diabetes mellitus and beyond .NEJM 2006 355; 507-510.

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Complications of Diabetes Mellitus

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Diabetes mellitus is associated with several complications throughout the course of the disease. At present short-term control of diabetes can be achieved in almost all cases by the use of dietary regimen, exercise and drugs. On long-term basis, majority of the patients fail to comply with the strenuous therapeutic regimen and the ideal control of blood sugar during day and night is compromised. Postprandial hyperglycemia is recognized to be an important factor contributing to vascular complications and increased mortality. Diabetes is more dreaded for complications, which invariably set in as the diabetic state continues. Though the DCCT and UKPDS trials have demonstrated that the incidence and severity of all complications can be brought down, complete prevention cannot still be guaranteed in any particular case. On account of this, long-standing diabetic patients constitute a sizeable proportion of chronic morbidity requiring regular and expensive therapeutic interventions. In many diabetics the disease may be first detected when the patient presents with a complication.

A. Acute Complications

1. Metabolic derangements
 - a. Diabetic ketoacidosis and coma.
 - b. Hypoglycemia
 - c. Hyperosmolar nonketotic coma
 - d. Lactic acidosis
2. Infections
 - a. Medical: Acute infections such as skin infections, respiratory tract infections, urinary tract infections, genital infections such as balanoposthitis, vulvovaginitis, and rhinocerebral mucormycosis.
 - b. Surgical: Boils, carbuncles, cellulitis, superficial and deep abscesses, gangrene, foot infections, necrotizing fasciitis.
3. Acute events occurring as a result of the long-term complications
 - a. Ischemic heart disease-acute
 - b. Renal failure
 - c. Peripheral vascular occlusion
 - d. Loss of vision
4. Obstetric Complications
 - a. Intrauterine fetal death
 - b. Hydramnios, more frequent
 - c. Higher frequency of pre-eclampsic toxemia
 - d. Large baby (> 4 kg) giving rise to complications during delivery and perinatally
 - e. Infections of the genital tract
 - f. Worsening of the diabetic state during pregnancy and postpartum.

B. Long-term Complications

1. **Cardiovascular:** Earlier onset of atheroma, ischemic heart disease, cerebrovascular accidents, high incidence of hypertension (about 30% of diabetes have hypertension).
2. **Neurological:** Peripheral neuropathy, autonomic neuropathy and mononeuritis multiplex including cranial nerve palsies, urinary retention and incontinence, diabetic autonomic diarrhea.
3. **Peripheral occlusive vascular diseases.**

TABLE 91.1

Major associated complications seen in long standing diabetic subjects at the time of first examination in a tertiary care hospital at Trivandrum

Complication	%
Nephropathy	70
Hypertension (> 140/90)	50
Carotid artery disease	18
Peripheral vascular disease	21
Retinopathy	20
Coronary artery disease (ECG criteria)	12
Elevated LDL (> 150 mg%)	12
Hypertriglyceridemia (> 200 mg%)	18

Ref: Poulouse K.P. Personal communication (2004)

- Renal:** Recurrent urinary infections, chronic pyelonephritis, papillitis necrotians, diabetic glomerulosclerosis, end stage renal failure.
- Ocular:** Cataract, retinopathy, iridocyclitis, glaucoma, refractive changes induced by treatment
- Respiratory:** Pulmonary tuberculosis, other infections.
- Alimentary:** Xerostomia, stomatitis, gingivitis, dental sepsis, loosening of teeth, halitosis, hepatomegaly, gastric dilataion, nocturnal diarrhea, and paralytic ileus
- Bone and joints:** Osteoporosis, osteoarthritis, and neuropathic joints (Charcot's joint).
- Skin:** Chronic fungal infections of skin, moniliasis of the mucous membranes of the genitalia and mouth, pruritus vulvae, necrobiosis lipidica diabetorum, trophic ulcers of the feet, scleredema
- Drug induced complications:** Hypoglycemia, drug allergy, toxicity to liver and bone marrow.

Even though the major long term complications produces clinical deterioration in the patient, sometimes they may be ignored and the patient may not seek medical attention, as shown in Table 91.1.

Metabolic Emergencies in Diabetes

All these situations are life-threatening. Hence awareness; early diagnosis and appropriate management are necessary to cut down the morbidity and mortality. Metabolic emergencies in a diabetic can be classified as:

1. Diabetic ketoacidosis and coma
2. Hypoglycemia
3. Hyperosmolar nonketotic coma and
4. Lactic acidosis

HYPOLYCEMIA

Hypoglycemia is the fall of blood glucose levels below 50-60 mg/dL at which level symptoms occur in normal persons. However the development of symptoms also

depends on the prevailing blood glucose levels and individual susceptibility. Factors such as age, medication and co-morbid conditions influence the clinical manifestations. In those who have chronically elevated blood glucose levels, even reduction of glucose to normal values may precipitate symptoms. Clinically it is characterized by a varying degree of neurological dysfunction and is responsive to the administration of glucose. The clinical manifestations are extremely varied and depend upon the rate of fall of blood glucose levels and the release of counter regulatory hormones.

Early recognition of the condition is essential since severe forms of hypoglycemia are life-threatening and delay in instituting therapy can result in permanent brain damage or loss of life. In many instances slow onset hypoglycemia is recognized by the patient from his past experiences.

Recent onset of episodes of hypoglycemia in a patient on therapy may be a pointer to renal insufficiency. The insulin requirements go down and necessary changes in dose have to be made. The excretion of oral hypoglycemic drugs is impaired and such drugs are better avoided in a diabetic with renal insufficiency.

CLINICAL FEATURE

This varies from patient-to-patient and the circumstances in which an attack is provoked, generally depending on the rate of fall of blood glucose and the individual endocrine status. The hypoglycemic episodes with insulin usually occur at predictable time intervals in relation to their peak action. Hypoglycemia due to oral drugs can occur any time 30-60 minutes after ingestion. Unlike insulin induced hypoglycemia, it may present with bizarre symptoms and elude recognition. The presentation may mimic cerebrovascular accident at times. Persistence of hypoglycemia over prolonged periods is another feature which should be borne in mind. Recurrence after initial correction is also common.

With a rapid fall in the blood glucose as happens during insulin therapy manifestations due to epinephrine release are prominent, while with a gradual fall in blood glucose the picture is predominantly due to decreased cerebral function presenting with varying neurological deficits (Table 91.2).

Symptoms of Hypoglycemia

1. Adrenergic symptoms: Palpitation, sweating, tremors, anxiety.
2. Neuroglycopenic symptoms: Tiredness, dizziness, drowsiness, seizures, coma.

Hypoglycemia usually manifests abruptly, unlike hyperglycemia which is more gradual in onset.

Physical examination reveals cold extremities, excessive sweating, tachycardia, elevated blood pressure and mental agitation. As the condition proceeds the patient

TABLE 91.2

Precipitating factors for hypoglycemia

- I. Meal-medicine mismatch:
 - a. Decreased food intake, missing a meal or its delay, diarrhea, vomiting.
 - b. Increased physical activity (unplanned, excessive strenuous physical activity) without reduction of the dose of drugs or adjustments in food intake.
 - c. Increased dose of either insulin or oral hypoglycemic agents
- II. Decrease in insulin requirements, which can occur when a juvenile diabetic goes into remission (*honeymoon phase in type-1 diabetes*), or soon after delivery in a pregnant woman (due to the drop in the placental hormones) or with the elimination of stress and control of infection.
- III. Renal and hepatic insufficiency which decrease the insulin requirements.
- IV. Drug interactions e.g. quinine, newer quinolones.
- V. Excessive alcohol consumption

becomes drowsy and comatose. Generalized convulsions may occur. The pupils are dilated and plantar response is extensor. Atypical features may occur at times.

At the suspicion of hypoglycemia, glucose should be administered after taking blood for glucose estimation. Venous blood glucose below 60 mg/dL suggests hypoglycemia. In severe cases the value may be below 40 mg/dL and at times glucose may be undetectable. In any doubtful situation, the response to glucose can be taken as a reliable test for the diagnosis of hypoglycemia.

Symptoms of hypoglycemia vs blood glucose levels

Plasma glucose (1 mmol/L = 18 mg/dL)	mg/dL	mmol/L	
	66	3.9	Counter regulation starts
	60	3.3	Autonomic symptoms
	50	2.8	Neuroglycopenic symptoms such as difficulty to concentrate, confusion, weakness, drowsiness, blurring of vision, dizziness and dysphasia
	40	2.2	Lethargy
	31	1.7	Coma
	20	1.1	Convulsions
	11	0.6	Permanent brain damage
	0	0	Death

The persistence of hypoglycemia for over six hours may lead to permanent CNS damage. Recurrent attacks may also contribute to impairment of mental faculties in children and the elderly. Hypoglycemia impairs the quality of life. Sudden death due to cardiac arrhythmias ('dead in bed' syndrome) may occur due to the abrupt

catecholamine surge associated with falling serum potassium levels, which can precipitate fatal arrhythmias. ECG may show QTc prolongation.

Management of Hypoglycemia

Management consists of emergency measures to correct the blood glucose levels and maintenance to avoid recurrence. If the patient can swallow, 50 g of glucose dissolved in 200 mL water should be given orally. Symptoms start improving within 5-7 minutes and patient becomes normal within 20-40 minutes. If glucose is not ready at hand, sucrose, sweet articles of food or even cereal foods can be given. Mild cases respond successfully. This method should be advised to all diabetic patients so as to avoid more serious consequences.

If the patient is unconscious, parenteral glucose should be administered. About 15-20 g. of glucose is usually needed. This is best administered by I V infusion of 200-250 mL of 10% dextrose, which is safe and effective.

An alternative is to give **glucagon** given IM in a dose of 1.0 mg and repeated 15 minutes later. It is effective in raising blood sugar. This is a useful method if the drug is available and in conditions, where IV injections are not possible due to technical reasons. Glucagon may be repeated after 15 min if response is poor. Glucagon injections are ineffective in cases of alcohol-induced hypoglycemia.

After initial correction of hypoglycemia, the patient is kept under observation for 3 to 4 hours, till he recovers completely and is fit for discharge. This is particularly important for those who are on long acting sulphonyl-ureas. Follow up action consists of detecting the precipitating cause for hypoglycemia and avoiding these factors.

Prevention

All patients should be informed about the clinical picture of hypoglycemia and taught how to recognize an impending attack and take corrective steps. They should be given identity cards indicating the disease, medication received and the address of the personal physician.

Hypoglycemic episodes are frightening to the patients and therefore, unless the warning symptoms are explained to them and corrective measures advised, many of them fail to comply with the prescribed regimen thereafter.

Recurrent Severe Hypoglycemia

Severe recurrent hypoglycemia is common among type-1 diabetes patients as well as among those with late stage of type 2 diabetes. The most frequent cause is exogenous insulin, which, unlike endogenous insulin does not get

suppressed when the blood glucose starts falling. The other reason is the failure of the counter regulatory hormone response. The hypoglycemia is not recognized by the patient at its onset. This state is called as 'hypoglycemic unawareness'. A vicious circle develops and episodes of hypoglycemia recur.

Hypoglycemia Unrelated to Diabetes Mellitus

In resting adults, over 60% of glucose is used by the CNS and the remainder by other tissues such as muscles, bone marrow and kidneys. Fasting hypoglycemia may result from reduction in hepatic gluconeogenesis and/or excessive glucose utilization. The former is due to hepatic diseases. The latter is due to tumours, which use up large amounts of glucose or non-beta cell tumors, which produce one or other insulin like growth factors.

Test

Plasma insulin is measured when blood sugar level is less than 45mg/dL. In those in whom insulin levels are high, the probabilities are insulinoma, factitious hypoglycemia, ingestion of sulphonylurea drugs and the presence of anti-insulin antibodies. These can be differentiated by determining C-peptide, proinsulin, and insulin antibody concentration. Insulinomas produce insulin and also proinsulin. The hallmark of Insulinoma is failure to suppress insulin production in the presence of hypoglycemia.

Anti-insulin antibody is more commonly seen in SLE, rheumatoid arthritis, Graves' disease and benign monoclonal gammopathy. Rarely it may be an isolated disorder.

Antibody induced hypoglycemia: Autoimmune insulin syndrome is a rare cause of hypoglycemia. This is characterized by late postprandial hypoglycemia and polyclonal insulin-binding antibodies. The antibodies trap insulin and release it after varying intervals, giving rise to hypoglycemia.

Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) is caused by gross derangement of carbohydrate and fat metabolism brought on by severe deficiency of insulin. This is characterized by hyperglycemia, presence of excess ketone bodies in blood and urine, and metabolic acidosis. In the early stages, the ketosis may be mild and easily correctable, but later it becomes clinically pronounced and resistant to therapy. Diabetic ketoacidosis is a common medical emergency encountered in the medical casualties of all major general hospitals in India. The term diabetic coma was used to denote extreme ketoacidosis. This term is not commonly in vogue at present.

Pathogenesis

Insulin deficiency may be absolute or it may be a conditioned deficiency brought on by the precipitating factors. Severe insulin deficiency results in hyperglycemia. Hyperglycemia leads to hyperosmolarity of the plasma, which causes a shift of intracellular fluid to the extracellular compartment with consequent cellular dehydration. Osmotic diuresis leads to loss of water and sodium from the extracellular compartment. Severe loss of water and electrolytes result in the shrinkage of extracellular fluid volume and hypotension. Reduction of renal blood flow impairs renal function.

In the presence of insulin deficiency fat cells undergo lipolysis. This releases excess of fatty acids which reach the liver but they are only incompletely metabolized. Due to this, large amounts of ketone bodies are formed.

Apart from insulin deficiency, other concomitant metabolic derangements also contribute to the severity of ketosis. Growth hormone and glucocorticoids which antagonize the action of insulin are produced in excess. These enhance gluconeogenesis, lipolysis, and ketogenesis in the liver. Lipolysis leads to production of free fatty acids (FFA). Glucagon directs the FFA to enter the mitochondria for beta-oxidation leading to excess production of ketone bodies such as acetone, acetoacetic acid and β -hydroxy butyrate. All the ketone bodies are excreted in urine. Acetone being volatile is present in the expired air and this imparts a fruity smell to the breath. Acidosis gives rise to peripheral vasodilatation which aggravates hypotension and leads to shock. The plasma bicarbonate level is reduced progressively as ketosis worsens.

Body potassium: Another serious metabolic consequence is the abnormal shift of potassium. Potassium moves out of the cells into the extracellular compartments leading to hyperkalemia. Potassium is lost in urine, resulting in the net loss of potassium from the body even in the presence of hyperkalemia. When the metabolic abnormality gets corrected with insulin, fluids and electrolytes, the glucose and potassium re-enter the cells. This leads to severe hypokalemia, which may be fatal, if undetected and treated promptly.

The anion gap is increased. Serum magnesium concentration falls. Total body phosphorus is also lowered. The erythrocyte 2,3- diphosphoglycerate levels are also lowered and as a consequence the oxygen dissociation curve is shifted to the left. This leads to tissue anoxia. Once ketosis develops, if left untreated, it proceeds leading to diabetic coma.

Causes of diabetic Ketoacidosis: All diabetics are predisposed to ketoacidosis, especially those with type-1 DM. In a few cases the diagnosis of diabetes may be made for the first time when the patient presents in coma, especially in children.

Precipitating Factors

1. Withdrawal or reduction in insulin dosage.
 2. Infections.
 3. Trauma or surgery
 4. Medical emergencies like acute myocardial infarction and cerebrovascular accidents.
 5. Large carbohydrate intake.
 6. Drugs which aggravate the diabetic state, e.g. corticosteroids.
 7. Psychological stress.
- In the majority of cases, the condition is precipitated by sudden withdrawal of insulin in the presence of an offending factor.

CLINICAL FEATURES

Since the metabolic derangement takes time to develop, the onset of ketosis is gradual over a few days, but in some young diabetics it may occur more rapidly. The early symptoms are those of uncontrolled diabetes such as extreme fatigue, polyuria, vomiting, and insomnia. Drowsiness and altered behavior should draw attention to the possibility of ketoacidosis. The clinical state steadily deteriorates. Some cases present with abdominal symptoms like severe pain and distension, which may be mistaken for surgical emergencies.

The fully established case presents a characteristic picture. The patient is dehydrated, drowsy, or deeply comatose. The respiration is deep and sighing and this is known as **Kussmaul's respiration**.

(Adolf Kussmaul (1822-1902) was a German physician. He has described three important clinical phenomena-pulsus paradoxus, Kussmaul's sign in pericardial tamponade and Kussmaul's respiration in metabolic acidosis).

A fruity smell of acetone may be detectable in the breath. Eyeball tension is low and blood pressure is low. The limbs are flaccid and deep reflexes are sluggish. Plantar response is upgoing. The abdomen may be distended due to gastric dilation or paralytic ileus, which results from autonomic neuropathy. Initially the pupils are normal, but they may dilate, when the coma becomes deep. In some cases fundal examination may reveal lipemia retinalis (milky plasma in the retinal vessels).

Diagnosis

Any deterioration of the general condition, loss of control of the diabetic state, bizarre symptoms, fatigue, vomiting and altered behavior occurring in a diabetic should be investigated for ketoacidosis.

The diagnosis should be established by urine examination and blood biochemistry. Urine shows sugar and acetone. Acetoacetic acid and acetone can be detected by *Rothera's test* or *Acetest tablets* or Ketostix. The tests can be semi-quantitated by noting the speed of development and depth of colour and also testing the urine in progressive dilutions. Acetone disappears on boiling.

Plasma ketones can also be detected by Ketostix or chemical methods. Acetoacetic acid can be tested also by the Gerhardt's test (ferric chloride test). Drugs like captopril which are eliminated in urine, give rise to false positive tests for acetone. Blood sugar is considerably elevated in most cases, but in some the elevation may be only moderate. Serum triglycerides are elevated (Table 91.3).

Differential Diagnosis

The diagnosis is easily suspected if coma occurs in a known case of diabetes, but the previous history may not be forthcoming always. So also the diabetic may develop other disorders leading to coma e.g. cerebrovascular accident. Diabetic coma has to be differentiated from hypoglycemic coma, cerebrovascular accidents, other causes of metabolic coma, head injuries, poisoning, and intracranial infections like meningitis and encephalitis. In cerebrovascular accident, diabetic ketosis may also develop as a complication. Another point to be remembered is that in cerebral hemorrhage and subarachnoid hemorrhage temporary glycosuria may develop even in non-diabetics, but this passes off when the acute stage is over. Moreover, this is not usually associated with ketonuria and acidosis. Other common causes of ketoacidosis are starvation and severe vomiting. In this glycosuria does not occur and blood glucose levels are low. Other causes of metabolic acidosis such as renal failure, lactic acidosis, poisoning by acids and salicylates and circulatory shock has to be excluded.

Hypersmolar nonketotic coma is rare in comparison to diabetic coma. The former is characterized by dehydration, hypotension, and disturbances of higher functions, ending in coma. This is more frequent in subjects with type 2 DM. In this condition the blood glucose is very high, often above 400 mg%. Ketonuria and metabolic acidosis are not present.

MANAGEMENT

- The principles of management include;
1. Correction of dehydration
 2. Control of hyperglycemia.
 3. Correction of electrolyte disturbances and acidosis.
 4. Attention to precipitating factors like infection, injury or stress
 5. Supportive measures.
 6. Long-term management.

Diabetic ketoacidosis is a medical emergency requiring hospitalization for treatment. In comatose patients, nasogastric tube is introduced to aspirate the stomach contents. In many cases the stomach may contain large amounts of fluid due to gastroparesis and therefore it is advisable to empty the stomach. Oral feeds are not permitted due to the possibility of aspiration pneumonia. Milder forms of ketoacidosis can be treated by

TABLE 91.3

Clinical and biochemical data to assess the severity of diabetic ketoacidosis

	Mild	Moderate	Severe
Symptoms	Increasing polyuria, thirst, weakness, tiredness	Severe polyuria, polydipsia, rapid breathing, smell of acetone in breath, weakness; somnolence, vomiting	Symptoms of moderate ketosis with drowsiness progressing to stupor and coma
Signs	Flushed face and skin tachycardia, slight smell of acetone in breath	Kussmaul's breathing, loss of skin turgor, soft eyeballs small pulse volume, heavy odour of acetone in breath, drowsiness, and weakness	Severe dehydration, hypotension, extreme tachycardia, air hunger, coma
Urine			
Glucose	2%	Above 2%	Above 2%
Acetone	+++	+++ in 1:4 dilution	+++ in 1:8 dilution
Serum			
Acetoacetate	Positive in undiluted serum (3-6 mmol/L)	Positive in 2-3 fold dilution (6-12 mmol/L)	Positive in 1:4 dilution (above 12 mmol/L)
Plasma bicarbonate	Above 18 mEq/L	10-18 mEq/L	Below 10 mEq/L
Potassium	Normal	Often elevated	Usually elevated
Sodium	Normal	Normal	Normal
Hematocrit	Normal	Elevated	Elevated
pH	Normal	7.2	7.1 or less
Approximate water deficit	1-2 liters	3-4 liters	5-8 liters
Approximate sodium deficit	Less than 100 mmol	100-250 mmol	250-480 mmol

conservative measures and if the patients can tolerate oral food and fluids, this route can be employed for correction.

Correction of dehydration: Fluid and electrolytes should be replenished by I V normal saline as early as possible and this is the most effective single step to arrest further deterioration and bring about recovery. The approximate fluid deficit ranges from 2-8 liters depending on the severity of the condition. The speed of administration of isotonic saline for a moderately severe case is given below:

1st liter	30 min
2nd liter	1 hour
3rd liter	1 hour
4th liter	2 hours
5th liter	3 hours
6th liter	4 hours (Total infusion of 6 liters in 11-12 hours)

Blood glucose and plasma bicarbonate are estimated at 2-hourly intervals. When the blood glucose falls below 250 mg/dL, 5% glucose solution may be given instead of saline. This helps to prevent hypoglycemia and also provide water for correcting cellular dehydration. By this time oral intake is increased and intravenous administration, tapered off.

A serious complication that may develop during fluid and electrolyte replacement is cerebral edema which may

even go on to coning of the brainstem. This is more frequent in children and newly diagnosed diabetics. Symptoms of increased intracranial tension usher in after the initial period of recovery. Unless this complication is kept in mind and promptly managed by the use of intravenous mannitol and other measures, mortality will be high.

Insulin: Diabetic coma is the most urgent indication for soluble insulin. Insulin has to be given intravenously in moderate and severe cases. In mild cases insulin may be given intramuscularly.

Dose: Since large intermittent doses may lead to complications such as late hypoglycemia, hypokalemia, hyperlactatemia and osmotic disequilibrium, the present trend is to use smaller doses, 2-10 units per hour continuously as slow intravenous infusion. In some cases higher bolus doses may be required. Action of insulin lasts only for few minutes if given intravenously. In mild cases the same dose can be given I M hourly.

Soluble insulin is diluted with saline to give 0.1unit/mL and administered in the drip or by intermittent injections in a dose of 6 units/hour (0.1 unit/kg/h for children) till the blood glucose comes down to 180 mg/dL. Thereafter the dose of insulin is reduced to 3 units/h. It is ideal to reduce the blood glucose to 90 mg/dL (5 mmol/L). In insulin-resistant cases as detected by blood

sugar estimation at 1 hr and 2-hr intervals, larger doses should be started without delay. It should be the aim to correct the metabolic abnormality within the shortest period, since prolongation of the coma may give rise to irreversible cellular damage. Insulin infusion is continued till the patient is able to take oral feeds and is fit for subcutaneous insulin.

If intramuscular injections of insulin are used the dose is 20 units as loading dose and 6 units every hour to be reduced to 6 units every 2 hours when the blood glucose falls below 180 mg/dL. Once the emergency is tided over, the patient should be put back on his regular insulin regimen.

Electrolyte disturbances: In addition to severe loss of sodium, there is also gross potassium deficit. The serum potassium level does not reflect the total body content since there is shift of intracellular potassium to the extracellular compartment. In the early phases the serum potassium level is high. With the normalization of metabolism with insulin and fluid replacement, potassium re-enters the cells. At this stage serious hypokalemia may supervene. Administration of potassium early in the regimen prevents this complication. If serum potassium is above 4-5 mmol/liter, potassium chloride administration is not started till the potassium falls with therapy. The dose and frequency are adjusted by 2-hourly serum potassium estimations. It is desirable to maintain the serum potassium levels between 4 and 5 mmol/L. Potassium replacement is crucial to prevent death due to hypokalemia during recovery. In a severe case, approximately 100-200 mmol of potassium may be necessary in the first 24 hours. Electrocardiogram monitoring is a helpful bedside method to indicate the effects of hypo- and hyperkalemia on the heart.

Administration of bicarbonate: There is considerable controversy regarding the use of bicarbonates in DKA. It need not be given as a routine. Its use results in a fall of serum potassium, shift of oxygen dissociation curve to the left resulting in tissue hypoxia and CSF disequilibrium. The indications for use of bicarbonates are

1. severe acidosis with plasma bicarbonate level less than 10 mmol/L
2. patients with DKA complicating AMI and
3. in patients with associated lactic acidosis.

Sodium bicarbonate is given slowly in doses of 55-100 mmol (200-300 mL of 2.74% NaHCO_3 solution). As the condition improves, the dose is reduced. Foci of infection, which may act as the precipitating factor should receive attention from the beginning.

Other supportive measures include proper care of the mouth, attention to the bladder and bowels, maintenance of fluid balance charts, and prevention of decubitus ulcers. When the patient improves, he is rehabilitated and his

usual antidiabetic regimen is restored. With modern lines of therapy almost all cases of diabetic coma can be saved if the condition has not advanced too far. Many of the deaths may be accountable to the underlying conditions, which have precipitated diabetic coma, such as myocardial infarction, stroke or infections.

Mild forms of DKA if detected early, can be managed at home using soluble insulin and, if needed, the insulin analogues such as insulin lispro, which are more prompt and predictable in action.

Prevention of Recurrence

The patient should be advised on the regular use of insulin and other anti-diabetes drugs. The fact that insulin should be continued during intercurrent illness has to be stressed. Frequent monitoring of blood glucose levels and urine examination for acetone should be done when the diabetic gets stressful situations, particularly infections.

HYPEROSMOLAR NON-KETOTIC COMA

Syn: Hyperosmolar hyperglycemic non-ketotic state (HHNKS)

This is a serious emergency seen occasionally in the elderly diabetics. It is commonly precipitated by infections, myocardial infarction, burns, trauma, surgical stress, renal failure, pancreatitis and the use of drugs like thiazide diuretics, steroids, phenytoin and propranolol. In this condition probably small amounts of endogenous insulin are present so that lipolysis does not occur, but glucose metabolism is greatly deranged. Blood glucose levels often exceed 300 mg/dL and go up above 600 mg/dL. Ketosis is absent and this distinguishes HHNKS from diabetic coma. Normal osmolality of the plasma is ± 290 mOsm/L. In hyperosmolar non-ketotic state the plasma osmolality rises above 300 and in severe cases, may exceed 370 mOsm/L. There is profound cellular dehydration. The hematocrit is high. When the fluid loss becomes severe, hypernatremia develops. Sodium ions are critically important in determining plasma osmolality. Body potassium is lost and a total deficit of 200-300 mmols may occur.

Clinical Features

The condition starts with extreme weakness and drowsiness and the patient gradually sinks into coma. Other neurological manifestations such as seizures, ataxia, hemiparesis, aphasia and mental disturbances may be present. Though thirst is present in the early stages, it disappears later. Respiration is normal or depressed. Apart from these features, the picture may resemble diabetic coma.

Diagnosis

Hyperosmolar non-ketotic coma should be suspected in all cases of coma occurring in diabetics, without demonstrable ketosis. Plasma osmolarity can be calculated from the plasma levels of sodium, potassium, glucose and urea using the following formula:

Plasma Osmolarity in mOsm/L= 2 (Na⁺ + K⁺) +

$$\frac{\text{Glucose in mg/dL}}{18} + \frac{\text{urea in mg/dL}}{5.6}$$

Some authors do not include K in the calculation.

Treatment

Principles of management include correction of the extreme fluid depletion and the hyperosmolar state. Insulin is administered in small doses as soon as the condition is recognized. Small doses are preferable since these patients are very sensitive to even small doses of insulin. Soluble insulin is given in doses of 5-10 units per hour intravenously as an infusion till the blood sugar comes to normal. Alternatively, 20 units of soluble insulin may be given intramuscularly, followed by, small doses of 5-10 units every second hour intramuscularly.

Hypotonic fluids are administered to lower the osmolarity. Half normal saline is the fluid of choice. About 6-8 liters may have to be given over 24 hours. Monitoring of central venous pressure is essential in the elderly to avoid fluid overload and cardiac failure. In patients with shock isotonic saline should be infused till the central venous pressure begins to rise.

Potassium should be replaced early during the treatment and it should be monitored with serum potassium estimations.

The prognosis is grave and mortality may be 20-40%. Prompt and early treatment results in recovery.

LACTIC ACIDOSIS (LA)

Normal level of serum lactate is between 0.4 and 1mmol/L in the fasting state and it may go up to 2 mmol/L after

meals (5 to 18 mg/dL). This is maintained by the balance between the production and utilization of lactate. Though lactate is produced in all the tissues, the brain, red blood cells and skeletal muscles account for the major part of this metabolite. Lactate is used for energy metabolism by several tissues under different circumstances. 70% of the lactate is cleared by the liver and 30% by the kidneys. Lactic acidosis has been divided into types A and B. In type A there is hypotension and tissue anoxia. Type B is further subdivided into types β_1 , β_2 and β_3 depending upon the etiology. LA may be primary when tissue perfusion is poor as in shock states. It may occur secondary to metabolic derangements as in uncontrolled diabetes, especially when treated with phenformin.

In diabetic lactic acidosis the blood lactate level is increased above 5 mmol/L and the arterial pH is below 7.25 (Table 91.4).

DIABETIC LACTIC ACIDOSIS

The hypoxic state produced by aberration in tissue metabolism probably contributes to the lactic acidosis associated with severe diabetes. Biguanides, especially phenformin aggravate this condition by inhibiting gluconeogenesis and mitochondrial electron transport chain. Due to this complication, phenformin is not routinely used at present. Metformin can also rarely produce lactic acidosis in patients with renal failure but the risk is quite low in normal subjects.

Clinical Features

In 80% of the patients the condition starts with gastrointestinal problems, followed by sudden alteration in the sensorium leading to loss of consciousness, hypotension, Kussmaul's breathing, hypothermia, severe dehydration and circulatory collapse. Diagnosis should be confirmed by estimating plasma lactate which is above 5 mmol/L. The lactate pyruvate ratio would be above 15. Arterial pH falls below 7.25 and plasma bicarbonate falls below 18 mmol/L. The anion gap which measures the

TABLE 91.4 Classification of lactic acidosis (Cohen and Woods, 1976)			
Type A (Tissue hypoxia)	Type B (without tissue hypoxia)		
	β_1 (Common disorders)	β_2 (Drugs and toxins)	β_3 (Hereditary form)
Cardiogenic shock	Diabetes mellitus	Biguanides	Type 1 glycogen storage disease
Endotoxic shock	Renal failure	Sorbitol	Fructose 1-6 diphosphatase deficiency
Severe anemia	Liver disease	Xylitol	Methylmalonic acidemia
Left ventricular failure			(Leigh's syndrome)
	Infections	Salicylates	
	Leukemia	Methanol	

unmeasured anions in blood would be above the normal range of 8-12 mmol/L.

In the absence of ketonuria, an increased anion gap in a diabetic is almost diagnostic of lactic acidosis. Mortality exceeds 50% in most series, if untreated.

Treatment

The principles of treatment comprise correction of shock, tissue hypoxia and acidosis. Toxic metabolites may be removed by hemodialysis. Insulin therapy speeds up recovery from lactic acidosis. Thiamine has been used with benefits especially in alcohol induced lactic acidosis. However its value remains doubtful. Sodium bicarbonate is given to counteract acidosis (buffer action). It should be used with great caution since volume overload, worsening of acidosis and rebound alkalosis may develop. The total dose of bicarbonate can be calculated from the formula.

Total requirement of bicarbonate (mmol) = (25- plasma bicarbonate) $\times$ body weight in kg $\times$ 0.3

Note: Carbicarb (a mixture of sodium carbonate and sodium bicarbonate) can also be used as a buffering solution IV. It is seldom used in practice.

OTHER ACUTE PROBLEMS IN THE DIABETIC

Somogyi effect (Posthypoglycemic hyperglycemia): Insulin treated patients may show wide fluctuation in blood glucose levels, especially hyperglycemic episodes following periods of hypoglycemic episodes. The counter regulatory hormones that are secreted abruptly give rise to this phenomenon.

Dawn phenomenon: This is hyperglycemia occurring around 3-4 am, which is due to partial insulin resistance caused by release of growth hormone. An additional bed time dose of insulin controls the hyperglycemia.

Rhinocerebral mucormycosis: This presents as a fulminant infection of the nasal cavity and paranasal sinuses with extension into the cranial cavity. This is seen more commonly in association with diabetic ketoacidosis. It gives rise to facial edema, cranial nerve palsies and coma. The organism belongs to the order mucorales in the class zygomycetes. Unless detected early and treated promptly the condition is fatal. Strong clinical suspicion and demonstration of the fungus helps to make early diagnosis. Amphoterecin B is the drug of choice.

Necrotising Fasciitis is fulminant infection in the fascial compartments of the limbs caused by mixed bacterial flora. It presents as acute painful infection of the limb or other sites, rapidly leading to suppuration. The rise in pressure in the fascial compartments may lead to vascular occlusion and extensive gangrene if not attended to early

with antibiotic therapy and surgical decompression of the fascial compartment.

Long-term Complications of Diabetes Mellitus

The chronic complications of diabetes have been classified into microvascular and macrovascular complications. The microvascular complications are specific for diabetes and they constitute diabetic nephropathy, retinopathy neuropathy and also the dilated cardiomyopathy. The macrovascular complications on the other hand, are not exclusive to diabetes. They tend to start even before the onset of florid diabetes. These include coronary artery disease, cerebrovascular disease and the peripheral vascular disease. Diabetes accelerates their progression and extent considerably.

Pathogenesis of diabetic complications: Several factors contribute to the total picture. These include:

Hyperglycemia: Hyperglycemia raises the intracellular glucose concentration in insulin independent tissues such as nerves, glomeruli, lens and retina. Aldose reductase, the rate-limiting enzyme in the polyol pathway catalyzes the reduction of glucose to sorbitol, which is subsequently converted to fructose. Sorbitol does not easily cross the cell membranes. It accumulates intracellularly and leads to cellular damage through its osmotic effects (e.g. in the lens): by altering the redox state of pyridine nucleotides (by increasing the NADH/NAD ratio); and by depleting the intracellular myoinositol levels.

Glycosylation of Proteins: The attachment of glucose to amino groups of protein leads to the formation of Schiff base products or early glycation products. The glycation of proteins leads to alteration in the functions of proteins. It is also responsible for the free-radical mediated damage to the tissues. The early glycosylation products undergo 'Amdori rearrangement' to form stable products termed **the advanced glycosylation end products (AGE)**. Specific AGE receptors are found in several cells such as the macrophages and endothelial cells where they mediate the release of cytokines and reactive oxygen species leading to cellular damage.

The other important factors which are involved in the pathogenesis of both the microvascular and macrovascular complications of diabetes are hypertension, hyperlipidemia, smoking and hypercoagulability.

CARDIOVASCULAR SYSTEM

Atherosclerosis sets in early and it tends to be diffuse and extensive. Ischemic heart disease is common. Ischemic heart disease in the diabetic differs from that in the non-diabetic by the involvement of both the sexes in the same

proportion and the occurrence of painless infarction. Some diabetics develop congestive cardiac failure in the absence of hypertension and demonstrable coronary artery disease. Such cases may be termed diabetic cardiomyopathy. Mortality from cardiovascular disease is 2-3 times more common in the diabetics as compared with normal. The target levels for control of blood pressure and lipids in the diabetics are lower than those in non-diabetics. The ideal levels to be achieved are: BP 130/80, LDL < 100 mg/dL, HDL > 40 mg/dL and HbA_{1c} < 7%.

Management of acute myocardial infarction in the diabetic is the same as in the nondiabetic. Since ketoacidosis may be precipitated by myocardial infarction, strict control of diabetes using insulin is needed in the acute phase. Hypoglycemia should be avoided since it may lead to extension of infarct. Diabetes is not a contraindication for angiography, angioplasty or bypass grafting.

Peripheral Vascular disease: Peripheral vascular disease occurs in 20% of the chronic diabetics. Affection of the upper limb is rare and the reasons for this not clear. Occlusion of the femoral artery and its branches may occur. The foot becomes ischemic. Intermittent claudication may develop. Associated sensory neuropathy predisposes to minor trauma leading to fulminant infection and gangrene. Calcification of the arteries in the legs and feet may be demonstrable in X-ray. Monkeberg's sclerosis affects several arteries.

Strict measures to control blood glucose and lipid levels and regulated exercise programmes help to give symptom relief in the early stages. Cessation of smoking is absolutely necessary for recovery. Lipid lowering drugs such as atorvastatin 10 to 20 mg or more at bed time and gemfibrosil normalize the lipid levels. Regression of the arterial narrowing does occur. Surgical measures include balloon angioplasty and bypass grafting. Once gangrene supervenes the management of the local condition is essentially surgical.

CEREBROVASCULAR DISEASE

In India 8-32% of stroke patients have diabetes and cerebrovascular disease is encountered in about 10% of all diabetic patients. The most common age group for strokes in diabetics is the sixth decade. Study by Poulouse K.P from Trivandrum showed that carotid artery atherosclerosis was present in 18% of patients with type 2 DM above the age of 55 years. It was 6 times more common in diabetes compared to non-diabetes (Int J: Diab. in developing countries 2002, vol 22). The presence of hypertension increases the risk of development of stroke. Thrombotic strokes are more common. The severity of neurological deficit is greater and the rate of recovery is poorer in a diabetic. The risk of a second episode within six months is very high and prophylactic use of antiplatelet agents is indicated.

DIABETIC RETINOPATHY

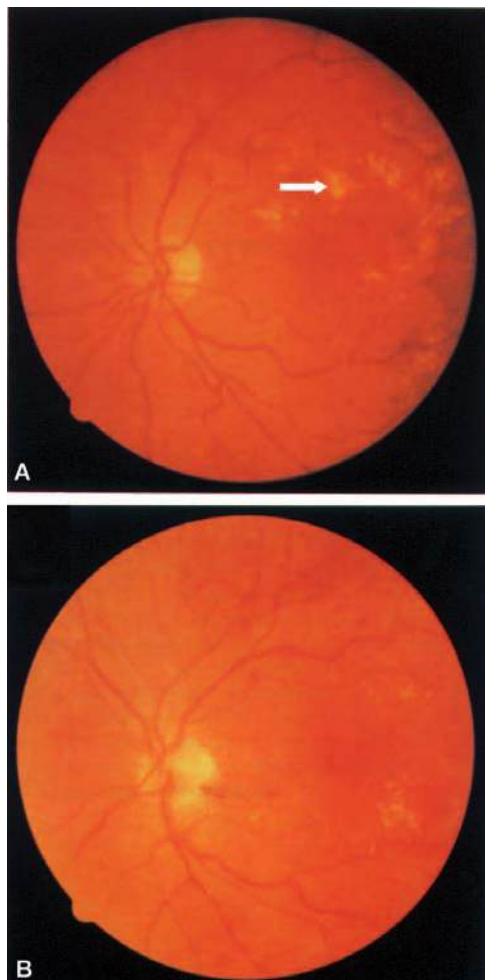
Diabetic retinopathy is now becoming the leading cause of blindness in most of the developing countries. The risk 8% developing diabetic retinopathy is directly related to the duration of the disease. In type 1 diabetes of 15 years or more duration the chance of having any form of retinopathy is 98% and about one-third of such patients have proliferative disease. In type 2 DM of 15 years duration the prevalence is 78%. A third have macular edema and a 6th have proliferative retinopathy. Insulin requiring diabetes have higher incidence of retinopathy compared to those controlled on diet and exercise without drugs.

Recent introduction of corneal confocal microscopy has helped to study the morphology of structures in the cornea including the nerves. The corneal structures are highly magnified up to a resolution of 1-2μ. The lesions can be quantitated and followed up.

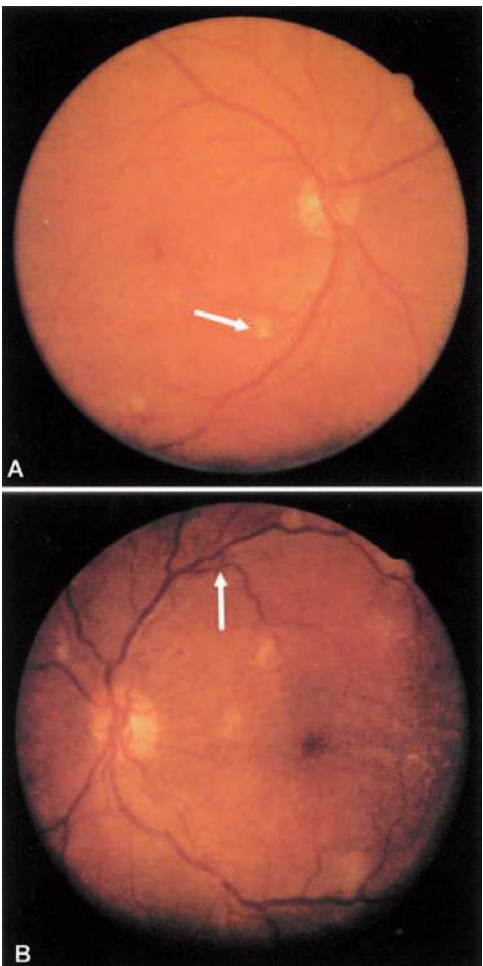
The lesions of diabetic retinopathy can be divided into two broad categories namely background or nonproliferative (NPDR) and proliferative diabetic retinopathy (PDR) (Table 91.5).

Fluorescein angiography is a reliable method to delineate retinal lesions. The earliest sign of retinal change is increased capillary permeability that is evidenced by the leakage of dye into the vitreous humor after fluorescein injection. Occlusion of the retinal capillaries follows, with subsequent formation of sacular and fusiform aneurysms. Arteriovenous shunts also occur. There is proliferation of the lining endothelial cells with loss of pericytes that supports the vessels. Hemorrhages in the inner retinal areas are dot shaped, while bleeding in the more superficial nerve fibre layers appear flame shaped, blot shaped or linear. Preretinal hemorrhages are boat shaped. The exudates are of two types. The cotton-wool spots are microinfarcts. Non-perfused areas surrounded by a ring of dilated capillaries and hard exudates represent leakage of proteins and lipids from damaged capillaries which can best be assessed by fluorescein angiography (Figs 91.1 to 91.4).

TABLE 91.5	
Lesions in diabetic retinopathy	
Background (NPDR)	Proliferative (PDR)
Increased capillary permeability	New vessels
Capillary closure and dilatation	Scar (retinitis proliferans)
Microaneurysms	Vitrear hemorrhage
Arteriovenous shunts	Retinal detachment
Dilated veins	
Hemorrhages (dot and blot)	
Cotton-wool spots	
Hard exudates	



Figs 91.1A and B: Preproliferative retinopathy. Fundus—note: hard exudates (arrow)



Figs 91.2A and B: Preproliferative retinopathy (A) note: cotton wool patches (arrow) (B) more advanced stage note: neovascularisation from veins (arrow)

The increased capillary permeability leads to development of retinal edema and is often associated with hard exudates. If the edema involves the macular region visual acuity may be affected severely and sometimes even permanently. The fundamental characteristic of proliferative retinopathy is new vessel formation and scarring. The stimulus for new vessel formation is retinal hypoxia secondary to capillary occlusion. Vascular endothelial growth factor (VEGF) plays a major role. Two serious complications of proliferative retinopathy are vitreal hemorrhage and retinal detachment, which can cause sudden loss of vision (Figs 91.1A to 91.2B).

The treatment of diabetic retinopathy: This consists of retarding its progression by strict glycemic control, control of blood pressure, cessation of smoking and correction of hyperlipidemia. Laser photocoagulation is used for decreasing the incidence of hemorrhage and scarring when new vessel formation occurs. Pan retinal photocoagulation is often used to diminish the retinal demands for oxygen in the hope that the stimulus for neovascularization may

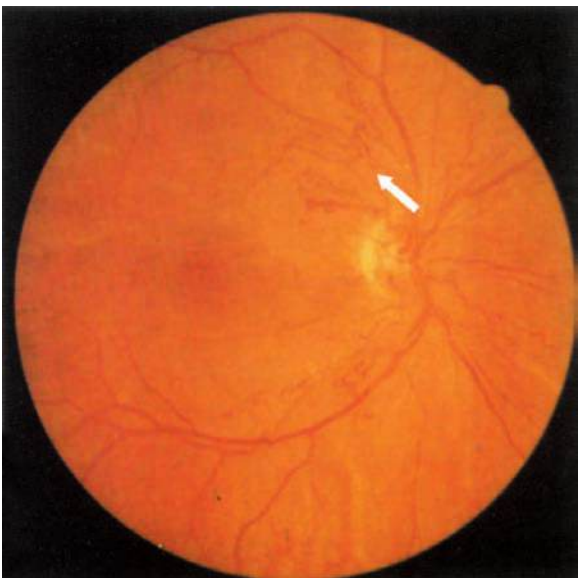
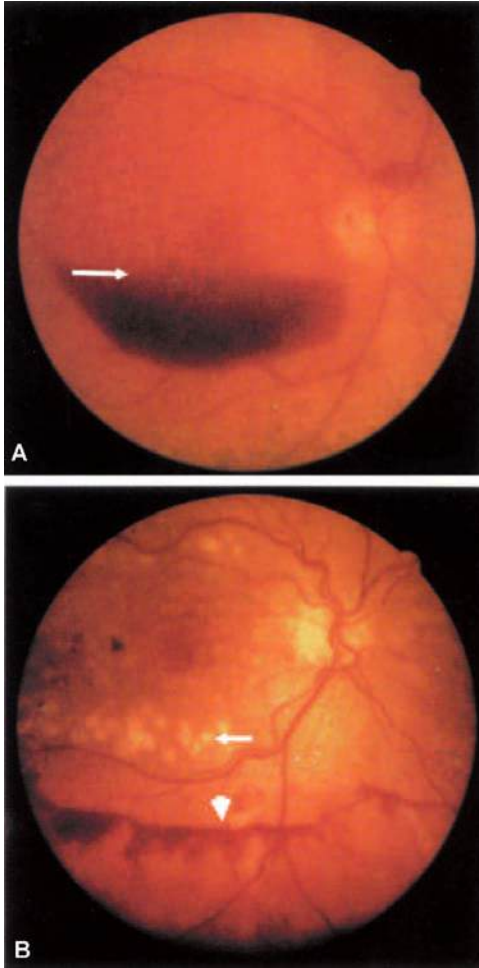


Fig. 91.3: Proliferative retinopathy. Note: regular looped vessels arising from the disc and normal vessels (arrow)



Figs 91.4A and B: (A) Preretinal hemorrhage—note: horizontal upper border (B) advanced diabetic retinopathy with laser scars (arrow). Also note absorbed pre-retinal hemorrhage (arrow head)

be decreased. Definite guidelines are available for the prevention and management of diabetic retinopathy. Persons who have no retinopathy as detected by fluorescein angiography should be screened by an ophthalmologist at intervals of three years. Those with retinopathy should be screened at intervals of 6-12 months for prophylactic and therapeutic photocoagulation of lesions.

(Ref. Navced Younis et al The Lancet: 2003; 361: 195-200)

Surgical techniques used for treatment of non-resolving vitreal hemorrhage and retinal detachment include pars plana vitrectomy. Newer, but experimental approaches include PKC-beta inhibitors like ruboxistaurin, which block the hyperglycemia-induced toxic PKC (protein kinase C) pathways.

Other Complications Affecting the Eye

Refractive errors are common due to changes in osmolarity of the aqueous humor altering the convexity of the

lens when the blood glucose levels change widely. This is a common phenomenon when an uncontrolled diabetic undergoes proper therapy, especially with insulin. This is called *insulin presbyopia*. When the lens adjusts to the normal glucose levels, the vision corrects itself.

Cataract: Senile cataract is preponed by 10 years or more in the uncontrolled diabetic. Posterior capsular cataract is more common. Management is similar to that of cataract in the non-diabetic.

In type 1 diabetic patients, snowflake opacities may develop in the lens due to severe hyperglycemia.

Diabetic Nephropathy

Renal complications of diabetes mellitus have been studied extensively in both types of diabetes by close follow-up over prolonged periods. Five distinct phases in the course of the disease have been identified (see also Chapter 174).

Stage I (Hyper filtration-hypertrophy stage): This stage is characterized by 20-40% increase in glomerular filtration rate (GFR) compared to normal age-matched controls, elevated renal plasma flow and an increase in kidney size by 30%. There is increase in the glomerular size and volume with elevated intraglomerular pressure. These changes are reversible with good glycemic control.

Stage II (Stage with structural glomerular lesions): The hemodynamic changes of the earlier stage and structural glomerular changes begin to appear during this stage in the form of basement membrane thickening and mesangial expansion. During the later part of this stage urinary albumin excretion may also increase transiently (normal < 7 µg/min) during periods of poor glycemic control and exercise.

Stage III (Stage of microalbuminuria): This stage is characterized by the appearance of microalbuminuria. i.e. albumin excretion is in the range of 30-299 mg/day or 20-200 µg/minute. Estimation of urinary albumin/creatinine ratio is emerging as the best way to assess microalbuminuria since this will eliminate fallacies due to urinary dilution or concentration. Microalbuminuria appears primarily due to decreased concentration of anionic heparan sulfate proteoglycans in the glomerular basement membrane. The urinary albumin excretion varies greatly depending upon the time of the day, exercise, posture, and glycemic control. Hence it should be measured at least 2-3 times before microalbuminuria is confirmed. At this stage the blood pressure starts to rise. The risk of overt nephropathy increases 25-30 times once this threshold of albumin excretion is crossed. However, interventions such as strict glycemic control, aggressive antihypertensive therapy and dietary protein restriction have been shown to retard the progress. Microalbuminuria

is an independent marker of cardiovascular risk of ischemic heart disease.

Stage IV (Overt nephropathy): This stage is characterized by the appearance of dip stick positive proteinuria (>550 mg/day). Hypertension is invariably present and retinopathy is also present in over 90% of the patients. Absence of retinopathy should alert the physician towards a nondiabetic cause for the renal disease. Once the overt proteinuric phase begins, there is a steady decline in renal functions with the GFR falling on an average by about 1 ml/min/month. A plot of the reciprocal of serum creatinine against time usually yields a straight line and allows the prediction of the rate of deterioration. Development of nephrotic range proteinuria portends a poor outcome.

Stage V (End stage renal disease): This stage is characterized by the presence of uremic symptoms, fluid retention and edema. At this stage abnormalities of several other organ systems may be obvious. Cardiac insufficiency, peripheral neuropathy, gastroparesis, cystopathy and other extra renal vascular disease may occur. Median survival in untreated patients is less than a year. Such patients require renal replacement therapy in the form of repeated hemodialysis, continuous ambulatory peritoneal dialysis or renal transplantation.

In type 2 diabetes, since the onset of the disease is not acute and since the diabetes can remain unrecognized for a long period of time many patients may present with nephropathy even at the time of first diagnosis. The presence of other disorder such as essential hypertension, urinary tract infection and other forms of kidney diseases hasten the progression of nephropathy.

Management

Even though there is no specific treatment for diabetic nephropathy, early detection and meticulous control of diabetes can reverse microalbuminuria and the progression of nephropathy can be slowed. Hypertension should be treated aggressively with the target blood pressure being <130/85 mm Hg. ACE inhibitors and angiotensin receptor blockers (ARBs) have been shown to slow the progression of nephropathy. They may also be useful in normotensive subjects with microalbuminuria. ACE inhibitors include captopril 12.5-75 mg, lisinopril 2.5-20 mg, Ramipril 1.25-5 mg or perindopril 2-4 mg given daily. Angiotensin receptor blockers (ARBs) like losartan (25-100 mg), Irbesartan (150-300 mg), Candesartan 8-12 mg, Valsartan 80-160 mg or telmisartan 40-80 mg are equally effective in retarding renal lesions. These drugs have been found to be useful to retard diabetic nephropathy also in normotensives. While administering them, renal function should be monitored in the initial phases to avoid hypotension and deterioration of renal function. There is risk of hyperkalemia which should also be monitored. Restriction

of dietary protein helps to retard the progression of renal failure.

URINARY TRACT INFECTIONS

Urinary tract infections are very common in diabetics since glucosuria predisposes to recurrent urinary infection. All common organisms causing urinary infection in non-diabetics are seen in the diabetics as well. In addition, candida may also become invasive. Severe urinary infection may give rise to pyelitis, pyonephritis and perinephric abscess. Papillitis necroticans is the condition in which the renal papillae undergo necrosis in the presence of fulminant infection. Fleshy bits are passed in the urine. At times these may give rise to urinary obstruction and reflex anuria.

Balanoposthitis: This is acute or chronic infection of the glans penis (balanitis) and prepuce (posthitis) occurring commonly in diabetics with glycosuria. This condition gives rise to secondary phimosis. In addition to local cleaning and application of nystatin ointment, strict control of glycosuria is required for full recovery. In many cases the first indication of the loss of control of the diabetic state may be the occurrence of balanoposthitis.

NEUROPATHY

The most common neurological complication is peripheral neuropathy. Metabolic neuropathy may develop because of hyperglycemia and this subsides with proper control of diabetes. The other type is mononeuritis multiplex which is produced by occlusion of the vasa nervorum of the nerve trunks. This does not clear up promptly with treatment. Clinical presentation may be varied. Symmetrical distal sensory neuropathy with pain, numbness, paresthesia, glove and stockings sensory loss and areflexia is the common pattern seen in diabetics.

Motor paralysis leads to foot drop, weakness and wasting of the quadriceps, wasting of small muscles of hands and feet and clawing of the feet. Entrapment neuropathies are also not uncommon. Patients may develop carpal tunnel syndrome. As a result of sensory motor neuropathy, pressure sores may develop over the metatarsal heads.

In chronic cases, with loss of sensation, the mid-tarsal and ankle joints may undergo degeneration (Charcot's joints). The third or sixth cranial nerves may be paralyzed (cranial neuritis). Pupillary abnormalities and disturbances of accommodation may also occur.

Sometimes diabetics develop lancinating pain, motor weakness, sensory ataxia and bladder derangements as in the case of tabes dorsalis (**diabetic pseudotabes**) (Table 91.6).

Diabetic amyotrophy consists of gross weakness and wasting of the proximal groups of muscles of the pelvic girdle, quadriceps and the ilio-psoas. Clinical features are

TABLE 91.6

Classification of diabetic neuropathy

A. Diffuse

1. Distal symmetric sensorimotor polyneuropathy
2. Autonomic neuropathy
 - a. Sudomotor
 - b. Cardiovascular
 - c. Gastrointestinal
 - d. Genitourinary
3. Symmetric proximal lower limb motor neuropathy (amyotrophy)

B. Focal

1. Cranial neuropathy
2. Radiculopathy/plexopathy
3. Entrapment neuropathy
4. Asymmetric lower limb motor neuropathy

pain, paresthesia and loss of tendon jerks without any objective sensory loss. This is seen more commonly in elderly subjects. Diabetic amyotrophy has to be differentiated from a primary myopathy and neuropathy. With proper control of the diabetic state; amyotrophy clears off completely unlike myopathy and neuropathy. Diabetic amyotrophy is probably due to microvasculitis in the lumbosacral plexus.

The gold standard to detect and quantify the severity of diabetic neuropathy includes electrophysiological tests and quantitative sensory tests of thermal and pain perception by small fibres. Sural nerve biopsy and electron microscopy helps to demonstrate the morphological changes.

Autonomic neuropathy is common in diabetes. Presence of autonomic neuropathy should be looked for since the warning signs of hypoglycemia may not develop in such patients. Common manifestations of autonomic neuropathy are impotence in males, orthostatic hypotension, nocturnal diarrhea, disorder of sweating and atonia of the bladder. There is impairment of autonomic control of the heart. Absence of sinus arrhythmia and loss of normal response to Valsalva's maneuver clinically indicate autonomic dysfunction of the heart. Subjects with cardiac autonomic neuropathy are under high risk of sudden cardiac death.

Once established, diabetic neuropathy tends to persist. Meticulous control of diabetes is of definite benefit. Analgesics, antidepressants and antiepileptic drugs such as carbamazepine help to relieve the pain and insomnia. Empirically high dose of vitamins B₁, B₁₂ and B₆ have been widely used based on clinical impression without much objective evidence. Electrical stimulation of the site of pain using a cutaneous nerve stimulator helps to relieve pain in some cases. More recently local application of capsaicin has been used with some benefit. Several drugs such as antioxidants, neurotropic peptides, nerve growth factor, prosaposin, memantine, gabapentin, frisiium,



Fig. 91.5: Trophic ulcer R foot—note the indolent deep ulcer

duloexitine, pregabalin and erythropoietin have been employed from time to time with marginal benefit.

Diabetic Foot

Foot problems give rise to severe morbidity in diabetic patients. Diabetes accounts for up to 50-80% of non-traumatic amputations. The life time risk of developing foot lesions in the diabetic is 12-25%. The factors contributing to the foot problems are:

1. neuropathy – sensory, motor and autonomic
2. ischemia and
3. trauma – physical, mechanical, thermal, continuous mechanical stress, uneven weight bearing.
4. infection

Ulceration of the foot in a diabetic usually results from the combination of neuropathic damage, tissue ischemia and excessive pressure loading, often with superimposed infections (Fig. 91.5).

Neuropathy predisposes to ulceration by reducing perception of pain and trauma inflicted by foreign bodies and walking with tight or ill-fitting shoes. Motor neuropathy leads to involvement of the small muscles of the feet altering the posture of the feet and leading to abnormal pressure distribution on to vulnerable areas, particularly over the metatarsal heads and heels. This leads to formation of callus which can breakdown and lead to ulceration. The other factors which contribute to abnormal distribution of foot pressure, in addition to motor neuropathy are limited joint mobility and local deformities, including Charcot's arthropathy. Removal of callus redistributes the pressure and reduces the risk of subsequent ulceration.

Ischemia: Tissue ischemia is a very important factor in the development of foot ulcers in the presence of neuropathy. Apart from major vascular occlusions, defects



Fig. 91.6: X-ray diabetic foot—note the resorption of the phalanges and distal parts of the metatarsals

in microcirculation which occur in diabetes, contribute to the development of ulceration and failure of established ulcers to heal.

Infections: Infection in diabetic foot ulcers is commonly due to mixed pyogenic anaerobic organisms, some of which may be gas forming. Infection of the deeper tissue may lead to thrombosis in the vessels. Abscess formation may also occur which may compress the plantar arch and reduce blood supply to the forefoot and toes. This may lead to gangrene of the toes and osteomyelitis of the bones, necessitating amputation. Systemic signs such as fever may be absent even with deep-seated infections. X-ray may show resorption of bones (Fig. 91.6).

MANAGEMENT

Prevention of foot ulcers is very important and meticulous care has to be taken. The foot has to be inspected everyday for any evidence of injury, washed clean, wiped dry and powdered. Walking on barefoot should be avoided. Footwear has to be well fitting and specially designed in case of deformity. Callosities or fissures in the skin have to be taken care of. Use of hot water, heating pads, or corn plasters is to be avoided. Smoking should be stopped and meticulous control of hyperglycemia and hyperlipidemia is to be achieved.

If ulcers are present, specimens from the depth of the ulcer should be sent for bacterial culture and sensitivity. Parenteral antibiotics are to be administered based on the organisms isolated. Local antibiotics are not very helpful. Delay in treatment will also cause rapid spread of infection leading to necrotising myofasciitis resulting in large ulcers. X-ray of the foot is necessary to assess the

involvement of the bones and joints. Deep abscesses may need drainage. Full debridement of ulcers is required till granulation tissue is seen and they should be packed with gauze soaked in antiseptic cream. Deep infections with osteomyelitis and gangrene may require amputation.

Other Complications

Puritus vulvae and **recurrent vaginitis** are distressing conditions associated with glycosuria. The common organism is *Candida albicans*. Strict control of diabetes and use of antifungal creams or tablets help to relieve the condition.

Tuberculosis

Diabetics are more susceptible to develop tuberculosis, especially pulmonary and pleural forms. Successful treatment should aim at simultaneous attention to both the diabetes and tuberculosis. The therapy for tuberculosis is the same as for non-diabetics.

Autonomic disturbances take the form of gastroparesis and paralytic ileus which give rise to bloating of the abdomen and this may mimic a surgical emergency. Correction of the diabetic state, especially ketoacidosis may relieve the condition. Prokinetic drugs such as domperidone may be of help at times.

Nocturnal diarrhea may occur in the uncontrolled diabetic and may be mistaken for infective diarrhea. Control of the diabetic state and antidiarrheal drugs such as codeine phosphate given in a dose of 30–40 mg oral bedtime may give relief. Loperamide which is an opiod derivative also reduces intestinal motility and this may be used as a short-term measure. Toxic megacolon is a serious side effect. Non-pharmacological measures such as dietary regulation and timing of the diet may help in some cases.

Dawn Phenomenon: This is hyperglycemia occurring around 3–4am which is due to partial insulin resistance caused by release of growth hormone. An additional bed time dose of insulin controls the hyperglycemia.

Necrobiosis lipoidica diabetorum: This is a skin condition associated with diabetes mellitus. It may occur only in less than 1% of diabetics, but above 80% of patients with necrobiosis may have diabetes. These lesions appear as shiny yellow plaques over the shin. There may be underlying telangiectasia. These lesions are susceptible to chronic ulceration as a result of repeated trauma.

Acanthosis nigricans, a velvety pigmentation of the nape of the neck, axilla and flexural zones may be associated with insulin resistance and diabetes, especially in the obese. Indirectly it indicates excess insulin secretion.

Scleredema diabetorum diffuse non-pitting induration of skin over the nape of the neck and Dupuytren's contracture may develop in some.

Rhinocerebral mucormycosis: This presents as a fulminant infection of the nasal cavity and paranasal sinuses, with extension into the cranial cavity. This is seen more commonly in association with diabetic ketoacidosis. It gives rise to facial edema, cranial nerve palsies and coma. The organism belongs to the order mucorales in the class zygomycetes. Unless detected early and treated promptly the condition is fatal. Amphotericin B is the drug of choice. The newer antifungals such as voriconazole are also effective.

Necrotising fasciitis is the fulminant infection in the fascial compartments of the limbs caused by mixed bacterial flora. It presents as an acute painful infection of the limbs or other sites, rapidly leading to suppuration. The rise in pressure in the fascial compartments may lead to vascular occlusion and extensive gangrene, if not attended to early.

Prevention of Diabetes Mellitus

The prevalence of diabetes, especially type 2 has increased considerably and reached epidemic proportions and is likely to quadruple itself by the turn of the century. Such a situation demands that we should contain this problem by concentrating on preventive strategies. Since the two types of diabetes are different entities, the approach to their prevention would also be different.

Type 1: Several advances have taken place in the understanding of the pathogenesis and natural history of type 1 diabetes, particularly in its preclinical phase. Coupled with this, the advances in the field of immunology and the development of the concept of immunomodulation and immunosuppression in autoimmune disorders have opened up newer vistas in its prevention. Recent experimental work on mice shows that autoimmune type 1 diabetes can be corrected by the transplantation of islet cells along with splenic cells and immunomodulator adjuvants. Stem cells of the spleen can home to the pancreas and develop into mature functioning islet cells. These landmark studies show promise for cure of type 1 diabetes in future.

(Ref. Douglas A Melton- Reversal of type 1 diabetes in mice. N. Eng. J Med 2006; 355: 89-90)

Type 2: The potential for primary prevention of type-2 DM exists in the high risk groups such as (i) persons with a family history of diabetes, (ii) obese individuals (iii) women with bad obstetric history and (iv) hypertensive patients. In these populations, screening for IGT should

be repeated at regular intervals. Enormous benefits could be achieved from preventive programs aimed at a balanced nutrition, avoidance of obesity, promotion of physical activity and reduction of smoking. Though studies have shown that administration of metformin, acarbose and thiazolidinediones during the stage of impaired glucose tolerance (IGT) and impaired fasting glucose IFG can all prevent the onset of florid diabetes, drugs are not generally recommended for this purpose as lifestyle modifications have been shown to be as effective and cheaper. Cases of pre-diabetes have to be managed on individual levels as the condition warrants.

Pancreatic transplants have been carried out in diabetics since 1966. It provides euglycemia and an insulin independent state. Such a state is achieved and maintained along with the use of immunosuppressant drugs. It is done in most cases simultaneously along with a renal transplant. The three main types of pancreas transplant are:

1. Simultaneous kidney pancreas transplant
2. Pancreas after kidney transplant
3. Pancreas transplant only

The choice of the type of transplantation depends upon the patients' kidney status. Simultaneous kidney pancreas transplant is the commonly performed procedure.

Islet Cell Transplantation

In this, cadaver pancreas is removed enbloc and their islets are separated out using collagenases. These isolated islets are then injected into the portal vein by percutaneous transhepatic procedure under fluoroscopic guidance. These injected islets get trapped in the hepatic sinusoids where they establish vascularity. This is associated with risks of liver failure, portal vein thrombosis and portal hypertension. Major indications for islet cell transplantation are cases of type-1 diabetes with any one of the following indications: 1. unawareness of hypoglycemia 2. brittle diabetes with frequent episodes of hypoglycemia and/or ketoacidosis and 3. progressive diabetic complications such as retinopathy, nephropathy and neuropathy. Today most islet transplants are done in conjunction with renal transplants, although people are focusing on solitary islet cell transplants. $2-7 \times 10^8$ islet cell are required to make effective transplantation. About 50% continue to have functioning pancreas without insulin dependence 5 years after transplantation. The immunosuppressive drugs used for renal transplants are not effective in suppressing the immune response against islet cells.

92

Fibrocalcific Pancreatic Diabetes and Other Causes of Melliturias

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Chapter Summary

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Pathology

The pancreas shows intra- and interacinar fibrosis with moderate round cell infiltration. The acini and islets undergo total atrophy and replacement by fat. The ducts are dilated and numerous intraductal calculi made up of calcium carbonate and traces of phosphate are seen to occupy the head and body of the organ. The calculi show a protein core with deposition of calcium in the interstices. The beta cells of the islets are reduced and this accounts for the diabetic state. The liver shows mainly glycogen infiltration and rarely fatty changes and cirrhosis. In long-standing cases the kidneys, retina, and peripheral nerves show lesions similar to those seen in maturity onset diabetes. The parotid glands are prominent and they show ductal dilation and round cell infiltration.

Syn: Calcific pancreatitis, Chronic relapsing pancreatitis, Pancreatic disease of the tropics, Fibrocalculeous pancreatic disease (FCPD).

Geographical Distribution

Chronic relapsing pancreatitis is confined almost exclusively to the tropics, mainly Africa, India, Indonesia and Malaysia. In India most of the cases have been reported from the midland and the hilly tracts of the southern districts of Kerala and Tamil Nadu. Smaller numbers have been reported from many other parts, especially Karnataka and Orissa. The incidence of FCPD seems to have come down in Kerala in recent years.

Etiology and Pathogenesis

Almost all cases belong to the poor socioeconomic groups, which consume cassava as the staple food. The cyanide present in cassava is thought to be responsible for its toxic effects. However some groups who did not consume cassava also had increased incidence of FCPD. This finding made the cassava theory unpopular. Currently, several genes are thought to be responsible for FCPD. The main gene incriminated is the SPINK-1 (Serine protease inhibitor ksazal-1) gene.

Clinical Features

The disease affects children and young adults in the age groups of 15-35 years. Both sexes are equally affected. In one-third cases, previous history of painful episodes of recurrent pancreatitis may be available. The pain is of a colicky or gnawing nature felt over the epigastrium. This differs from that of peptic ulcers in having no relation to food and not being relieved by antacids. Pressure over the epigastrium gives prompt relief. The physical appearance of these subjects is diagnostic. They show extreme emaciation, distension of the upper abdomen, cyanotic hue of the lips, and bilateral painless parotid enlargement. Growth and development are reared. Women develop secondary amenorrhea. Urinary bladder is grossly distended and atonic. The patients generally seek treatment for diabetes or its complications (Figs 92.1 to 92.3).

The diabetic state is often severe, requiring high doses of soluble insulin for control. In the majority of cases the fasting and postprandial blood glucose levels are high. With the passage of time, the diabetes becomes brittle in many cases.

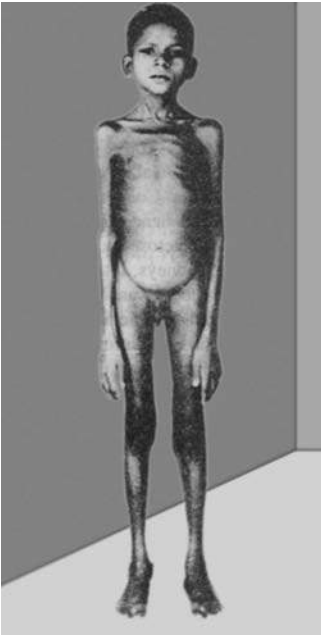


Fig. 92.1: Pancreatic diabetes—male aged 24 years



Fig. 92.2: Pancreatic diabetics a group from a village

Laboratory features: Fasting and postprandial blood glucose levels are in the ranges of type 1 diabetes. Pancreatic enzymes are lowered. Plasma immunoreactive insulin is reduced.

Diagnosis: The disease should be suspected when a young individual presents with abdominal pain and juvenile diabetes. Plain X-ray of the abdomen reveals radio-opaque calculi in the pancreas. CT scan of the abdomen confirms the diagnosis. The calculi are found mainly in the head and body of the organ. They are of varying size and shape and may show translucent centers (Fig. 92.4).

Complications: Complications are due to diabetes, pancreatic calculi, and pancreatic exocrine dysfunction.



Fig. 92.3: Pancreatic diabetes with cataract



Fig. 92.4: Pancreatic diabetes—plain X-ray of abdomen (Note calculi across L1-L2 vertebrae)

1. Diabetic complications are similar to the complications seen in maturity onset diabetes.
2. Complications due to calculi and exocrine dysfunction include obstructive jaundice, recurrent attacks of pancreatitis, and malabsorption state. Steatorrhea manifests if the diet contains normal amounts of fat or excess fat.
3. Carcinoma pancreas.

Prognosis: With adequate control of diabetes by diet and insulin many cases survive up to the fifth or sixth decade. With proper control of the disease, women resume menstruation. Pregnancy and normal childbirths can be achieved with proper management. The children born to such parents do not have predisposition to develop the same disease. Early onset of microangiopathy shortens life

considerably. Some develop pancreatic cancer on follow-up.

Treatment

The treatment is only symptomatic. Control of the diabetic state is similar to the other forms of juvenile diabetes. Since they are mostly insulin-dependent, oral hypoglycemic drugs are ineffective. Generally, the insulin requirement is high and proper control can be achieved only by giving repeated doses of soluble insulin.

Abdominal pain of recurrent pancreatitis is very disabling and response to common antispasmodics like atropine and propantheline bromide is unsatisfactory. During acute attacks the cases have to be managed on the same lines as acute pancreatitis. In intractable cases with demonstrable calculi, surgical removal of the stones and dilation of the sphincter of Oddi have been beneficial in many cases. When signs of malabsorption are present, dietary management and administration of pancreatic enzymes are indicated.

Other Causes of Melliturias

Though glucose is the most common sugar present in urine, other sugars may be encountered at times. Some are present due to inborn metabolic errors whereas others are of the 'overflow' type. In the latter type, sugars appear in urine whenever the blood levels rise above the renal threshold even in the absence of metabolic abnormalities.

Identification of the sugar is important since many cases of innocent melliturias may be wrongly treated as diabetes mellitus with disastrous consequences. A positive Benedict's test with negative diastix should suggest the possibility of non-glucose reducing substances in urine. These include sugars like lactose, fructose, galactose, pentose, and other substances like ascorbic acid, aspirin, and PAS. The final identification of these substances is by chemical methods or chromatography.

LACTOSURIA

Newborn babies ingesting milk may develop lactosuria. The urinary level of lactose increases with the quantity ingested. Lactosuria is common in women during pregnancy and lactation. All these are nonpathological.

FRUCTOSURIA

After intake of large amounts of fructose-containing foods like berries, grapes, and honey even normal persons develop fructosuria, the alimentary fructosuria.

Rarely fructosuria is due to deficiency of the specific enzyme, fructokinase in the liver. This is called essential fructosuria. This condition is benign since most of the

ingested fructose can be utilized by other metabolic pathways.

Hereditary fructose intolerance is a more serious metabolic error caused by the deficiency of *hepatic fructose-1-phosphate aldolase*. This is transmitted as an autosomal recessive. These subjects develop postprandial hypoglycemia. The clinical picture varies with age. The severe form presents in infancy. The baby is normal when breastfed, but vomiting and diarrhea occur when fructose-containing foods, or sucrose and sorbitol (which yield fructose on digestion) are introduced into the diet. The baby fails to thrive. Other accompaniments of the condition are hepatomegaly, jaundice, evidence of hepatic dysfunction, postprandial hypoglycemia, renal tubular acidosis, aminoacidurias and lactic acidosis. If left untreated, the condition proceeds to portal or biliary cirrhosis. If the abnormality is recognized early and fructose is avoided, all the lesions clear up. In older children and adults the disease presents with nausea, abdominal pain, distension, and diarrhea. Since sugar and sweets precipitate these attacks; such persons learn to avoid these items. Hepatic involvement is less marked, but uricosuria and renal stones are more common.

Diagnosis: This should be suspected clinically from the history. Precipitation of hypoglycemia by small doses of fructose (0.25 g/kg body weight in adults or 3 g/m² body surface in children) establishes the diagnosis. In normal subjects hypoglycemia is induced only by large doses of fructose.

Hereditary fructosuria has to be distinguished from other metabolic disorders like galactosemia and tyrosinosis.

GALACTOSEMIA

Normally lactose present in milk is converted into glucose and galactose by intestinal lactase. Galactose is absorbed and converted to glucose in the liver. Conversion into glucose is defective in galactosemia and hence the concentration of galactose-1-phosphate and galactose increase in blood and tissues such as liver, brain, kidneys, intestines, and lens.

Galactosemia is transmitted as an autosomal recessive trait. In the fully developed form classical galactosemia presents with cataract, mental retardation, hepatic cirrhosis, and death in early life. The enzyme galactose-1-phosphate uridyl transferase is deficient. The severe form manifests within a few days of birth with intolerance to milk, vomiting, refusal to feed, and failure to thrive. Jaundice, hepatomegaly, and hepatic dysfunction develop early. Cataracts develop within weeks or months. As the child grows up, mental deficiency becomes evident. Recurrent bacterial infections (*E. coli*) are common and may be fatal.

In the atypical form of galactosemia, the enzyme galactokinase is deficient. Galactokinase is required to convert galactose into galactose-1-phosphate and in its absence galactose accumulates in blood and tissues. The only complication in this disorder is cataract formation.

Diagnosis: Urine shows galactose. Diagnosis is established by demonstrating the deficiency of galactose-1-phosphate uridyl transferase in erythrocytes.

Treatment consists of dietary measures to avoid milk and milk products, and this results in dramatic improvement. Even in advanced cases dietary management leads to regression of symptoms except the cataract.

PENTOSURIA

Pentosuria can be due to ingestion of excessive pentoses found in grapes, cherries, plums, etc. and this is known as alimentary pentosuria. The pentoses are arabinose, apiose, rhamnose, ribose, and xylose. Essential pentosuria is an inherited disorder transmitted as an autosomal recessive trait and the urinary pentose is 1-xylulose. It is caused by the deficiency of xylitol dehydrogenase. This condition is clinically silent and no treatment is required. The pentosuria is controlled by avoiding fruits.

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Other Metabolic Disorders

K.V. Krishna Das

10

Chapter Summary

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INBORN ERRORS OF METABOLISM: GENERAL CONSIDERATIONS

Inborn errors of metabolism (IEM) are genetically determined interruptions of one or several related metabolic pathways. Clinical symptoms result from several abnormal metabolic processes. These include:

1. Deficiency of an enzyme required for normal metabolism.

2. Toxicity due to accumulation of intermediary compounds due to defective metabolism, including acute intoxication.
3. Energy deficiency
4. Organomegaly
5. Profound central hypotonia and
6. Malformations

Inborn errors of metabolism are mostly recessive disorders with clinical symptoms occurring in homozygous individuals. The genetic defects involve homozygous (autosomal) or hemizygous (X-linked) mutations in genes encoding proteins with single enzymatic function. Other abnormalities include interruption in other biochemical pathways.

Though individually the inborn metabolic disorders are rare, when considered collectively, their incidence is higher. The mode of presentation may give a clue to the metabolic disorder. Positive family history helps in diagnosis. Parental consanguinity and neonatal death of siblings or maternally related male members are factors which favour a diagnosis of IEM.

At present several types of IEM are correctable by therapeutic measures or by bone marrow or stem cell

transplantation. Acute presentations of IEM in neonates fall into one of the following five syndromes:

1. The baby is intoxicated:- During the prenatal period it is apparently normal, but soon after birth it starts deteriorating, especially when external feeding is established.
2. Energy deficient conditions:- These results from recurrent hypoglycemia and/or lactic acidosis.
3. Prominent visceral involvement (i.e.) isolated hepatic, or cardiac failure
4. Floppy baby from the birth often, with seizures
5. Multiple malformations

Metabolic defect should be suspected when an infant which is normal at birth fails to thrive, or develops metabolic acidosis and features such as persistent vomiting, organomegaly, developmental abnormalities, convulsions and urinary abnormalities such as peculiar odour, colour change and others. In some instances, the defect occurs in several children in the same family. It is important to make early diagnosis since in many cases dietary modification and supplementation with the missing cofactor help to overcome the defect and prevent permanent damage.

With the development of methods to detect enzymic defects and more advanced biochemical techniques, several metabolic disorders have been brought to light. Though many of these disorders are rare, their investigation has helped in improving the understanding of several metabolic pathways. Many of these metabolic defects are genetically inherited and, therefore, genetic counseling is important in their prevention. Diagnosis of these metabolic disorders early in life and avoidance of the offending articles in diet or biochemical correction of the abnormality helps to restore normalcy.

Table 93.1 gives a list of the important metabolic disorders. For full description, the student may consult larger textbooks on the subject.

It is now possible to identify the abnormal gene and its product which leads to the clinical abnormality.

Many of the inherited metabolic disorders are correctable by bone marrow or stem cell transplantation. In some cases replacement of the missing enzyme therapy using recombinant enzyme is possible but such treatment is expensive. In Hurler's syndrome, stem cell transplantation using cord blood alters the natural history of the disease, if undertaken early in life.

The Metabolic Syndrome

Syn: Reavens syndrome, Syndrome X

This condition has gained prominence in modern times since it is a common forerunner of ischemic heart disease, diabetes mellitus and atherosclerosis. This condition is amenable to life style modifications and has been extensively studied and criteria for early diagnosis have

TABLE 93.1

Some important inherited metabolic disorders

1. Abnormalities of glycogen metabolism
Glycogenoses
Glycogen storage disease
Type I (von Gierke's)
Type II (Pompe's)
Type III (Cori's, Forbe's)
Type IV (Andersen's)
Type V (McArdle's)
Type VI (Her's)
Type VI a
2. Abnormalities of purine metabolism:
Gout, Lesch-Nyhan syndrome, myopathy, and combined immunodeficiency
3. Abnormalities of pyrimidine metabolism:
Orotic aciduria
4. Lysosomal storage diseases:
 - a. Mucopolysaccharidoses (MPS):
MPS IH-Hurler' syndrome (Gargoylism)
MPS IS (Scheic's syndrome)
MPS II (Hunter's syndrome)
MPS III (Sanfilippo-A, B, and C)
MPS IV (Morquio)
MPS VI (Maroteaux-Lamy)
MPS VII (Sly)
 - b. Mucolipidoses (ML): Mucolipidoses types I, II, III, and IV, mannosidosis, fucosidosis, and aspartyl glucosaminuria.
5. Lipid storage disorders:
Gaucher's disease
Neimann-Pick disease
Farber's lipogranulomatosis
Krabbe's disease
Metachromatic leucodystrophy
Multiple sulfatase deficiency
Fabry's disease
GM1 gangliosidosis
GM2 gangliosidosis infantile
Tay-Sachs disease
Juvenile Tay-Sachs diseases (Sandoff's)
6. Disorders of amino acid metabolism:
Hyperphenylalaninemia (phenylketonuria-PKU)
Tyrosinemia
Histidinemia
Disorders of enzymes concerned with the urea cycle leading to increase in citrulline, argininosuccinic acid, and ornithine in blood.
Disorders of lysine metabolism: Periodic hyperlysinemia, persistent hyperlysinemia, and hyperpipecolatemia.
Disorders of branched-chain amino acid metabolism: Maple-syrup-urine disease, isovaleric acidemia, propionic acidemia, methyl malonic aciduria and biotin responsive multiple carboxylase deficiency.
Disorders of sulfur-containing amino acids: Homocystinuria, cystinosis, and alkaptonuria.
Disorders of fat metabolism: Hyperlipidemias-Fredrickson's types 1, 2a, 2b, 3, 4, and 5.
Hemochromatosis
Wilson's disease
Disorders of heme metabolism.
Porphyrias

TABLE 93.2

Criteria for diagnosis of the metabolic syndrome

1. Impaired fasting plasma glucose (FPG) ≥ 100 mg/dL
2. Obesity with the waist circumference > 102 cms in males and 88 cms in females
3. Plasma triglycerides > 150 mg/dL
4. HDL cholesterol < 40 mg/dL in men and < 50 mg/dL in women
5. Blood pressure $> 130/85$ mm Hg

been laid out. The occurrence of the metabolic syndrome is very common, and it is estimated that 22-39% of the adult population in developed countries have this condition. Prevalence varies depending on the definition used and on ethnicity.

Several criteria for the diagnosis of metabolic syndrome have been put forward by WHO, International Diabetes Federation (IDF) and American Association of Endocrinologists (Table 93.2).

The combination of

1. Abnormal glucose tolerance
2. Abdominal obesity
3. Dyslipidemia
4. Hypertension and
5. Coronary artery disease, is together referred to as the *metabolic syndrome* or the *insulin resistance syndrome*. Indians express this syndrome in an exaggerated manner, and this is probably one of the reasons for the increasing prevalence of type 2 diabetes and coronary artery disease in the Indian subcontinent and especially those who have settled in more affluent countries. The exact genesis of the syndrome is not well understood. Inheritance of polygenic predisposition, abnormal intrauterine programming and sedentary life style are but some of the hypotheses put forward to explain the syndrome. The central underlying feature of this syndrome is insulin resistance.

The major components are obesity, hypertension, dyslipidemia and glucose intolerance (the deadly quartets) and coronary artery disease. The diagnosis requires the presence of at least 3 of the 5 major criteria. Individuals with metabolic syndrome are at increased risk of developing diabetes, cardiovascular events (accelerated atherosclerosis) hypercoagulability and endothelial dysfunction.

The association between the metabolic syndrome and abdominal obesity is well proven. It is possible that in the metabolic syndrome the various endocrine secretions of the adipocytes could play a role in the pathogenesis. Recent reports also reveal a link between both high birth weight as well as low birth weight amongst infants as pre disposing factors for the development of metabolic syndrome and type 2 diabetes in adulthood.

Several other manifestations are linked to insulin resistance. These include: 1. polycystic ovarian syndrome 2. fatty liver 3. hyperuricemia 4. microalbuminuria 5. markers of reduced fibrinolysis such as plasminogen activator inhibitor-1 and 6. endothelial damage.

In subjects who have any one component of this syndrome, it is important to look for other components also since they cluster together. Management consists of full investigations for all the component abnormalities, dietary regulation, physical exercise, control of lipid abnormalities and regular monitoring.

HYPERLIPIDEMIAS

General Considerations

The exogenous lipids: A liberal diet supplies about 100 g of triglycerides and 1 g of cholesterol daily. After absorption they circulate in blood as chylomicrons from which the fatty acids pass to muscle cells and fat cells where they are utilized for energy or re-esterified into triglycerides. The remaining portion of the chylomicron which is rich in cholesterol esters is taken up by the liver for the formation of bile acids and the rest passes unaltered in bile. Free fatty acids liberated from fat depots are also metabolized in the liver to form triglycerides, phospholipids, and cholesterol which circulate in blood as lipoproteins.

The endogenous lipids: The liver synthesizes triglycerides from surplus carbohydrates obtained from diet. The triglycerides are esterified and released into circulation as very low density lipoproteins (VLDL). The triglyceride is split off and it enters the adipocytes. The VLDL remnant which contains mainly cholesterol esters gets physically transformed into low density lipoprotein (LDL). Around 75% of circulating cholesterol is present in the form of LDL, and this is the form in which cholesterol is supplied to extrahepatic tissues like the adrenal cortex, muscle cells, renal cells, and lymphocytes for the formation of cell membranes, and hormones. Unesterified cholesterol which is liberated into plasma from disintegrating hepatic parenchymal and phagocytic cells constitutes high density lipoproteins (HDL). The levels of cholesterol and triglycerides in plasma show considerable variation in health. Cholesterol levels above 200 mg/dL and triglyceride levels above 150 mg/dL indicate hyperlipidemia in adults. The cholesterol of atheromatous lesion is derived principally from plasma.

HDL is protective against atheroma, whereas LDL favours atherogenesis. Lipoprotein abnormalities are particularly marked in the metabolic syndrome (syndrome X) in which the HDL level is reduced. In the presence of hypertriglyceridemia, a decrease in cholesterol content of HDL results from decrease in the cholesteryl-ester content of HDL lipoprotein core making the particle small and

TABLE 93.3

Properties of the major lipoprotein fractions

Lipoprotein	Major lipid	Major apoproteins	Sp. gr.	Electrophoretic mobility
Chylomicron	Dietary triglyceride	AI, AII, BI, CI, CII, CIII	Below 1.006	No movement
VLDL	Endogenous triglyceride	B, CI, CII, CIII, E	Below 1.006	Pre-beta
LDL	Cholesterol esters	B	1.019 to 1.063	Beta
HDL	Cholesterol esters	AI, AII	1.063 to 1.210	Alpha
Remnants and triglyceride	Cholesterol esters	B, CIII, E	Less than 1.019	Slow pre-beta

dense. This leads to increase in the clearance of HDL from the circulation and the serum level of HDL falls.

Small dense LDL: This form of LDL increases when the triglyceride levels rise. This leads to depletion of unesterified cholesterol and phospholipids with either no change or an increase in LDL triglyceride.

Small dense LDL is more atherogenic than buoyant LDL due to the following reasons.

1. It is more toxic to the endothelium
2. It is able to pass more easily through the endothelial basement membrane
3. It adheres to glycosaminoglycans
4. It has increased susceptibility to oxidation
5. It is more selectively bound to scavenger receptors on monocyte derived macrophages. Presence of small dense LDL is common in syndrome X (Table 93.3).

CLINICAL CONSIDERATIONS

The blood levels of cholesterol and triglycerides give valuable information for the assessment of errors of lipid metabolism. LDL and HDL together account for 90% of the cholesterol in the plasma. Lipids are present in circulation as lipoproteins and free fatty acids (non-esterified fatty acids) bound to albumin. The lipoproteins are formed by the combination of the lipids, triglycerides, phospholipid, and cholesterol with specific apoproteins. These have been classified as very low density lipoproteins (VLDL, pre-beta) low density lipoproteins (LDL, beta lipoproteins), or high density lipoproteins (HDL, alpha lipoproteins) based on ultracentrifugal studies and electrophoretic patterns. The LDL and HDL particles are heterogeneous. The terms “pre-beta”, “beta”, and “alpha” refer to the bands seen on electrophoresis.

The role of HDL is probably to transport cholesterol and remove lipids from the arterial walls. The HDL reduces uptake of LDL by cells. Increase in levels of LDL and VLDL and decrease of HDL are associated with higher incidence of atheroma and its complications. Specific subclasses are selectively related to coronary heart disease. HDL has a protective role against atherogenesis. In coronary heart disease the concentration of HDL fraction is particularly low. Raised concentration of

LDL is readily decreased by controlled diet and appropriate drugs. Reduction of saturated fats in the diet and increase in the proportion of mono- and polyunsaturated fats help to lower LDL levels.

Trans-saturated fats produced by hydrogenation of vegetable oils are particularly atherogenic. These fats, prepared in large amounts commercially are used for the production of margarines, artificial butter, bakery products, deep fried fast foods and others. Regular physical exercise helps to lower LDL cholesterol and raise HDL cholesterol to a limited extent.

High levels of LDL (above 500-700 mg/dL) lead to acute pancreatitis.

Lipoprotein (a) [LP (a)] is a genetically determined fraction, with less of environmental influences. In Asian Indians it is a very powerful predictor of coronary artery disease. Concurrent high levels of triglycerides and LDL increase the risk. LP(a) is highly thrombogenic, atherogenic and antifibrinolytic. Its atherogenic risk is 10 times that of LDL. Due to this high risk, LP(a) is called the “**deadly cholesterol**”. Measurement of LP(a) is advisable for all persons with family history of premature atherosclerosis.

Hyperlipidemias may be primary or secondary. In the primary hyperlipidemias genetic factors may be prominent. Environmental factors such as obesity, high saturated fat diet, and smoking aggravate the disorder. Primary hyperlipidemias may be further classified into three groups.

Primary Hyperlipidemias

Group I: This consists of hypercholesterolemia (280-400 mg/dL, 7-10 mmol/L) with a clear serum, normal triglyceride levels, and increase in LDL (beta lipoproteins). In the majority of cases environmental factors like high saturated fat diet and smoking are seen to aggravate the condition. For a long time the condition is asymptomatic, but 50% develop ischemic heart disease by the age of 50 years.

The condition occurs as an autosomally dominant inherited disorder in 5% of subjects. They show very high serum cholesterol levels (320-640 mg per dL in

heterozygotes and 640-1280 mg/dL in homozygotes). Xanthomas and arthritis are common. Xanthomas are deposits of cholesterol seen as yellowish nodular masses which vary in size from a few millimeters to several centimeters. They develop insidiously and are painless. The common types are *xanthoma tendinosum* (over the tendo-Achilles, extensor tendons of the hand, etc), *xanthoma tuberosum* over the bony prominences (around the elbow, knees, iliac crest, etc), *xanthoma planum* (plaque-like), striate xanthoma along the palmar creases, or as papular eruptions (*eruptive xanthoma*). Sometimes they ulcerate and discharge greasy material. Some may be calcified. Histology shows collections of lipid-laden cells.

Many subjects may show *xanthelasma*. These are yellowish plaque-like lesions seen on the medial aspects of the upper and lower eyelids. Though these show a strong association with hypercholesterolemia, they may also be seen in persons with normal cholesterol levels.

Corneal arcus occurs as a greyish ring along the periphery of the cornea. A clear zone of cornea can be seen outside the arcus and this feature distinguishes corneal arcus from other lesions like *Kayser-Fleischer ring*. Corneal arcus is seen to develop in the majority of persons with age, but premature occurrence of arcus has been associated with the presence of hypercholesterolemia, especially LDL cholesterol, but in several reports from India this association has not been seen.

Group II: In this type of disorder there is predominantly hypertriglyceridemia. The serum is cloudy, triglycerides and pre-beta lipoproteins are increased but cholesterol is normal or only moderately increased. Common associations are obesity, diabetes mellitus, and gout. There is a strong tendency to develop ischemic heart disease.

Group III: Consists of chylomicronemia and this results from the deficiency of extrahepatic lipoprotein lipase. This is rare.

Frederickson's classification: Frederickson has suggested a classification of hyperlipidemia which includes six groups based on the serum levels of lipids and lipoproteins, estimated in the fasting state.

Management of primary hyperlipidemias: Many cases can be controlled by dietary management. Excess weight should be reduced. Groups I and II benefit by the avoidance of dietary cholesterol and restriction of fat to supply less than 15% of the total calories. Lipids should be supplied as polyunsaturated fats. Foods such as egg yolk, butter, margarine, hydrogenated oils, lard, suet, cakes and biscuits made with these fats, whole milk, cream, fatty meat, chocolates, coconut oil and foods fried in saturated fats should be avoided. Some cases show an abnormal elevation of serum lipids with the intake of alcohol and refined carbohydrates. Such cases benefit by restriction of alcohol and refined carbohydrates. Group III

Frederickson's classification		
Types	Lipoproteins	Groups
Type 1	Chylomicron	Group III
Type 2a	LDL	Group I
Type 2b	LDL and VLDL	Group II
Type 3	Remnants	
Type 4	VLDL	
Type 5	VLDL and chylomicrons	

hyperlipidemias respond to reduction of fat below 15% of their dietary intake.

As important as the diet are exercise programs. Weight reduction and aerobic exercises help to normalize several of the hyperlipidemias. Proper exercise regimen and avoidance of smoking reduce the coronary risk further.

The desirable level of total cholesterol for Indians is ideally 150-200 mg/dL. Decreased level of HDL below 35 mg/dL is an independent risk factor for atherosclerosis. Presence of low HDL levels is an indication for active lowering of total cholesterol and LDL. Levels of triglycerides above 200 mg/dL especially when accompanied by a low HDL/LDL ratio increases the risk of coronary atheroma six fold. The LDL particle size also influence the risk factor, smaller size being more harmful.

Drug therapy: Drugs are employed when dietary measures alone are inadequate. Cholestyramine, which is an anion exchange resin, in a daily dose of 16-32 g in 3-4 divided doses helps to control the hyperlipidemia in group I. It acts by inhibiting the absorption of bile acids and cholesterol. It is very effective in type 2 hyperlipidemia, but is contraindicated in types 3, 4, and 5.

Clofibrate, which is a branched chain fatty acid, reduces VLDL and it is effective in lowering plasma triglycerides in types 3 and 4, when given in doses of 0.5 g 3-4 times a day. Clofibrate is indicated in severe hyperlipidemia where the risk of atheromatous occlusions, xanthomatosis and pancreatitis is high (Frederickson's types III, IV, and V). Adverse side-effects of clofibrate include gastrointestinal upsets, increased incidence of cholelithiasis, and increased frequency of malignant neoplasms. Nicotinic acid in a dose of 0.5 to 1 g or more thrice daily augments the lipid lowering effects of other drugs in groups I and II hyperlipidemias. Gemfibrosil in a dose of 0.8 g bd is an effective lipid lowering agent.

Exercise and cessation of smoking help to increase HDL cholesterol, and reduce triglycerides and VLDL. High fiber diet, guar gum powder, fenugreek seeds and bittergourd (Karela) are known to lower serum LDL levels.

The statins: These are inhibitors of HMG (hydroxymethyl glutaryl) coenzyme reductase. They inhibit cholesterol biosynthesis in the liver thereby reducing LDL cholesterol. Other actions of statins include modulation of macrophage activity, changing immune functions of lymphocytes,

reduction of inflammatory activity and improvement in hemorrheological factors. There are several members in this group—lovastatin, simvastatin, pravastatin, Rosavastatin, atorvastatin and others. The newer members have got greater clinical activity. The dose range from 10-40 mg once a day. Effective lowering of cholesterol and LDL reduce the risk of thromboembolic occlusions of coronary and cerebral arteries. Maintenance of serum lipids at lower normal levels has also been shown to lead to regression of atheroma. Statins are indicated to normalize lipid levels in both genetic and secondary hyperlipidemias. It is better to start with lower doses and work up the dose to adjust the lipid levels depending upon the clinical condition and changes in serum lipids. Several large clinical trials have established the beneficial role of statins in reducing the incidence of coronary artery disease, cerebrovascular disease and major acute cardiac events such as myocardial infarction and sudden death. The evidence base for regular use of statins for secondary and primary prevention of atheroma is strong. There are reports of the use of large doses of statins (up to 80 mg daily) in the metabolic syndrome improving the results and prognosis. Side effects include reversible myositis, headache, rise in hepatic enzymes, abdominal pain and others.

Probucol

This drug lowers LDL predominantly. It is an alternate drug in those whose response to statins is inadequate or those who cannot tolerate statins. The dose is 500 mg bd oral.

Probucol has no effect on triglycerides. It may lower HDL slightly. Side effects are mild, mainly gastrointestinal. Rarely, prolongation of the Q-T interval and cardiac arrhythmias may develop. Therefore regular ECG monitoring is required.

Cholesterol Absorption Inhibitor

EZETIMIBE selectively inhibits the absorption of cholesterol by the brush border of the small intestinal epithelium. Triglycerides, fatty acids and fat soluble vitamins are not affected. Its main use is in combination with statins when their effect is suboptimal.

Omega-3 fatty acids: Eicosa pentaenoic acid (EPA) and docosahexaenoic acid (DHA), 2-7 g/day given orally reduces blood levels of triglycerides and cholesterol and thereby lower the coronary risk. Fish oils and fish produce similar beneficial effects.

Secondary Hyperlipidemias

Secondary hyperlipoproteinemias outnumber the primary type. In the majority of cases LDL cholesterol is increased in the serum. The risks of coronary, cerebral, renal and peripheral arterial disease are high irrespective of the primary cause and this risk can be brought down by appropriate therapy.

Causes: The secondary types are seen in diabetes mellitus, hypothyroidism, nephrotic syndrome, biliary obstruction, pancreatitis or as a side effect of drugs such as estrogens and corticosteroids.

In all subjects with hyperlipidemias primary causes should be looked for and attended to.

HEMOCHROMATOSIS

Syn: Bronzed diabetes

This is a metabolic disorder associated with marked increase in iron store in the body. Two forms are known 1. genetic 2. acquired. The genetic hemochromatosis is an autosomal recessive disorder showing varied phenotype manifestations and varying expressivity in different families. Homozygous disease occurs in 3-5/1000. Carrier frequency is 1/10 to 1/5 among the Caucasian population and this is one among the more common genetic abnormality in them. HLA-A3 and B14 are more frequently associated with genetic hemochromatosis.

Underlying defect is the pronounced increase in intestinal absorption of iron through an up regulation of the duodenal metal transporter gene caused by mutation of HFE gene, which is located on chromosome 6 near the HLA locus. Its product is widely expressed in several tissues. More than 80% of affected subjects show a homozygous point mutation (G-A at nucleotide 845) in HFE gene. This results in a cytosine to tyrosine replacement at amino acid 282 (c 282 y). This abnormality can be demonstrated in the laboratory and is used for genetic screening. The HFE product binds to transferrin receptor. Several mutations are known to produce hemochromatosis. Mainly four types of hereditary hemochromatosis are identified. These include:

- a. HFE related
- b. Juvenile type
- c. Transferrin receptor 2 (TfR₂) related and
- d. ferroportin related iron overload

Normal iron absorption is 1-2 mg/day. In hemochromatosis it goes up to 6 mg/day and the body stores may reach up to 60 g against the upper limit of normal of 4 g.

The secondary type is due to iron overload.

Pathogenesis

The main defect is loss of regulation of intestinal absorption of iron resulting in increased absorption of dietary iron. This iron is taken up by several parenchymal tissues and macrophages which results in toxic damage. The pathological changes include cellular dysfunction, necrosis, and fibrosis. Liver and pancreas are most severely affected. The skin, myocardium, and endocrine glands like the adrenal cortex, testes, pituitary and thyroid are affected with varying severity. The condition remains asymptomatic till the total body stores of iron reach 15-20 g.

The liver is enlarged, firm to hard in consistency, and the cut section is brown. The hepatocytes and Kupffer's cells show stainable iron. Eventually, portal cirrhosis develops. Cirrhosis develops when the hepatic iron content exceeds 400 $\mu\text{mol/g}$, i.e. 22.4 mg/g of dry liver tissue. Acinar cells of the pancreas and less frequently the islet cells show hemosiderin. Diabetes may develop. There is increase in iron in several organs. Skin shows increased pigmentation due to deposition of melanin.

Clinical Features

Males are affected five times more frequently than females. Symptoms generally start in the fourth and fifth decades. These include lethargy, loss of libido and impotence, pigmentation, hepatomegaly, and diabetes. The combination of pigmentation and diabetes is referred to as **bronzed diabetes**. Cirrhosis of liver and testicular atrophy occur in advanced cases. Severity of the diabetes is variable. Cardiac enlargement, cardiac failure, heart block and arrhythmias occur in 10-15% of cases. Arthropathy develops due to deposition of calcium pyrophosphate and hemosiderin in the synovium. In long-standing cases hepatocellular carcinoma may develop.

Course and Prognosis

Mean survival in untreated cases is 5 years after diagnosis. Death is caused by infection, cardiac failure, hepatic failure, hepatic carcinoma or diabetic complications. Modern treatment has improved the outcome considerably.

Diagnosis

Hemochromatosis should be considered in all patients presenting with hepatic cirrhosis, diabetes, skin pigmentation, and cardiac abnormalities. In hepatic cirrhosis due to any cause there is accumulation of iron in the liver and this should be distinguished from primary hemochromatosis.

Serum iron is usually above 175 $\mu\text{g/dL}$, TIBC is 200 $\mu\text{g/dL}$ and transferrin saturation is about 60% and often even 100%. Serum ferritin may be increased to 1000 ng/mL in severe cases and in the absence of significant hepatocellular damage, this reflects the enormous iron load.

The 24-hour urinary excretion of more than 2 mg iron following intramuscular injection of 0.5 g of desferrioxamine is suggestive of excessive iron stores. Values greater than 10 mg indicate idiopathic hemochromatosis.

Treatment

Simple venesection to remove 500 mL blood once in two weeks or at shorter intervals help to prolong life by a mean of 8.2 years and improves hepatic function. Venesection is indicated when the serum ferritin level exceeds

1000 ng/mL. The hematocrit is adjusted to around 35% by venesection. Each venesection removes 250 mg of iron. When the iron stores become normal (ferritin drops to 50 ng/mL) progression of cirrhosis may halt. Rarely it may regress and the pigmentation may also come down. There is a general reluctance to do venesection at frequent intervals in them. An established case may require removal of several liters of blood at regular intervals of 5-7 days before the clinical benefits become evident.

The iron chelating agent desferrioxamine has been used when venesection is contraindicated by the presence of anemia, but the drug is less effective. Diabetes is controlled on its own merits. In secondary hemochromatosis desferrioxamine is effective.

WILSON'S DISEASE

Syn: Hepatolenticular degeneration;
Westphal-Strumpell pseudosclerosis

It is an inborn error of metabolism of copper inherited as autosomal recessive. The abnormal gene is present in chromosome 13 and it is identified as ATP7B. This disease is present not uncommonly in many communities in India. Normally copper which is absorbed from the gut is initially bound loosely to albumin, but very soon it binds firmly with ceruloplasmin, which is a globulin produced in the liver.

In Wilson's disease absorption of copper is normal or increased. There is defect in excretion of copper into the bile. Ceruloplasmin in the plasma is absent or considerably reduced. Production of ceruloplasmin is normal but its degradation is accelerated. Therefore the serum copper remains loosely bound to albumin and gets deposited in various organs such as the liver, brain, cornea, kidneys heart, and muscles. This leads to the damage of parenchymal tissues. The most prominent lesions are cirrhosis of the liver and damage to basal ganglia and renal tubules. Cirrhosis of the liver is more common in children.

Clinical Features

The presentation may be predominantly hepatic, neurological or mixed. Hepatic manifestations include recurrent episodes of acute hepatitis like picture, acute liver failure, chronic hepatitis, eventual cirrhosis, portal hypertension and chronic hepatic failure. Hematemesis, portal systemic encephalopathy and coma may follow.

In the brain, copper is deposited mainly in the basal ganglia, cerebellum, and cerebral cortex. This manifests as involuntary movements, extrapyramidal features, dystonias, dementia, cerebellar disturbances, and convulsions. Renal tubular damage results in generalized aminoaciduria. Phosphaturia occurs resulting in osteomalacia and renal rickets. Other renal functions remain unaffected (See also chapters 84 and 191).

Deposition of copper in the Descemet's membrane layer of the cornea appears as a brownish yellow ring (Kayser-Fleischer ring) which merges to the limbus without a clear intervening zone. This has to be distinguished from corneal arcus in which a clear zone of cornea intervenes between the ring and the limbus. Kayser-Fleischer ring is best studied by slit-lamp examination. Presence of Kayser-Fleischer ring is associated with definite neurological damage. At times Wilson's disease may present with acute viral hepatitis like picture.

Diagnosis

Wilson's disease should be suspected in all young patients below the age of 40 years who present with hepatic dysfunction and/or neurological disorder, especially affecting the extrapyramidal system and cerebellum. Presence of Kayser-Fleischer ring is diagnostic. Diagnosis should be confirmed by estimating serum copper and ceruloplasmin and demonstrating high copper content in liver tissue obtained by biopsy.

Serum ceruloplasmin is low. Normal value is 18-65 mg/dL. Total serum copper is below 80 µg/dL. Normal value is 100-200 µg/dL. Amount of copper bound to ceruloplasmin is low whereas the unbound copper is higher than normal. Urinary copper excretion is high—more than 100 µg/24 hours. (Normal 0.32 µg/24 hrs). Hepatic copper is elevated — often above 250 µg/g dry weight. Normal 20-45 µg/g.

CT scan in Wilson's disease shows general cerebral atrophy with basal ganglia having low attenuation signals. MRI is more helpful. Subtle changes in signal activity occur in the basal ganglia in symptomatic and even presymptomatic stages. PET scan shows diffuse reduction of glucose metabolism.

Course and Prognosis

The disease steadily progresses to end fatally in 5-14 years. Hepatic failure, hematemesis, or neurological deterioration account for the majority of deaths.

Treatment

Treatment aims at increasing the elimination of excess copper that is stored in tissues. Elimination is increased by chelating agents like penicillamine (dimethyl cysteine-Distamine, Cuprimine). The dose is 1-4 g daily given orally before food and at bed time. It leads to urinary loss of copper. Adverse side effects include nephrotoxicity, agranulocytosis, arthralgia, lupus-like syndrome, lymphadenopathy, rashes, and thrombocytopenia. These are seen on starting the therapy. Side effects may necessitate temporary withdrawal of the drug. Many toxic effects are dose-related. Interruption of therapy leads to relapse of symptoms and therefore treatment has to be life

long. Even during pregnancy penicillamine can be continued.

Triethylene tetramine (Trientine) dihydrochloride is another chelating agent given in a dose of 400-800 mg orally thrice daily before food. It is not freely available.

Trientine enhances copper excretion and decreases intestinal absorption. Zinc given as zinc acetate blocks intestinal absorption by inducing metallothionein synthesis in intestinal cells. The dose is 150 mg oral daily in divided doses. Zinc is safe and can be given on a long term basis for treatment as well as prevention in susceptible subjects. Potassium sulfide given orally is effective in inhibiting absorption of copper from foods. Therapy can be monitored clinically and by biochemical tests for free copper in the serum, urinary copper, and hepatic transaminases. Another drug is tetrathiomolybdate which prevents absorption of copper and also makes the circulating copper unavailable to be deposited in tissues. Side effects include anemia which is due to overzealous elimination of copper from the body. Liver transplantation may be needed in some cases.

Screening of Relatives

Since asymptomatic siblings show abnormality of copper transport, they have to be investigated with estimation of serum ceruloplasmin and hepatic copper. Early treatment helps to prevent the development of organ damage.

Porphyrrias

These are rare metabolic errors involving enzymes concerned with the heme synthetic pathway. Heme is synthesized in every cell, 85% being in erythroid cells. Out of this 85% is used for the creation of different cytochromes. Most of these disorders are inherited, but porphyria cutanea tarda can be acquired. The synthesis of heme involves 8 steps and each step is enzymically mediated. These are:

Glycine

(1)

Delta-aminolevulinic acid

(2)

Porphobilinogen

(3)

Polypyrrrole

(4)

Uroporphyrinogen III

(5)

Coproporphyrinogen III

(6)

Protoporphyrinogen III

(7)

Protoporphyrin III

(8)

Heme

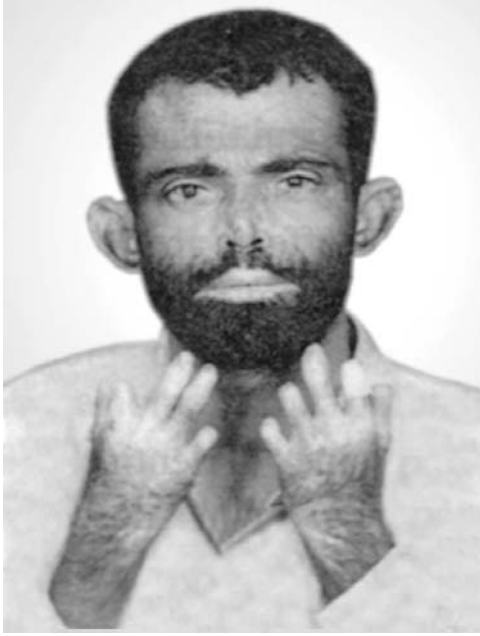


Fig. 93.1: Congenital erythropoietic porphyria

Note: (1) Ulceration and scarring face, (2) Ulceration and mutilation of ears, (3) Mutilation of hands and fingers

In porphyrias, the skin and nervous system are predominantly involved. Excess porphyrins in the skin induce photosensitization and cause further damage. The pathogenesis of neural lesions is not fully understood.

Porphyrias can be classified in different ways:

1. Depending on the organ in which excess of metabolites are produced.
2. Clinical manifestations, and
3. Specific enzyme defects.

Clinical Classification

1. Cutaneous manifestation without neurological features: Congenital erythropoietic porphyria, erythrohepatic porphyria (erythropoietic protoporphyria), porphyria cutanea tarda.
2. Neurological features without skin lesions: Acute intermittent porphyria.
3. Those that produce either cutaneous or neurological and cutaneous manifestations: Variegate porphyria (porphyria variegata), hereditary coproporphyria.

Among the porphyrias the most commonly encountered one is acute intermittent porphyria.

ACUTE INTERMITTENT PORPHYRIA

It occurs worldwide and in India the condition has been reported from all parts of the country. It is inherited as autosomal dominant. Women suffer more than men. Basic defect is a gross reduction (below 50%) of uroporphyrinogen I synthase which is required for the conversion of

porphobilinogen to polypyrrole (step 3). Urine contains the porphyrin precursors porphobilinogen (PBG) and delta-aminolevulinic acid (ALA) even when the patient is asymptomatic. During an acute attack, levels of porphyrin precursors such as δ -aminolevulinic acid and porphobilinogen increase and these are excreted in large amounts in urine. These precursors are neurotoxic, especially to the autonomic and peripheral nervous systems. In addition, urinary uro- and coproporphyrins also may increase.

Clinical Features

This condition may remain latent for long periods without recognition. Acute episodes are precipitated by several factors. Important among them are:

1. Drugs—barbiturates, sulpha drugs, griseofulvin, phenytoin, female sex hormones and several others.
2. Dietary factors—starvation or excess eating; and
3. Infections.

The acute attack is characterized by neurological phenomena and acute abdominal pain. Excitement, behavioural disturbances, depression, suicidal tendency, delirium, convulsions, and coma are frequent. Peripheral neuropathy and mononeuropathies may be prominent in some cases. Autonomic neuropathy results in gastrointestinal dysfunction, urinary retention, hypertensive crises, disordered sweating, and tachycardia.

Abdominal pain may be so severe as to be mistaken for a surgical emergency. Severe constipation or diarrhea may occur. Gastrointestinal fluid losses lead to hyponatremia and dehydration.

Diagnosis

Acute intermittent porphyria should be considered in the differential diagnosis of all bizarre neurological and neuropsychiatric disorders, severe abdominal pain, and autonomic disturbances.

Diagnosis is established by urine examination. Freshly passed urine is colourless but on standing for a few hours at room temperature it becomes portwine in colour and this should be looked for in all cases. Porphobilinogen (PBG) in urine can be demonstrated by Watson-Schwartz test, i.e. the urine gives a pink colour with Ehrlich's aldehyde reagent just as in the case of urobilinogen. On extracting the pigment with chloroform, PBG is not extractable, whereas urobilinogen is. The amount of PBG can be estimated quantitatively.

Apart from acute intermittent porphyria, PBG may occur in urine in hepatic diseases, drug toxicity, porphyria variegata and hereditary coproporphyria. Specific diagnostic test is the demonstration of diminution of uroporphyrin I synthase in erythrocytes.

Treatment

Symptomatic management during an attack: The offending drugs should be stopped. Phenothiazine (chlorpromazine) administered in a dose of 50 mg intramuscularly relieves abdominal pain and hypertension. Maintenance of fluid and electrolyte balance helps to tide over the crisis. High carbohydrate intake and propranolol give symptomatic relief. Hematin (heme arginate) infusion given IV gives relief in acute attacks. The dose is 3 mg/kg once daily IV $\times$ 4 days (maximum 250 mg/day). This may be repeated if necessary. Aspirin, morphine, guanethidine, reserpine, and penicillin can be safely used for suitable indications.

Prophylaxis should be in the form of avoidance of precipitating factors. Relatives should be screened for the enzyme deficiency and susceptible persons should be warned to avoid the offending drugs.

DISORDERS OF AMINO ACID METABOLISM

These are a heterogeneous group of rare disorders clinically characterized by mental retardation and a shortened life span, generally inherited as autosomal recessive and ranging in severity from mild to very severe forms.

Phenylketonuria (PKU)

Syn. Hyperphenylalaninemia

This is one of the most widespread metabolic errors occurring in infancy. It is an autosomal recessive disorder caused by the deficiency of hepatic phenylalanine hydroxylase which is required for the conversion of phenylalanine into tyrosine. In the well developed case there is severe mental retardation, seizures, microcephaly, hypopigmentation of skin and hair, and eczema. Ingestion of phenylalanine in milk and milk products aggravates the symptoms. Death occurs due to intercurrent infections. Phenylacetic, phenylpyruvic, and phenyllactic acids, which are metabolites of phenylalanine, occur in excessive quantities. These impart a musty odour to the urine and give a green colour with 5% ferric chloride solution within 2-3 min.

Avoidance of milk and other phenylalanine containing diet from the first month of life prevents the development of symptoms. Even in established cases withdrawal of dietary phenylalanine improves the symptoms.

Diagnosis

The urine is screened by ferric chloride test for metabolites of phenylalanine. The Guthrie test which is a filter paper spot test using one drop of blood is done as a screening test for the presence of excess amounts of phenylalanine in blood. In infants with a positive Guthrie test quantitative estimation of amino acids in blood is done.



Fig. 93.2: Ochronosis. Note the dark pigmentation of the hands, face and pinna of the ears

Serum phenylalanine is above 20 mg/dL in severe PKU, whereas normally the levels of phenylalanine and tyrosine do not exceed 1 mg/dL.

Treatment

Dietary measures using diets which are low in phenylalanine (200-800 mg/day) help to keep the serum level below 12 mg/dL. This is continued for the first 8-10 years of life. Tetra hydrobiopterin has been tried as an alternate treatment for mild forms of phenyl ketonuria. Tetrahydrobiopterin is a natural co-factor of aromatic amino acid hydroxylases and nitric oxide synthase. Mild cases may respond but many of the severe cases do not. This depends on the specific genotypes.

Alkaptonuria

This is caused by deficiency of homogentisic acid reductase (homogentisate 1,2 dioxygenase). Homogentisic acid is a metabolic product of tyrosine. The urine turns black on standing due to oxidation of homogentisic acid. **Ochronosis** is dark pigmentation of cartilage tissues.

Clinical features of alkaptonuria include arthralgia, arthropathies, pigmentation of the sclera and cartilages, especially of the pinna of the ear, renal stones, cardiac dysfunction and others. In spondylitis occurring in alkaptonuria, the sacro-iliac joints are not affected. This feature distinguishes the condition from ankylosing spondylitis (Fig. 93.2).

A new drug has been introduced **niticinone**. The dose is 0.7mg/ day for 7 days followed by 2.8 mg/day for 3 days. It reduces the level of homogentisic acid in urine. Long term results are awaited.

Inherited Disorders of Connective Tissue

K.V. Krishna Das

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General Considerations

The term connective tissue includes cartilage, bone, tendons, fascia, ligaments, and vascular walls. The connective tissue consists mainly of the fibrous proteins—collagen and elastin and the amorphous complex carbohydrates, hyaluronic acid, proteoglycans and glycoproteins, together called the ground substance. Functions of connective tissue include: (i) formation of an elastic covering, e.g. dermis; (ii) protection of vital structures, e.g. skull; (iii) acting as levers for aiding muscular action, e.g. long bones, and (iv) provision of deformable elastic cushions to bear stress and aid in joint movement, e.g. cartilage.

Collagens are a class of proteins, each being determined by a single gene. Two major types are pericellular and interstitial collagens. Pericellular collagen (types IV and V) occurs in basement membranes and intercellular tissues. The major collagen of skin, bones, articular cartilage, tendons, and fascia is interstitial collagen (types I, II, III). The collagens are formed from procollagens by complex enzymatic processes.

Developmental disorders involving the collagens may be hereditarily transmitted. The manifestation and severity differ on account of differences in penetrance and expression of single genes or genetic heterogeneity.

Major Disorders of Collagen

OSTEOGENESIS IMPERFECTA

This disorder is described in section 12, chapter 114.

Ehlers-Danlos Syndrome (EDS)

This is a disorder of types I and III interstitial collagen. Ehlers-Danlos syndrome comprises of at least eleven heritable disorders of connective tissue leading to defects in synthesis or structure of collagen. The abnormality is in the metabolism of fibrillar collagen. Mutations in the type V collagen gene account for up to 50% of classic EDS. Other abnormalities such as defects in tenascins which are extracellular matrix proteins can lead to clinically distinct recessive forms of the syndrome. Clinical features include hyperextensibility of the skin, laxity of joints with tendency to subluxate, purpura, bruises, subcutaneous nodular calcification, and violaceous subcutaneous nodules called molluscoid pseudotumours, delayed wound healing, and kyphoscoliosis. The genetics of this disorder is heterogenous and on this basis EDS may be subclassified into autosomal dominant, autosomal recessive and X-linked types.

Marfan's Syndrome

This name is derived from the first description of the disease by the French pediatrician Antoine Jean-Bernard Marfan (1858-1942). The main pathology is caused by quantitative deficiency of fibrillin-1 which is an extracellular matrix protein. This deficiency sets in motion structural changes in later life and results in multi-system connective tissue abnormalities. The skin texture and elasticity are normal. The basic mechanism is altered regulation of transferring growth factor β , (TGF β)-a family of cytokines that affect cellular performance. The gene is located on chromosome 15q21. More than 500 mutations have been reported. In this disorder a wide spectrum of clinical abnormalities exists. The condition is inherited as autosomal dominant. 25% give a family history and 25% is sporadic.

Clinical Features

Bony abnormalities: These include disproportionately long limbs compared to the trunk (dolichostenomelia),

arachnodactyly (spider fingers), pectus excavatum, pectus carinatum, kyphoscoliosis, increased joint laxity, recurrent dislocations, genu recurvatum and flat feet. The arm span is greater than height by 7.5 cm. Arm span/height ratio is >1.05.

Ocular lesions: The classic feature is ectopia lentis occurring in 60% of cases, the displacement of the lens is upwards, unlike as in traumatic dislocation in which the dislocation is downward. Other features include high myopia and retinal detachment.

Cardiovascular lesions: Dilation of the aortic root, aortic regurgitation, aneurysms of the ascending aorta and sinus of Valsalva, dissecting aneurysms of descending aorta, mitral valve prolapse, mitral regurgitation and cardiac failure may occur. Respiratory manifestations include lung cysts and recurrent pneumothorax.

Differential diagnosis: Marfan's syndrome closely resembles homocystinuria which may present with skeletal and ocular abnormalities similar to those of Marfan's syndrome. The urine shows homocysteine in the latter.

Eunuchoid features: These may be mistaken for marfanoid features. In the former there is no arachnodactyly and other features of hypogonadism are present.

Diagnosis

Strong clinical suspicion is essential for diagnosis. If the terminal phalanx of the thumb projects beyond the medial border of the closed fist, it suggests Marfan's syndrome. The wrist sign is overlap of the thumb and little finger when wrapped around the wrist.

Diagnostic criteria have been postulated. Metacarpal index measured on X-ray of the hand is diagnostic.

Prognosis

Progressive dilation of the aortic root, aortic and mitral incompetence, aneurysm of descending aorta and heart failure account for death.

Treatment

There is no curative treatment. The orthopedic, ocular and cardiovascular lesions demand special attention. Medical treatment consists of beta adrenergic blockers such as atenolol given in doses of 25-50 mg od or bid. This reduces the tension on the aorta and delays dilation.

Enalapril and other antihypertensive drugs may be employed. Patients with Marfan's syndrome should avoid isometric exercises and competitive sports since sudden death may occur.

Surgery on the aortic aneurysm and valves are indicated during the course of the disease. Ectopia lentis has to be treated surgically.

Homocystinuria and Hyperhomocysteinemia

Genetically determined homocystinuria occurs in 1/100000 live births and leads to a 40-fold increase in total serum homocysteine (t Hcy). The total pool is the sum total of all forms of homocysteine.

In the plasma homocysteine occurs in four forms:

1. Free thiol—1%.
2. Disulfide bound to plasma proteins, especially albumin—70-80%.
3. Dimer homocysteine.
4. Combination with other thiols including cysteine to produce homocysteine-cysteine mixed disulphide (20-30%).

During the metabolism of methionine, homocysteine is formed. Homocysteine is metabolised further in two ways.

1. In the liver it is remethylated by betaine-homocysteine methyl transferase. Betaine (trimethyl glycine) acts as the donor of the methyl group.
2. In most other tissues the remethylation is catalysed by methionine synthase and N-methyltetrahydrofolate acts as the donor. The latter depends on dietary folate for its formation. Vitamin B₁₂ is an essential cofactor for methionine synthase activity.

Normal fasting plasma level of t Hcy is 5-15 µmol/L. The arbitrary value for hyperhomocysteinemia is elevation above 15 µmol/L of homocysteine, after methionine loading. The levels in the different grades of hyperhomocysteinemia are:

- Mild—16-30 µmol/L
- Moderate—31-100 µmol/L
- Severe—above 100 µmol/L

The term homocystinuria refers to a group of rare inborn metabolic disorders resulting in high level of circulating homocysteine > 100 mmol/L and urinary homocysteine.

Homocysteine in urine can be detected in many metabolic abnormalities. Most common among them is *cystathionine betasynthase deficiency*, which is an autosomal recessive disorder. This deficiency leads to failure of homocysteine to react with serine to form cystathionine and further conversion to cysteine. Two molecules of homocysteine get converted to homocysteine by disulphide oxidation. Normally homocysteine is not detectable in plasma or urine by ordinary chemical methods. In cystathionine beta-synthase deficiency plasma and urinary levels of homocysteine increase and become detectable. In some genetic variants of homocystinurias the metabolic abnormality can be corrected by administration of large doses of pyridoxine, whereas the others are not correctable. Increased levels of homocysteine interferes with normal cross linking of

collagen and this may be a likely mechanism for the production of the ocular and skeletal abnormalities. Excess homocysteine reacts with cysteine residues thereby disrupting the structure and function of fibrillin 1, the main component of the lens zonules (suspensory ligaments). Four vitamins- Folic acid, vitamin B₁₂, vitamin B₆ and vitamin B₂ are involved in the intermediate metabolism of homocysteine.

Pathological homocystinuria is characterized by disruption of the zonular fibers of the lens, osteoporosis and thromboembolism affecting arteries and veins.

Causes of Hyperhomocysteinemia

- A. Genetic enzyme defects in homocysteine metabolism
- B. Nutritional deficiencies of vitamin cofactors, e.g.: folate, vitamins B₁₂ and B₆.
- C. Diseases—Pernicious anemia, hypothyroidism, renal failure, malignancies such as acute lymphatic leukemia and breast cancer, and severe psoriasis.
- D. Drugs—Folate antagonists such as methotrexate, phenytoin and carbamazepine Vitamin B₆ antagonists such as theophylline, tobacco smoke.
- E. Elderly age.

Measurement of plasma homocysteine is done by high performance liquid chromatography (HPLC).

The patient should fast for at least 12 hours to avoid variations caused by the meal.

In chronic renal disease hyperhomocysteinemia occurs. This acts as an independent risk factor for cardiovascular complications.

Hyperhomocysteinemia leads to a prothrombotic state by the following mechanisms.

1. Increases platelet aggregation
2. Activates factors V, X and XII, and
3. Inhibits protein C.

In addition hyperhomocysteinemia is a strong independent risk factor for osteoporotic fractures in elderly men and women. The exact mechanism is not clear, possibly, homocysteine-related collagen cross-linking in bone may be responsible.

Clinical Features

In some of the western societies hyperhomocysteinemia is reported to be around 5%. Vitamin B₁₂ deficiency leading to hyperhomocysteinemia, venous thrombosis and pulmonary embolism has been reported from India.

(Ref. Dani S J, et al. Hyperhomocysteinemia masquerading as pulmonary embolism; JAPI 2003;51:914-916).

Higher prevalence (13-47%) has been reported among groups of patients having symptomatic atherothrombotic disease. Genetically determined type is characterized by marfanoid body features, subluxation of the lens, and mental retardation. Vascular thrombotic episodes are more frequent.

Acquired hyperhomocysteinemia has assumed great epidemiological importance on account of its association with coronary, cerebral and other vascular thrombotic episodes.

Pyridoxine responsive patients have milder forms of the disease compared to pyridoxine non-responders. Bony abnormalities include osteoporosis of the spine and long bones, scoliosis, marfanoid features, pectus excavatum and pectus carinatum. Some children may develop mental retardation and seizures.

The characteristic feature is premature vascular disease. If the condition remains untreated, 20% die before 30 years of age. The homocysteine levels show relationship with coronary artery disease, peripheral artery disease, stroke or venous thrombosis. The vascular damage is mediated by oxidative injury to the endothelium. The embolic complications predominate over atherosclerotic complications.

Diagnosis is suggested by the presence of homocysteine in urine detected by cyanide-nitroprusside reaction which is a simple way of detecting increased amounts of sulphhydryl compounds. This test is not specific.

Management

Several attempts are being made to reduce the risk of vaso-occlusive diseases by lowering plasma homocysteine levels by dietary supplementation with folic acid, 400 µg/day, vitamin B₁₂ 100 µg/day and vitamin B₆ 25 mg/day. Several studies are at present looking into the effect of this vitamin supplementation on the risk of atherogenesis and stroke in the young.

In genetic homocystinuria dietary restriction of methionine and oral supplementation of folate and pyridoxine are beneficial. Cysteine and betaine are found to lower plasma homocysteine levels.

Food articles such as egg, milk and meat are rich in methionine and these should be avoided.

Low methionine dietary formulas are available for treating affected children.

Endocrinology

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Endocrinology: General Considerations

K.P. Poulose, B. Jayakumar

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General Considerations

Approximately 10% of the population in India suffers from endocrine/metabolic diseases other than diabetes mellitus and the proportion of various endocrine/metabolic diseases is given below.

• Goiter	54%
• Diabetes mellitus	20%
• Hormone related reproductive disorders	10%
• Adrenal/pituitary disorders	4%
• Nutritional/metabolic disorders	10%

Endocrine diseases account for 7-10% of patients admitted in hospitals. The prevalence varies from states to states as well as cities and villages.

Physiology

Endocrine system consists of specialised tissue organised in different anatomical sites in the form of glands such as thyroid and adrenals or distributed diffusely as identifiable cells in various organ systems, such as the gut, brain, kidneys, lungs and others. The latter are called paracrine cells. Hormones secreted by the former group reach the circulation directly since these glands are devoid of ducts. Their main action is at distant sites, and many have generalised systemic effects in addition to specific effects on the target tissues, e.g.

1. Thyroid hormone stimulates general metabolism, growth and maturation.

2. Glucocorticoids act as stress hormones, take part in several immunological functions and also influence the blood sugar level.

Effects of hormones on target tissue are mediated through the action on specific receptors which modulate cellular processes, often through the medium of several chemical messengers.

Hormones from the paracrine cells diffuse out and their action is mainly on the neighbouring cells, but they can also have distant effects. The paracrine tissue consists of amine precursor uptake decarboxylase cells (APUD cells). Some of the hormones produced by this system are listed below:

Gut: Gastrin, cholecystokinin, vasoactive intestinal peptide (VIP), motilin, bombesin, substance P and others.

Kidneys: 1, 25 dihydroxy cholecalciferol, erythropoietin, renin, prostaglandins PGA and PGE, kallikrein, insulin like growth factors and others.

Lungs: Dopamine, substance P, prostaglandins, thromboxanes, adrenocorticotrophic hormone, parathyroid hormone, antidiuretic hormone, melanocyte stimulating hormone and others.

Hormones can be chemically classified as peptides, steroids and amines.

Functions of the endocrine system may be considered under the following headings:

1. Maintenance of cellular constancy of the body.
2. Maintenance of the constancy of body fluids (micro-homeostasis).
3. Control of metabolic processes.
4. Growth and differentiation of tissues.
5. Reproduction and
6. Adaptation to changes in the external environment (fluid, food, and electrolyte availability)

Hormones or chemical messengers which are secreted by endocrine cells are released into circulation in response to specific signals. Endocrine dysfunction may manifest as overt clinical disorders such as Cushing's syndrome and acromegaly or silent biochemical abnormalities like hyperglycemia or failure of control mechanisms as in gonadal disturbances.

Biological responses are also under control of other substances such as the neurotransmitters like catecholamines and acetylcholine, prostaglandins, histamine, kinins, cytokines and several others. Intracellular chemicals like cyclic 3, 5 adenosine monophosphate (cyclic AMP), cyclic 3, 5 – guanosine monophosphate (cyclic GMP) and calcium act as second messengers for exerting the biological activity of hormones on cells.

Developmentally, the origin of the endocrine system can be traced back to all the three germ layers.

The endocrine glands can be broadly grouped into:

The pituitary – thyroid – gonadal – adrenal axis (classical endocrine system). These glands act in unison through feedback control and modulate biological activity of distant target cells and organs.

The neuroendocrine system derived from neurectoderm: This is composed of neurosecretory cells. The central component of this system is formed by the brain-pituitary system and the peripheral component is made up of diffusely scattered paracrine cells in many organs. The paracrine system is seen mainly in the gastrointestinal tract adrenal medulla, and the ‘C’ cells of thyroid. These paracrine cells are amine precursor uptake and decarboxylase (APUD) cells which is necessary for the formation of amine or peptide hormones.

Tissues which produce humoral substances which circulate along with the known hormones, e.g. prostaglandins and kinins: These exert strong physiological responses and tend to modulate hormone effects.

Hormone Metabolism

Synthesis, storage, release, and transport to the site of action are the processes undergone before a hormone activates its target. After exerting their effects, the hormones are metabolized to inactive products or they are continually excreted. The concentration of a hormone in blood is governed by its rate of synthesis, release, metabolism and elimination. Many hormones function in closed loop systems, i.e. rise in level of the hormone in the blood exerts feedback inhibition on its controlling hormone. Many endocrine glands exhibit diurnal rhythmicity (sleep-wake cycle), pulsatility with regular periodicity, and regulation of secretion in response to substrate augmentation. Hormones like steroid hormones and thyroid hormones are bound to carrier proteins of high affinity for transport. The hormone is biologically inactive in the bound form and it has to be split to restore its activity.

Hormone Actions

Hormones modulate both the intracellular and extracellular activities of cells so that the different cells in an organ or tissue behave as a synchronous macrocellular complex. As a general rule, hormones do not initiate biochemical processes primarily, but they only regulate the rate of the reactions in responsive cells. Hormones produce measurable specific effect in organs, cells, cellular organelles, enzymes, genes or membranes. The specificity of hormone response is achieved by three mechanisms such as (i) specific target tissue, (iii) appropriate receptor stimulation, and (ii) the capacity of the cells to respond specifically to receptor activation. Hormone effects are generally brought about by conformational changes in protein molecules of the receptors or enzymes in the target cell. The receptor shows increase and decrease in number (up regulation and down regulation) and alteration in their sensitivity to the hormone. Alteration in number and the sensitivity of the receptor also grossly influence the final result produced by the hormone. In type 2 diabetes the basic abnormality is the resistance of the receptors to secreted insulin. Modification of receptor function to increase the sensitivity to insulin by drugs brings about relief. The hormonal effects often lead to acceleration of some biochemical reactions or metabolic pathways with inhibition of others.

One of the main functions of the endocrine system is communication of information between cells. Polypeptide hormones and catecholamines act on the cell surface through specific receptors and activate intracellular second messengers like cyclic AMP, calcium or enzymes. These in turn regulate the activities of the cell. Peptide hormones bring about rapid responses in tissues within seconds or minutes.

Steroid hormones exert their action within the cell by influencing specific receptors which bind to nuclear chromatin. The hormone receptor complex regulates protein synthesis. Thyroid hormones enter the target cells and bind directly to receptor proteins in the chromatin. Such interactions which affect nuclear processes are relatively slow, taking a few hours at times.

Hormone Receptors

The responsive cells contain specific sites of binding of active hormones. The hormones bring about their effect or response in target cells through the receptors. The binding to receptors takes place very quickly. Loss of cellular receptors leads to unresponsiveness to the hormone. Changes in receptor affinity or number also modify the magnitude of hormone responses. The biological effects of a hormone depend on:

- i. its affinity for receptors,
- ii. intrinsic agonist property,
- iii. its concentration at the site of action, and
- iv. its rate of degradation.

The number of hormone receptors on a cell far exceeds that required for bringing about a response. When 5-10% of available binding sites on the cells are occupied, the hormones exert their maximal effect. The remaining number act as spare receptors. Receptors have strict structural specificity, saturability, high affinity and often tissue specificity for target cell responsiveness. The surface receptors are regulated by metabolites such as cyclic GMP within the cell. At times, the receptors may become antigenic and stimulate the production of antibodies. These antibodies react with the receptors and interfere with their functions.

Hormone agonists (optimal inducers) are substances which directly stimulate hormone action by stabilisation of hormone-receptor complex in an active conformational state. Hormone antagonists (anti-inducers) specifically block the effect of an agonist by binding with hormone receptors.

Endocrine disorders result from excessive or diminished secretion of hormones, or abnormalities in responsiveness of tissues. Progressive rise in hormone levels may reduce tissue sensitivity (negative cooperativity).

Clinical Aspects of Endocrine Disorders

11

Symptomatology

Endocrine disorders may manifest with dysfunction of the gland at fault or secondary disturbances in other endocrine glands. Sometimes the presenting symptom may be a remote effect due to defective regulation of a metabolic process, e.g. secondary amenorrhea in hypopituitarism or Cushing's syndrome. The structural changes in the endocrine glands do not always correlate with the severity of dysfunction. For example, gross functional defects may result form microadenomas of the pituitary whereas large tumours may remain silent.

Abnormalities of growth: The rate of growth may be altered in physiological (e.g. puberty) or pathological conditions. Heredity and environmental factors play a major role in determining growth and development. Abnormalities of growth are common in endocrine disorders. Growth is brought about by increase in number and size of body cells. When considering disorders of growth, rate of growth is a more reliable parameter, than the actual size of an individual. The maturation of organs and systems in the body constitutes development.

Endocrine dwarfism: It may be accompanied by abnormalities of sexual function and secondary sexual characteristics e.g. hypothyroidism, hypopituitarism,

gonadal dysgenesis (XO), pseudohypoparathyroidism and adrenogenital syndrome. Hypothalamic syndromes and Cushing's syndrome are causes of impaired growth. *Disparity between age and height, disparity in bone age, alteration of skeletal proportions and disorder in sexual development* are features which suggest endocrine aetiology. Endocrine causes of dwarfism have to be differentiated from constitutional dwarfism, primary bone diseases, malnutrition, metabolic disorders, and severe systemic diseases like renal and hepatic failure.

Excessive height: It may result from accelerated growth hormone activity or abnormalities of adrenal, ovarian or testicular hormones. Pituitary disorders cause gigantism or acromegaly. Hypogonadism causes abnormal increase in height and is associated with eunuchoidism (arm span considerably greater than height and lower segment longer than upper segment). Disorders like Marfan's syndrome and homocystinuria cause abnormally tall stature with other associated congenital abnormalities. Though gigantism is commonly the result of excessive growth hormone activity occurring in young age, rarely it may be secondary to other cerebral disorders as well.

Obesity: Increase in weight by 10% or more above the ideal weight caused by excessive accumulation of fat is called obesity. Endocrine causes include Cushing's syndrome, hypothalamic syndromes, insulinomas, hypothyroidism, polycystic ovarian syndrome and familial hyperlipidemia (type IV). Obesity is associated with delayed puberty in children. It is now known that many cases of apparently dietary obesity in young persons may have abnormalities of adrenocortical function.

Polyphagia: Polyphagia or increased appetite is a common feature of diabetes mellitus and hyperthyroidism and it is accompanied by loss of weight. Polyphagia leading to gain in weight is seen in acromegaly and insulinomas. Hypothalamic disorders like craniopharyngioma and Laurence-Moon-Biedl syndrome may give rise to polyphagia, galactorrhea, hypogonadism, and somnolence.

Loss of weight: Significant weight loss (>5-6%) inspite of increased intake of food is suggestive of diabetes mellitus, thyrotoxicosis and pheochromocytoma. Loss of weight is accompanied by loss of appetite in disorders like Addison's disease, pan-hypopituitarism, anorexia nervosa and psychiatric illnesses.

Non-specific symptoms: like anorexia, nausea, vomiting, and diarrhoea with considerable weight loss may be the features of metabolic disturbances occurring in diabetic ketoacidosis, adrenal crisis, thyroid storm or hypercalcemia.

Fatigue and weakness: These are the presenting symptoms in diabetes mellitus, Addison's disease, hypothyroidism, hypopituitarism, hyperthyroidism. Cushing's syndrome, hyperparathyroidism, and hypogonadism.

Polyuria: Polyuria of more than 3L/day of recent onset should suggest diabetes mellitus, diabetes insipidus or hypercalcemia. Other rare endocrine causes include primary hyperaldosteronism and hypokalemic nephropathy. Polyuria is generally accompanied by polydipsia. Psychogenic polydipsia (increased thirst) is not an uncommon disorder and this has to be distinguished from a primary endocrine abnormality.

Skin changes: Several endocrine disorders lead to characteristic abnormalities on the skin and mucous membranes. In many cases, these precede the other features of endocrinopathies. *Hyperpigmentation* affecting the skin folds, pressure points, and the oral mucous membranes and gums is seen in Addison's disease. Cushing's syndrome is accompanied by increased pigmentation. Pregnancy, thyrotoxicosis, and use of oral contraceptives lead to spotty brown pigmentation over the face (chloasma). Acanthosis nigricans which appears as velvety hyperpigmented thickened plaques in the flexural areas and nape of the neck occurs in Cushing's syndrome and juvenile myxedema.

Vitiligo (hypopigmentation of the skin): This may occur in many endocrine disorders like Addison's disease, hypothyroidism, and hypopituitarism which have an autoimmune basis. Vitiligo may be localised or generalised.

Pallor of the skin may occur in hypothyroidism or myxedema. Panhypopituitarism also leads to hypodepigmentation and loss of hair and the skin does not tan on exposure to sunlight.

Abnormalities of hair: Hirsutism is excessive hair growth in women and children occurring over the androgen sensitive areas such as face, axilla, and pubis. Hirsutism may be primary (idiopathic) or secondary to endocrine disorders. Growth of hair is determined by genetic, endocrine, and other factors. Hirsutism commonly occurs in women at puberty, pregnancy or menopause. In hyperandrogenism, it is an early symptom. In such cases it may be accompanied by other features like virilism in which there is change of voice, clitoromegaly, baldness, and malodorous perspiration. Secondary hirsutism occurs in hyperfunction of the adrenal cortex, polycystic ovaries (**Stein Leventhal syndrome**), testicular and ovarian tumours and bronchogenic carcinoma with endocrine manifestations. Therapy with glucocorticoids, and other drugs such as phenytoin and diazoxide also gives rise to hirsutism.

Loss of hair (alopecia): Androgenic tumours and hyperfunction of the adrenal cortex give rise to frontal baldness. Generalized loss of hair over the head and eyebrows are suggestive of myxedema. Hypopituitarism and hypogonadism are accompanied by absence, or loss of facial, axillary, and pubic hair. Many non-endocrine

disorders like cirrhosis liver and malnutrition are also characterized by loss of hair.

For descriptions of alopecia see Section 18 Chapter 215.

Gynecomastia: Benign glandular enlargement of male breast is called gynecomastia. The glandular tissue is hypertrophied in true gynecomastia. Accumulation of fat in the region of the breasts is called pseudogynecomastia. Bilateral breast enlargement (usually painless, at times tender) occurs physiologically during adolescence. Pathologically gynecomastia occurs in testicular disorders like dysgenesis, atrophy and tumours, systemic diseases associated with disturbances of gonadal hormones (e.g. hepatic failure) and as adverse side effects of drugs like estrogens, spironolactone, digitalis, reserpine, phenothiazines, cimetidine, ketoconazole, busulfan and several others. In most instances the gynecomastia recedes when the cause is removed, but sometimes it tends to persist.

Galactorrhea: This refers to the condition where there is abnormal (unphysiological) secretion of milk. Normal secretion of milk occurs only during lactation and pregnancy. Galactorrhea is a common finding which may not be disclosed by the patient and, therefore, this has to be specifically looked for. Newborn infants may show galactorrhea at times (witch's milk). Hyperprolactinemia, acromegaly, thyroid disorders (hypothyroidism and rarely thyrotoxicosis), feminizing adrenal tumours, corpus luteum cysts, and rarely choriocarcinoma may present with galactorrhea. Drugs like phenothiazines, metoclopramide, digoxin and many others may give rise to galactorrhea.

Disorders of sexual maturation: Normally boys attain sexual maturity before the age of 18 years and girls do so before the age of 16.

Precocious puberty: Sexual maturation before the age of eight years constitutes precocious puberty. Though rarely this may be a familial trait, more often it is due to some serious organic disease. Hypothalamic disturbances, congenital virilizing adrenal hyperplasia, adrenal tumours, and gonadal neoplasms are commonly associated with sexual precocity. Androgen therapy gives rise to sexual precocity in boys. Juvenile hypothyroidism in boys may be associated with pituitary enlargement and sexual precocity. Precocious puberty leads to premature fusion of the epiphyses and this results in dwarfism.

Delayed puberty (infantilism): When there is failure to attain sexual development by the age of 18 years in boys and 16 years in girls, it is delayed puberty. Though it may be a familial trait in some, often it is a manifestation of genetic or gonadal disturbances. In India, non-endocrine causes like malnutrition or undernutrition are also responsible for delayed puberty. Hypothalamic lesions, pituitary lesions and gonadal dysgenesis (Klinefelter's

syndrome) are the common causes of infantilism in boys. Failure to attain puberty by the age of 18 is seen in girls with gonadal dysgenesis (Turner's syndrome), pituitary and hypothalamic diseases and polycystic ovarian syndrome. Rare causes include congenital absence of uterus and vagina and pseudohermaphroditism.

Disturbance of sexual function: Impotence is the inability to get penile erection sufficient to perform the sexual act. Proper penile erection is a complex processes requiring vascular, neural, and endocrine mechanisms. The sex drive is termed *libido*. Impotence and loss of libido are commonly caused by psychogenic factors, but endocrine disturbances like testicular atrophy, Addison's disease, thyrotoxicosis, and feminizing tumours of the adrenal cortex may be associated with this symptom. Autonomic neuropathy occurring in diabetes mellitus, chronic alcoholism, central nervous system lesions, and therapy with several drugs are the other common causes of impotence.

Skeletal manifestations: Several endocrine disorders give rise to changes in the bones which may be the presenting manifestations. The predominant manifestations of metabolic bone disorders are bone pains and muscular weakness. When patients present with bone pains, bone cysts, pathological fractures, bony deformities or 'X-ray evidence of bony abnormalities, hyperparathyroidism, osteomalacia, rickets and osteoporosis should be looked for. Cushing's syndrome and hyperthyroidism may occasionally manifest with severe osteoporosis.

Urinary calculi: Several metabolic disorders lead to recurrent stone formation in the kidneys or other parts of the urinary tract. Calcium stones are seen in hyperparathyroidism, hypervitaminosis D and sarcoidosis. Idiopathic hypercalcuria is a common cause of recurrent calcium stones in male children.

Metabolic abnormalities such as cystinuria, renal tubular acidosis, gout and oxaluria, may all be associated with urolithiasis.

Tetany: Tetany may occur classically in hypocalcemia and less commonly in hypomagnesemia. It is clinically characterised by *carpopedal spasm*, *Chvostek's sign*, and *Trousseau's sign*. Tetany is commonly seen in hypoparathyroidism, pseudo-hypoparathyroidism, osteomalacia, rickets, alkalosis and acute pancreatitis. Tetany is rapidly correctable by the intravenous administration of 10 mL of 10% calcium gluconate. Tetany unresponsive to the administration of calcium should suggest the possibility of hypomagnesemia.

Psychiatric symptoms: Psychiatric symptoms may be prominent in several endocrine disorders. Confusion, behavioural disturbances, somnolence or coma may be seen in hypoglycemia, diabetic coma, hypopituitarism,

hypothyroidism, Addison's disease, water intoxication, and hypercalcemia. Mental changes are also common in hyperthyroidism, Cushing's syndrome, and hypoparathyroidism. In many cases the higher functions return to normal when the endocrine disorder is controlled, but this need not be so in all cases.

Physical Examination

The total clinical effect produced by an endocrine disturbance is determined by the age of onset, severity of hormone dysfunction, duration of the disorder, compensatory mechanisms, and the behaviour of the target organs. Several other factors like generic behaviour, nutritional status, intercurrent illnesses, and therapy modify the expression of symptoms. Familial incidence is seen in disorders like diabetes mellitus, thyroid disorders, pure gonadal dysgenesis, Kallmann's syndrome, Laurence-Moon-Biedl syndrome and multiple endocrine adenomatosis.

Growth and development: Disorders of growth are common in many endocrine disorders.

Secondary sexual characters: Disorders of sexual development may take the form of sexual precocity, heterosexual signs (appearance of features of the opposite sex), delayed puberty, or regression of secondary sexual characters.

Anthropometry: In addition to height and weight, measurement of skeletal proportions is of great value in diagnosis. At birth the ratio of the upper segment to the lower segment is 1:7:1 with the pubic symphysis taken as the reference point. The two segments become equal by the age of 10 years and this proportion is maintained throughout. The arm span equals the height in adults. The infantile proportion is retained in conditions such as juvenile hypothyroidism and chondrodystrophies which interfere with growth in early age. In hypopituitarism and other causes of generalized short stature, the growth retardation is proportional and the ratio is maintained. The lower segment and arm span are disproportionately increased in eunuchoidism, because of delay in closure of the epiphyses.

Cardiovascular abnormalities: Various grades of hypertension may be present in pheochromocytoma, hyperaldosteronism and congenital adrenal hyperplasia. The hypertension may be paroxysmal as in the case of pheochromocytoma or persistent as in the others. Malignant hypertension occurring in young subjects should raise the possibility of an endocrine cause.

Orthostatic hypotension may be a prominent symptom in Addison's disease, hypopituitarism, and diabetic neuropathy. It may also occur less commonly in

pheochromocytoma. Cardiovascular manifestations may be prominent in thyrotoxicosis and myxedema.

The integument: The texture and pigmentation of the skin should be looked for. Black freckles and ‘café’ au lait’ (Fr. coffee with milk) spots are seen in gonadal dysgenesis, neurofibromatosis, and some types of sexual precocity. Hirsutism is common in virilizing conditions. Presence of acne is a sensitive index of excessive androgen activity.

Breasts: Careful examination of breasts for recent change in size, tenderness, pigmentation and galactorrhea is absolutely essential in all cases. Enlargement and hyperpigmentation of breasts occur in pregnancy, trophoblastic tumours, luteinising tumours, Cushing’s syndrome and estrogen therapy. Though the breasts are large in size in testicular feminization, the nipples and areola are immature. In Sheehan’s syndrome the areola may undergo depigmentation.

Musculoskeletal system: Several endocrine disorders give rise to characteristic abnormalities. Excessive muscle weakness, hypotonia and localised hypertrophy or atrophy are suggestive of diseases of the thyroid or adrenal cortex. In juvenile myxedema, hypertrophy of the calf muscle may be present in a few e.g. **Hoffmann’s syndrome**. **Adrenogenital syndrome** is characterized by hypertrophy of the muscles in children – (**Infant Hercules**). Myopathy is characteristic of thyrotoxicosis.

Periodic paralysis (episodes of paralysis mainly involving peripheral muscles lasting for few minutes to hours) may occur in thyrotoxicosis, hyperaldosteronism and others.

Ocular manifestations: Exophthalmos (abnormal protrusion of eyeball) and ophthalmoplegia may be present in thyrotoxicosis and pituitary tumours. Cataract occurring prematurely may point to diabetes mellitus or hypoparathyroidism. Visual field defects are common in space occupying lesions in the region of the pituitary and hypothalamus.

External genitalia: State of development of the external genitalia gives indication of the hormonal status in the early developmental period. Fusion of the labia and enlargement of the clitoris in female babies with or without formation of a penile urethra at birth, are indicative of excessive androgenic activity during early fetal development. Development of clitoromegaly is the result of androgen overactivity later in life. Pelvic examination is necessary for the assessment of the size of the uterus and ovaries and vaginal development. Examination of vaginal epithelium and cervical mucus gives evidence of activity of the ovarian hormones.

Small penis (less than 2.5 cm in length and flaccid) may be due to abnormalities of testosterone biosynthesis, organ unresponsiveness, gonadal dysgenesis, hypo-

TABLE 95.1

The time of appearance of the ossification centre and its fusion in normal subjects

Bone	Epiphyseal appearance	Fusion with diaphysis
Head of humerus	1st year	18-20th year
Medial epicondyle of humerus	4-6th year	18-20th year
Lower end of radius	End of 1st year	17-19th year
Lower end of ulna	5- 6th year	17-19th year
Head of femur	1st year	14-17th year
Lower end of femur	Before delivery	20th year
Patella	Before 2-6 year	Puberty
Lower end of tibia and fibula	1st year	17th year

thalamopituitary disorders or rarely defective development. Testicular size is objectively assessed by measurement. Normal adult testis measures 5cm in length and its volume is 15 to 25 mL. The testes are small and firm in Klinefelter’s syndrome whereas they are small and soft in acquired testicular atrophy.

Bone age: This is a common parameter used for assessing the maturity of the skeleton. Appearance of the centres of ossification and fusion of epiphyses occur regularly at definite periods during the growth of the individual. These are under hormonal control. Abnormalities in the growth of the skeleton provide evidence of endocrine dysfunction. Radiography of selected bones are routinely done for this purpose. In hypothyroidism occurring in early life, centres of ossification fail to appear. Cushing’s syndrome, hypopituitarism and hypogonadism lead to delay in epiphyseal fusion. The epiphyses appear and fuse prematurely in hyperthyroidism and sexual precocity (Table 95.1).

Laboratory Investigations

The function of any endocrine gland can be assessed by:

- 1. Quantitative estimation of its hormones and their metabolites.
- 2. Biochemical tests which reflect the metabolic abnormality, e.g. blood glucose in diabetes mellitus, serum calcium in parathyroid disorders.
- 3. Imaging procedures which reveal the morphology and function of the endocrine glands and other tissues, and
- 4. Assessment of the functional reserve of the glands by appropriate stimulation and suppression tests.

Estimation of Hormones and their Metabolites in Body Fluids

The levels of hormones in blood and body fluids are very low. Non-peptide hormones are present in body fluids in

microgram (10^{-6} g) concentration whereas peptide hormones are present only in the range of nanogram (10^{-9} g) or picograms (10^{-12} g) per unit volume. Several techniques are used for their estimation. These are:

- a. Bioassay,

b. Spectrophotometric and fluorimetric assay,

c. Radioimmunoassay (RIA),

d. Enzyme – linked immunosorbent assay (ELISA) and

e. Chemoluminiscent assay

Adrenal steroids like plasma cortisol and its metabolites – 17-ketosteroids, 17-ketogenic steroids and 17-hydroxysteroids are estimated by spectrophotometric analysis.

Radioimmunoassay (RIA) which has revolutionised the diagnosis and management of endocrine diseases is the most extensively used method for quantitation of hormones in clinical practice. By this method almost all hormones which exist even at picogram levels can be estimated. This method was devised by Berson and Yalow in 1959 and they were awarded the Nobel Prize in medicine in 1977.

Enzyme-linked immunosorbent assay (ELISA) is used instead of RIA in many cases. Though ELISA has some advantages over RIA, so far ELISA has not been able to achieve the type of exquisite sensitivity required for measuring picogram quantities of substances and, therefore, many hormones cannot be estimated by this technique.

Imaging of endocrine glands is done in several ways. Imaging techniques are employed when surgical or other methods of ablative therapy are contemplated.

Commonly used imaging procedures are as follows:

- a. Radiography – plain and contrast studies

b. Isotope scanning – dynamic* and static studies

c. Ultrasonography of neck, abdomen and pelvis.

d. Computerized tomography.(CT)

e. Magnetic resonance imaging (MRI)

f. Angiography to detect abnormal vascularity

* After the injection of the appropriate isotope, images of the organ are taken at one second or at shorter intervals (perfusion phase or vascular phase) and later, after minutes or hours (static phase). Isotope scans give structural and functional details.

The hormone secretion from these glands can also be estimated by selective catheterisation of their efferent veins.

Stimulation and suppression tests: These are useful to assess the functional reserve and autonomy of the different endocrine glands and integrity of their feedback control.

Acronyms commonly used in endocrinology	
ACTH	- Adrenocorticotrophic hormone
ADH	- Antidiuretic hormone
CRH	- Corticotropin releasing hormone
FSH	- Follicle stimulating hormone
GH	- Growth hormone
GHRH	- Growth hormone releasing hormone
GHRIH	- Growth hormone release inhibiting hormone
GnRH	- Gonadotropin releasing hormone
hCG	- Human chorionic gonadotropin
IGF-1	- Insulin-like growth factor-1
LH	- Leuteinising hormone
PIH	- Prolactin inhibiting hormone
PRH	- Prolactin releasing hormone
TRH	- Thyrotropin releasing hormone
TSH	- Thyroid stimulating hormone
T3	- Tri-iodothyronine
T4	- Tetra-iodothyronine

Types of Hormones and their Patterns of Secretion

Polypeptides	GHRH, GHRIH, TRH, ADH, Oxytocin, GH, IGF-1
Single chain peptide	CRH, ACTH, prolactin
Glycoproteins	LH, FSH, TSH, hCG
Steroids	Cortisol, estrogen and androgens
Amines	Dopamine
Iodinated tyrosine	T3, T4

Pattern of Secretion of Hormones

Continuous secretion	T3,T4
Intermittent pulsatile	LH, FSH, GH, prolactin
Circadian rhythm	
• Highest at early morning	Cortisol
• Highest at midnight	Melatonin
• Low at midnight	ACTH
Variable secretion rate	Stress-related hormones

Hypothalamus, Pituitary and their Disorders

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Physiological Considerations

The main seat of neuroendocrine coordination is the hypothalamus. The higher neural centres influence it through the monoaminergic pathways. Physical and chemical stimuli also influence the hypothalamus through the blood perfusing it. The supraoptic and paraventricular nuclei respond to these stimuli by the production of hormones vasopressin and oxytocin. These are bound to carrier proteins – neurophysins – and in this form they travel down the pituitary stalk to be stored in the posterior pituitary. The releasing hormones which help to release the tropic hormones of the anterior pituitary are secreted by the hypothalamus. These pass down the hypothalamo-hypophyseal portal circulation to exert their action on the anterior pituitary.

The pituitary gland weighs 0.5 to 1.g. (usually 0.6g)
It consists of two portions. (i) adenohypophysis which is

composed of columns of epithelial cells derived from the primordial foregut and (ii) neurohypophysis which is formed from a diverticulum arising from the floor of the third ventricle. The neurohypophysis (posterior pituitary) stores the secretions of the supraoptic and paraventricular nuclei of the hypothalamus.

Blood supply to the hypothalamus and pituitary is derived from the superior and inferior hypophyseal arteries which are branches of the internal carotid artery. The radicles of these vessels lie in close relation to the axons of the peptidergic neurons of the hypothalamus which transfer their secretions into the blood that perfuse them. From these radicles the hypothalamo-hypophyseal portal system arises and it terminates around the epithelial cells of the anterior pituitary. The releasing and inhibiting hormones secreted by the hypothalamus reach the pituitary through this system and exert their control. Blood returning from the pituitary reaches the hypothalamus and the pituitary secretions are able to influence the hypothalamus through this pathway.

Pituitary Gland

Histology: This consists of three types of cells- acidophils, basophils and chromophobes. The acidophil cells (eosinophilic cells) which form about 60-75% of the total number of epithelial cells are situated in the posterolateral aspect of the gland. They secrete growth hormone (GH) and prolactin (PRL). The basophils secrete follicle stimulating hormone (FSH), luteinising hormone (LH), thyroid stimulating hormone (TSH), adrenocorticotrophic hormone (ACTH) and melanocyte stimulating hormone (MSH). The chromophobe cells are either precursors of secretory cells or are cells which are depleted of their secretions. Based on electron microscopic findings the cells of the pituitary can be classified as somatotrophs, lactotrophs, thyrotrophs, gonadotrophs, corticotrophs, and melanotrophs.

Lactotrophs form 15-20% of the total number of cells and they are distributed throughout the gland. Their number

increases during pregnancy. Somatotrophs make up about 50% of the cells of the anterior pituitary. Corticotrophs form less than 10% of cells and are situated anteromedially. Gonadotrophs which form 10% of cells are mainly distributed in the lateral wings, and thyrotrophs are found mainly in the inferomedial and superior parts of the gland.

Hormones of the Pituitary

Type of cells	Percentage	Secretion
Acidophils (eosinophils)	60-75%	
Lactotrophs	15-20%	Prolactin
Somatotrophs	50%	GH
Basophils	25%	
Corticotrophs	10%	ACTH
Gonadotrophs	10%	FH, LH
Thyrotrophs	5%	TSH
Melanotrophs	—	MSH

Hypothalamic Hormones

Growth hormone releasing hormone (GHRH) stimulates the release of growth hormone from the anterior pituitary.

Corticotropin releasing hormone (CRH) and **vasopressin** stimulate the release of ACTH from the pituitary

Thyrotropin releasing hormone (TRH) is a tripeptide found in the median eminence of the hypothalamus and in several other parts of the nervous system. This stimulates the pituitary to enhance the secretion of TSH

and prolactin (PRL) in normal individuals. Only TRH modulates the release of prolactin.

Gonadotropin releasing hormone (GnRH) is a decapeptide which releases both follicle stimulating hormone (FSH) and luteinising hormone (LH) from the adenohypophysis. This is also referred to as luteinising hormone releasing hormone (LHRH). Sex steroids exert a negative feedback on the hypothalamus and pituitary and influence the secretion of FSH and LH. However, estrogens from the developing graafian follicles exert a positive feedback on the hypothalamus and pituitary and thereby enhance the secretion of GnRH and gonadotropins.

Growth hormone release inhibiting hormone (GHRH) or Somatostatin (SS) is a polypeptide hormone with 14 amino acids. In addition to the hypothalamus, several other cells in other locations like stomach, duodenum, upper jejunum and islets of Langerhans are found to contain SS. The hormone exerts a general inhibiting effect on the surrounding endocrine and exocrine tissues. Somatostatin has a short biological life and hence it is unlikely to exert its effect on distant tissues. The growth hormone response brought about by stimuli like exercise, hypoglycemia, arginine and sleep is inhibited by SS. It also reduces the thyroid stimulating hormone (TSH) response to injected TRH. In the stomach and intestine, the production of gastrin, gastric inhibitory polypeptide, hydrochloric acid and vasoactive intestinal polypeptide is diminished. The secretion of insulin and glucagon from islet cells is reduced. The exocrine pancreatic secretions like bicarbonate and enzymes are inhibited (Table 96.1).

Hypothalamic hormones, their action on the pituitary and the peripheral hormones liberated		
Hypothalamic hormones	Action on pituitary	Peripheral hormones released (or) Peripheral effect
Thyrotropin releasing hormone (TRH) (1)	Thyroid stimulating hormone (TSH) (1)	T3,T4 and prolactin (1)
Gonadotropin releasing hormone (GnRH), (LHRH) (1)	Releases luteinising hormone (LH), and follicle stimulating hormone (FSH) (1)	Estrogens and androgenic steroids (2)
Growth hormone releasing hormone (GHRH)	Growth hormone (1) secreted	Somatomedin (IGH-1) (1)
Growth hormone releasing inhibiting hormone (GHRH-somatostatin) (1)	G H inhibited TSH response to TRH reduced	
Prolactin inhibiting factor (PIF) (3)	Prolactin (PRL) (1) inhibited	Prolactin level kept at normal levels
Corticotropin releasing hormone (CRH) (1)	Adrenocorticotrophic hormone (ACTH) (1)	Cortisol mainly (2)
Vasopressin (antidiuretic hormone ADH) (1)	-	Action on the renal tubules
Oxytocin (1)	-	Uterine contraction
Note: (1) peptide (2) steroids (3) amine		

Antidiuretic hormone (ADH) or Arginine vasopressin:

Arginine vasopressin is the natural ADH in humans, whereas in the pig it is lysine vasopressin. This is stored in the posterior pituitary. The term 'vasopressin' denotes its ability to raise the blood pressure of experimental animals and humans in pharmacological doses. The synthesis and release of vasopressin are regulated by osmotic and non-osmotic stimuli. During periods of fluid deprivation the release of ADH increases 3-5 times the basal levels and this helps to conserve fluid by the kidneys. Half-life of ADH in circulation is 7-20 minutes. Under basal conditions, osmotic mechanisms predominate over non-osmotic mechanisms. Changes in serum osmolality by 1 to 2% lead to alteration in the volume of the osmoreceptors in the anterior hypothalamus and this triggers the supraoptic nucleus. However, under conditions of stress, volume receptors in the atrium and pulmonary veins are also activated. When there is a fall in blood pressure, receptors in the carotid and aortic sinuses are stimulated and they augment the secretion of vasopressin. Other factors which stimulate vasopressin secretion are psychological and physical stresses. Once triggered, the non-osmotic mechanisms are capable of stimulating the synthesis and secretion of vasopressin.

Vasopressin exerts its main effect on the distal convoluted tubules and collecting tubules of the kidney and increases the reabsorption of water. The hormone activates the adenylate cyclase system in the cells lining the tubules and makes them more permeable to water by increasing the size and number of pores. In addition, vasopressin stimulates the smooth muscles of the arterioles in the mesentery, coronary circulation and skin. Intestinal smooth muscle is also stimulated to activity. The main source of vasopressin for therapeutic use is synthetic and the preparation is I-deamino-8 arginine vasopressin (DDAVP). It is used mainly for the treatment of diabetes insipidus. In other conditions like hemophilia, DDAVP is finding increasing use. In conditions of intractable hypotension vasopressin is used with benefit. Vasopressin is also employed to reduce portal hypertension and esophageal variceal bleeding.

Oxytocin: This hormone enhances uterine contraction during labour and also in the postpartum period. This helps in delivery and postpartum hemostasis. Oxytocin also enhances the release of milk from the breast during suckling.

The production of oxytocin is controlled mainly by stimuli arising from the breast during suckling. The impulses reach the hypothalamus through the spinal cord and stimulate the production of oxytocin. Distension of the female genital tract stimulates oxytocin production whereas stress and emotional disturbances inhibit it. Oxytocin is used mainly to induce labour and stimulate uterine contraction after delivery. Estrogens also stimulate the release of oxytocin.

Hypothalamic Disorders

Hypothalamic disorders result from destruction of the neurons which secrete the hormones or from alterations in the afferent impulses from the higher neural centres into the hypothalamus.

Reduction of hypothalamic neurons may either be due to lack of development as in **Kallmann's syndrome** or destruction by disease processes such as encephalitis, meningitis, tumours or ischemia. Hypothalamic disturbances may lead to deficiency of the releasing hormones and consequent hypothyroidism, hypogonadism, hypoadrenocorticism and dwarfism. In general, hypothalamic lesions induce only partial failure of the target glands unlike lesions of the pituitary. Hypothalamus exerts a tonic inhibitory control on prolactin secretion, hypothalamic lesions result in uncontrolled production of prolactin. This may lead to galactorrhea, amenorrhea, and hypogonadism.

Hypothalamic function is regulated by feedback impulses from the target glands and also by impulses from higher neural centres. Other stimuli arising from the osmoreceptors and glucoreceptors situated in hypothalamus and alteration in the physical and chemical characteristics of blood influence hypothalamic activity. Functions such as temperature regulation, eating, satiety, and thirst are controlled by regulatory centres situated in the hypothalamus. Important disorders of the hypothalamus are psychogenic **amenorrhea, anorexia nervosa and deprivation dwarfism** in children. Impairment of inhibitory inputs from other areas of the brain may lead to precocious puberty and excessive secretion of ADH (**the syndrome of inappropriate secretion of ADH-SIADH**) (Fig. 96.1).

Diseases of the Posterior Pituitary

DIABETES INSIPIDUS (CRANIAL DIABETES INSIPIDUS)

Normally, antidiuretic hormone (ADH) is secreted in response to physiological stimuli such as osmolality, hypovolemia, hypotension, and psychological stress. This hormone (ADH) plays a major role in maintaining serum osmolality within a narrow range. Normal blood level of arginine vasopressin is 1-3 IU/mL. Failure of secretion of ADH from the supraoptic nucleus leads to the development of central diabetes insipidus. The clinical abnormality becomes evident only when about 99% of the neurons in this region are lost. Several conditions may lead to diabetes insipidus.

Clinical Features

Diabetes insipidus presents with gross polyuria, thirst and polydipsia. The urine volume may vary from 2.5 to 10 litres or more in 24 h and the osmolality may fall below



Fig. 96.1: Anorexia nervosa. Note emaciation, breast is developed pubic hair is present, refusal to eat

200 mOsm/kg. Majority of those patients have normal thirst mechanisms and they make up the fluid loss by taking adequate quantity of water and salt and thus prevent the development of dehydration and hyponatremia. In this condition plasma osmolality is raised whereas the urinary osmolality is low. When the free intake of water and salt is diminished as in coma or due to other causes, severe dehydration and hypovolemia develop. In moderately

severe cases the osmolality of plasma ranges from 400 to 600 mOsm m/kg. In well compensated patients, apart from the history and the gross polyuria with dilute urine (specific gravity around 1004), no other abnormality may be evident. In those subjects in whom the disease is secondary to other disease processes, the primary abnormality may be evident. In idiopathic cases MRI may reveal evidence of neurohypophysitis.

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Causes of Pituitary Diabetes Insipidus

Pituitary diabetes insipidus

Head trauma (closed and penetrating)	Vascular
Neoplasms	Sheehan's syndrome
Primary	Aneurysm (internal carotid)
Craniopharyngioma	Aortocoronary bypass
Pituitary-adenoma (suprasellar)	Hypoxic encephalopathy
Dysgerminoma	Pregnancy
Meningioma	Idiopathic
Metastatic deposits (lung, breast)	Congenital malformations
hematological (lymphoma, leukemia)	Septo-optic dysplasia
Granulomas	Midline craniofacial defects
Neurosarcoidosis	Holoprosencephaly
Histiocytosis	Hypogenesis, ectopia of pituitary
Xanthoma disseminatum	Genetic causes
Infections	Autosomal dominant (AVP-neurophysin gene)
Chronic meningitis	Autosomal recessive (AVP-neurophysin gene)
Viral encephalitis	Autosomal recessive-Wolfram-(4p – WFS 1 gene) disease
Toxoplasmosis	X-linked recessive (Xq28)
Inflammatory	Deletion chromosome 7q
Lymphocytic Infundibulo-neurohypophysitis	
Wegener's granulomatosis	
Lupus erythematosus	
Scleroderma	
Chemical toxins	
Tetrodotoxin	
Snake venom	

Diagnosis

Diabetes insipidus should be diagnosed by the history and the presence of polyuria with fall of specific gravity of urine. The urine volume does not fall and the specific gravity does not rise with fluid deprivation. Since fluid restriction may be hazardous in these subjects, it has to be done only under close supervision. Other conditions producing polyuria with low specific gravity of the urine such as nephrogenic diabetes insipidus and psychogenic polydipsia have to be differentiated.

Differential Diagnosis

Nephrogenic diabetes insipidus: The renal tubules are refractory to the action of normal levels of circulating ADH. This may be congenital as in primary nephrogenic diabetes insipidus or secondary to diseases such as chronic renal failure, diabetes mellitus, hypercalcemia, hypokalemia and sickle cell anemia or due to drugs such as lithium and demeclocycline.

Primary polydipsia (psychogenic polydipsia): Compulsory water drinking is a part of complex psychiatric disturbances in which the patient drinks large amounts of water. The disorder may show remission and exacerbation.

Investigations

Cranial or central diabetes insipidus can be distinguished from nephrogenic diabetes insipidus and primary polydipsia by simple laboratory tests.

1. **Measurement of 24 hour urine volume:** If the urine volume is less than 2 litres, diabetes insipidus is unlikely. It is to be remembered that mild cases may present with lower urine volumes, but in times of stress such as diarrhea or excessive sweating, hypovolemia, shock and hyponatremia ensue early.
2. **If the osmolality of early morning urine** exceeds 800 mOsm/kg, it almost rules out diabetes insipidus.
3. **Water deprivation test and vasopressin administration:** Fluid deprivation for 8 hours is done under medical supervision, only dry food is given. Since this is hazardous, it should not be continued if the body weight falls by 5% or 2 kg. Urine osmolality is measured hourly till steady values are obtained in three consecutive samples. Then 5 units of aqueous vasopressin or desmopressin 1 µg is given parentally. Osmolality of plasma and urine is determined hourly for further three hours. In central diabetes insipidus the rise in urine osmolality after vasopressin exceeds 9% whereas in patients with nephrogenic diabetes insipidus the rise is less than 9%. With desmopressin 1µg I.M. or 20 µg intranasal, the increase in urine osmolality exceeds 50% whereas in nephrogenic

diabetes insipidus it is below 45%. Patients with psychogenic polydipsia require longer periods of fluid deprivation for obtaining steady urine osmolality, since they tend to be fluid overloaded. Fluid deprivation results in rise of urine osmolality in this condition.

X-ray of the skull may reveal conditions such as histiocytosis, secondary deposits or hematological malignancies which cause destructive lesions of skull bones. CT or MRI scan will be more specific in delineating the lesion.

The prognosis of diabetes insipidus depends upon the primary cause. As such, diabetes insipidus does not shorten life expectancy, if it is identified and promptly managed.

Treatment

Cases with moderate or severe disease require specific therapy.

Vasopressin analogues: At present the synthetic analogue DDAVP (desmopressin) arginine vasopressin is used. It is given as nasal spray or instillation. It has duration of action for 12 to 24 hours and many cases require only one or two doses daily. Moreover, DDAVP is devoid of the pressor activity. It is absorbed even in the presence of nasal congestion. Parenteral preparations are available for use in more severe cases or in emergencies. Dose of DDAVP is 5-10 µg as nasal installation twice a day.

Several non-hormonal substances which act on the nephrons by different mechanisms effectively reduce the urine volume in pituitary diabetes insipidus. These are listed below:

- a. **Chlorpropamide** (250 to 500 mg/day), clofibrate and carbamazepine bring about reduction in urine volume in mild and moderate cases.
- b. **Thiazide diuretics** are effective in bringing down urine volume.

These drugs, being cheaper and more easily available, are generally used except in rare occasions when hormonal replacement becomes inevitable.

VASOPRESSIN EXCESS

Syn: Syndrome of inappropriate ADH secretion (SIADH)

Normally secretion of ADH depends upon plasma osmolality and blood volume. When this mechanism fails, or ectopic sources secrete ADH, the *syndrome of inappropriate ADH* secretion results. This syndrome is not rare in clinical practice. Adults and children may be affected. This is an important cause of hyponatremia in many chronically ill-patients.

Causes

- **TUMOURS:** carcinoma lung, carcinoid, leukemia, lymphoma and thymoma
- **DRUGS:** vasopressin, chlorpropamide, carbamazepine, clofibrate, vincristine, cyclophosphamide, thiazides, nicotine and demeclocycline
- **PULMONARY DISORDERS:** pneumonia, pleural effusion and tuberculosis
- **NEUROLOGICAL DISORDERS:** meningitis, encephalitis, Guillain-Barré Syndrome
- **METABOLIC** Acute intermittent porphyria
- **ENDOCRINE DISORDERS:** Addison's disease
- AIDS and AIDS related complex.
- **IDIOPATHIC**

Clinical Features

The symptomatology is vague and it is likely to be missed unless the condition is strongly suspected. There is dilutional hyponatremia. When the level of serum sodium falls to 120-125 mmol/L, somnolence, anorexia, confusion, and depression may be observed. These are manifestations of cerebral edema when the serum sodium suddenly falls to 125 mmol/L, or less. When the sodium level falls below 120 mmol/L, coma, convulsions and focal neurological deficits may develop. Severe hyponatremia with serum sodium below 110 mmol/L is usually fatal if undetected, due to brainstem herniation.

Diagnosis is by estimating serum sodium level, which is below 125 mmol/L with high urine sodium level above 20 mmol/L. Plasma osmolality must be less than 270 mOsm/kg with normal renal, adrenal and thyroid functions. Urine osmolality is more than 100 mOsm/kg.

Treatment

The syndrome of inappropriate secretion of ADH is only a manifestation of other serious underlying diseases and, therefore, the problem should receive total attention. Mild hyponatremia responds to fluid restriction of 0.5 to 1L/day in addition to the previous days' urine output. Administration of demethylchlortetracycline (demeclocycline) which produces nephrogenic diabetes insipidus is effective in some cases. The dose is 600-1200 mg/day. In severe cases presenting with convulsions, coma or hemiparesis, urgent infusion of hypertonic saline (3-5%) is indicated. Too rapid a correction results in central pontine myelinolysis. Intravenous saline containing 500 mmol/L is infused slowly till the plasma sodium rises above 125 mmol/L, thereafter oral supplements are continued. 100 mL of 3% saline contains 50 mmol of sodium chloride.

Tolvaptan is a selective non-peptide oral vasopressin V2-receptor antagonist which promotes aquaresis (excretion of electrolyte-free water). This drug is useful in the management of hyponatremia (Na^+ level < 135 mmol/L)

which is a predictor of death in chronic heart failure and cirrhosis liver. The excretion of water is not associated with electrolyte excretion. The dose is 15 mg daily orally to start with and increased up to 60 mg/day. The effect wanes off, if tolvaptan is stopped. Adverse side effects include increased thirst, dryness of mouth and polyuria. Tolvaptan is indicated in SIADH and severe fluid overload states such as chronic heart failure, cirrhosis liver and others.

Anterior Pituitary and its Disorders

GENERAL CONSIDERATIONS

Hormones of the anterior pituitary are polypeptides with one or more chains. They can be grouped into three classes.

1. **Corticotropin group:**
 - a. Corticotropin (Adrenocorticotrophic hormone ACTH)
 - b. Melanocyte stimulating hormone (MSH), lipotropins (LPH)

Corticotropin and lipotropins form the major bulk, MSH is present only in small quantities. Endogenous opioid peptides (endorphins) are derived from the lipotropins. The adenohypophysis can maintain its functional capacity even if 50% of its tissue is lost, but beyond this its function suffers.
2. **Glycoprotein hormones:**
 - a. Follicle stimulating hormone (FSH)
 - b. Luteinizing hormone (LH or Interstitial cell stimulating hormone)
 - c. Thyroid stimulating hormone (TSH)
3. **Somatotropin – mammotropin group:**
 - a. Growth hormone (GH)
 - b. Prolactin (PRL)

Adrenocorticotropin (ACTH)

ACTH is a single chain polypeptide with 39 amino acids. The hormone can be estimated by radioimmunoassay. Blood levels show considerable variation, values being highest early in the morning (40-80 pg/mL). ACTH release is facilitated by the corticotropin releasing factors of the hypothalamus and inhibited by increasing levels of circulating plasma cortisol. ACTH production goes on independent of feedback inhibition and diurnal variation during periods of stress. It exerts action on the adrenal cortex and extra-adrenal tissues. ACTH promotes the synthesis of glucocorticoids and androgens by the adrenal cortex. Aldosterone secretion is only marginally affected.

Other effects of ACTH include lipolysis and increase in pigmentation brought about by stimulation of the melanocytes. Normally these extra-adrenal effects of ACTH are not pronounced, but when ACTH production

is increased as in Addison's disease and Nelson's syndrome, pigmentation becomes prominent. The role played by lipotropins in man is not understood.

Glycoprotein Hormones

The pituitary glycoprotein hormones are *thyroid stimulating hormone* (TSH), *follicle stimulating hormone* (FSH), and *luteinizing hormone* (LH). The placental glycoprotein hormone *human chorionic gonadotropin* (HCG) resembles LH in function. All these hormones act through the adenylate cyclase mechanism.

Thyroid stimulating hormone (TSH) (Syn: Thyrotropin) The TSH acts mainly on the thyroid to increase its vascularity and size. It enhances all aspects of thyroid function such as iodine uptake, synthesis of thyroglobulin, and release of thyroxine. TSH secretion is increased by TRH and inhibited by increasing levels of circulating thyroxine and tri-iodothyronine. The inhibitory effect of circulating thyroid hormones on TSH is stronger than the stimulatory effect of TRH on the pituitary. Plasma TSH level is about 0 to 5 μ U/mL. Basal TSH levels are considerably increased and TSH response to TRH is amplified in primary hypothyroidism. The TSH Levels are very low and often undetectable in primary thyrotoxicosis. Moreover, the TSH response to TRH is also negligible.

Gonadotropins

GnRH produced by the hypothalamus influences the synthesis and secretion of LH and FSH. LH is stimulated to a greater degree than FSH. Secretion of LH and FSH is inhibited by rising levels of estrogens, progesterone and testosterone in blood, except during the preovulatory phase. During the preovulatory phase a high level of estrogens produces a positive feedback on the hypothalamus and pituitary, and this result in excessive production of LH.

Gonadotropins increase the synthesis and secretion of sex steroids and promote gametogenesis. The Pituitary produces FSH and LH, and chorionic gonadotropins (HCG) are produced by the placenta. FSH and LH secretion occurs in spurts in females. FSH facilitates the maturation of graafian follicles by acting on the granulosa cells of the ovary. LH also acts on the granulosa cells to enhance estrogen production. Acting on the interstitial cells of the testes, it increases the secretion of testosterone. Spermatogenesis is stimulated. Increase in LH levels in the mid-cycle phase leads to rupture of the mature follicle and liberation of ovum. In addition, it leads to luteinization of the ruptured follicle. LH is responsible for continued development of the corpus luteum till the placenta takes over this function during pregnancy. LH also maintains the steroidogenic function of the placenta.

Somato-mammotropin Group of Hormones

Growth hormone (GH): GH is a single polypeptide with 191 amino acids. The quantity of GH exceeds that of the other pituitary hormones. Human pituitary contains 6-10 mg of extractable GH. Normal daytime circulating level of growth hormone is $< 0.5 \mu\text{g/L}$.

Post-mortem pituitary was a major source of this hormone used for diagnostic and therapeutic purposes. This has led to the spread of disease such as slow virus infections of the CNS.

Fasting level of GH in the plasma is below 4 ng/mL. Secretion occurs in bursts lasting 1-2 h. Maximal secretion occurs during the stages III and IV of NREM sleep. Factors such as exercise, hypoglycemia and rise in amino acid levels enhance secretion. Secretion of GH by the pituitary is increased by its releasing hormone (GRF) and inhibited by somatostatin secreted by hypothalamus.

GH promotes linear growth in prepubertal children by its anabolic activity and effect in cartilage growth. Another metabolic effect includes lipolysis which leads to the increase of serum free fatty acids, which in turn inhibit glucose uptake by cells. This partly accounts for the anti-insulin activity of GH.

GH acts on the liver and other tissues to stimulate the production of *insulin-like growth factor (IGF-1)*, also known as *Somatomedin-C* which is responsible for growth promoting activity. Serum level of IGF-1 is an indicator of overall GH secretion. Whereas GH secretion occurs in spurts, IGF-1 level does not show marked diurnal variation.

Prolactin (PRL): Prolactin resembles GH closely. Prolactin level can be estimated by radioimmunoassay. This hormone is also secreted in bursts lasting for a few minutes to hours, maximal secretion occurring during sleep. Hypothalamus exerts an inhibitory effect on PRL secretion through *prolactin inhibitory factor (PIF)*. It is most likely that prolactin-releasing factors also exist. Thyrotropin releasing hormone also stimulates release of prolactin. Neuroendocrine reflexes caused by suckling and stimulation of breast in females also help to release PRL. Prolactin exerts its main action on the breast which is primed by the action of estrogens, progesterone, GH, and cortisol. Prolactin stimulates the synthesis of milk proteins. The physiological role of PRL in male is not clearly known.

Basal PRL level is about 10-20 ng/mL in men and non-pregnant women. Towards the end of pregnancy, levels as high as 200 ng/mL are observed. During puerperium, values fall to non-pregnant levels even though lactation is continued. Prolactin is released during suckling and this prepares the breast for the next feeding.

Insulin like Growth Factors (IGFs) (Somatomedin-C)

IGFs are substances which act as intermediaries to exert the action of other hormones like growth hormone and insulin. IGF participates in the growth and functions of almost all organs in the body. The three peptide hormones or growth factors namely insulin, IGF-1 and IGF-2 have approximately 50% of the amino acids in common. Interaction of growth hormone with its hepatic cell receptors stimulates the expression of IGF-1 gene and release of IGF-1. Levels of IGF-1 in the liver and serum inhibit further growth hormone release. The mechanisms of regulation of IGF-2 are not known.

Whereas insulin which is secreted by the beta cells of the islets of Langerhans as a prohormone initially, gets cleaved at the C-peptide, the IGFs which are synthesised primarily in the liver retain the C-peptide moiety. Insulin present in pico molar concentrations in plasma has a half-life of minutes, whereas IGFs circulate in nanomolar concentrations bound to IGF binding proteins secreted by the liver. This binding limits the availability of IGFs to the target cells. They act in an autocrine or paracrine manner.

Physiological Role and Mechanism of Action

Insulin acts primarily on the liver, muscles and adipose tissue. IGF take part in the metabolism of all tissue cells. Both the IGFs are important for embryonic development. After birth IGF-1 seems to have a predominant role in regulating growth. The exact function of IGF-2 is not known. IGFs bind specifically to IGF receptors which are distinct from insulin receptors. Once the insulin receptor or IGF receptor is activated, similar metabolic processes are evoked within the large cells. Insulin regulates metabolic functions whereas IGF-1 regulates growth and differentiation in postnatal life. Mechanisms of action of insulin and IGF-1 differ. Liver and fat express both insulin and IGF-1 receptors. Insulin controls hepatic glucose production and lipolysis by signalling exclusively through insulin receptors. So also insulin stimulated uptake of glucose by cells is solely mediated by insulin receptors.

IGF-1 mediates many, if not most of the metabolic actions of growth hormone. It stimulates bone formation, protein synthesis, glucose uptake in muscle, neuronal survival and myelin synthesis. It also reverses negative balance during starvation and inhibits protein degradation in muscles.

Locally produced IGFs have important actions in several organs. Growth hormone, parathyroid hormones and sex steroids regulate the production of IGFs in bone, whereas sex steroids are the main regulators of IGFs in the reproductive system. The exact role of the locally produced IGFs has not been fully elucidated.

Pathological conditions associated with abnormalities of IGF-1 include **Laron's dwarfism**, Type 2 **diabetes mellitus**, Type 1 **diabetes mellitus**, insulin resistance

states and others. IGF-1 is secreted by some tumours whose growth rate is modified by this hormone.

IGF-1 in Therapy

1. **Dwarfism**

Laron's dwarfism is a growth hormone deficiency syndrome in which insensitiveness to growth hormone exists as a result of unresponsiveness of the receptors. In these subjects IGF-1. 150 mcg/kg body weight per day given S.C. increases height velocity by three times that of normals i.e. 10.8 cm vs. 3 cm/year.

2. **Insulin resistant states**

Type 2 DM: IGF-1 has been proposed as therapy for severe insulin resistance states since its actions resemble those of insulin and may therefore bypass the defects that block the action of insulin. In doses of 100 mcg/kg body weight given subcutaneously, it decreases serum insulin levels by 60-80% and improves glucose utilisation both in diabetes mellitus and impaired glucose tolerance. In Type 2 DM, the resistance is overcome.

In Type 1 DM: IGFs exert their action by:

- Decreasing the secretion of GH.
- Increasing the sensitivity to insulin and
- Decreasing insulin requirements.

3. **Osteoporosis**

IGF-1 which has anabolic activity has been used as an adjunct in the management of osteoporosis.

4. **Regulation of growth of baby after birth** by mediating the metabolic effects of GH.

- Stimulates bone formation
- Protein synthesis
- Glucose uptake in muscle
- Myelin synthesis

Side Effects of IGF-1

Intravenous injection may cause anaphylaxis and cardiovascular problems including asystole and hypertension which are secondary to hypophosphatemia. Multiple subcutaneous doses given for more than 10 days may give rise to temporomandibular pain, facial and hand edema, weight gain, dyspnea, tachycardia, raised intracranial tension, gynecomastia and Bell's palsy. All of these regress on withdrawal of therapy.

Investigations in Hypothalamo-pituitary Disorders

These are designed to detect the morphological and functional abnormalities. Tumours may present as space occupying lesions with pressure effects on neighbouring neural structures. Endocrine disturbances resulting from increased or decreased secretion of hormones are also seen commonly, but these may not be constant. Some tumours

secrete excess of hormones while others compress normal tissue and suppress its function. The investigations may be grouped under three heads – neurological, imaging and hormonal studies (Table 96.2).

1. Neurological investigations:

Perimetry: Pressure of tumours in the region of the pituitary causes compression of the optic chiasma and leads to defects in the visual field. These can be documented by perimeter.

Visual Evoked potential studies will be of further help to record involvement of the optic nerve and its pathway.

2. Imaging studies:

- Lateral view skiagrams of the skull may show enlargement of sella, double flooring, destruction of clinoid processes or suprasellar calcification. More detailed information of this area may be obtained by cone views of the pituitary fossa.
- CT scanning coupled with contrast studies: These studies give definite information in almost all cases.
- Isotope scanning procedures help to reveal regional vascularity and focal lesions.
- MRI with gadolinium contrast is superior to CT to detect smaller lesions especially in the posterior fossa.

3. Hormonal studies:

- Radioimmunoassay: Anterior pituitary hormones and secretion of its target glands can be measured precisely by radio immunoassay.
- Feedback control: Integrity of hypothalamo-hypophyseal system can be assessed by tests involving suppression or stimulation tests.
- Indirect indices of hormonal disorders: When the measurement of hormones in blood is not practical, e.g. ADH, the functions of the target organs are studied. For example in diabetes insipidus, studies of concentrating function of the kidney give valuable information.

Diseases Affecting the Pituitary

PITUITARY HYPERFUNCTION

Excessive activity of pituitary hormones may result from several causes. These are:

- Tumours of the pituitary:** Tumours can arise from the different cellular constituents of the pituitary. Pituitary tumours may be isolated or they may form part of multiple endocrine adenomatosis in which the parathyroid and pancreatic islets may also show tumours.
- Defective regulatory control** by the hypothalamus: Diseases of the hypothalamus may result in increased secretion of the release hormones or decreased

secretion of inhibitory hormones acting on the pituitary.

- Ectopic secretion of pituitary hormones:** Hormones of the pituitary or their analogues may be secreted by malignant neoplasms as a paraneoplastic phenomenon, e.g. chorionic gonadotropin and luteinising hormone may be secreted by hepatoblastoma, and PRL, GH and ACTH may be produced by carcinoma of the bronchus.

Well defined clinical syndromes are common and can occur due to excess of PRL, GH and ACTH. Thyroid stimulating hormone (TSH), FSH and LH are less commonly involved and they may not produce typical clinical syndromes at times.

Hyperprolactinemia

Prolactin (PRL) excess is the most common disorder resulting from over activity of the pituitary. About one-third of women with long-standing menstrual disorders show excessive PRL activity. Hyperprolactinemia is less common in males. Prolactin is released sparingly into circulation, because its secretion is under inhibition by a hypothalamic prolactin inhibitory factor.

Causes

- Prolactinomas arising from the pituitary – the most common pituitary tumour.
- Several lesions of the thoracic wall and conditions which stimulate the breasts lead to over secretion of PRL.
- Tumours and inflammatory lesions of the hypothalamus may result in excessive liberation of PRL by the pituitary. In empty sella syndrome the pituitary stalk is compressed due to cisternal herniation into the pituitary fossa and the inhibitory factor for prolactin secretion falls.
- Several drugs such as chlorpromazine, oral contraceptives, reserpine, haloperidol, and digoxin may lead to the release of excess amounts of prolactin.
- Increased amounts of PRL are seen in other endocrine disorders such as hypothyroidism. Pregnancy may be associated with PRL overactivity.

Clinical Features

About 50% of patients with hyperprolactinemia develop galactorrhea and menstrual irregularities. Hirsutism may develop. Women show an ovulation and infertility.

Signs of local pressure on the neural structures such as the optic chiasma, optic tract and third ventricle lead to focal neurological defects such as visual field defects, obstructive hydrocephalus and others. Generalized increase in intracranial tension gives rise to headache and papilledema. Prolactin suppresses the release of

TABLE 96.2

Tests of pituitary function			
Hormone to be estimated	Test	Blood samples	Interpretation
Growth hormone	Insulin tolerance test: Regular insulin (0.05-0.15 u/Kg IV)	-30, 0, 30, 60 min for glucose and GH	Glucose < 40 mg/dL; GH should be >3 mcg/L
	GHRH test: 1 ug/Kg IV	0, 15, 30, 45, 60, 120 min for GH	Normal response is GH>3 mcg/L
	L-Arginine test:30 g IV over 30 min	0, 30, 60, 120 min for GH	Normal response is GH > 3 mcg/L
	L-dopa test: 500 mg PO	0, 20, and 60 min for TSH and PRL	Normal prolactin is >2 mcg/L and
Prolactin	TRH test: 200-500 mcg IV		Increase > 200% of baseline
ACTH	Insulin tolerance test: Regular insulin (0.05-U/Kg IV)	-30, 0, 30, 60, 90 min for glucose and cortisol	Glucose <40 mg/dL Cortisol should increase by > 7 mcg/L or to > 20 mcg/dL
	CRH test: 1 ug/kg bovine CRH IV at 0800 h	0, 15, 30, 60, 90, 120 min for ACTH and cortisol	Basal ACTH increase 2-to 4-fold and peaks at 20-100 pg/mL Cortisol levels > 20-25 mcg/dL
	Metyrapone test: Metyrapone (30 mg/kg) at midnight	Plasma 11-deoxycortisol and cortisol at 8 AM ACTH can also be measured	Plasma cortisol should be <4 mcg/dL to ensure an adequate response Normal response is 11-deoxycortisol >7.5 mcg/dL or ACTH > 75 pg/mL
	Standard ACTH stimulation test: ACTH 1-24 (Cosyntropin) 0.25 mg IM or IV	0, 30, 60 min for cortisol and aldosterone	Normal response is cortisol > 21 mcg/dL and aldosterone response of >4 ng/dL above baseline
	Low-dose ACTH Test: ACTH 1-24 (Cosyntropin) 1, mcg IV or 3-day ACTH stimulation test consisting of 0.25 mg ACTH 1-24 given IV over 8 h each day	0, 30, 60 min for cortisol 3rd day	Cortisol should be > 21 mcg/dL
Thyroid function test (TFT)	Basal thyroid function tests: T ₄ , T ₃ , TSH, free T ₃ , free T ₄	Basal tests	
	TRH test : 200-500 mcg IV	0, 20, 60 min for TSH and PRL	TSH should increase by >5 mU/L unless thyroid hormone levels are increased
LS, FSH	LH, FSH testosterone, estrogen	Basal tests	Basal LH and FSH should be increased in postmenopausal women Low testosterone levels in the setting of low LH and FSH
	GnRH test: GnRH 100 mcg IV	0, 30, 60 min for LH and FSH	In most adults, LH should increase by 10 IU/L and FSH by 2 IU/L
Multiple hormones	Combined anterior pituitary test: GHRH (1 mcg/kg), CRH (1 mcg/kg) GnRH (100 mcg) TRH (200 mcg) are given IV	-30, 0, 15, 30, 60, 90, 120 min for GH, ACTH, cortisol, LH, FSH and TSH	Normal responses are variable Combined or individual releasing hormone responses must be elevated in the context of basal target gland hormone values and this may not be diagnostic (see text)

luteinising hormone and therefore prolactinomas are associated with loss of libido, impotence and azoospermia in men. 95% of prolactinomas are benign. The ratio of incidence of microadenoma in females and males is about 20:1, while no gender difference is seen with macroadenoma.

Diagnosis

Basal serum PRL levels above 20 ng/mL which fail to increase with the administration of TRH, suggests the possibility of prolactinomas. In moderate or large sized tumours the value may go up above several hundred ng/mL. There is generally a direct relationship with the level of prolactin and tumour size. Serum prolactin levels also help to assess the improvement with therapy. Hyperprolactinemia is often associated with thyroid dysfunction. Hence such cases should also be investigated for abnormalities of thyroid function. Other tests of pituitary function should also be done when macroadenoma bigger than 1 cm in diameter are present, in order to assess the degree of suppression of other hormones by the tumours.

CT and MRI may reveal almost all the macroadenomas. MRI can detect only over 70% of the microadenomas. In patients with clinical features and raised hormonal levels suggesting prolactinoma, about 30% of microadenomas may not be readily demonstrable by direct imaging.

Treatment

Dopamine agonists arrest the growth of the tumour, lower the secretion of prolactin and bring about clinical and biochemical relief in more that 80% of cases. Among the dopamine agonists, **bromocriptine** which is a derivative of ergot is most popular in India.

The drugs have to be given on a long-term basis, often for several years. After 2 years of successful therapy the dose can be reduced on a trial and error basis.

In the case of microadenomas medical treatment may be sufficient, but in the case of macroadenomas if tumour regression is not complete or if local complications develop, surgical or radiation therapy may have to be

undertaken. Irradiation with a dose of 3.5-5 Gy over 4-6 weeks is effective but it is only rarely required.

Other dopamine agonists include **cabergoline**, **quinagolide** and **pergolide** Table 96.3.

If with treatment of the prolactinomas the sexual function does not recover, accompanying hypogonadism or menopause has to be suspected.

Usually medical treatment is very satisfactory. Macroadenomas shrink to a considerable extent in more than 70% of cases. Those who desire pregnancy should be informed that there is a small chance of the tumour enlarging during the early weeks of pregnancy.

When the tumour produces pressure effects and threatens vision, surgical removal is the treatment of choice. The procedure commonly employed is transphenoidal microsurgery.

Even in patients with focal neurological deficits medical treatment can be given a fair trial since dramatic improvement is the rule.

Gigantism and Acromegaly

Effects of excessive amount of growth hormone (GH) depend on the age of onset of the disease. *Onset before closure of the epiphyses leads to gigantism and later onset after closure of epiphyses results in acromegaly.*

Causes: Hyperplasia or adenoma of the pituitary affecting the acidophils, chromophobes or both lead to hypersecretion of GH. In 80% of cases the underlying tumour is a somatotroph adenoma, in 10% it is non-somatotroph adenoma and in 10% it is of mixed type. Rarely may it is due to abnormality of the hypothalamus or ectopic hormone production. The total clinical picture results from the local effects of the tumour and endocrine effects of GH. The tumour compresses the neighbouring cells in the pituitary and leads to suppression of gonadotrophs and thyrotrophs. Mixed acidophil adenoma produces both GH and PRL. Large-sized tumours may present as space occupying lesions.

GIGANTISM

Onset of growth hormone excess before the age of 10 years leads to gigantism. This disorder is caused in the

Dopamine agonist drugs		
Dopamine agonist drugs	Dose orally	Side effects
Bromocriptine	2.5-15 mg/day given in divided doses daily	Gastrointestinal intolerance, fatigue, postural hypotension and nasal blockage
Cabergoline	250-1000 µg/week given as 2 doses in a week, maximum dose up to 3.5 mg/week	This is also an analogue of bromocriptine. Better than bromocriptine with fewer side effects, but more expensive, can be given weekly
Quinagolide ⁴	50-150 mg once daily	This is a non-ergot drug
Pergolide	25-50 µg daily	Long acting ergot derivative with potency 100 times that of bromocriptine, side effects few

majority of cases by hyperplasia of the eosinophilic cells of the pituitary. There is disproportionate growth in height and size. Maximal linear growth occurs in the bones of the extremities so that the arm span exceeds the height and the lower segment exceeds the upper segment. Early during the disease muscular hypertrophy and sexual precocity may be evident. Later, features of acromegaly may also develop. Growth hormone exerts its effect on tissue cells through the medium of insulin like growth factors.

ACROMEGALY

Acromegaly develops when growth hormone excess develops after the fusion of the epiphyses. This is seen in adults, between the ages of 20-50. Both sexes are affected. The hormone level may go above 30 mU/L (normal 2 mU/L) (Figs 96.2 to 96.5).

CLINICAL FEATURES

The onset is insidious. There is enlargement of soft tissues and bones of the hands, feet, and skull. The face is elongated and the features are coarse. Lips, tongue, nose, salivary glands and lacrimal glands are enlarged. The mandible is prominent and prognathic. Growth of the mandible leads to separation of the lower incisors. The larynx is enlarged and the voice becomes husky. Thyroid may enlarge under the influence of GH, but there is no hyperfunction. During the active stage, excessive sweating occurs. Spine may show kyphosis, enlargement of vertebrae and osteoarthritis.

Arthritis with hypertrophy and edema of periarticular tissues may occur around the peripheral joints. Bony prominence and attachments of muscles to bone become hypertrophied. Though the bones increase in thickness, unlike in gigantism, the length does not increase. There is generalized enlargement of all viscera. The changes in



Fig. 96.3: Acromegaly male 45 side view.
Note: The prognathic mandible



Fig. 96.4: Acromegaly large legs and feet
Note: Normal for comparison



Fig. 96.2: Acromegaly male 45



Fig. 96.5: Acromegaly large hands
Note: Normal for comparison

the heart include enlargement, specific cardiomyopathy and congestive cardiac failure. The nerves are also thickened which may lead to entrapment neuropathies such as carpal tunnel syndrome. Increase in collagen fibres in the nerves may result in peripheral neuropathy. Though the muscles are hypertrophied, they may be weak due to proximal myopathy. Glucose intolerance develops in 25-30% of cases and many proceed to overt diabetes mellitus. Males complain of loss of libido and impotence. Females develop amenorrhea. Gynecomastia and galactorrhea may be seen in some cases.

Course and Prognosis

The endocrine disturbances and local pressure effects progress in cases with pituitary tumours. Death occurs due to raised intracranial tension, diabetic complications, cardiac failure or infections. The course depends on the nature of the pituitary tumour and its growth. In many cases the conditions may burn out. Factors which contribute to increased mortality include higher prevalence of hypertension, diabetes, cardiomyopathy and sleep apnea.

Diagnosis

Acromegaly should be suspected clinically from the appearance of the patient. The diagnosis has to be established by investigations.

1. Imaging procedures: X-ray of skull reveals enlargement of the sella turcica. AP or transverse diameter of more than 16 mm is diagnostic of pituitary fossa widening. Prominence of the bony points of the skull and enlargement of the frontal air sinuses are suggestive points. X-ray of chest may reveal cardiomegaly. X-ray of mandible reveals separation of teeth especially incisors. Hands and feet show tufting of the phalanges and enlargement of soft tissues.
CT or MRI give definite localization of the lesions. MRI of pituitary with contrast administration is the most sensitive method for diagnosis. Adenomas > 2mm in size can be visualized. More than 75% of patients with acromegaly have macroadenomas >1cm diameter at the time of diagnosis.
2. GH estimation: Basal GH levels in blood are elevated. The diagnostic finding is the failure of suppression of GH levels by a glucose load. The patient undergoes an oral GTT with 75-100 g glucose and blood is collected over 120 minutes. In normal subjects the GH levels fall below 2 µg/L. The blood glucose and GH are estimated simultaneously. Other pituitary hormones may also show alterations like PRL, IGF and TSH.
3. Estimation of insulin like growth factor – 1 (IGF-1) is helpful. IGF-1 levels also correlate with the activity of the disease. Normal levels of IGF-1- range from 0.35-1.9 U/mL in men and 0.45-2.2 U/mL in women.

Treatment

Aim of therapy is to correct the biochemical and morphological abnormalities and remove the tumour if pressure effects are evident.

Surgery is the method of choice if there are no contraindications. Impairment of vision is an indication for urgent surgery. The GH levels fall rapidly after surgery. Transphenoidal surgery is the treatment of choice, the GH level and IGH-1 level falling soon after the surgery. 40-50% attain long-term cure. The rest may get varying degrees of benefit.

Irradiation: The pituitary can be irradiated by implantation of radon seeds or yttrium. Alpha particles and protons have been employed in addition to conventional radiotherapy.

Drug therapy: In cases where surgery is contraindicated, *bromocriptine* reduces GH levels in about 50% of cases. Medication has to be continued in a dose of up to 10 mg/day for several months. Unlike in the case of prolactinomas, drug therapy is less effective than surgery. Hence its main role is in cases unsuitable for surgery or surgical failures.

Several newer modalities of drug therapy have been introduced recently. These include:

Somatostatin Receptor Ligands

1. **Octreotide** which is a synthetic analogue of somatostatin is 45 times more potent than the latter in inhibiting GH release. It is given in doses of 100-200 µg as SC injections 8 hourly. Continuous medication is required. Cholelithiasis is one of the major adverse side effects. The physical abnormalities regress with successful therapy. Though the diabetic state may improve in many cases, it may persist in some. Total blindness may not recover. Complications like cardiomyopathy, diabetes mellitus, and neuropathy can be avoided by early treatment. Other preparations include
2. **Octreotide LAR.** 10-40 mg IM injection once in 4 weeks
3. **Lanreotide 30 mg IM** every 10-14 days or
4. **Lanreotide gel 60-120 mg** deep SC injection once in 4 weeks.

Growth Hormone Receptor Antagonist

Pegvisomant 10-40 mg SC injection daily. This is a pegylated growth hormone analogue.

Dopamine Agonists

Cabergoline 1-4 mg oral weekly

The choice of the preparation and monitoring of therapy are highly specialized procedures to be undertaken by trained endocrinologists.

Ref: Shlomo Melmed. Acromegaly: N. Eng JI Med 2006; 355:2558-73.

CUSHING’S DISEASE

This term is given specifically to the condition in which a pituitary adenoma produces excess ACTH and leads to hypercortisolism.

Harvey Cushing described this condition in 1912 and demonstrated its cause as a primary pituitary tumour responsible for producing adrenal cortical hyperplasia, 20 years later. Cushing’s disease is due to hypersecretion of adrenocorticotropin. Microadenomas of the anterior pituitary secrete ACTH. They do not enlarge the sella turcica. The pathological mechanism is probably the failure of negative feedback exerted by circulating cortisol on the hypothalamus. In most of the cases the lesions start as hyperplasia which passes on to microadenomas which are less than 1 cm in diameter. Normal diurnal rhythm of ACTH secretion is abolished and the ACTH response to stress and hypovolemia is also lost.

Due to stimulation by ACTH, bilateral hyperplasia of the adrenal cortex and Cushing’s syndrome result.

Treatment

The ideal treatment is trans-sphenoidal microadenectomy. An alternative line of therapy is bilateral adrenalectomy followed by pituitary irradiation. When surgery and irradiation of the pituitary are contraindicated, drugs which inhibit cortisol secretion are used (*metyrapone*, *ketoconazole*). Some cases of Cushing’s syndrome due to ACTH secreting tumours of the pituitary may respond to *bromocriptine* or *cypheptide*.

In some cases of Cushing’s disease, bilateral adrenalectomy may be followed by enlargement of the pituitary tumour and associated hyperpigmentation. This is called *Nelson’s syndrome*.

Pituitary incidentalomas – The term incidentaloma refers to an incidentally detected lesion with no symptoms. Autopsy studies show an incidence of 10-20%.

Hypopituitarism

When there is failure of one or more cell types of the pituitary to secrete normally, hypopituitarism results. It is unusual to get deficiencies of single hormones. More often several hormones are deficient. The condition commonly presents as dwarfism in children and as hypogonadism in adults.

Hypopituitarism may result from primary lesions of the pituitary or secondary to lesions of the hypothalamus. Head injury, surgery, irradiation, chronic infections and tumours in the suprasellar region may lead to damage to the hypothalamus. Congenital lesions of the hypothalamus leading to diminution or absence of gonadotropin releasing hormone (GnRH) and growth hormone releasing hormone (GHRH) may occur. *Kallmann’s syndrome* is a

congenital deficiency of LHRH associated with anosmia and demonstrable defects in midline neural structures. Sheehan’s syndrome is the condition of hypopituitarism resulting from infarction of the adenohypophysis, usually precipitated by massive hemorrhage, particularly associated with hemorrhagic complications of pregnancy. Simmond’s disease described by Morris Simmonds a German Physician (1855-1925) is panhypopituitarism caused by complete atrophy of the adenohypophysis.

Adult Panhypopituitarism

Symptoms depend on the type and severity of cell failure, age of the patient and the age of onset of the disease. The condition becomes overt only when more than 75% of cells are destroyed. In panhypopituitarism growth hormone is affected first followed by gonadotropins, TSH and ACTH deficiency and consequent secondary adrenal deficiency occurs only when the pituitary function is grossly affected. Hypoprolactinemia manifests only during the puerperium as failure of lactation.

Etiology of Hypopituitarism

Developmental/Structural causes

- Transcription factor defect, Pituitary dysplasia/aplasia
- Congenital CNS mass, encephalocele
- Primary empty sella syndrome

Congenital hypothalamic disorders (septo-optic dysplasia, Prader-Willi Syndrome, Laurence-Moon-Biedl syndrome, Kallmann’s syndrome)

Traumatic

- Surgical resection,
- Radiation damage,
- Head injuries

Neoplastic

- Pituitary adenoma
- Parasellar masses (meningioma, germinoma, ependyoma and glioma)
- Rathke’s cyst
- Craniopharyngioma
- Hypothalamic hamartoma, gangliocytoma
- Pituitary metastases (breast, lung, colon, carcinoma)
- Lymphoma and leukemia
- Meningioma

Infiltrative/inflammatory diseases

- Hemochromatosis, lymphocytic hypophysitis, sarcoidosis, histiocytosis X, granulomatous hypophysitis

Vascular causes

- Pituitary apoplexy
- Sheehan’s syndrome due to massive intrapartum hemorrhage resulting in pituitary infarction
- Sickle cell disease
- Atrophy of the pituitary-Simmond’s disease

Infections

- Fungal (histoplasmosis)
- Parasitic (toxoplasmosis)
- Tuberculosis
- Pneumocystis carinii
- Miscellaneous causes

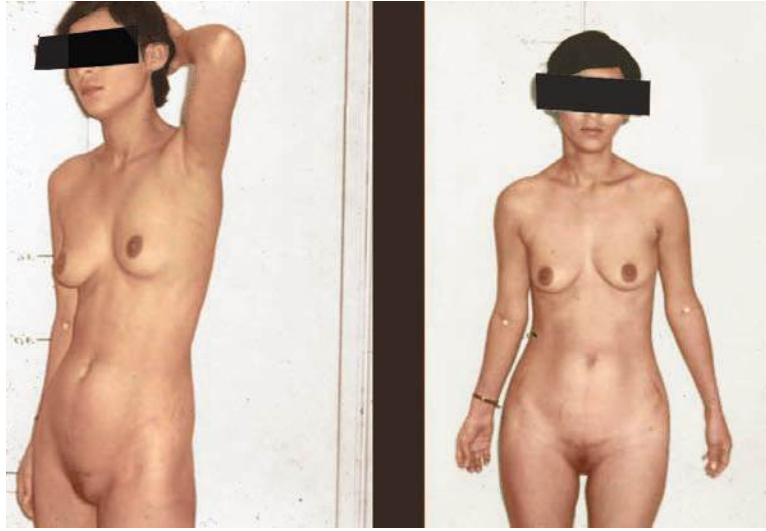


Fig. 96.6: Sheehan's syndrome. Note: The absence of hair in the axilla and pubic region

Clinical Features

One of the common modes of presentation is **Sheehan's syndrome** in which the hyperplastic pituitary of pregnancy which is vulnerable for ischemic damage undergoes infarction due to postpartum hemorrhage and shock. The earliest manifestation is failure of lactation. The patient develops amenorrhea, genital atrophy, loss of axillary and pubic hair, and loss of libido. Men with hypopituitarism present with testicular atrophy, loss of libido, and absence of spermatogenesis. Failure of ACTH secretion leads to secondary adrenal cortical failure. As the hypopituitarism advances, thyroid hormone deficiency also manifests. It is rare to get classical myxedema. The symptoms of GH deficiency are usually evident clinically. The symptoms of GH deficiency include lack of strength due to reduction in muscle mass, increased insulin sensitivity and mild refractory anemia (Fig. 96.6).

Differential Diagnosis

Panhypopituitarism has to be differentiated from other causes of dwarfism, general debility and asthenia. In *anorexia nervosa* which affects young women between the age of 15 and 30 may mimic hypopituitarism. In *anorexia nervosa* all the pituitary hormones except GH are decreased. With weight loss of more than 20% amenorrhea may also develop. Unlike hypopituitarism, the pubic and axillary hairs are retained. Moreover, emaciation is more suggestive of *anorexia nervosa* (Fig. 96.1).

Investigations

The diagnosis of panhypopituitarism is established by estimating the pituitary hormones and the hormones of the target glands.

Stimulation tests reveal the functional integrity of the target glands.

- ACTH secretion:** When adrenal response to ACTH is established, insulin induced hypoglycemia may be used to test the pituitary reserve of ACTH. If plasma cortisol rises above 20 mcg/dl following insulin, there is normal reserve of ACTH in pituitary.
- TSH reserve:** This can be easily assessed by administration of TRH. This could also elucidate the PRL secretory status of pituitary.

Management

This consists of replacement of the hormones of the target organs.

Cortisol deficiency is corrected with 12.5-25 mg of cortisol or its equivalent of other synthetic steroids. Glucocorticoids should be replaced before supplementation of thyroxine and gonadotropins in order to avoid the development of adrenal crisis. Glucocorticoid replacement should be increased during periods of acute stress like operations and infections. Mineralocorticoid replacement is not usually needed since this hormone is not markedly deficient in hypopituitarism. Thyroid replacement is best achieved with synthetic thyroxine started in a dose of 50-100 µg/day and raised to a dose of 150-200 µg slowly.

Testosterone replacement improves vigour, vitality, and libido. The oral preparation is methyl testosterone. Alternatively, testosterone can be given intramuscularly as depot injections. Estrogens and progesterone therapy prevent atrophy of the breasts and vaginal mucosa and also osteoporosis.

Gonadotropin therapy: Gonadotropin replacement is essential for return of ovulation and spermatogenesis. Short courses of admixture of FSH and LH (menotropins) followed by human chorionic gonadotropins (HCG) are used to induce ovulation (Table 96.4).

Protracted hypopituitarism can lead to premature atherosclerosis and increase in cardiovascular mortality.

TABLE 96.4

The details of pituitary hormone therapy	
Hormone deficit	Hormone replacement
ACTH	Hydrocortisone (10-20 mg AM; 10 mg PM) Cortisone acetate (25 mg AM; 12.5 mg PM) Prednisone (5 mg AM; 2.5 mg PM)
TSH	L-Thyroxine (0.075-0.15 mg daily)
FSH/LH	Males Testosterone enanthate (200 mg IM every 2 weeks) Testosterone skin patch (5 mg/d) Females Conjugated estrogen (0.65-125 mg qd for 25 days) Progesterone (5-10 mg qd) on days (16-25) Estradiol skin patch (0.5 mg, every other day) For fertility: Menopausal gonadotropins, human Chorionic gonadotropins
GH	Adults: Somatotropin (0.3-1.0 mg SC qd) Children: Somatotropin (0.02-0.05 (mg/kg per day)
Vasopressin	Intranasal desmopressin (5-20 µg twice daily) Oral 300-600 µg qd

(Ref. Kalman Kovaes, Sheehan's syndrome The Lancet 2003;361:520-2).

CHILDHOOD HYPOPITUITARISM

Hypopituitarism starting in childhood presents with a wide spectrum of disorders such as dwarfism (GH deficiency), hypogonadism (LH and FSH deficiency), hypothyroidism (TSH deficiency) or a combination of these.

Etiology

In general the etiological factors operating in adults are seen in children as well. In addition, hypopituitarism may be part of a general abnormality in the CNS like absent septum pellucidum. Growth hormone deficiency may develop as a familial trait transmitted as an autosomal recessive. Vaginal breech delivery may be complicated by growth hormone deficiency in the child as a result of mechanical distortion of the skull and consequent damage to the pituitary stalk.

Clinical Features

The child is normal at birth. Growth retardation is evident at the age of 2 or 3 years when the growth rate falls to 50% of the normal. Such children are obese with abnormal, deposition of body fat. When there is associated hypothyroidism, retardation of bone growth is more severe. In spite of growth retardation, these children have normal intelligence, but they may develop psychological



Fig. 96.7: Dwarf normal age-matched woman for comparison (30 years)

disturbances due to their physical appearance. Hypogonadism leads to delay in the fusion of epiphyses. Such children continue to grow for longer periods, thus attaining taller stature than children whose gonadal function is normal.

Hypopituitarism has to be distinguished from other common causes of growth retardation. Pathological causes of dwarfism include malnutrition, severe systemic illnesses, malabsorption state, skeletal disorders, corticosteroid therapy and deprivation dwarfism. Deprivation dwarfism occurs in children brought up in family circumstances under great stress, especially without maternal care.

Dwarfism

This is defined as shortness of stature that is below the third percentile for children of similar age and ethnic group. Genetic and environmental factors influence growth. This is a common problem in pediatric practice. In many cases short stature is seen in families without any demonstrable pathology. Pathologically dwarfism may result from several groups of conditions (Fig. 96.7).

- A. Major constitutional disorders:** Generalized malnutrition, rickets, malabsorption states, congenital cyanotic heart disease, severe respiratory, hepatic or renal disease, and long-term corticosteroid therapy.
- B. Inherited and genetic disorders:** Achondroplasia, fragilitas ossium, aminoacidurias, other metabolic defects, Turner's syndrome, pseudohypoparathyroidism and renal tubular acidosis.
- C. Endocrine disorders:** Cretinism, juvenile hypothyroidism, adrenogenital syndrome, precocious puberty,

hypopituitarism, hypothalamic disturbances, idiopathic hypoparathyroidism. The term Fröhlich's syndrome (*dystrophia adiposo genitalis*) refers to the combination of dwarfism, obesity, hypogonadism and diabetes insipidus and is produced by craniopharyngioma or chromophobe adenoma.

- D. Psychogenic dwarfism or deprivation dwarfism:** This is probably an emotionally mediated disorder unassociated with malnutrition, in which maternal deprivation leads to a selective deficiency of growth hormone. Provision of maternal care and emotional support improves the growth hormone levels and promotes growth.
- E. Laron dwarfism:** This is an autosomal recessive disorder characterised by small face and mandible, prominent forehead, saddle nose, discoloration of teeth, sparse hair, retarded growth of hair and teeth and small hands and feet. Serum GH levels are increased, but insulin like growth factors (IGF) are lower than normal. Receptor insensitivity is the mechanism underlying this disorder.

Investigation and Treatment

Management of a case of dwarfism depends upon the clinical findings and endocrine investigations.

When dwarfism is due to deficiency of growth hormone, the treatment of choice is human recombinant growth hormone (HGH) given in a dose of 0.02-0.2 IU/kg twice a week or 150-300 ug I.M. injection daily. Growth hormone therapy has different goals in children and adults. In children it increases linear growth, restores body composition and improves the quality of life and self image. In adults the main effects are restoration of body composition, reduction of fat tissue, improvement of muscular and cardiac function, beneficial effects on serum lipids and improvement in the quality of life.

Side effects include arthralgia, myalgia, and edema. Initial spurt of growth is remarkable and a linear growth of 12 to 15 cm may be obtained in one year, but the growth rate slows down later and at this stage higher doses of hormone are needed.

Concurrent use of anabolic steroids helps to improve growth and bring about a positive anabolic response. Commercially available GH is prepared by recombinant DNA technique or synthetic processes.

Empty Sella Syndrome

(Syn: Subdiaphragm cistern, Intracellular-subarachnoid Space, Intracellular cyst)

Definition

This is a rare disorder in which the pituitary fossa is enlarged with accumulation of cerebrospinal fluid at the expense of pituitary tissue, which may be reduced to a small remnant. The condition may be primary in which anatomical defects occur in the diaphragm sellae or secondary to surgery or irradiation on the region of the pituitary. The suprasellar subarachnoid space herniates through defects in the diaphragm sellae. The sella turcica becomes filled with CSF enclosed in an arachnoid-lined sac. This causes pressure effects on the pituitary stalk resulting in hyperprolactinemia and galactorrhea.

Diagnosis

The condition may be associated with normal endocrine profile in 60% of cases. In 40% of cases growth hormone response to stimuli and levels of gonadotropins may be reduced.

X-ray skull may show either a normal sella or an enlarged sella with thinned out dorsum sellae. Bony erosion is absent. The diagnosis is confirmed by air-encephalography which shows absence of diaphragm sellae and presence of CSF in the sella turcica. CT scan with metrizamide cisternography or MRI confirms the diagnosis.

Treatment

Hormonal replacement is undertaken if endocrine deficiency exists.

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Pineal Gland and its Disorders

K.P. Poulse, B. Jayakumar

Chapter Summary

General Considerations: Pineal Gland 624

Disorders of the Pineal Gland 624

General Considerations: Pineal Gland

(Syn. Pineal body)

Anatomy: The pineal gland which weighs 120 mg lies beneath the posterior border of the corpus callosum and between the superior colliculi. Embryologically it develops from the ependyma lining the roof of the third ventricle.

Two types of cells are found in the pineal gland - the pinealocytes which form the majority and the neuroglial cells. The pinealocytes produce indolamines mainly **melatonin** and peptides such as vasotocin. Melatonin diffuses into the bloodstream. Secretion increases soon after the onset of darkness, peaks between 2 and 4 A.M. and falls off thereafter.

In infancy, melatonin levels are high (325 pg/mL). They fall off with age to 10-60 pg/mL in young adults. Exposure to light inhibits secretion. The effects on tissues are receptor mediated.

Possible physiological effects of melatonin include:

1. Hypnotic: increased propensity to sleep.
2. Control of circadian rhythm, e.g. temperature regulation.
3. Possible role in cyclical mood changes.
4. Sexual activity and reproductive function.
5. Anti-proliferative action in cancer.
6. Enhancement of the immune response.
7. Modulation of aging response and protection of cells and damage.

Diminished levels of melatonin may be associated with acceleration of the aging process.

In addition to melatonin, three hypothalamic hormones (TRH LH-RH and somatostatin) and an octapeptide, arginine vasotocin (vasopressin), -have also been detected in the pineal gland. During infancy, the pineal is relatively large. With age, it involutes.

Disorders of the Pineal Gland

1. **Calcification of the pineal gland:** This occurs in the matrix of ground substance secreted by pinealocytes. Calcification begins in early childhood and is completed by about puberty. Calcification is not associated with any functional disturbance.
2. **Tumours:** The pineal may be the seat of tumours. These may be pinealoma, teratoma, glial tumours or vascular tumours.

Tumours lead to mechanical effects due to pressure and endocrine disturbances. Pressure effects include rise in intracranial tension, internal hydrocephalus due to pressure on the aqueduct of Sylvius, and paralysis of upward gaze due to oculomotor involvement (**Parinaud's syndrome**). Ataxia, visual disturbances and signs of hypopituitarism may occur.

Endocrine disturbances manifest as abnormalities of sexual maturation such as sexual precocity, delayed puberty, and hypogonad states, evidence of hypothalamic involvement like diabetes insipidus, polyphagia, somnolence, obesity or behavioural disturbances are seen in 70% of patients with pinealomas and precocious puberty.

Treatment

Surgical treatment is beneficial in trained hands, though the procedure is difficult. Pineal tumours are partially radiosensitive and irradiation is effective. Chemotherapy with carboplatin, etoposide, vincristine, and bleomycin has also been found to be successful. Prognosis is good with a 5 years survival of 70-85%.

Thyroid and its Disorders

K.P. Poulouse, K.V. Krishna Das

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General Considerations

At present thyroid disease from the second most common endocrine disorder in India next only to diabetes mellitus. If asymptomatic endemic goiter is also included, thyroid disease may even rank as the most common endocrine disease. The prevalence of iodine deficiency disorders is very high. With the introduction of iodised salt, the prevalence of iodine deficiency disorders is coming down.

Anatomy: The thyroid gland weighs 15 to 25 g, and it is made up of an isthmus and two lateral lobes. The isthmus lies just below the cricoid cartilage. The gland lies deep to the strap muscles of the neck enclosed in the pretracheal fascia which anchors it to the trachea, so that the thyroid moves up on swallowing. The width and length of isthmus averages 20 mm, thickness 2-6 mm. The lateral lobes from superior to inferior pole measure 40 mm, breadth is 15-20 mm and thickness 20-39 mm. The parathyroid glands which are four in number are embedded in the substance or sheath of the thyroid, behind the lateral lobes. The thyroid develops as early as the third or fourth week of gestation. The thyroid is formed as an outgrowth on the ventral wall of the pharynx in association with the

parathyroids which are derived from the third and fourth branchial arch. The 'C' cells which produce calcitonin are formed from the cells of the ultimobranchial body. Persistence of the remnants of the thyroid stalk may give rise to the pyramidal lobe, which lies just to the left of the midline extending upwards from the isthmus or to thyroglossal cyst. Failure of the thyroid stalk to descend results in the formation of lingual thyroid.

In the fetus the thyroid hormones are synthesized under the influence of TSH only by about the eleventh or twelfth week of gestation. Hence in the first trimester the fetus is totally dependent on maternal thyroxine. For proper development of mental and motor skills, adequate thyroid hormone concentration is necessary, whose synthesis depends on the availability of maternal iodine status. Initially, there is synthesis of T4 only in the fetus (TSH dependent) and inactive T3 (reverse T3) is formed from T4.

Iodine metabolism and hormone synthesis: The average Indian diet contains variable quantities of iodine ranging from very low values to more than 200 µg/day. Ingested iodine is reduced to iodide in the gastrointestinal tract and absorbed throughout the gut, the maximum being in the small intestine. Thyroid traps this iodine.

Daily dietary requirement of iodine varies with age

Children < 5 years of age	90 µg
6-12 years	120 µg
> 12 years	150 µg
Pregnancy and lactation	200 µg

In iodine deficiency the level of iodine in urine is < 100 µg/L

Plasma inorganic iodide level is usually less than 1.0 µg/dL. About 90% of the total body iodine is in the thyroid gland.

Thyroxine (T4) and tri-iodothyronine (T3) are formed by sequential reactions occurring in the thyroglobulin molecule under the control of TSH. The follicular cells synthesize thyroglobulin and store it within the follicles as colloid. This colloid acts as a reservoir of thyroid hormones.

Release of thyroid hormones from thyroglobulin: The follicular cells take up thyroglobulin colloid droplets and release T3 and T4 by their degradation. The thyroglobulin molecule is split by proteases and peptidases into T3 and T4 which are released into circulation and this is controlled by TSH. The total T4 secretion is about 60-120 µg and T3 is 20-30 µg per day. In the peripheral tissues T4 is converted into T3. 80% of circulating T3 is derived from de-iodination of T4 in the peripheral tissues and the rest from the thyroid gland. The turnover of T4 from thyroglobulin is only 1% per day and thus the large store of hormone provides prolonged protection against disorders of thyroid hormone synthesis. Total T4 stored in thyroid gland is about 5 mg, which is adequate for 50 days.

Plasma transport: Around 75% of thyroxine (T4) circulates in blood bound to *thyroxine binding globulin* (TBG) which is an alpha-globulin, 15% is bound to pre-albumin, now called transthyretin and the rest to albumin. Tri-iodothyronine (T3) also remains bound to TBG in the plasma. The plasma level of T4 is 5-10 µg/dL and that of T3 is 150-250 ng/dL. The sum total of T4 and T3 bound to the carrier protein is referred to as plasma protein-bound iodine (PBI). The normal range is 4-8 µg/dL. In serum, the free T4 is 0.03% of total T4 and free T3 is 0.3% total T3. The levels of T4 and T3 are regulated by the TSH from the anterior pituitary and TRH from hypothalamus. Rising levels of thyroid hormones inhibit TSH secretion. Both T4 and T3 are de-iodinated in the cells by the microsomal enzymes (deiodinases types 1, 2 and 3) and the iodides are excreted in urine (70 µg/day). T3 is bound to specific nuclear DNA thyroid hormone receptors and it is carried by cytosolic binding proteins into the cell nucleus.

Deiodinases are expressed in liver, kidney, pituitary and thyroid. The metabolic effects of thyroid hormone are initiated by the binding of T3 to the nuclear receptors. T3 has 15 fold higher binding affinity to intranuclear receptors compared to T4.

Actions of Thyroid Hormones

1. Increases cellular oxidation in all tissues.
2. Increase of protein breakdown.
3. Increases the turnover of carbohydrates and lipids.
4. Calcium is mobilized from bone.
5. The cardiovascular effects consist mainly of increase in heart rate and cardiac output.

Calcitonin: Calcitonin is a 32 amino acid peptide hormone formed in the parafollicular cells (C cells) of the thyroid. Calcitonin inhibits bone resorption and release of calcium from bone, thereby helping to lower calcium levels in blood. Catabolism of bone is significantly reduced. Levels of calcitonin increase during hypercal-

cemia and the secretion stops when the calcium levels fall. High levels of calcitonin are seen in patients with medullary carcinoma of the thyroid, however, in this condition there is no hypocalcemia. Human calcitonin gene is located in the short arm of chromosome 11. Glucocorticoids, glucagon and gastrin increase calcitonin secretion. It is also secreted by insulinomas, vasoactive intestinal polypeptide secreting tumours (VIPomas) and some lung tumours. Calcitonin has therapeutic use in the management of acute hypercalcemia, osteoporosis, and Paget's disease of bone.

Calcitonin Gene Related Peptide (CGRP)

This is a 37 amino acid peptide formed from the pre-procalcitonin gene located on chromosome 11. Final targets of action of this peptide are the C-cells of the thyroid and neural tissue. In the C-cells the product is calcitonin, whereas in neural tissue the product is pro-CGRP, which is a neurotransmitter influencing the sensory system. It is also a very powerful vasodilator which is concerned with the regulation of regional blood flow.

ASSESSMENT OF THYROID FUNCTION

Clinical examination is most valuable in all cases. Though several classic features such as lid lag and thyroid bruit specifically point to florid hyperthyroidism, in marginal cases the clinical symptomatology shows considerable overlap with normals or other non-thyroid disorders. Many tests are available to assess thyroid function but no single test is totally satisfactory.

THYROID FUNCTION TESTS

Isotopic Tests

- a. Estimation of T3, T4 and TSH by radioimmunoassay or ELISA
- b. Estimation of free T3 and T4
- c. TRH stimulation test
- d. Thyroid scan
- e. ¹³¹I uptake studies, TSH stimulation and T3 suppression tests. These are seldom done at present.

Non-isotopic Tests

- a. Demonstration of thyroid autoantibodies.
- b. Imaging procedures of the neck. USS, CT and MRI
- c. Biopsy of thyroid—fine-needle aspiration cytology (FNAC) or open biopsy.

Radioactive iodine uptake test: The amount of radioactivity concentrated by the thyroid following oral administration of ¹³¹I, after 2 and 24 hours is measured. In Indians, the normal ranges are 10 ± 5% at 2 h and 42 ± 7% at 24 h. The uptake values are high in hyperthyroidism and are low in hypothyroidism. Since this test is likely to

Alteration of T3, T4 and TSH values in common thyroid disorders			
(Total or free)	T3	T4	TSH
Graves' disease	High	High	Low
T3-toxicosis	High	Normal	Low
Primary hypothyroidism	Low	Low	Very high
Secondary and tertiary hypothyroidism	Low	Low	Low

be altered in several non-thyroidal diseases, and by drugs containing iodides, this is not routinely done except under special circumstances. These include:

- 1. Factitious hyperthyroidism
- 2. Acute and subacute thyroiditis
- 3. Hashitoxicosis and
- 4. For calculating the therapeutic dose of ¹³¹I in thyrotoxicosis.

Normally iodine uptake is suppressed by exogenous administration of T3 or T4. In Graves' disease (primary hyperthyroidism) T3 and T4 fail to suppress iodine uptake. In hypothyroidism, in order to identify the site of lesion as the thyroid, pituitary or hypothalamus, the effect of TSH or TRH respectively on iodine uptake by the thyroid is studied. In primary hypothyroidism the values do not change, whereas in pituitary or hypothalamic disease, the iodine uptake is increased by TSH or TRH respectively.

Estimation of T4, T3 and TSH: These hormones can be directly estimated by radioimmunoassay or ELISA. The total plasma level of T4 is 4-8 µg/dL and T3 is 150-250 ng/dL. Normal range of TSH is upto 5 µU/mL (Table 98.1).

Free T3/T4 estimation: The values of total serum T3 and T4 may be altered by many drugs, which interfere with TBG binding (estrogen increases, androgen decreases) and in conditions like pregnancy and hypoproteinemic states. In these situations free hormone concentrations correlate better with the metabolic state than the total hormone concentrations because they are unaffected by changes in

binding protein concentration or affinity. Free T3/T4 is the preferred test now and can be measured by RIA/ELISA.

TRH stimulation test: 100-200 µg of TRH is injected intravenously after estimation of basal TSH level in the serum. At 20, 40 and 60 minutes post-injection, TSH levels are estimated. Normally there is a two-fold rise. In Graves' disease the TSH response to TRH is minimal. In hypothalamic hypothyroidism, the basal level of TSH is low, but TRH causes more release of TSH. In pituitary disease, the basal as well as post-injection level of TSH remains the same at a low level.

Thyroid scintiscanning: Scanning offers a visual display of the size and shape of the thyroid gland. It is employed in different situations (Table 98.2).

- 1. It provides an objective assessment of the morphology of the gland.
- 2. It locates ectopic foci of thyroid tissue.
- 3. The functional activity of thyroid nodules can be evaluated (hot or cold nodules).
- 4. In the investigation of masses in the neck or mediastinum, scintiscanning is useful to detect their nature (e.g. retrosternal thyroid).
- 5. Metastasis from thyroid carcinoma can be visualized.

Originally ¹³¹I was used for visualizing the thyroid, the scan being done after 24 hours of administration. At present technetium pertechnetate which has a half-life of 6 hours is used for this purpose. With technetium scanning can be done soon after the injection of the radioisotope.

Additional laboratory investigations include haematological tests and estimation of the levels of serum calcium, sodium, CPK and proteins.

Fine-needle aspiration biopsy is a very valuable preoperative procedure done routinely. A correct diagnosis can be obtained in over 80% of cases. False negative results occur more frequently than false positive ones. The diagnostic accuracy of FNAC is about 95%, specificity 92% and sensitivity is around 83%.

Results of various isotopic tests in thyroid disorders				
Disease	RAIU	T4 (RIA)	T3 (RIA)	TSH
Graves' disease	H	H	H	L
Iodine deficiency goiter	H	N	N/M	N
Primary hypothyroidism	L	L	L	H
Suprathyroidal hypothyroidism	L	L	L	L
Subacute thyroiditis	L	N/H	N/H	N/L
Factitious hyperthyroidism	L	H	H if T3 is taken	L

Key: N : normal, H: high, M: marginal change, L: low

Ultrasound/ CT/ MRI Scanning US scanning provides an accurate indication of the size and is useful for differentiating cystic from solid lesions. CT and MRI are useful in the evaluation of retrosternal and retrotracheal extension of the gland, so also compression of trachea, extent of intrathoracic extension of thyroid malignancy and infiltration to adjacent structures. MRI gives better delineation of soft tissue involvement like infiltration of nerves.

Demonstration of thyroid auto-antibodies: Different types of antibodies are demonstrable in patients with thyroid diseases. These include antibodies against thyroglobulin, intracellular microsomal antigen (thyroid peroxidase) and nuclear components. Their presence is diagnostic in many disorders, especially chronic lymphocytic thyroiditis (Hashimoto's disease) and *postpartum thyroiditis*.

All autoantibodies against thyroid cells are IgG. Some antibodies are stimulatory, whereas others are inhibitory with reference to thyroid function.

1. Stimulating - TSH receptor antibodies (Thyroid stimulating immunoglobulin)
2. Destructive
 - a. Thyroid peroxidase (TPO) or antimicrosomal antibodies – the antigen is the thyroid peroxidase enzyme.
 - b. Antithyroglobulin antibodies

TPO antibodies may be present in normal elderly women in upto 20% of cases.

Thyroid stimulating immunoglobulins are TSH receptor antibodies (TSH R Ab).

Since low levels of antibodies are present in normal individuals, the absolute concentration becomes more important. Antibodies are estimated by various methods—immunofluorescence, hemagglutination, radioimmuno assay (more precise) and ELISA techniques. Antibodies are produced due to a secondary response to thyroid injury. The thyroid antibodies most frequently estimated are those directed against thyroglobulin and against thyroid peroxidase. The latter correlates better with thyroid dysfunction and its presence tends to correlate with damage to thyroid tissue and lymphocytic infiltration. The mechanisms of autoimmune destruction of the thyroid probably involve both cellular and humoral components (Table 98.3).

Goiter

Enlargement of the thyroid gland is known as goiter. A benign diffuse enlargement not caused by inflammation or tumour is called *simple goiter* or *nontoxic diffuse goiter* (NTDG).

TABLE 98.3

Frequency (%) of the presence of antibodies in various thyroid disorders

	TSH receptor antibodies	(Thyroglobulin) antibodies	(Thyroid peroxidase) antibodies
Normal	0	5-20	8-27
Graves' disease	80-95	50-70	50-80
Autoimmune thyroiditis	10-20	80-90	90-100
Thyroid cancer	0	20-40%	+
Pregnancy	0	14	14
Type 1 diabetes mellitus	0	40	40
hTgAb : human thyroglobulin antibodies			
hTPOAb: human thyroid peroxidase antibodies. The figures denote the percentage frequency.			

* Serum thyroglobulin (Tg) estimation is done as a follow up in patients with well differentiated thyroid follicular carcinoma. However, serum Tg can also be elevated in goiter, hyperthyroidism and inflammatory conditions of the thyroid.

Causes of goiter

1. *Simple (non toxic) goiters* may occur due to different causes:
 - i. *Physiological goiter*— This is simple enlargement of the thyroid in puberty and pregnancy. It generally subsides when the physiological stress is over, or it may persist. The term physiological goiter is being questioned.
 - ii. *Parenchymatous goiter or colloid goiter*: — Iodine deficiency, iodine excess, dyshormonogenesis, and intake of goitrogens cause thyroid enlargement, the acini being filled with colloid. In some, the cause may not be evident.
2. Goiter due to thyroiditis—acute, subacute or chronic.
3. *Nodular goiter*—single or multiple nodules.
4. *Toxic goiter*—primary (Graves' disease) or secondary (Plummer's disease).

SIMPLE GOITER

This may be endemic or sporadic. Puberty goiter, colloid goiter and parenchymatous goiter are included in this group. The thyroid gland is diffusely enlarged, painless and non-tender. It may be soft or firm in consistency. The term physiological goiter is being discarded since it is doubtful whether the thyroid enlarges due to physiological reasons. Many of these show occult or overt iodine deficiency. Similarly many of the previously labelled puberty goiters were actually due to autoimmune thyroiditis.

Etiology: Simple goiter is the result of relative iodine deficiency which occurs during periods of increased

demand for thyroid hormones, such as menarche and pregnancy. Diffuse colloid goiters are common in younger subjects and are unusual above the age of 40 years. By the age of 35-40 years, the diffuse goiter becomes multinodular. Retrosternal extension may be present, occluding the thoracic inlet.

The gland enlarges due to hyperplasia and hypertrophy. When the stress is over or it is corrected, the cells undergo hyperinvolution and this leads to the formation of colloid goiter. These subjects are clinically euthyroid. Thyroid function is preserved by the preferential production of excess T3 instead of T4. In many cases the thyroid gland reaches large sizes.

It is possible that repeated cycles of hyperplasia and hyperinvolution may lead to the formation of multinodular goiter later.

Treatment

Administration of thyroxine (up to 0.3 mg/day) brings about a favourable response in 60% of subjects. The gland shrinks within 3 months of starting treatment. Treatment has to be continued for 1-2 years or more. Complete regression of the goiter is rare. Abrupt withdrawal of the drug causes rapid enlargement of the gland.

ENDEMIC GOITER

This is a major public health problem all over the world, especially in India. Iodine deficiency manifests in various ways and goiter is the most easily recognized form. Endemic cretinism, which is also common, leads to severe morbidity in these zones. About 54 million people in India have goiter and the number at risk is estimated to be above 167 million.

It is also estimated that there are 2.2 million cretins and 6.6 million children with mild neurological defects in India attributable to iodine deficiency. The spectrum of abnormalities due to iodine deficiency is now grouped under the title '**iodine deficiency disorders' (IDD)**.

An area is termed endemic for goiter when 10% or more of the population is affected. Important among the well recognized goiter belts of the world are the high mountain regions of Andes, Alps and Himalayas, region of the Great lakes of USA, and several pockets in Africa (Zaire). The broad belt covering the mountain ranges of Afghanistan to the sub-Himalayan regions of India, Pakistan, Nepal, Bangladesh and Myanmar extends up to Malayasian archipelago and Indonesian islands. Apart from these well recognized regions, many other states in India, such as Haryana, Rajasthan, Uttar Pradesh, Orissa, Madhya Pradesh, Tamil Nadu and Kerala also show areas of iodine deficiency. In these endemic belts the daily iodine intake is generally less than 50 µg. The drinking water is very low in iodine content. Normal daily requirement of iodine is 150- 200 µg for adults.

Dietary sources of iodine such as sea fish, milk, and eggs may be absent in the diet of the people in these areas.

Pathology

The thyroid gland is enlarged with hypertrophy and hyperplasia of the cells. The euthyroid state is maintained in many subjects because of the increased production of T3. The plasma inorganic iodide levels are low. The absolute iodine uptake by the thyroid is maintained normal by increasing the plasma clearance rate of iodide. PBI is also normal. Urinary iodide excretion is low. Plasma T4 is normal but T3 may be high. Correction of iodine deficiency leads to resolution of the goiter. Alternatively, the cells may undergo hyperinvolution. In this case the acini become filled with colloid and diffuse colloid goiter may develop. With repeated episodes of iodine depletion and repletion, multinodular goiter may develop.

Iodine deficiency during pregnancy leads to abnormalities in the mother and baby. Neonatal and infantile iodine deficiency leads to a spectrum of clinical abnormalities ranging from latent to overt thyroid disorders. Cretinism occurring as a result of iodine deficiency is widespread, and this is one of the correctable causes of abnormality in growth and development in the endemic areas.

Preventive Measures

Several strategies have been tried on a national and international basis for correcting widespread iodine deficiency.

Fortification of common salt with iodide (1 part to 100,000 parts) and distribution in endemic areas has been partially successful in many regions. Table salt fortified with iodine is freely available in India at present. In remote areas where access to medical help is not easy, one of the strategies to prevent iodine deficiency states is the injection of iodized oil. Intramuscular injection of oil containing about 500 mg of iodine once in three years offers effective personal protection.

Provision of iodide promptly reduces the goiter rate and incidence of cretinism in endemic areas. An adverse effect of iodine supplementation is the development of acute hyperthyroidism (**Jod Basedow phenomenon**) very rarely. This is due to the proliferation of thyroid cells during the iodine deprivation period and also the formation of hyperfunctioning nodules leading to hyperthyroidism on supplementing iodine.

Excessive supplementation of iodine in regions with only marginal iodine deficiency may lead to subclinical hypothyroidism and autoimmune thyroiditis rarely (see also chapter 32).

SPORADIC GOITER

The etiology of sporadic goiter is not fully clear. The possible causes include increased iodine demand during

pregnancy or puberty, presence of goitrogens in the diet and genetic factors.

Exogenous goitrogens include common drugs such as thiocarbamides (antithyroid drugs), chlorpropamide, PAS, amiodarone, glutethimide, iodine on a long-term basis, reserpine, phenylbutazone and lithium carbonate. Items of food like cabbage, turnips, soyabean flour, and cassava may act as goitrogens. Cabbage contains thiocyanates which inhibit iodine uptake by the thyroid. Cassava (tapioca) contains cyanogenic glycosides such as linamarin and lotaustralin, which liberate hydrocyanic acid on acid hydrolysis in the stomach.

Goiter may be the result of defective hormone synthesis. Such defects may involve pathways like oxidation, organification, coupling of iodine or proteolysis. The condition manifests as large goiters which show increased iodine uptake. Features of hypothyroidism or cretinism may be evident in some cases. Clinically retrosternal extension of the goiter can be demonstrated by asking the patient to raise both arms above the head for 30 seconds, when the neck veins will engorge with plethoric appearance of face (*Pemberton's sign*).

In cases of dyshormonogenesis, monoiodotyrosines or diiodotyrosines may be elevated in blood depending upon the enzymopathy. In many cases the goiter is familial.

Management: It is essential to detect the cause and tackle the same. Mild iodine deficiency and drug induced goiters respond to medical therapy. Established goiters which do not respond to medication have to be treated by surgical excision. Since thyroid carcinomas are not rare, all goiters should be investigated, including needle aspiration biopsy. Indications for surgery include cosmetic disability, pressure effects, retrosternal extension, suspicion of malignancy and progressive enlargement.

Hyperthyroidism

Persistent, elevation of the synthesis and release of thyroid hormones T4 and/or T3 leads to hyperthyroidism. It may be due to several causes. Hyperthyroidism affects approximately 2% of women and 0.2% of men.

Causes of Hyperthyroidism

Common Causes

- i. Toxic diffuse goiter (*Graves' disease*) -80%
- ii. Toxic multinodular goiter (*Plummer's disease*) -5%
- iii. Toxic adenoma (*autonomous hot nodule*)

Rare Causes

- i. Neonatal hyperthyroidism due to transplacental transfer of long acting thyroid stimulator (LATS), now designated as thyroid stimulating immunoglobulins (Tslg)
- ii. Thyrotoxicosis factitia caused by the self administration of thyroid hormones.
- iii. Iodine induced hyperthyroidism (*Jod Basedow phenomenon*), rarely seen in regions where iodised salt is

distributed, or also with the use of drugs like amiodarone and radiopaque contrast dyes.

- iv. Hashimoto's thyroiditis may be associated with thyrotoxicosis (**Hashitoxicosis**).
- v. Ectopic secretion of TSH like substances by trophoblastic tumours, e.g. hydatidiform mole or chorio-carcinoma or hyperemesis gravidarum in which chorionic gonadotropins are elevated.
- vi. TSH secreting tumours of the pituitary.
- vii. Tumours such as ovarian teratomas containing thyroid tissue (*struma ovarii*) and metastases from follicular carcinoma of thyroid.
- viii. Acute or subacute thyroiditis may give rise to transient hyperthyroidism. Postpartum thyroiditis occurring as painful enlargement of the thyroid within 6 months of delivery may also be accompanied by hyperthyroidism
- ix. Pituitary resistance to thyroid hormone.

DIFFUSE TOXIC GOITER

Syn: Graves' disease, Parry's disease, Basedow's disease

The disease is quite common in general practice, but the severity may vary. Females are affected more with a peak incidence between 20 and 40 years. Though neonates of thyrotoxic mothers may suffer from hyperthyroidism, usually the condition subsides within 3-6 weeks of birth.

Etiology

The exact etiology is not fully understood. The consensus is that Graves' disease is an autoimmune disorder. Several genetic susceptibility loci and environmental factors are likely to contribute to the development of the disease for e.g. HLA 138, HLA DR3, HLA DR2, CTLA-4 (cytotoxic T lymphocyte associated- 4) gene regions. There is a 50% concordance in monozygotic twins and 5% in dizygotic twins. There is also strong association with other autoimmune diseases like pernicious anemia, type 1 DM, myasthenia gravis, Addison's disease, systemic lupus erythematosus (SLE), idiopathic thrombocytopenic purpura (ITP) and rheumatoid arthritis. Various immunoglobulin antibodies are found directed against antigens in the thyroid cells, orbital tissues and dermis. In some cases thyroid stimulating immunoglobulins (autoantibodies) are demonstrable. These are immunoglobulins of IgG class and have TSH-like action. They cross the placenta and lead to hyperthyroidism in the fetus and neonates as well.

Thyroid stimulating immunoglobulins (TSI) are of two types

- a. (TSH receptor antibodies) TSH RAb compete with TSH at the TSH receptor sites in the thyroid cell membrane and behaves like TSH. The serum levels of TSI correlate with the severity of hyperthyroidism, the more the level of TSI, more severe is the disease.
- b. Inhibiting or blocking antibodies such as TSH R IAB which may block the ligand binding site and act as

TSH agonists. TSH receptor is an autoantigen, and its gene structure and chromosomal location is identified now as (14q 31). TSH R IAb is seen in 15% of patients with myxedema.

Pathology

Thyroid is diffusely enlarged due to hyperplasia of acinar cells and increased vascularity. Histologically the acinar cells are hyperplastic, with accumulation of the colloid. Varying degree of lymphocytic infiltration is also seen. Microsomal and antithyroglobulin antibodies are also found in many patients with Graves’ disease, but in lower levels than in Hashimoto’s disease.

Thyroid associated eye disease is a frequent manifestation of thyroid disorders, particularly hyperthyroidism. Extraocular muscles are the target of autoimmune response. There is evidence of retro-orbital inflammation characterised by focal edema, glycosaminoglycan protein deposition, followed by fibrosis. Retro-orbital tissue may act as an autoantigen which has immune reactivity similar to the TSH receptor. Glycosaminoglycans are secreted by the fibroblasts under the influence of cytokines from local lymphocytes.

The present consensus is that the immune system in the body recognizes an antigen common to the thyroid gland, retro-orbital tissues and skin and this is likely to be TSHR Ab and the level of TSH R Ab correlates with the severity of ophthalmopathy and dermopathy. The interstitium shows diffuse mononuclear infiltration, primarily by activated T-cells with some B-cells and occasional macrophages. The retrobulbar fibroblasts and skin fibroblasts are affected by the autoimmune processes. Graves’ ophthalmopathy and dermopathy are strongly associated (Table 98.4).

Clinical Features

Graves’ disease is more frequent in young women. The effect of thyroid hormone is to increase metabolism and sensitise the tissues to catecholamines. The condition is florid and easily detectable in many cases. The symptoms may be less obvious in others. The general symptoms

attributable to hypermetabolic state include loss of weight, intolerance to heat, increased sweating, excessive appetite, palpitation, tachycardia, exertional dyspnea, nervousness, tremor, diarrhea, easy fatigability, apprehension, and insomnia. Rarely mental changes like severe agitation and frank psychosis may be the presenting features.

Examination of the neck shows the thyroid to be diffusely enlarged, but sometimes it may be asymmetrical. It is soft, warm, pulsatile, and tender. Arterial thrills and bruit may be detectable. These phenomena indicate increased vascularity.

Several organs show abnormality. Though in most cases, many of them are detectable, the severity of involvement may not be uniform.

Thyroid associated eye disease may present in several ways, 90% have overt hyperthyroidism. 10% have no obvious thyroid dysfunction. Those with no signs of thyrotoxicosis are known as *ophthalmic or euthyroid Graves’ disease*. Among them 50% have autoimmune hypothyroidism, the remaining 50% have no detectable clinical or biochemical dysfunction of the thyroid. Main clinical features include diplopia with vertical separation of visual images, asymmetry of palpebral fissures, disorders of movement of the eyes and lids, and compression of the optic nerve (Fig. 98.1).

- 1. Sympathetic overactivity leads to lid lag, stare, increased watering, and infrequent blinking. These subside with correction of thyroid function.
- 2. There is abnormal protrusion of the eyeball (*exophthalmos*) and *partial or complete ophthalmoplegia*. Exophthalmos is generally bilateral, but can be unilateral or asymmetrical. It may precede overt hyperthyroidism. Exophthalmos is assessed by measuring

TABLE 98.4

Binding of thyroid hormones to various protein fractions in blood-%			
	TBG	TBA	TTH
T4	68	20	11
T3	69	11	9
TBG – Thyroid binding globulin TBA – Thyroid binding albumin TTH – Transthyretin 3-6% of plasma T3/T4 are bound to lipoproteins. TBG affinity for T4 is 20 times more than that for T3.			



Fig. 98.1: Bilateral exophthalmosma in a male thyrotoxic patient

the distance between the lateral angle of the bony orbit and the anterior part of cornea by **Hertel exophthalmometer**.

3. Papilledema may develop in advanced cases. Some cases may show optic atrophy.

Skin changes: The skin is soft and moist. The hair is soft. Sweating is excessive. The nails show thinning (*onycholysis*) and may get separated from the nailbed (*Plummer's nails*).

Sometimes localized myxedematous deposits may occur. The common site is the front of the leg (**hence called pretibial myxedema**). Over this site the skin is raised, nodular, indurated, and reddish brown in colour. The lesions may be pruritic. Examination reveals *peau de orange* (orange peel-like) appearance. In addition to the pretibial regions, thighs, genitalia, and lower abdomen may be affected. Pretibial myxedema is attributed to local nonresponsiveness of tissues to the thyroid hormones.

Some cases show clubbing of fingers and toes and hypertrophic osteoarthropathy (**thyroid acropachy**).

Changes in skeletal muscles: There is excessive fatigue and weakness. The proximal muscles of pelvic and pectoral girdles show myopathy characterized by selective weakness and atrophy and this may incapacitate the patient. The condition recovers completely when thyrotoxicosis is controlled. This is an example of reversible endocrine myopathy. Myasthenia gravis may coexist with Graves' disease and the relationship is more of a see-saw phenomenon — myasthenia *abating when thyrotoxicosis* is active and vice versa. Both conditions demand management on their own merits. Hypokalemic periodic paralysis may occur more frequently in thyrotoxic subjects.

Cardiovascular system: Cardiac output increases out of proportion to the rise in basal metabolic rate. Thyroxine has a direct chronotropic effect on cardiac tissues. Increase in workload leads to cardiac hypertrophy. Combination of excessive demand in the presence of reduction of reserve capacity of the myocardium leads to high output cardiac failure. Atrial fibrillation occurs in up to 25% of cases and this is resistant to drug therapy and cardioversion, till the thyrotoxicosis is also controlled.

Other arrhythmias such as paroxysmal tachycardia and atrial flutter are also common. Some patients develop effort angina.

Alimentary system: Abdominal cramps, diarrhea and vomiting are common features. The diarrhea is due to intestinal hurry. In many cases it takes the form of increased frequency of bowel movements, especially after food.

Reproductive system: In women the periods become scanty and fertility is reduced. In men libido and potency

may be altered variably. Gynecomastia may develop. Oligospermia may occur.

Bones: Osteoporosis may develop as a result of increased resorption of bones. Hypercalcemia and hypercalciuria may be demonstrable.

The general clinical picture produced by toxic diffuse goiter and toxic nodular goiter is similar in many respects. However, eye changes and pretibial myxedema are more common in toxic diffuse goiter. Association with other autoimmune diseases is more characteristic of Graves' disease, which is the more frequent form in younger age groups. Toxic adenomas occur usually at later age groups. In them cardiovascular manifestations are more prominent and sometimes may be the only clinical presentation. In toxic adenoma, local examination of the thyroid may not reveal generalized hypervascularity and bruit, but the condition can be easily diagnosed by palpating the nodules.

Sometimes the thyroid gland may produce excessive quantities of only tri-iodothyronine (T₃). Such a condition is called T₃ toxicosis, mostly seen in autonomous hot nodules or in iodine deficient areas.

Diagnosis

In florid cases clinical diagnosis is easy. Subclinical cases may be missed if thyrotoxicosis is not kept in mind. In all cases it is advisable to confirm the diagnosis and establish its severity by investigations.

Differential Diagnosis

When the symptoms are mild, hyperthyroidism may be mistaken for anxiety state, tuberculosis, diabetes or primary muscle disease. In anxiety state the palms are cold and moist, whereas in hyperthyroidism they are warm and moist.

Euthyroid Graves' disease: This is a condition in which exophthalmos is present with or without thyroid enlargement. There may not be signs of overt hyperthyroidism. ¹³¹I uptake is increased or normal, but the uptake is not inhibited by administration of T₃. Moreover, administration of TRH does not lead to elevation of TSH. T₃ and T₄ levels will be normal.

Laboratory Investigations

¹³¹I-uptake by the thyroid gland, levels of T₄ and T₃, are all increased. TSH is low and there is no increase in TSH levels when TRH is administered.

TREATMENT

Thyrotoxicosis may be treated with antithyroid drugs, irradiation by radioactive iodine or surgery.

Drug therapy: Drugs form the first line of management in the ordinary case. Antithyroid drugs block the synthesis of thyroid hormones by inhibiting thyroid peroxidase enzyme, thus blocking iodination of tyrosine. The drugs are started in a small dose and worked up to optimum response, and maintained for a period of 18-24 months. With improvement in the condition the dose can be tapered and maintained at a lower level. In 50% of cases remission is obtained during drug therapy. Many cases may relapse on withdrawal of therapy. Thiocarbamides, potassium perchlorate, and Lugol's iodine are also employed as antithyroid drugs.

Thiocarbamides: *Carbimazole, methylthiouracil and propylthiouracil* are the drugs in this class, of which methylthiouracil is seldom used at present. Carbimazole (Neomercazole) is most widely used on account of its effectiveness, relative safety and free availability. It is started in a dose of 10-15 mg 6 hourly as tablets. Carbimazole has mild immuno-suppressive effects while PTU in addition blocks the conversion of T₄ to T₃. As the desired effect is obtained, the dose is reduced and continued at a lower level to maintain euthyroid state.

Propylthiouracil is used at times when carbimazole is not tolerated. The daily dose is 150 mg 6 hourly as tablets. Both these drugs promptly block the formation of thyroxine and tri-iodothyronine, but do not prevent the release of hormone stored in the colloid. Therefore, it takes 2-3 weeks for the effect to be fully established. If found effective, the therapy should be continued for 12-18 months before reducing the dose and withdrawing it. Early withdrawal may lead to relapse. Even after the full course some cases may still relapse.

Adverse Side Effects

Thiocarbamides are toxic drugs and, therefore, close watch should be instituted when administering them. Adverse effects include fever, lymphadenopathy, splenomegaly, jaundice, leukopenia, thrombocytopenia, and **agranulocytosis**. Generally, adverse effects manifest during the early part of treatment. Reversible enlargement of the thyroid may occur during therapy and this subsides on stopping the drug. Enlargement of the thyroid may be troublesome at times. Another untoward side effect is the worsening of exophthalmos. Concurrent use of thyroxine sodium in a dose of 0.05 to 0.1 mg daily helps to reduce these side effects and continue anti-thyroid medication more smoothly.

Potassium perchlorate: It is an ion inhibitor which inhibits the transport of iodine to the thyroid. In an initial dose of 800 mg daily, the drug is very effective. As the condition improves, the dose is reduced. The action is rapid. Potassium thiocyanate is another drug in this category.

Iodine (inorganic or organic) given in pharmacological doses promptly blocks iodine uptake by the thyroid, formation of thyroxine and also release of preformed hormone from colloid. Iodine blocks the peripheral conversion of T₄ to T₃. For immediate effect iodine or iodides are preferable. Since the vascularity of the thyroid also comes down, it becomes less friable during surgery. Therefore, iodine is given as a preoperative drug for thyroidectomy, and also for the management of thyroid storm.

Dose: *Lugol's iodine* (iodine dissolved in potassium iodide solution containing 10 mg iodine in each drop) or saturated solution of potassium iodide which contains 50 mg iodine per drop is given in a total dose of 500 mg/day. Effect of iodine on the thyroid is not permanent. With continued use exceeding 2-3 weeks, the antithyroid activity wanes. Therefore, iodine or iodides are used only for short-term treatment. Sodium iodide can be given IV-1g/day.

Inorganic iodine is not routinely used because of toxicity and high incidence of recurrence. Organic iodine such as oral cholecystography dye can be used on a short-term basis. Iodine blocks the peripheral conversion of T₄ to T₃. Because of the rapid action iodides are most useful in the management of thyroid crisis. Since the entero-hepatic circulation of T₃ and T₄ is higher in thyrotoxicosis, it may be beneficial to use bile salt sequestrants like cholestipol hydrochloride along with carbimazole in the initial phase of treatment of resistant cases of thyrotoxicosis.

Steroids like dexamethasone which suppresses the peripheral conversion of T₄ to T₃ and secretion of T₄/T₃ are also found to be useful.

Pretibial myxedema responds to the local application of triamcinolone cream under occlusive dressing.

T₄ has a half-life of about 5 days in the body. Therefore, the effect of antithyroid drugs is not immediately evident. There is a latent period of 7-10 days before the symptoms are controlled. In order to reduce the distressing symptoms immediately, beta-adrenergic blockers like propranolol (up to 120 mg/day) may also be used. This promptly controls the tachycardia, palpitation, diarrhea, tremor, and exertional dyspnea. Excitement and insomnia are indications for drugs like phenothiazines (100 mg/day) or diazepam (20-30 mg/day).

Spontaneous development of hypothyroidism after antithyroid drug therapy for autoimmune thyroiditis denotes the presence of TSH blocking antibodies.

Surgery

Subtotal thyroidectomy is the operation of choice.

Indications for surgery are:

- i. Large goiter with pressure effects.
- ii. Nodular toxic goiter.

- iii. Failure of drug therapy or serious toxicity of drugs and
- iv. Poor drug compliance, socioeconomic factors, cosmetic reasons and desire for quick response.

The patient is given drug therapy before surgery to make him euthyroid. This is necessary to prevent *thyrotoxic crisis*. Two weeks prior to surgery carbimazole is replaced by potassium iodide 60 to 100 mg per day in order to reduce the size and vascularity of the gland. Surgery is effective in reducing toxic symptoms in almost all cases. Recurrence after surgery occurs in 10% cases. The immediate complications include recurrent laryngeal nerve palsy and damage to the parathyroid glands (2%). 40-45% of cases may develop hypothyroidism in 10 years, requiring thyroid supplementation.

Radio-iodine treatment: Currently ^{131}I treatment has practically replaced thyroidectomy in the treatment of Graves' disease in adults in many countries. Data from major centers shows that 50% of patients are treated with ^{131}I , 35% with surgery and only 15% with antithyroid drugs alone. In India radio-iodine treatment is available in many centers for routine use. ^{131}I is the commonly used preparation. ^{125}I can also be used for this purpose. ^{131}I has a half-life of 8 days while ^{125}I has a half-life of 60 days.

Indications for Radio-iodine Treatment

- i. Thyrotoxicosis with small or moderate sized gland.
- ii. Recurrent thyrotoxicosis.
- iii. Masked hyperthyroidism.
- iv. Thyrotoxic heart failure.
- v. Poor surgical risk.

Contraindications

- i. Pregnancy is an absolute contraindication since the isotope may reach the fetus and destroy its thyroid as well.
- ii. In severe thyrotoxic patients ^{131}I treatment may precipitate thyroid storm. Hence treatment has to be undertaken with caution.

^{131}I dose: The thyroid will be effectively irradiated with 7000 rads. For this dose, each gram of thyroid tissue should receive 150 microcuries of ^{131}I . The average total dose is 8-10 millicuries (300-400MBq-Mega Bequerel). However this dose leads to hypothyroidism in 30-70% of cases within 2-10 years. Hence lower doses are preferred in many centers. After an initial dose of 4-5 millicuries (150-200 MBq), the dose is repeated after three to six months. Even among those who were given the lower dose hypothyroidism may develop in 50% within 25 years. ^{131}I can be administered orally as a solution on an outpatient basis, but the urine and feces which contain high amounts of radioactivity have to be disposed safely. Antithyroid medication should be withdrawn four days before administering ^{131}I and this can be continued thereafter till

the patient becomes euthyroid. Women of child bearing age should be given ^{131}I within 10 days of onset of menstrual bleeding. In those with irregular menstrual periods pregnancy should be excluded by urine test before drug administration. They should avoid pregnancy for four months thereafter.

THYROTOXIC CRISIS

Syn: Thyroid storm

This is caused by sudden release of thyroid hormones from the gland, spontaneously or immediately after surgery. Thyroid crisis is more frequent if surgery is undertaken during active thyrotoxicosis. Thyroid storm can be precipitated by ^{131}I treatment also. This is a medical emergency.

Thyroid crisis should be suspected if the patient develops high fever, severe tachycardia, restlessness, heart failure, peripheral vascular collapse or psychotic behaviour.

Treatment

This is a medical emergency demanding urgent specific treatment.

1. Diazepam is given in doses of 5-10 mg IV to allay the agitation and quieten the patient. Tepid sponging helps to keep the temperature down from rising to hyperpyrexia levels.
2. I.V glucose saline drip is started and hydrocortisone 100 mg is given at 4-6 hour intervals to combat shock.
3. Sodium iodide is given IV in a dose of 300-600 mg 8 hourly till the metabolic crisis is controlled.
4. Beta-adrenergic blockers are very effective in reducing tachycardia and adrenergic symptoms. Propranolol given IV in doses of 1-4 mg stat over a period of 5 minutes is very effective and the effect lasts for 3-4 hours, after which it is to be repeated. In less severe cases propranolol can be given orally, in doses ranging from 120-240 mg in 24 hours upto 600-1200 mg.
5. If IV sodium iodide is not available, an effective anti-thyroid regimen is to give propyl thiouracil 100 mg 6 hourly along with potassium iodide 50-100 mg orally, rectally or through a Ryle's tube as the case may be. Iodine containing radio-contrast dyes such as *sodium iopodate* 500 mg orally daily will restore the serum T3 to normal in 2-3 days. Propranolol and sodium iopodate can be withdrawn after 14 days. Carbimazole can also be given 15-20 mg 6 h through a Ryle's tube.

HYPERTHYROIDISM DURING PREGNANCY

Both propyl thiouracil and carbimazole are effective. These drugs cross the placenta and appear in breast milk. Propyl thiouracil is preferred in pregnancy since the fetus receives only 0.025% of the administered dose whereas with carbimazole it receives 0.2%. Aplasia cutis of scalp

can develop in neonates with carbimazole. The minimum dose of these drugs required to keep the mother's thyroxine level at the upper limit of normal should be continued. After delivery baby should be fully investigated for thyroid function and appropriate management instituted. In general, hyperthyroidism naturally remits during pregnancy and relapses after delivery.

Toxic adenomas: These are usually autonomous and thyrotoxicosis due to this cause tends to be permanent and prolonged, without any natural remission. Specific anti-thyroid drugs are less effective. Beta-adrenergic blocking drugs may control the adrenergic symptoms. ^{131}I is the more effective therapy, but larger doses up to 10-50 millicuries may be required at times. Surgical removal is the better alternative.

Hyperthyroidism due to thyroiditis: Usually this is a transient phenomenon occurring in subacute thyroiditis or Hashimoto's thyroiditis. The condition is self-limiting, but some cases may go on to hypothyroidism, later becoming euthyroid. Specific antithyroid drugs may not be needed in many. Often beta-adrenergic blocking drugs are sufficient to control the symptoms.

Exophthalmos: There is no specific treatment for exophthalmos. During treatment of Graves' disease, the exophthalmos subsides in some, but in others it remains unchanged or worsens. The treatment of exophthalmos is only empirical since the pathogenesis is not fully understood. Radio-iodine treatment aggravates ophthalmopathy.

Irritation and watering of the eyes are benefited by the use of eyedrops containing corticosteroids, methyl cellulose or 5% guanethidine. Use of sun glasses with side shields and adoption of semi-upright position help to give further relief. Use of prismatic glasses helps to overcome diplopia. Injection of botulinum toxin to paralyse selected extraocular muscles has been tried as a measure to avoid diplopia. Diuretics are also beneficial in some cases.

MALIGNANT EXOPHTHALMOS

When exophthalmos is associated with reddening, edema and bulging of conjunctiva from under the lids and around the corneal limbus it is called malignant exophthalmos. If left untreated, this may lead on to corneal ulceration and blindness. This is also treated on the same line as for exophthalmos but prednisolone orally 90-120 mg daily is found to be beneficial. The eyes are protected from exposure keratitis by performing lateral tarsorrhaphy. Surgical decompression of the retro-orbital space (orbital decompression) is undertaken when the vision is threatened or papilledema develops. Irradiation of retro-orbital tissues may arrest the progression of exophthalmos and this is tried in severe cases where vision is in danger.



Fig. 98.2: Female thyrotoxicosis with exophthalmic ophthalmopathy

The dose required may be up to 2000 cGy given in 10-12 sittings. Plasmapheresis has been used as a temporary measure, with limited success (Fig. 98.2).

Long-term use of octreotide in a dose of 100-200µg daily by subcutaneous injection is beneficial in the management of troublesome exophthalmos.

Graves' ophthalmopathy is self-limiting. Once the active disease is controlled the orbital tissues undergo fibrosis, but full recovery may not occur.

Subclinical hyperthyroidism: This is defined as the condition in which the serum level of TSH is undetectable but with normal serum T4/T3. Subtle signs and symptoms of thyrotoxicosis may be present. Some patients may have atrial fibrillation. Even if asymptomatic, some authors advocate anti-thyroid medication to prevent future atrial fibrillation and osteoporosis, in addition to correcting the thyroid status, especially if the TSH levels are below 0.1µ unit/mL.

Hypothyroidism

Insufficient synthesis and release of thyroid hormones give rise to hypothyroidism. This may be congenital or acquired later in life. Congenital hypothyroidism leads to developmental abnormalities resulting in cretinism. When hypothyroidism occurs in juveniles or adults, a characteristic clinical picture develops in which there is accumulation of hydrophilic mucopolysaccharides in the ground substance of the dermis and several other tissues resulting in induration and coarsening of the skin and enlargement of organs like the tongue. This is called myxedema. Women are affected more with a 10% prevalence in adult women and 3% in adult men. Myxedema is associated with other autoimmune disorders like

diabetes mellitus, rheumatoid arthritis, and pernicious anemia.

There is another entity called subclinical hypothyroidism which is defined as mild TSH elevation with normal T3 and T4. They also may be symptomatic as florid hypothyroidism and they require treatment.

Causes of Hypothyroidism

Primary hypothyroidism—the thyroid gland is primarily at fault.

Non-goitrous

- Spontaneous atrophy (autoimmune)- Myxedema
- Congenital metabolic or other defects.
- Surgical removal or ^{131}I treatment.

Goitrous

- Dyshormonogenesis.
- Dietary iodine deficiency.
- Antithyroid drugs given to the mother during pregnancy.
- Drug induced: PAS, iodides, phenylbutazone, lithium carbonate, amiodarone and others and
- Hashimoto's disease.

Secondary hypothyroidism — In this condition the thyroid is normal but the regulating system is abnormal.

- Hypopituitarism
- Isolated TSH deficiency
- Abnormalities of the hypothalamus (neoplasm, sarcoidosis, encephalitis).

CLINICAL FEATURES

Clinical features of hypothyroidism depend on the age of onset of the disorder and the types.

Cretinism

The incidence of neonatal hypothyroidism in India is nearly 1 in 2500, whereas it has a worldwide incidence of 1 in 4000 on neonatal screening.

This results from hypofunction of the thyroid from birth. This may result from iodine deficiency occurring in endemic goiter belts. Babies born to hypothyroid women or those taking antithyroid drugs during pregnancy may develop cretinism. Though the abnormality is present at birth in many babies, symptoms manifest only after several months and, therefore, the condition may remain undetected in the newborn. The infant is dull and lethargic. Growth is retarded. Other features include large protruding tongue, broad flat nose, widely set eyes, sparse hair, dry skin, protuberant abdomen, and umbilical hernia. Abnormal persistence of physiological jaundice, croaky voice, constipation, somnolence and problems in feeding should raise the possibility of cretinism in the newborn. As the baby becomes older, retardation of growth and milestones become evident (Fig. 98.3).

Neurological abnormalities are prominent in some cases. These include deafness, spastic limbs, and at times,



Fig. 98.3: Cretin. Note: The retardation of growth and dull facies—normal of the same age for comparison on the right

coma. Mental development is severely retarded. If replacement thyroxine treatment is not given within the first 6-12 months, the newborn will lose 3-5 intelligence quotient (IQ) points every month from birth.

The appearance and ossification of several epiphyseal centers are delayed. Delay in the appearance of epiphyseal centers for carpal bones and delay in the eruption of teeth are useful diagnostic features to diagnose florid cretinism but for best results the diagnosis should be made much earlier with biochemical tests as early as possible in the child's life: Delay in diagnosis of even mild hypothyroidism in infancy leads to permanent impairment of the cognitive faculties in the child even though other functions may recover to varying degrees.

Treatment of Cretinism

The development of normal mental function in cretinism depends almost solely on the institution of treatment early in the neonatal period. Any delay in starting thyroid hormone replacement will lead to permanent disability. Therefore, the need to make an early diagnosis cannot be overemphasized. The dose for infants is 10-15 $\mu\text{g}/\text{kg}$ daily—the average infant may require 50 $\mu\text{g}/\text{day}$ and this may go up to even 0.1-0.2 mg/day as the child grows. The child's growth and bone development should be monitored by regular clinical and radiological examination. Undetected congenital hypothyroidism is one of the most frequent causes of remediable mental retardation in later life.

Routine estimation of TSH T4, and T3 in neonates is undertaken in many centers to exclude neonatal hypothyroidism. As a screening test, estimation of TSH

alone is carried out at times. The prospect for normal mental development is poor if treatment is not started before the first few months of life.

Myxedema

Primary hypothyroidism occurring in juveniles and adults leads to myxedema. Hypothyroidism is one of the common endocrine disorders seen in India.

CLINICAL FEATURES

Clinical features depend upon the degree of impairment of thyroid function and its duration. The onset is insidious and often unnoticed by the patient or relatives. Early manifestations include slowing of activities, lethargy, somnolence, constipation and generalized disinterestedness. Due to lowering of metabolism and accumulation of fluid and adipose tissue, considerable weight gain occurs. The patient becomes intolerant to cold and patient prefers to sit in the sun or near the fire. The hair is coarse, dry, and sparse. The scalp and eyebrows may become bald. The skin is lusterless, thick, and dry with scanty hair. Puffiness, coarseness and skin thickening are due to deposition of glucosaminoglycan. This is a diagnostic feature in a well developed case. The voice is croaky due to thickening of the vocal cords. Generalized non-pitting edema is common. Many show periorbital edema and macroglossia (Fig. 98.4).

Neurological features predominate in many cases.

Common presentations are slowness of mental and physical activity, slowed speech, muscle cramps, muscle hypertrophy, paresthesia and entrapment neuropathies.

Carpal tunnel syndrome is common. The tendon reflexes are altered. The relaxation phase is delayed. This abnormality is best seen in the ankle jerk. Nerve conduction velocity is reduced. Psychiatric disturbances (**myxedema madness**) are common. Unless treated early, severe cases go into somnolence, stupor, and coma.



Fig. 98.4: Myxedema: Male aged 50

Myxedema coma is precipitated by exposure to cold, infections, trauma or sedatives. Hypothermia and respiratory depression may develop. Sleep apnea may occur at times. **Myxedema coma** carries a high mortality rate.

Cerebellar dysfunction may develop, manifesting as truncal or limb ataxia and intention tremor. Unless hypothyroidism is kept in mind, these cases may be missed.

Cardiovascular manifestations include cardiomegaly, pericardial effusion, angina pectoris, mild or moderate hypertension, and predisposition to ischemic heart disease due to dyslipidemia. Cardiac failure is not uncommon.

Abnormalities of sexual function: Impotence occurs in men. Women may develop menorrhagia and girls may attain precocious puberty.

Hoffmann's syndrome: Muscle dysfunction is common in hypothyroidism. Hypertrophy of muscles associated with pseudomyotonia (slowness of contraction and relaxation) are features diagnostic of Hoffman's syndrome. Calf muscles are affected very frequently.

Pendred's syndrome: In this congenital condition, there is permanent deafness or deaf-mutism in addition to goitrous hypothyroidism. The defect is a block in the synthesis of thyroid hormone.

Laboratory Investigations

1. Both total and free serum T₃, and T₄, levels are low.
2. The TSH level is very high in primary hypothyroidism. Raised TSH level is the most readily available indicator for primary hypothyroidism. Levels of TSH above 20 mU/L and lowered levels of T₄ are virtually diagnostic. T₃ levels may be unreliable. TSH is low in pituitary or hypothalamic hypothyroidism. In hypothalamic hypothyroidism administration of TRH leads to the production of TSH and increase in T₄ and T₃ levels. Normal serum TSH is 0.4 to 4.0 μ U/L. TSH may be elevated in adrenal cortical (glucocorticoid) deficiency, renal failure and exposure to cold without hypothyroidism.
3. ¹³¹I uptake by the thyroid is low
4. Immunological markers: Titers of antithyroglobulin and antimicrosomal antibodies (TPO) are high, especially if the disease is of autoimmune origin. Antithyroid peroxidase antibodies are more consistently elevated.
5. Serum cholesterol level is raised above 300 mg/dL in many cases of myxedema. In pituitary hypothyroidism the cholesterol level is normal.
6. Creatine phosphokinase level is increased.
7. ECG shows slow rate, low voltage and ST and T wave changes.

The basal metabolic rate (BMR) is low. Since low BMR occurs in many other conditions, this finding is not specific and hence not used as a diagnostic test at present.

Diagnosis

Hypothyroidism should be suspected in all cases of rapid increase in weight without obvious edema, slowing of activity, tendency to fall asleep often, hoarseness of voice, recent onset of constipation and psychiatric disturbances, especially depression. Uncommon presentations include vague aches and pains, non-articular rheumatism, neurological phenomena such as carpal tunnel syndrome and cerebellar disturbances.

The clinical suspicion of hypothyroidism should be strong in all infants and children who fail to thrive and in whom milestones of development are delayed. Since hypothyroidism is a common cause of growth retardation in many communities in India, even a therapeutic trial with 0.05 mg thyroxine will not be out of place in areas where access to specialized endocrinology services are not available.

Differential Diagnosis

Myxedema has to be distinguished from other causes of edema such as nephrotic syndrome and chronic congestive cardiac failure.

Obesity due to any cause may mimic hypothyroidism. In many cases of obesity sub-clinical thyroid dysfunction may co-exist.

Secondary hypothyroidism which is caused by hypopituitarism is to be distinguished from primary hypothyroidism. In the former there is no myxedema, the skin is fine and hair is silky. There is no cardiomegaly. Evidence of hypo-adrenalcorticism and hypogonadism may be present in varying degrees. Diagnosis is established by estimating the level of TSH in serum, which is low in secondary hypothyroidism, and typically high in primary hypothyroidism. T3 and T4 are low. Functions of the adrenal cortex and gonads may also be affected frequently.

Course and Prognosis

The course of hypothyroidism is slowly progressive with fluctuations in thyroid function. Myxedema coma, ischemic heart disease or cardiac failure may prove fatal in some. Myxedema promptly responds to replacement therapy, but the condition recurs on cessation of medication. *Delay in instituting treatment in children results in permanent retardation of mental faculties, even though the physical and sexual characteristics may recover to variable extent with medication.*

Treatment

The principle of therapy is life-long replacement of thyroid hormone so as to produce full clinical remission and

achieve normal biochemical parameters as far as possible. Replacement therapy is started with synthetic **levothyroxine sodium (T4)**, available as 0.05 and 0.1 mg tablets given orally once or twice a day as required. The drug is freely available, cheap and free from serious side effects and very satisfactory for prolonged use. **Tri-iodothyronine (T3)** is available as tablets containing 25 µg. It is more rapid in action and, therefore, employed in emergency situations like myxedema coma.

Dosage Thyroxine is given in a dose of 1.6 µg/kg in adults orally as single daily doses. Average daily dose for adults is 0.1-0.2 mg of L- thyroxine sodium. T4 should be preferred for treatment of an ordinary case. T4 and T3 are available both for oral and parenteral use. In complicated myxedema, monitoring of treatment can be done by clinical assessment and TSH levels which should be kept at the lower levels of normal. When treating children, biochemical monitoring is necessary to achieve full success, whereas in the case of adults clinical assessment is adequate in most cases. But in those with co-existing lipid abnormalities, more meticulous correction of the hypothyroid state is beneficial. Failure to achieve full improvement with thyroxine supplementation should raise suspicion about concomitant diseases such as hypoadrenal corticism.

Since myxedema tends to be permanent, thyroid supplementation has to be life-long. With effective treatment the clinical abnormalities subside within 4-6 weeks, but they promptly return within weeks to months on stopping therapy. During periods of other intercurrent illness and other forms of stress thyroxine supplementation should not be interrupted.

In elderly subjects, due to the presence of co-existent ischemic heart disease, overdose of thyroxine may precipitate angina. It is essential to exclude ischemic heart disease by ECG before starting therapy. In the presence of ischemic heart disease the initial dose of thyroxine should be smaller and the optimum dosage has to be worked up. Hypothyroid subjects are very sensitive to exogenously administered thyroxine. Concurrent administration of beta blockers in doses which reduce the heart rate helps to avoid angina. The optimum dosage has to be worked out.

Overdose may lead to hyperthyroid symptoms.

Treatment of myxedema coma: Treatment of myxedema coma is a medical emergency. Coma is the result of a combination of factors such as heart failure, cerebral ischemia, hypothermia, and hypothyroidism.

The patient should be hospitalized. The drug of choice is tri-iodothyronine (T3) given IV in a dose of 20 µg stat and repeated 4 hours later. At present parenteral preparation of levothyroxine sodium is also available for use. The dose is 500 µg IV stat and thereafter, 100 µg/day. Hydrocortisone should be given along with thyroxine

replacement, in order to prevent hypoadrenal crisis and to help recovery from shock. The dose is 100 mg IV, 3-4 times a day. Dexamethasone 2 mg IV 6 h is a suitable alternative.

Supportive measures include gradual warm up of the patient, intravenous glucose drips, maintenance of proper ventilation and treatment of coexisting infections. Myxedema coma is a condition associated with high mortality and therefore best results are obtained if treatment is undertaken in well-equipped centers. If parenteral preparations of thyroxine are not available, administration of thyroxine through a nasogastric tube in doses of 0.1 mg three or four times a day is advised till the coma clears, and thereafter the dose is modified suitably.

Thyroid Hormone Resistance Syndrome (THRS)

This was first described in 1967. It is defined as an impaired response of the target tissues to thyroid hormone despite increased levels of T3 and T4, with normal TSH levels usually. These patients often present with symptoms of hypothyroidism. About 90% of THRS result from mutations in the gene encoding TR-B and mutant receptors have reduced affinity for T3 and are functionally deficient. Pattern of inheritance is autosomal dominant.

Three types have been described.

1. Generalised resistance to thyroid hormone by all tissues including the pituitary
2. Pituitary resistance to inhibition by thyroid hormone. TSH may be normal or increased in this type. Such patients may show thyrotoxic symptoms.
3. Selective peripheral tissue resistance to circulating thyroid hormone. They are clinically hypothyroid but T3, T4 and TSH levels are normal.

Treatment is difficult because thyroid hormone analogues designed to suppress TSH and relieve the hypothyroid symptoms lead to worsening of the cardiovascular manifestations.

All these patients may respond better to analogues of thyroxine. Patients with selective pituitary resistance may respond to dextrothyroxine or 3,5,3 tri-iodothyroacetic acid (TRIAC). It may be that a higher circulating concentration may initiate some degree of receptor binding to T4. Analogues of thyroid hormone with TR-B may eventually prove useful in treatment.

Ocreotide and bromocriptine are also used to suppress TSH secretion in patients with high TSH.

Thyroiditis

Acute Suppurative Thyroiditis

(Syn: Acute bacterial or pyogenic thyroiditis)

In general, the thyroid gland is resistant to suppuration on account of (1) its capsule (2) rich blood supply,

(3) rich lymphatic supply and (4) high iodine content. Pre-existing thyroid disease may predispose to suppuration.

Acute suppurative thyroiditis is caused by direct invasion by *pneumococcus*, *Staph. aureus* or *Str. hemolyticus*. Local symptoms include painful enlargement of the thyroid with other signs of acute inflammation. Clinical examination and ultrasonography will confirm the diagnosis. Systemic manifestations include fever and leucocytosis. Treatment is with appropriate antibiotics, sometimes requiring incision and drainage.

Subacute Thyroiditis

Mainly three forms are known:

1. Granulomatous thyroiditis
2. Lymphocytic thyroiditis, and
3. Postpartum thyroiditis

Chronic Thyroiditis

- a. Hashimoto's diseases, syn: Struma lymphomatosa
- b. Riedel's thyroiditis also known as Riedel's struma.

Subacute Granulomatous Thyroiditis

Syn: Giant cell thyroiditis, de Quervain's thyroiditis

It may follow an episode of upper respiratory infection. **Subacute granulomatous thyroiditis** is most probably viral in origin caused by Coxsackie, mumps or adenoviruses.

This is painful and the pain radiates to the mandible, neck or the ears. Low grade fever, myalgia and dysphagia may be present. 50% of patients show hyperthyroid features. The thyroid is tender, firm and asymmetrically enlarged. The ESR is elevated.

T4 and T3 levels are elevated, but radioactive iodine uptake is low. Antiviral antibodies may be demonstrable. Mainstay of treatment is to use analgesics and corticosteroids.

Initial dose of prednisolone is 10-20 mg tid for a few days, soon tapered off as a maintenance dose.

In the present AIDS era, *Pneumocystis carinii* thyroiditis which may occur in association with pneumocystis pneumonia has to be borne in mind.

Subacute Lymphocytic Thyroiditis or Painless Thyroiditis

Subacute lymphocytic thyroiditis is also known as silent or painless thyroiditis. This is characterised by an abrupt onset of hyperthyroidism, elevated T3 and T4 levels, low radioactive iodine uptake and a painless non-tender goiter. Autoimmunity is considered to be the cause and there is a high prevalence of thyroid autoantibodies in these patients. Viral antibodies are absent.

Since the hyperthyroidism is transient in both of these types, only beta-blockers are required to control hyperthyroid symptoms. Antithyroid drugs are not given.

Postpartum Thyroiditis

Thyroid dysfunction occurring within the first 6 months postpartum is called *postpartum thyroiditis* (PPT). The prevalence varies from 5-7%. PPT develops in 30-50% of women who have TPO antibodies. Most of the patients go into complete remission. PPT is twice as common in patients with type 1 diabetes mellitus and other autoimmune disorders compared to normals. Thyroid gland is enlarged and painless in the majority of cases, with elevated levels of T3/T4. Histology shows lymphocytic infiltration. Sometimes overt thyrotoxic symptoms develop. More than 80% of patients recover thyroid function within an year. Recurrence in subsequent pregnancies is common.

Unlike as in postpartum Graves' disease ^{131}I uptake is low in this condition.

Management

Thyrotoxic symptoms may have to be treated with beta adrenergic blockers. Later if hypothyroid symptoms develop, thyroxine has to be supplemented.

CHRONIC THYROIDITIS

Chronic Lymphocytic Thyroiditis

Syn: Hashimoto's disease-Autoimmune thyroiditis

Hashimoto's disease is an autoimmune disorder which has close relationship with Graves' disease. Autoimmune diseases like Sjögren's syndrome, pernicious anemia, myasthenia gravis and rheumatoid arthritis may co-exist. Other associations include MEN type II, POEMS syndrome, Turner's syndrome, Down's syndrome and Addison's disease. The peak incidence occurs in the fourth and fifth decades of life. Females are affected more than males.

The thyroid is diffusely enlarged, lobulated, firm or hard in consistency, and painless. More commonly it is associated with hypothyroidism. Rarely thyrotoxicosis may occur in Hashimoto's disease (**Hashitoxicosis**). The thyroid is infiltrated with lymphocytes. Large hyperplastic lymphoid follicles with germinal centers may be present. The thyroid cells tend to be slightly larger and have an acidophilic staining character (Hurthle or Askanazy cells).

The follicles contain very little colloid. Varying degrees of fibrosis may occur.

Most characteristic laboratory feature is the presence of high titers of circulating antibodies which include *anti-thyroglobulin antibodies* and *anti-microsomal antibodies*. Asymptomatic relatives of the patients may show low titers of the antibodies. Erythrocyte sedimentation rate is markedly elevated and serum gamma globulin is high.

Course: The condition may persist as such for many years. As a sequel, hypothyroidism may develop in many cases.

Treatment

Long-term suppressive medication with T4 in a dose of 0.1 - 0.2 mg daily leads to rapid resolution of the goiter.

Riedel's Thyroiditis

Syn: Fibrous thyroiditis; Woody Thyroiditis

This is extremely rare. The patients present with pressure symptoms due to the enlarged thyroid gland which is hard and immobile. 25% of patients may have hypothyroidism. Treatment is surgical removal.

Sick Euthyroid Syndrome

Trauma, stress and severe illness may induce alterations in the production, transport and metabolism of thyroid hormones especially the peripheral conversion of T4 to T3. The regulation of TSH secretion also becomes altered. These manifest as abnormalities of the serum levels of both bound and free T4, T3 and TSH. This condition is known as sick-euthyroid syndrome. The most consistent features are the low levels of T3 in the serum, with decreased, normal or elevated T4.

Different functional abnormalities may be encountered. Correction of the primary disorder helps to correct the thyroid dysfunction as well. The importance of recognizing this condition is to differentiate it from primary thyroid disorders.

Solitary Thyroid Nodule

Many patients may present with solitary thyroid nodule which demands investigation and appropriate management. Thyroid nodules may be solid or cystic. True solitary nodules may occur in 4 to 7% of the adult population.

Generally, functioning adenomas tend to be benign, whereas the chance of malignancy is more in the case of non-functioning nodules, often referred to as *cold nodules*, by isotope scanning. The problem is to distinguish benign lesions from malignant ones and to assess the functional status of the nodule. Clinical examination should include careful local examination of the thyroid, cervical lymph nodes, evidence for pressure effects on cervical structures, and mediastinal obstruction. Thyroid nodules occurring after irradiation of the neck may be papillary adenocarcinomas. Physical findings suggestive of malignancy include a firm or hard non-tender nodule, a recent history of mild or moderate enlargement, fixation to adjacent tissues and the presence of regional lymphadenopathy. Rapid painful enlargement occurring within days or weeks is suggestive more of hemorrhage into a nodule rather than malignancy.

Investigations should include ultrasonography, ^{131}I scintiscanning and fine-needle aspiration cytology (FNAC).

Solid nodules detected by ultrasonography are more likely to be malignant than cystic lesions. FNAC gives histological diagnosis in most of the cases. In case of doubt open biopsy of the nodule is required.

In order to distinguish whether a hyperfunctioning nodule is autonomous or thyrotropin dependent, tri-iodothyronine in a dose of 25 µg t.d.s is administered for five days and scintiscanning is repeated. Autonomous nodules are not suppressed.

Thyroid peroxidase cyto-immunochemistry with a monoclonal antibody (MOAb47) significantly increases the accuracy of FNAC in follicular lesions.

Treatment

The management of a solitary nodule is still a matter of controversy. Early surgery is recommended for solitary cold nodules and hard rapidly growing nodules. For normally functioning and non-autonomous nodules, a course of thyroid hormone 0.3 mg/day is given and in many cases the nodule may reduce in size. Thyroid hormone is of no use in the treatment of autonomous hyperfunctioning nodules. Such nodules can be irradiated with ¹³¹I given preferably after a course of T3 / T4 for 5 days. T3 suppresses iodine uptake by the normal tissue and thus ¹³¹I gets concentrated only in the autonomous nodule.

Autonomous thyroid adenomas may respond to local repeated injection of ethanol (0.4-2 mL) under ultrasonic guidance. Repeated injections may be necessary. Cystic nodular lesions require repeated aspiration followed by injection of sclerosing agents like tetracycline diluted in normal saline (100 mg/mL). Subcutaneous leakage may produce pain. Surgical removal is necessary if other measures fail.

Tumours of the Thyroid

Thyroid may be the seat of benign or malignant neoplasms. Most of the malignant tumours are primary, rarely metastases from the kidneys, breasts, and lungs may occur. Benign tumours are adenomas. Carcinomas are less common. They may be differentiated or undifferentiated. Irradiation to the tonsils, thymus, lungs or cervical lymph nodes during childhood may predispose to carcinoma of thyroid after a latent period of 10-20 years. Therapy with ¹³¹I has not been associated with increase in thyroid carcinoma, but follow-up of children in Marshall's islands where atomic bombs were tested and in the vicinity of the Chernobyl accident, external irradiation has been found to increase the incidence of papillary adenocarcinoma of the thyroid. Rarely thyroid may be the seat of lymphoma or sarcoma. The frequency of thyroid cancer is higher in females. It varies from 0.92-1.99% of cases in males and 0.9 to 5.71% in females. The highest

TABLE 98.5		
Data from Regional Cancer Center, Trivandrum on carcinoma thyroid		
Papillary Ca	–	65%
Follicular Ca	–	24%
Anaplastic Ca	–	5%
Medullary Ca	–	6%
Ref: Poulose K.P, Personal observation, on 350 patients seen between 1990 and 1994.		

TABLE 98.6	
The different types of MEN	
Multiple endocrine neoplasia (MEN)	
I.	Tumours of ant. pituitary, adrenal cortex, parathyroid, pancreas
II a.	Tumours of adrenal medulla, parathyroid, medullary Ca. thyroid
II b.	Tumours of adrenal medulla, medullary Ca. thyroid, neurinomas

frequency in India is observed in Kerala State as compared to other states according to a publication of the National Cancer Registry Programme instituted by the ICMR (Tables 98.5 and 98.6).

85% of thyroid cancers in children are papillary type. The peak incidence of anaplastic carcinoma is in the 7th decade and it is characterized by rapid growth of tumour. Lymphomas of the thyroid gland can also occur, and almost always associated with Hashimoto's disease.

Treatment is by total thyroidectomy followed by ¹³¹I. This isotope has no role in the treatment of anaplastic carcinoma. In cases of thyroid cancer the five year survival rate is above 80%. Although the incidence of some forms of thyroid cancer is related to radiation, studies in Kerala did not show any relationship of thyroid cancer to the higher background irradiation from the monazite sands of Kerala sea shores.

Medullary carcinoma of thyroid: Around 10-15% of malignant lesions of the thyroid are medullary carcinomas. The disease may be familial. Relatives of patients may show elevation of serum calcitonin levels, if they are harbouring latent tumours. Medullary carcinoma arises from the 'C' cells or parafollicular cells. Metastasis is common. Elevation of serum calcitonin level is diagnostic in the presence of a palpable thyroid nodule. Medullary carcinoma may secrete serotonin, prostaglandins and even ACTH. Such cases are associated with flushing and diarrhea.

Medullary carcinoma may co-exist with other endocrine tumours multiple endocrine neoplasia (MEN) such as bilateral pheochromocytoma and hyperparathyroidism (MEN IIa and IIb).

Treatment consists of surgical removal of the carcinoma. Medullary carcinoma does not respond to ¹³¹I therapy.

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Parathyroids and their Disorders

K.P. Poulse, B. Jayakumar

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General Considerations

Collip identified the active principle of the parathyroid glands in 1924. There are two superior and two inferior parathyroids together weighing 120 mg. The superior parathyroids develop along with the thyroid and the inferior parathyroids develop along with the thymus. Twigs from the superior and inferior thyroid arteries supply the parathyroids. Aberrant parathyroids may be seen at the tracheoesophageal groove, substance of the thyroid gland or thymus, retroesophageal space, anterior mediastinum, surface of the pericardium, carotid bifurcation, jugular foramen or pharyngeal mucosa. The parenchyma consists of chief cells arranged in trabecular, alveolar or acinar patterns with mature fat cells interspersed. Parathyroid hormone (PTH) is secreted by chief cells. In addition the glands contain large polyhedral oxyphil cells with bright eosinophilic cytoplasm which appear after puberty. Pre and pro-parathyroid hormones are precursors formed during the synthesis of PTH.

Parathyroid hormone (parathormone): This is a single chain polypeptide having 84 amino acids. Parathyroid hormone is secreted as a pre-pro-hormone with 115 amino acid residues in the endoplasmic reticulum. It is converted into a prohormone containing 90 amino acid residues. The active hormone contains 84 amino acid residues. In circulation PTH is metabolised to biologically inactive fragments. The circulating PTH is a mixture of polypeptide chains of different biological activity. Therefore the biological activity does not correlate strictly

with the total levels of PTH. The secretion of PTH is controlled by several factors. Circulating ionised calcium exerts the major control on PTH secretion and release. Fall in ionised serum calcium stimulates, and rise inhibits PTH secretion. This reciprocal relationship is maintained as long as the serum calcium level ranges between 7 and 15 mg/dL (1.74 to 3.75 mmol/L; 1 mmol/L Ca = 4 mg/dL). Rise in serum phosphate stimulates PTH secretion indirectly by decreasing calcium levels. Extracellular magnesium concentration can also influence secretion of PTH. The half-life of PTH is less than 2 minutes.

Ninety-nine percent of total body calcium remains as hydroxyapatite in bones. In the plasma 50% of the circulating calcium is in ionised form (i.e. free calcium), 40% is protein bound and 10% is complexed with citrate and phosphate ions. Calcium and phosphorus constitute 65% of the weight of bones. Hypoalbuminemia is the commonest cause of hypocalcemia. Therefore it is necessary to estimate the levels of serum albumin along with serum calcium levels before a diagnosis of hypocalcemia is made.

Calcium homeostasis: Normal calcium concentration is essential for bone formation, blood coagulation, cardiac contractility, neural function and secretory activities. Calcium stabilizes biological membranes and serves as a co-factor in cellular reactions. The plasma calcium level is maintained within a narrow range of 9-11 mg/dL.

Actions of PTH: The ultimate effect of this hormone is to conserve body calcium and increase its level in extracellular fluid. It exerts its influence in several ways. The action is receptor mediated.

1. Parathyroid hormone increases calcium resorption from bone, and raises serum calcium.
2. It increases tubular reabsorption of calcium.
3. It increases absorption of calcium from the intestine.
4. It increases the renal excretion of phosphate and hydroxyproline, resulting in decreased plasma phosphate.
5. It enhances the formation of 1,25 (OH)₂D₃ (calcitriol) in the kidneys.

- 6. It increases the secretion of acid and pepsin in the stomach.
- 7. It activates the cyclic AMP-adenyl cyclase system in its target cells (PTH receptors in kidney, osteoblasts and intestines).

PTH acts on bones to modulate both osteoblastic and osteoclastic activity, thereby controlling both formation and resorption. PTH acts on bone to modulate osteoblastic activity directly, and osteoclastic activity indirectly. Only the osteoblasts have receptors for PTH. Indirect activity on the osteoclasts is brought about by releasing cytokines which activate the osteoclasts to increase bone resorption. PTH does not have any direct effect on the intestine. With excess of PTH levels as in hyperparathyroidism bone remodelling is increased and there is increased release of calcium resulting in hypercalcemia. Enhanced absorption of calcium and phosphate is due to increase in the levels of 1,25 (OH)₂ D₃ caused by increased formation of 1,25 (OH)₂ D₃ by the renal tubules under the action of PTH.

The net effect on bones depends on factors such as the bone involved, the dose of PTH and the duration of exposure. In small doses osteoblastic activity is promoted. Higher levels of parathyroid hormone result in increased osteoclastic activity in bone, inhibition of collagen formation by osteoblasts, and accelerated osteolysis. The net result is the resorption of bone with release of calcium, products of collagen breakdown and alkaline phosphatase into bloodstream. Kidney tubules possess PTH receptors. Parathyroid hormone acts on the kidneys to conserve calcium and eliminate phosphate, bicarbonate, and sodium. The net effect on bone depends on the complex interplay of PTH, vitamin D and renal function (Tables 99.1 and 99.2).

Tests of Parathyroid Function

Biochemical Studies

Serum calcium: In normal adults the total serum calcium level is maintained between 9 and 11 mg/dL, regardless of the intake. As age advances, serum calcium level

TABLE 99.1	
Showing the main actions of PTH	
1.	Increases bone resorption - Serum calcium increased
2.	Increases calcium reabsorption from distal nephrons—urinary calcium decreased
3.	Inhibits phosphate reabsorption from proximal tubules—urinary phosphate increased
4.	Increases calcium absorption from gut indirectly by stimulating the production of 1,25 Vit D ₃ from kidneys
5.	Osteoblastic activity—increased in smaller dose and shorter duration
6.	Osteoclastic activity—increased in larger doses on prolonged exposure

TABLE 99.2		
The actions of PTH, Vitamin D and calcitonin		
	Serum Ca	Serum PO ₄
PTH	↑	↓
Vitamin D	↑	↑
Calcitonin	↓	↓
Calcium absorption		Not under PTH influence
50-60%	Proximal convoluted tubules	Not under PTH influence
20-30%	Henle's loop	Under PTH influence
15-20%	Cortical distal nephrons	

gradually falls in men but it increases in women. Several factors affect serum calcium level. These are serum protein concentration, pH of blood, postural variations, and the actions of PTH and vitamin D. While interpreting serum calcium values, all these factors have to be taken into account. Ionized calcium levels in plasma usually range from 4-5 mg/dL. When serum albumin levels rise above normal, serum calcium levels also rise at the rate of 0.8 mg/dL for every 1 g of albumin/dL. While collecting blood for calcium estimation venous stasis should be avoided (i.e.) blood should be collected from a free-flowing vein.

Serum phosphorus: In adults, the level of serum phosphate ranges from 2.5-4.8 mg/dL. The levels are higher in children (5.0 ± 1.6 mg/dL). Serum phosphate level shows marked diurnal variation. Several factors such as serum protein levels, calcium, renal function, age, sex, and diets rich in carbohydrates influence serum phosphate level. Blood has to be collected in the fasting state for phosphorus estimation. In hyperparathyroidism, serum phosphorus is low. 85% of body phosphate is in bones and 15% either in the inorganic or organic form is distributed in the intra- and extracellular compartments. Phosphate is an integral part of nucleic acids, ATP, phospholipids and creatinine phosphokinase.

Serum alkaline phosphatase: Total serum alkaline phosphatase, especially bone alkaline phosphatase reflects bone turnover in metabolic bone diseases. The normal adult value is 30-110 international units/litre (3-13 KA units/dL). The isoenzyme bone alkaline phosphatase is elevated in osteoclast overactivity.

Parathyroid hormone (PTH) levels in serum can be estimated by RIA. In hyperparathyroidism PTH is elevated and in hypoparathyroidism it is reduced. Parathyroid hormone levels estimated by RIA may not reflect true biological activity since a part of the estimated hormone may not be biologically active. It is more advantageous to estimate PTH and ionised calcium simultaneously. Presence of high levels of PTH along with high calcium levels suggests abnormality of control mechanisms. Elevated PTH levels in the presence of low calcium levels

suggest pseudohypoparathyroidism. In magnesium deficiency also PTH levels are low.

Serum vitamin D: In healthy subjects, total vitamin D level is 35.0 ± 3.4 ng/mL, 25 OHD₃ is 28.5 ± 2.0 ng/mL and 1,25 (OH)₂D₃ is 35.0 ± 3 pg/mL. In hypoparathyroidism and chronic renal failure, circulating levels of 1,25 OHD₃ are low. Dietary intake of calcium and phosphate also influences serum vitamin D levels.

Serum electrolytes: Since PTH inhibits the tubular absorption of bicarbonate it may lead to renal tubular acidosis. Hypercalcemia of primary hyperparathyroidism is often associated with hyperchloremic acidosis. This feature helps to distinguish primary hyperparathyroidism from hypercalcemia occurring in bony metastases or hypervitaminosis D in which there is mild alkalosis.

Urinary calcium: In health more than 95.0% of filtered calcium is reabsorbed by the tubules. If the intake of calcium is steady, urinary loss of calcium is less than 3-4 mg/kg of ideal body weight in 24 hours. In hyperparathyroidism, with sustained hypercalcemia, the daily urinary loss of calcium exceeds 300 mg. This gives a positive *Sulkowitch test*.

Urinary phosphate: Parathyroid hormone facilitates the excretion of phosphates in urine. 88% of the filtered phosphate is reabsorbed in the proximal and distal tubules and only 12% is excreted. When the dietary intake of phosphates is 1-1.5 g/day, the daily urinary loss is less than 1 g. Dietary phosphate is mostly absorbed and it tends to raise serum phosphate level. The urinary excretion therefore varies directly with dietary intake. Normal phosphate clearance, determined by simultaneous measurement of urinary and serum phosphate is 10.8 ± 2.7 mL/minute. The tubular reabsorption of phosphates exceeds 75-85% of the filtered load. Tubular reabsorption is reduced in hyperparathyroidism and thereby phosphate clearance is increased at least by 50%.

Urinary hydroxyproline: Normal adults eliminate 15-42 mg of hydroxyproline in 24 hours. This is increased in hyperparathyroidism and osteomalacia. Other conditions in which urinary hydroxyproline is altered include growth spurt and bone resorption.

Urinary cyclic-AMP: Measurement of urinary c-AMP levels gives useful clues regarding parathyroid function. Normal adults excrete 10 micromoles of c-AMP in 24 h (1.8 to 4.5 nanomoles/dL of glomerular filtrate). In primary hyperparathyroidism, urinary c-AMP levels are high. Administration of PTH raises urinary c-AMP levels in normals. This response is absent in pseudohypoparathyroidism. Urinary c-AMP levels are elevated in hypercalcemia secondary to bony metastases.

Suppression tests: Tests to determine the suppressibility of PTH are employed to differentiate various hypercalcemic states from hyperparathyroidism.

Calcium infusion test: Calcium infusion suppresses normal parathyroid, but not autonomous parathyroid glands. Normally PTH level falls at the end of calcium infusion, 15 mg/kg body weight given over 4 hours and it remains low for 12 hours. Urinary phosphate excretion falls by more than 30% during the infusion.

Cortisone test: Oral administration of prednisolone in a dose of 30 mg/day for ten days suppresses serum calcium levels in non-parathyroid causes of hypercalcemia, but not in primary hyperparathyroidism. With the advent of newer imaging techniques, these suppression tests are seldom done.

Stimulation tests of parathyroid function: These tests are employed to distinguish hypoparathyroidism from pseudohypoparathyroidism.

Ellsworth-Howard test: Normal subjects respond to the administration of 200-400 USP units or 50-80 BPC units of PTH by increasing the urinary levels of phosphate and c-AMP by about 100%. Subjects with hypoparathyroidism show exaggerated increase in these parameters. In patients with pseudohypoparathyroidism, this response is blunted.

Indirect tests of parathyroid function include estimation of bone mineral density and isotopic bone scans.

1. **Estimation of bone mineral density** by radiography and dual energy X-ray absorptiometry (DEXA)
2. **Isotopic bone scans** using ^{99m}Technetium phosphate compounds.

Imaging the parathyroids: This can be done by subtraction techniques using ²⁰⁷Thallium chloride and ^{99m}Technetium pertechnetate radionuclides or imaging with ^{99m}Technetium sestamibi. Initial scan with Technetium delineates the thyroid. Thallium is taken up both by thyroid and parathyroids. Computerised subtraction techniques allow localization of parathyroids.

CT/MRI is also helpful. Selective venous blood sampling for PTH is also useful for localizing the source of abnormal function. Ultrasound neck is also helpful with a sensitivity of 80%.

Primary Hyperparathyroidism

When pathological hypersecretion of PTH occurs persistently, it results in hyperparathyroidism. It is characterized by hypercalcemia, hypophosphatemia, metabolic bone disease, recurrent nephrolithiasis, renal damage, peptic ulceration and other complications. Adult women are more affected than men. Peak incidence is in the sixth decade 2-3 times more in women. Rarely primary hyperparathyroidism may occur in neonates. A wide spectrum of severity ranging from an asymptomatic illness to fatal hypercalcemic crisis may be seen. Though hyperparathyroidism is one of the common endocrine disorders, many patients may remain asymptomatic.

Causes: The main causes are:

1. Benign adenoma of one parathyroid gland seen in 85% of cases.
2. Hyperplasia of all the parathyroid glands (15%) or
3. Carcinoma of one of the glands (1%).

In 85% of cases the lesion is an *adenoma* which may vary in weight from 0.5 to 5 g. Histologically, the adenoma is composed of chief cells in the vast majority, but at times oxyphil cells or mixed cells may predominate. Adenomas remain well-encapsulated within a rim of normal tissue. Ectopic foci for parathyroid adenomas include thymus, thyroid, pericardium or retroesophageal space.

About 15% of cases are due to diffuse or nodular hyperplasia affecting all or most of the parathyroid glands. *Carcinoma* is rare forming only about 1%. When present, it affects only one gland. The degree of malignancy is low. Adenoma or carcinoma may be part of the multiple endocrine neoplasia syndromes. MEN-1 (pituitary and pancreas) and MEN-11 (medullary carcinoma of thyroid and pheochromocytomas) are genetically mediated autosomal dominant disorders.

CLINICAL MANIFESTATIONS

Classic description of hyperparathyroidism is that it is a disease of bones, stones, abdominal groans and psychic moans. The presenting symptoms may vary depending on hypercalcemia, renal involvement, bone involvement or other complications. Sometimes a tumour may be palpable in the neck or visualized radiologically in the mediastinum.

Hypercalcemia: Hypercalcemia manifests in several ways. Common symptoms include lethargy, polyuria, polydipsia, drowsiness, confusion, weight loss, generalized muscle weakness, hypertension and autonomic dysfunction such as anorexia, uncontrolled vomiting and constipation. Proximal muscle weakness may be prominent. Severe cases go into stupor and coma. Long-standing hypercalcemia leads to metastatic calcification in the lungs, cornea, kidneys, blood vessels and other organs. The corneal lesion is *band keratopathy* in which calcium deposition is best demonstrated by slit lamp examination. Cardiac dysfunction occurs. Ventricular systole is shortened. Electrocardiogram shows shortened QT interval and other non-specific changes.

Skeletal manifestations: Osteitis fibrosa cystica or diffuse loss of bone tissue such as osteoporosis or osteomalacia may occur. Osteitis fibrosa cystica is accompanied by severe localized bone pain, marked deformities, and pathological fractures. In osteitis fibrosa, the bone trabeculae are reduced. There is increase in multinucleated osteoclasts and fibrovascular tissue. Radiological abnormalities of bone include subperiosteal erosion of cortical bone, demineralization, local destructive lesions such as cystic changes—(*bone cysts and brown tumours*) and calcification of fibrocartilage. The phalanges show

loss of bone tuft and subperiosteal erosions, and these are diagnostic. Acromioclavicular joints, symphysis pubis and sacroiliac joints also show similar changes. Osteopenia is seen characteristically as punched out and mottled areas in the skull (*pepper pot skull*). The lamina dura of the teeth is lost. Joints may show chondrocalcinosis and degenerative changes. With successful treatment of hyperparathyroidism all the radiological abnormalities clear up.

Renal manifestations: Nephrolithiasis, nephrocalcinosis, and disorders of glomerulotubular function are common in longstanding cases. Renal calculi are made up of a mixture of calcium oxalate and calcium phosphate. Renal stones tend to be recurrent. Hypercalcemia predisposes to urinary infection. Nephrocalcinosis is usually associated with bony changes such as osteitis fibrosa cystica. Glomerular filtration rate is reduced. Blood urea and serum creatinine are elevated. Tubular dysfunction also occurs. Correction of hypercalcemia reverses the functional defects in the kidneys.

Alimentary manifestations: Hypercalcemia increases gastric acid production and thus predisposes to peptic ulceration. Zollinger-Ellison syndrome may co-exist (multiple endocrine neoplasia type I). Hypercalcemia leads to chronic pancreatitis, pancreatic calcification or acute hemorrhagic pancreatitis.

Diagnosis

Primary hyperparathyroidism should be suspected in all cases of hypercalcemia, recurrent urinary calculi, osteitis fibrosa, peptic ulcer, pancreatitis, myopathy, chondrocalcinosis and vague constitutional symptoms. All cases presenting with dehydration, polydipsia, nocturia, anorexia, confusion, joint stiffness and hypertension, in which other causes are not evident, should also be investigated for primary hyperparathyroidism.

Biochemical tests: The diagnosis is confirmed by the presence of hypercalcemia and hypophosphatemia. Serum alkaline phosphatase and urinary hydroxyproline excretion are elevated. Urinary c-AMP excretion is elevated. Parathyroid hormone levels are elevated. Higher levels of 1.25 Vitamin D are also present.

Demonstration of tumour or hyperplasia: Large parathyroid tumours may produce indentation on the barium-filled esophagus, demonstrable by barium swallow examination. Ultrasonography, CT scan with contrast imaging and MRI demonstrate the lesion in most cases. Radioactive thallium technetium subtraction scanning may be employed to locate the tumour. Selective venous blood sampling from the neck and mediastinum to detect a gradient in PTH levels helps to assess the functional status of the lesion as well.

TABLE 99.3

Changes in blood levels of parathormone (PTH), serum calcium, phosphorus and creatinine in various parathyroid disorders

Diagnosis	PTH	Calcium	Phosphorus	Creatinine	Congenital abnormalities
Primary hyperparathyroidism	H	H	L	N	Nil
Secondary hyperparathyroidism	H	L/N	H	H	Nil
Tertiary hyperparathyroidism	H	H	H	H	Nil
Hypoparathyroidism	L	L	H	N	Nil
Pseudohypoparathyroidism	N/H	L	H	N	Present
Pseudopseudohypoparathyroidism	N	N	N	N	Present

Key: H: high, N: normal, L: low

Differential diagnosis: Primary hyperparathyroidism has to be distinguished from secondary hyperparathyroidism and all other causes of hypercalcemia. In secondary hyperparathyroidism, though PTH levels are high, serum calcium values are not elevated, but phosphate is elevated e.g. renal rickets.

Common causes of hypercalcemia are disseminated malignancy involving bone, hypervitaminosis D, thyrotoxicosis, Addison's disease and prolonged immobilisation. Rarely hypervitaminosis A, sarcoidosis, multiple myeloma and thiazide drugs may be the cause of hypercalcemia. Sometimes hypercalcemia runs in families (familial hypocalciuric hypercalcemia). This is due to an autosomal dominant mutation of calcium sensor that results in inappropriate secretion of PTH and enhanced renal calcium reabsorption. Idiopathic hypercalcemia is a rare disorder of infancy, often associated with congenital cardiovascular defects. Hypercalcemia of malignancy seen in bony metastasis and multiple myeloma is either due to local osteolytic lesions releasing cytokines like (IL6, and TNF β) which enhance bone reabsorption or due to release of PTH related polypeptide PTHrP which is a PTH like humoral factor (Table 99.3).

Prognosis

The course of hyperparathyroidism tends to be progressive. If detected and treated early, the condition subsides. Skeletal changes revert to normal but advanced renal lesions fail to clear up and, therefore, it is essential to start treatment before renal damage is established.

Treatment

Surgical removal of the adenoma is the treatment of choice. In the case of hyperplasia, all the glands are removed except for a portion of one gland which is left behind. All cases should be investigated for multiple endocrine

neoplasia and appropriate treatment is indicated if this is detected. Serum calcium level above 11 mg/dL, evidence of bone disease, recurrent renal stones, reduction of glomerular filtration rate below 60 mL/min and uncontrollable peptic ulcer are indications for early surgery.

After successful parathyroidectomy, the serum PTH falls by 50% within 10 minutes and the serum calcium falls to normal within 24-36 hours. This does not happen if surgical removal is inadequate. Some cases develop postoperative tetany due to hypocalcemia. This is managed by giving intravenous infusions of calcium gluconate or calcium chloride (1 mg/mL of fluid), the total dose and duration of therapy being decided by clinical progress. One ampoule of calcium gluconate contains 10 mL, each mL containing 137.5 mg of the drug. If hypocalcemia tends to persist, it is managed on the lines indicated for hypoparathyroidism.

At times magnesium deficiency may be the cause of postoperative tetany. Serum magnesium levels are low (normal values 0.7-1.2 mmol/L or 2-3 mg/dL). Mild cases respond to oral supplementation with magnesium chloride. In severe cases magnesium sulfate can be given intramuscularly repeatedly or as intravenous infusion lasting for 8-12 hours. The total dose is decided by the serum magnesium levels. A severe case may require 2 mmol/kg body weight. Magnesium sulphate is available as 20% solution or 50% solution. Parenteral magnesium therapy should be closely monitored, since serum levels above 4 mmol/litre lead to neuromuscular paralysis.

Medical treatment: Mild cases with moderate hypercalcemia, elderly patients, and those who are poor surgical risks have to be managed medically. In such cases the intake of calcium should be restricted to 200 mg or less by avoiding dairy products. Serum calcium can be lowered by the regular administration of potassium phosphate 1-2 g daily. The patient should be carefully followed up for

detecting metastatic calcification. Peptic ulceration should be managed on its own merits. Liberal intake of fluids (3.5-4.5 litres per day) and calcitonin injections at intervals help to reduce the risk of urinary calculi.

Acute Hypercalcemia and its Management

Normal serum calcium levels range around 2.6 mmol/L (10.4 mg/dL) when the serum albumin levels are normal, i.e. 4g/dL. Acute hypercalcemia usually results from hyperparathyroidism or disseminated secondaries in bones. Serum calcium levels above 3.5 mmol/L (14 mg/dL) lead to life-threatening situations demanding emergency management.

In hyperparathyroidism PTH is elevated. In bony secondaries PTH-related protein secreted by the tumour is elevated whereas PTH values are normal or reduced. Both PTH and PTH-related protein lead to resorption of bone by osteoclasts, increase in the renal tubular absorption of calcium and decrease in the reabsorption of sodium and water. As a result polyuria and dehydration develop. Clinical abnormalities are referable to gastrointestinal, cardiovascular, renal and central nervous systems.

Gastrointestinal symptoms	: Anorexia, nausea, vomiting, constipation and at times acute pancreatitis.
Cardiovascular system	: ECG abnormalities such as Q-T prolongation and increased sensitivity to digoxin.
Excretory system	: Polyuria, polydipsia, nephrocalcinosis and renal failure.
Central nervous system	: Apathy, drowsiness, confusion, coma.

Treatment

- 1. The patient is rehydrated by IV infusion of normal saline. Often 2.5-4 litres may be needed.
- 2. Frusemide given in a dose of 20-40 mg IV helps to increase urinary excretion of calcium. Thiazide diuretics are contraindicated since they enhance distal tubular absorption of calcium.

Drugs which Inhibit Osteoclast Activity

Calcitonin: Both salmon calcitonin and human calcitonin are available for use. Calcitonin is given in a dose of 4 MRC units/kg SC or I.M every 12 hours. It is rapid in action but weaker compared to bisphosphonates. If the response is inadequate the dose may be increased to 8 units/kg. Preparations for nasal spray IV and rectal use are also available.

Bisphosphonates: Etidronate, pamidronate and alendronate are available for use as oral or IV preparations.

Dosage:

Etidronate	7.5 mg/kg daily orally × 6 months
Pamidronate	15-45 mg I.V daily for 6 days
Alendronate	40 mg/day orally before food—10 mg tablets are available.

Other analogues such as ibandronate oral and zoledronate (IV) are also available at present. They also lower serum calcium levels. On a long-term basis they also suppress osteoclastic activity.

Mithramycin (Plicamycin) is given as IV infusion in a dose of 25 µg/kg over 4-6 hours. The serum calcium level starts falling within 12 hours of start of therapy and it continues to fall for 2-3 days. The effect of a single dose lasts for several days. Toxic side effects include nausea, thrombocytopenia and nephrotoxicity.

Sodium phosphate: This is given as IV infusion. Solution containing 11.5 g NaH₂PO₄ and 2.58 g KH₂PO₄/L is given IV as infusion in a volume of 500 mL over 4 hours. It reduces serum calcium level rapidly. Phosphate promotes the deposition of calcium in bones. Though it may be used in a life-threatening emergency, it is associated with adverse side effects.

Disodium acetate: Rapid IV infusion in a dose of 200 mg/kg over 30-60 minutes lowers serum calcium rapidly. Excessive dose should be avoided since it leads to hypocalcemia, tetany and coagulopathies.

Glucocorticoids: Hypercalcemia caused by lesions other than hyperparathyroidism temporarily responds to corticosteroids.

In life-threatening emergencies, calcium can be removed from the system by dialysis procedures using calcium free dialysing fluids.

Secondary and Tertiary Hyperparathyroidism

These are seen in conditions where there is resistance to the action of PTH. Increased levels of PTH are seen in the presence of persistent hypocalcemia. Increased secretion of PTH is the result of chronic stimulation by hypocalcemia.

Secondary hyperparathyroidism is seen in rickets, osteomalacia, malabsorption syndrome, chronic renal failure, and skeletal fluorosis. Removal of the primary cause early in the disease may correct the parathyroid dysfunction also but this is not invariably so. Though, in the initial stages the parathyroids are stimulated by hypocalcemia, later on, the glands become autonomous because of the development of adenomas. This condition is known as **tertiary hyperparathyroidism**.

Biochemical profile includes normal or low serum calcium with elevated serum phosphate. In tertiary hyperparathyroidism, serum calcium may rise. Bone changes are the result of excessive parathyroid activity and calcium deficiency. Serum alkaline phosphatase is high.

Therapy is intended to correct hypocalcemia which is the chronic stimulus for stimulation of the parathyroids. Surgical removal of the adenoma may be indicated in tertiary hyperparathyroidism.

Humoral Hypercalcemia of Malignancy

This refers to the condition in which PTH like substances (peptides or prostaglandins) are secreted by other tumours like carcinomas of the breast, kidneys, lungs and uterine cervix, lymphomas, and also leukemias. Often this leads to severe and fulminant hypercalcemia. Malignancies may also cause hypercalcemia by local bone destruction (e.g. myeloma, breast cancer) or by release of PTH related proteins (e.g. lung, kidneys, squamous cell cancers) or by activating lymphocytes to release interleukin 1 and tumour necrosis factor.

Hypoparathyroidism

Definition

Deficiency in the secretion of parathyroid hormone (PTH) leads to hypoparathyroidism. This is characterized by hypocalcemia, hyperphosphatemia and low levels of circulating PTH. The hyperphosphatemia leads to calcification of the basal ganglia in 50% of cases. Soft tissue calcification may also occur.

Etiology

1. Accidental surgical removal of parathyroids or interference with their blood supply during surgery in the neck.
2. Idiopathic atrophy of the parathyroids.
3. Destruction of the parathyroid by carcinomatous secondaries, infarction, radioiodine therapy or irradiation of the neck.
4. Neonatal hypoparathyroidism may occur as a transient phenomenon in premature infants and infants of mothers with hyperparathyroidism or diabetes mellitus.
5. Autoimmune hypoparathyroidism.
6. Developmental defects as in DiGeorge syndrome.
7. Rare causes- hemochromatosis, Wilson's disease with copper deposition in the parathyroids.
8. Hypomagnesemia.

Postoperative hypoparathyroidism may be transient or permanent. Idiopathic hypoparathyroidism may run in families. It may be associated with other congenital abnormalities involving maldevelopment of the third and fourth pharyngeal pouches such as **DiGeorge syndrome**

in which the thymus and parathyroids are absent. Other immune-mediated endocrinopathies such as Addison's disease, hypothyroidism, hypofunction of ovaries, and pernicious anemia may coexist. Antibodies against parathyroids and other organ specific antibodies may be present.

Clinical Manifestations

Clinical features depend upon the onset, duration and the severity of hypocalcemia. Prominent features include tetany, dental abnormalities, subcapsular cataracts, myocardial dysfunction and neurological abnormalities.

Tetany is due to hypocalcemia. It manifests as muscle cramps, paresthesia of the hands, feet and mouth, *spasmophilia* (*carpopedal spasm*, *bronchospasm* and *laryngospasm*) and severe neuromuscular irritability. Physical exertion, emotional stress, hyperventilation, vomiting, and ischemia to the limb may precipitate *tetany*. In less severe and chronic forms of hypocalcemia tetany may remain latent.

Latent tetany can be identified by eliciting the *Chvostek's sign*, *Trousseau's sign*, and also by *electromyography*. Hyperexcitability of the facial muscles manifesting as contraction of the facial muscles on gentle tapping over the facial nerve in front of the tragus of the ear is the *Chvostek's sign*. *Trousseau's sign* is elicited by making the forearm ischemic by applying a sphygmomanometer cuff to the arm and keeping the pressure above systolic blood pressure for five minutes. The hand goes into painful carpopedal spasm and assumes the *accoucheur's hand position*. Laryngeal spasm gives rise to inspiratory dyspnea or stridor (*laryngismus stridulus*).

Hypocalcemic tetany has to be differentiated from tetany occurring in alkalosis, hypokalemia and hypomagnesemia. When serum magnesium falls below 0.8 mmol/L PTH secretion is depressed and this leads to secondary hypoparathyroidism. Parenteral replacement of magnesium restores parathyroid function.

Common neurological manifestations of hypocalcemia include convulsions which are unresponsive to conventional anticonvulsant therapy, paresthesia and psychiatric behaviour. Other manifestations such as papilledema and extrapyramidal disturbances like chorea, parkinsonism, and athetosis may develop. Soft tissue and basal ganglia calcification can occur.

The skin is dry and scaly. The hair is brittle and coarse. Deformity and moniliasis of the nails are common. The enamel of the teeth is pitted, dental roots are short and blunt, and early loss of teeth is common. Subcapsular posterior or anterior zonular cataracts develop.

Cardiac abnormalities may occur. Chronic hypocalcemia may lead to cardiac failure and tetany. Diuretics further aggravate the hypocalcemia. The electrocardiogram shows prolonged QT interval. The acute manifestations of hypo-

parathyroidism are corrected dramatically by the intravenous administration of calcium. Intravenous administration of 10% calcium gluconate, calcitriol and oral maintenance doses of calcium gluconate restore cardiac function.

Diagnosis

Presence of hypocalcemia with hyperphosphatemia should arouse suspicion of hypoparathyroidism, if renal disease can be excluded. Other causes of hypocalcemia are rickets, malabsorption states, hypoproteinemia, acute pancreatitis, and extreme dietary deficiency of calcium. The total serum calcium is low in hypoproteinemia since the fraction bound to albumin is reduced, even though the ionized calcium is kept normal. Tetany does not occur in this condition. In acute pancreatitis transient hypocalcemia develops which is self-limiting. In rickets and osteomalacia both calcium and phosphorus are low. Diagnosis of hypoparathyroidism can be confirmed by demonstrating low levels or absence of PTH. The response to therapeutic administration of PTH is dramatic.

Pseudohypoparathyroidism (PSHP)

Syn: PTH resistance syndrome

The term *pseudohypoparathyroidism* refers to the condition in which the target tissues become resistant to the action of PTH. As a result, there is overactivity and hyperplasia of the parathyroids with excessive secretion of PTH. In spite of the raised blood levels of PTH, the clinical and biochemical features are those of hypoparathyroidism. In most cases it is an inherited disorder associated with short stature, brachydactyly, round face, obesity and webbing of the neck. Vitamin D deficiency, hypomagnesemia, chronic renal failure, and other renal tubular defects give rise to PTH resistance.

This is characterised by biochemical features of genuine hypoparathyroidism with elevated PTH levels. In the two major forms of this (Type 1 and Type II) disorder, correction of hypocalcemia results in alteration of symptoms and suppression of PTH levels, however the resistance continues. The common disorder PSHP type Ia is characterised by short stature, brachydactyly, round facies, obesity, short fourth metacarpal bone, webbing of the neck, mental retardation, and subcutaneous calcification. The term *Albright's hereditary osteodystrophy (AHO)* has been used to describe the somatic features of Type Ia. This is due to defective functioning of guanine nucleoside coupling protein (GS protein). These patients may also have resistance to other hormones like TSH, glucagons, LH and ADH. Diagnosis is made by estimation of GS protein in red cells. In Type Ib PSHP the somatic features of Type Ia are absent. Several other types of PSHP like Type II have been described.

Pseudopseudohypoparathyroidism Some of the relatives of subjects with pseudohypoparathyroidism show skeletal changes, but none of the biochemical abnormalities of hypoparathyroidism. This condition is called pseudopseudohypoparathyroidism.

Treatment of hypoparathyroidism Aim of treatment is to normalize serum calcium levels without increasing urinary loss. Though correction of hypocalcemia is easy, in the absence of PTH, considerably large amounts of calcium are lost in urine. Therefore, even with low-normal levels of serum calcium, nephrolithiasis may develop. Intestinal absorption of calcium can be enhanced by the administration of vitamin D. This corrects hypocalcemia, but not other metabolic abnormalities. It is desirable to keep serum calcium levels between 8.5 and 9 mg/dL by adjusting the dose of vitamin D. Several preparations are available. Vitamin D₂ 50,000 to 100,000 U/day or the metabolically active product 1-25(OH)₂ cholecalciferol (calcitriol) in doses of 0.25-0.5 µg given orally daily helps to improve serum calcium level. Result of vitamin D₃ therapy is not always predictable, since individual variations are common. Vitamin D preparations take a few weeks to exert their full effect. Loss of control may develop even after long periods of satisfactory control. Along with vitamin D₃, approximately 1.0 g of elemental calcium should be provided in the diet. This will be provided by 2.5 g calcium carbonate, 3g calcium chloride, 8 g calcium lactate or 11 g of calcium gluconate. Hypomagnesemia confers resistance to vitamin D which clears up on supplementation of magnesium orally or parenterally.

Treatment of tetany: Slow intravenous injection of 20 mL of 10% calcium gluconate solution promptly relieves tetany. The relief is maintained by giving an intravenous drip containing calcium gluconate 15 mg/kg body weight. Intravenous calcium injection is quite safe even though it may cause a feeling of heat over the body, which could be disturbing to the patient, unless informed beforehand. In subjects receiving digitalis therapy it may precipitate fatal arrhythmias like ventricular fibrillation. Supplementation of oral calcium carbonate or gluconate along with alpha calcidol serves to increase serum calcium on long term basis.

Alkalotic Tetany

In hysterical subjects who hyperventilate, alkalotic tetany may develop. Alkalosis enhances neuromuscular excitability. This can be prevented by the inhalation of 5% carbon dioxide or re-breathing into the same bag. For tetany due to metabolic alkalosis infusion of isotonic saline is the most effective measure. In alkalosis produced by the excessive administration of alkalis, relief is obtained by giving ammonium chloride orally in a dose of 2 g 6 h.

100

Disorders of the Adrenal Cortex and Adrenal Medulla

R.V. Jayakumar, A.G. Unnikrishnan,
K.P. Poulose**Chapter Summary**

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Introduction

The adrenal glands are two paired glands, which produce hormones necessary for metabolism as well as hemodynamic stability. Several disorders of the adrenals exist, and these range from autoimmune adrenal damage to neoplastic transformations of the glands.

Basic Considerations

Anatomy: The adrenals are paired glands each weighing about 4.7 g. Section of the gland shows an outer cortex and inner medulla. Histologically, three zones are visible in the cortex; the zona glomerulosa, zona fasciculata and zona reticularis from without inwards (Fig. 100.1). The arterial supply is derived from several branches of the phrenic, renal, ovarian or spermatic arteries and aorta. Venous drainage on the left is into the left renal vein and on the right to the inferior vena cava.

Embryology: The fetal adrenal cortex is formed during the fourth to sixth week of gestation from the celomic mesoderm of the posterior abdominal wall. The permanent adrenal cortex is formed from the small basophilic cells, which appear five weeks later. The adrenal medulla develops in the seventh week from sympathogonia that

migrate from the neural crest into the fetal adrenal cortex. The adrenals are relatively bigger at birth, but with the passage of time the size reduces since the inner zone of acidophilic cells undergo involution.

Physiology: Several hormones are produced by the adrenal cortex. The cortex synthesizes cholesterol and also takes cholesterol from the circulation for the production of its hormones. Synthesis of hormones takes place in several steps. The trophic hormone produced by the anterior pituitary-adrenocorticotrophic hormone (ACTH) stimulates the adrenal cortex to secrete hormones. Adrenal medulla secretes adrenaline and noradrenaline.

Adrenocorticotrophic hormone (ACTH) secreted by the anterior pituitary stimulates secretion of adrenal cortical hormones (glucocorticoids and sex hormones) by acting on specific receptors present on the adrenal cortex through the mechanism of c-AMP (Fig. 100.2).

Steroid hormone secretion, role of ACTH, transport and metabolism: The secretion of cortisol (the most physiologically important steroid hormone) occurs only in response to stimulation by ACTH. In health the levels of cortisol are highest in the morning. Plasma cortisol reciprocally influences adrenocorticotrophic hormone, i.e. higher cortisol levels inhibit and lower levels stimulate production of ACTH and also stimulate the melanocytes and activates tissue lipase. Within 2-3 hours of falling asleep the ACTH levels progressively rise and reach the highest level about an hour or so before waking up. During waking hours ACTH levels progressively fall to reach the minimum before falling asleep. The secretion of ACTH and cortisol is increased in response to different stress factors such as trauma, fever, surgery, hypoglycemia, severe anxiety, and several others. The circadian rhythm disappears during periods of stress and in adrenal tumors.

About 75% of cortisol circulates in blood bound to transcortin, which is a glycoprotein. 15% is loosely bound to albumin and 10% circulate in the free state unbound and the latter accounts for the metabolic activities of the hormone. When plasma cortisol level is high (e.g. Cushing's syndrome), plasma transcortin is saturated and

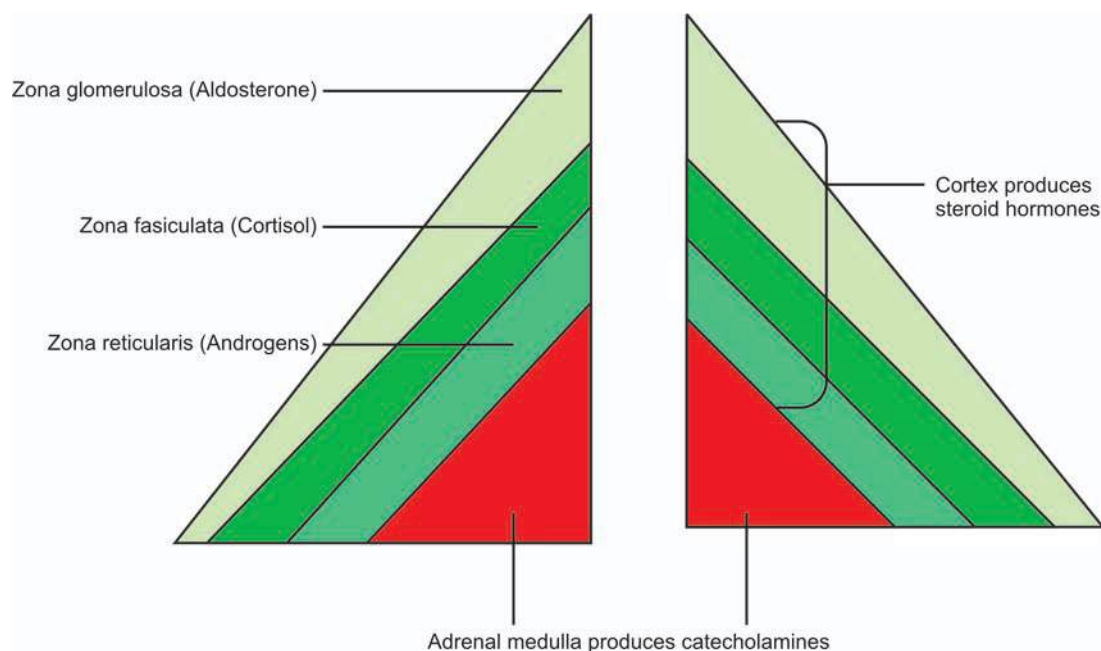


Fig. 100.1: A diagrammatic representation of the layers of the adrenal gland

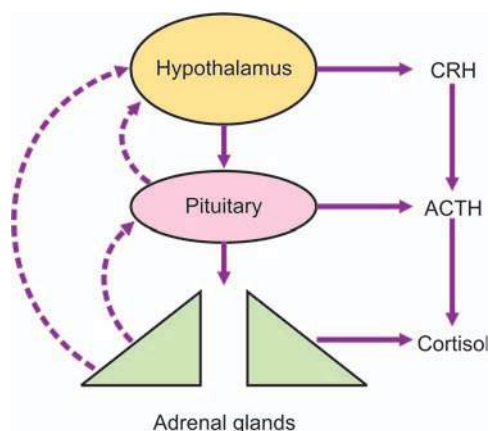


Fig. 100.2: Diagram showing the hypothalamic-pituitary axis controlling the adrenal gland. Note the feedback loops that exist; CRH-corticotrophin-releasing hormone, ACTH-adrenocorticotrophic hormone. Broken lines indicate negative feedback loops

the level of unbound cortisol increases. This appears in excessive amounts in urine. Steroid hormones are inactivated mainly in the liver. Other tissues such as muscles, skin, fibroblasts, intestine and lymphocytes also metabolize them.

ADRENAL CORTICAL HORMONES

Based on their main functional activity, cortical hormones can be grouped as glucocorticoids, mineralocorticoids, and sex hormones (androgens and estrogens). Glucocorticoids are secreted by zona fasciculata, mineralocorticoids by zona glomerulosa and sex hormones by zona reticularis

TABLE 100.1

Secretory rates of adrenal cortical hormones

Adrenal cortical hormones	Secretory rate in mg/24 h
Cortisol (hydrocortisone)	12-30
Corticosterone	1-4
Aldosterone	0.05-0.15
Deoxycorticosterone	0.05-0.2
Dehydroepiandrosterone	15-50

(Table 100.1 and Fig. 100.2). The adrenal medulla produces the catecholamines, adrenaline and noradrenaline.

Glucocorticoids: The important members of this group are cortisol (hydrocortisone), corticosterone and 11-dehydrocorticosterone. Normal cortisol level at 8 AM is 140-700 nmol/L (5-25 mcg/dL) and it falls to 0.8 mcg/dL at midnight, highest concentration is around 4 AM.

Glucocorticoids promote gluconeogenesis and lead to hyperglycemia. Other major effects include increase of protein catabolism, suppression of ACTH, anti-inflammatory and anti-allergic action, immunosuppressant effects and reduction in the size of circulating lymphocyte pool and lymphatic organs (lympholysis). In addition, glucocorticoids exert minor effects such as induction of several enzymes, stimulation of hematopoiesis, fat deposition over the trunk, uricosuria, elimination of water load, production of a feeling of well being, reduction in circulating eosinophils and maintenance of the capacity

for muscular work. Glucocorticoids are used therapeutically for replacement therapy and in many other conditions. Several synthetic analogues are available for therapeutic use.

Mineralocorticoids: Aldosterone is the most important member in this group, the other being deoxycorticosterone (DOC). These exert their main action on epithelial membranes of the skin, gastrointestinal tract and kidney. The main action is conservation of sodium and chloride and elimination of potassium. Excessive activity of these hormones causes retention of sodium and chloride, edema and potassium loss. Aldosterone secretion is stimulated by angiotensin II which is the final product of the renin angiotensin system initiated by the afferent arterioles of the renal glomeruli. ACTH does not exert any appreciable effect on the secretion of aldosterone.

Details of the rennin-angiotensin system are given in chapter 168.

All available preparations of adrenocortical hormones are synthetic products. Comparison of the potency of natural and synthetic corticosteroids (for equivalent dose) is given in Table 100.2. Betamethasone and dexamethasone differ structurally by a single methyl group and hence their pharmacological effects are also slightly different. Both have the same bioavailability. Betamethasone has a longer half-life and larger volume distribution.

Sex hormones: Adrenal cortex secretes sex steroids (both androgens and estrogens), which are small in amount compared to the secretion of gonads. Under normal conditions they play only a minor role in the development of secondary sex characters. When the secretion is increased under pathological conditions, they may produce virilization and less commonly feminization, which is more evident in the male. Adrenal estrogen-secreting tumours can lead to gynecomastia in males and precocious puberty in girls. In adult women, excessive secretion of adrenal androgens leads to amenorrhea, hirsutism and infertility.

TABLE 100.2

The relative potency of the different corticosteroid for mutations

Steroid preparation	Glucocorticoid activity	Mineralocorticoid activity
Cortisol (Hydrocortisone)	1	1
Cortisone	0.7	0.7
Aldosterone	0.3	300
Fludrocortisone	-	125
Prednisolone	4	0.25
Dexamethasone	25	< 0.1
Betamethasone	25	< 0.1
Triamcinolone/methyl prednisolone	5	< 0.1

Investigation of Adrenal Cortical Disorders

Serum Cortisol: This is the simplest examination, and can be carried out by radioimmunoassay (RIA). The test results depend on the time of sampling. Normally, serum cortisol levels are highest early in the day, and then decline over a period of time to reach a nadir in the late night. If measured at 8.00 am, the normal cortisol levels in the serum range from 5 to 25 µg/dL. However, if measured at 4.00 pm, the normal values would range from 2 to 8 µg/dL. At midnight, for instance, the serum cortisol levels are expected to be below 5 µg/dL. This circadian variability of normal cortisol values is useful in the diagnosis of states of cortisol excess, i.e. endogenous Cushing's syndrome. In this situation, there is a continuous, non-circadian production of cortisol from the adrenal glands and thus the evening cortisol value could be above normal, sometimes even higher than the morning cortisol value.

Urinary cortisol: Level of free cortisol excreted in urine depends on the plasma level of unbound cortisol. Normal range is 55-193 nmol (20-70 µg) in 24 h. This is a very sensitive test for the diagnosis of Cushing's syndrome in which the urinary cortisol is increased.

Aldosterone and its derivatives: Normal plasma concentration estimated by RIA is 10 ng/dL, and the urinary excretion is 5-19 µg/day.

Secretory activity of the adrenal cortex: Cortisol secretory rate can be determined isotopically. Normal value is 250-840 µmol/24 h (i.e.) 150-30 mg cortisol in 24 hours.

Other hormones: Dehydroepiandrosterone sulphate (DHEAS) can be estimated by RIA. The values of DHEAS are extremely high if there is a DHEAS-producing adrenal tumour. DHEAS estimation helps to differentiate androgen secretory tumour of adrenal from that of an ovarian tumour.

ACTH Testing: This is a useful test to detect the adrenal reserve. While a simple serum cortisol level might suffice to pick up adrenal insufficiency, if the value is less than 3 µg/dL at 8 am, many a time the serum cortisol level could be normal, but the adrenal may be damaged, and might therefore lack the capacity to augment the adrenal secretion in response to stress or conditions of increased hormone requirement. In order to pick up these cases, where the adrenal reserve capacity is compromised, ACTH testing is useful. The estimation of plasma and/or urinary steroids before and after ACTH administration reveals the responsiveness of the adrenal cortex to ACTH. A simple method is to administer 250 µg of synthetic ACTH (Synacthen) intramuscularly and to sample serum cortisol at 30 minutes and 60 minutes. Levels greater than 20 µg/dL exclude impairment of adrenal reserve (double the base line value).

TABLE 100.3

Interpretation of diagnostic tests in hyperadrenocortical states

Test	Normal subjects	Pituitary cause (Cushing's disease)	Adrenal tumour and hyperplasia	Ectopic ACTH production
Urinary 17 KGS	Normal	H	H	H
Plasma ACTH	Normal	H	L	H
Suppression by Dexamethasone 1 mg screening test	Suppression of plasma cortisol	No suppression	No suppression	Nil
2 mg/day × 3 days	Suppression	No suppression	Nil	Nil
8 mg/day × 2 days	Suppression	Suppression	No suppression (tumour) Suppression (hyperplasia)	No suppression

Dexamethasone suppression test (DST): Exogenous or endogenous glucocorticoids normally suppress ACTH secretion. This feedback inhibition is lost in Cushing's syndrome. Dexamethasone is given in a dose of 0.5 mg 6h for 2 days. Urinary 17-OHCS comes down below 2.5 mg/day in normals and plasma cortisol falls below 2 mg/dL on the second day of the test. In the overnight version of the dexamethasone suppression test (*o-DST*) plasma cortisol is estimated at 8 am after taking 1 mg of dexamethasone during the previous night at 11 pm. If plasma cortisol is less than 5 µg/L Cushing's syndrome can be excluded. Several other modifications of this test are available at present. Normal subjects show prompt suppression even when small doses of dexamethasone (single dose of 1 mg) are administered. In adrenal hyperplasia, suppression can be achieved only with higher doses (8 mg/day for 2 days) while in the case of adrenal adenoma, carcinoma and ectopic sources of ACTH, cortisol production is not suppressed even by higher dose of dexamethasone. After the estimation of basal cortisol values, in the high dose, DST 2 mg dexamethasone is given every 6 hours for 2 days and cortisol estimations are repeated and in the overnight high dose DST, 8 mg of dexamethasone is given at 11 pm and serum cortisol measured at 8.00 am on the next day: Values more than 50% of the basal value indicate non-suppression (Table 100.3).

Demonstration of the lesion: Adrenals can be visualized radiologically especially if they are calcified. In many cases the tumors are 4 to 6 cm in diameter by the time they show endocrine abnormalities. Adrenals can be well visualized by CT scanning and MRI and these should be done to demonstrate the anatomy of the gland. Even much small tumours can be visualized. Isotope scanning after administration of ^{123}I or ^{131}I metaiodobenzyl guanidine (MIBG) helps to show up the adrenals. Sampling of blood from the adrenal veins helps to identify the abnormal gland in cases where there is a difficulty in localizing

which adrenal (right or left) is the source of excess hormone production.

Diseases of the Adrenal Cortex

CUSHING'S SYNDROME

Syn: Hypercortisolism

Hypercortisolism may develop either due to primary disease of the adrenal cortex such as adenoma, carcinoma or hyperplasia or due to stimulation of the gland by ACTH secreted by the pituitary or ectopic ACTH-like substances produced as paraneoplastic processes. The term **Cushing's disease** refers specifically to the pituitary dependent hyperadrenal corticism. In addition corticosteroids administered therapeutically can give rise to iatrogenic Cushing's syndrome.

Cushing's syndrome is caused by persistent over secretion of glucocorticoids. In addition to increased levels of cortisol in blood, loss of the normal diurnal rhythm is also a prominent feature.

Causes of Cushing's Syndrome

- Pituitary Cushing _ ACTH dependent
- Adrenal Cushing – non-ACTH dependent
- Ectopic Cushing – ACTH or ACTH like substances dependent
- Iatrogenic Cushing – Externally administered glucocorticoids (Table 100.4).

Clinical Features

The symptoms are mainly due to excessive production of glucocorticoids. Almost all features can be attributed to gluconeogenesis, excessive protein catabolism and androgenic effects of cortisol.

General features: The affected subject is plethoric with rounded appearance of the face (moon face). There is a characteristic obesity with deposition of fat over the neck, shoulders, abdomen, and hips. Often, this results in a

TABLE 100.4

The etiology of Cushing's syndrome

ACTH-dependent causes:

Bilateral adrenal hyperplasia: 70% of these are secondary to a small adenoma involving the basophils (Cushing's disease) or chromophobes in the pituitary. Sometimes the abnormality is in the production and release of CRF from the hypothalamus.

Ectopic ACTH secretion: This is seen as a paraneoplastic syndrome in bronchogenic carcinoma, medullary carcinoma of thyroid, carcinoids, pancreatic carcinoma, ovarian carcinoma, neuroblastoma and ganglioma.

ACTH –independent causes:

1. **Adenomas or carcinomas** of the adrenal cortex and micronodular hyperplasia.
2. **Iatrogenic:** Use of physiological or pharmacological doses of glucocorticoids over prolonged periods.

Cushing's syndrome is not uncommon in India. It has been reported from all parts of the country. Pituitary-dependant adrenal hyperplasia and adrenal tumours are more frequent in women in the fourth and fifth decades.

typical crest of fat on the nape of the neck, and this is referred to as “**buffalo hump**” (Fig. 100.3).

The integument: Hirsutism develops in many cases and it is particularly disturbing in women. Face, chest, and other regions are affected most. Acne may develop. The hairline may recede over the temporal regions (temporal baldness) or even general baldness may result. Skin shows painless striae, which develop as reddish streaks over the thighs, gluteal regions, abdomen, axillae, and outer aspect of the arms. Striae are formed as a result of rupture of subcutaneous collagenous tissue. In severe cases the overlying skin may be stretched and thinned out and it tends to rupture and ulcerate. Repair of wounds is considerably delayed. Wound dehiscence is common after surgery. Scar formation is poor. Bruising, purpura, and melanotic pigmentation are seen in some cases. Some cases show secondary polycythemia (Fig. 100.4).

Other features: Hypertension and its complications are common. Muscles are easily fatigable, flabby and atrophic. Proximal muscles show myopathic changes. Psychiatric symptoms like depression and melancholia may be the presenting features in some. Amenorrhea and clitoromegaly develop in women. In women with over-production of androgen hormones infertility may occur. Males show loss of libido and impotence. Bones show osteoporosis, which is more prominent in the axial skeleton. Fractures are common (Fig. 100.5).

Biochemical abnormalities: Secondary diabetes develops in many of these patients. Hypokalemia, and fluid retention may develop.

Pituitary Cushing's Syndrome (Cushing's Disease):

This is the common variety of Cushing's syndrome, next



Fig. 100.3: Cushing's syndrome. Note: truncal obesity and buffalo hump (arrow)



Fig. 100.4: Cushing's syndrome: striae on abdominal wall (arrow)



Fig. 100.5: Cushing's syndrome osteoporosis: Compression fracture of vertebra (arrow)

only to iatrogenic Cushing's syndrome. Usually it is caused by pituitary microadenoma. Insidiously developing diabetes, hypertension and cushingoid habitus, with mild hyperpigmentation are characteristic. Rarely pituitary macroadenoma (>1 cm in size) may occur and in this situation, features of tumour enlargement like visual field defects and headache may be present.

Carcinoma of the adrenal cortex: These tumours are rapidly progressive with local invasion and distant

metastases early in their course. Some tumours do not produce hormones whereas others produce both cortisol and sex hormones. Over 80% of estrogen-producing tumours are malignant.

Iatrogenic Cushing's syndrome: This may occur at all ages in both sexes but it is more prominent in young adults. Daily administration of 5-10 mg or more of prednisolone or its equivalent for a period of more than 3-6 months can give rise to Cushing's syndrome. Though it was considered that only moderate or high doses of glucocorticoids led to hypercortisolism now it is known that even small doses given as aerosols or surface applications can, at times lead to the condition, on prolonged use. The full-fledged case resembles classic Cushing's syndrome. The clinical features are variable in many cases. Regression of symptoms occurs within months of withdrawal of the drug, but established diabetes may not clear up promptly, especially so if there is a family history of diabetes.

Ectopic ACTH secretion: Carcinomas of the bronchus, neural tissue, ovaries and gastrointestinal tract may give rise to ACTH like substances. This syndrome is seen more in older age groups. It is characterized by rapidly developing pigmentation, hypokalemia, and marked alkalosis. In many the complete picture of Cushing's syndrome may not develop. Cushing's syndrome may be the presenting condition in many neoplasms. The primary lesion may not be evident at the beginning but in some cases clinical features produced by the primary lesion may also occur simultaneously. Presence of digital clubbing and osteoarthropathy in any case of Cushing's syndrome, should suggest pulmonary malignancy as the underlying cause.

Important clinical features of Cushing's syndrome

- Truncal obesity
- Moon facies
- Hypertension
- Osteoporosis
- Protein depletion
- Glucose intolerance
- Purple striae
- Muscle wasting and weakness

Diagnosis

Clinical diagnosis is easy in florid cases. It has to be supported by biochemical investigations. Cushing's syndrome has to be differentiated from simple obesity, hirsutism, functional ovarian tumours, diabetes mellitus, and hypertension. In borderline cases, continued observation and repetition of tests might be required to establish the diagnosis.

Work up of Cushing's syndrome is shown in Figure 100.6. Radiological studies, ultrasonography, CT

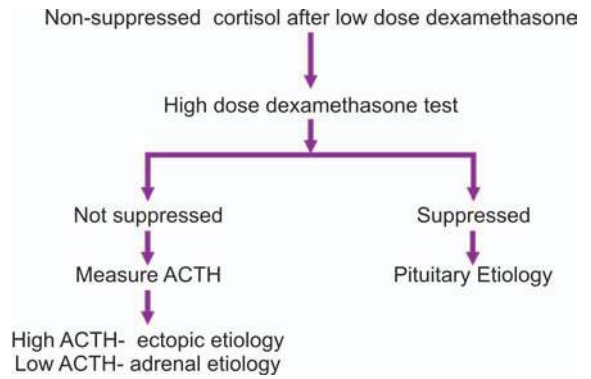


Fig. 100.6: Flow chart for the diagnosis of Cushing's syndrome

scan, MRI and estimation of cortisol levels in the adrenal veins identify the site of tumour or hyperplasia.

Course and prognosis: Cushing's syndrome due to primary adrenal disease or pituitary lesions is fatal if left untreated, though rarely spontaneous remissions may occur. Death is due to diabetic complications, hypertension, hypokalemia, infections or the physical effects of the underlying neoplasm.

TREATMENT

Surgical removal of the adrenal tumour is the treatment of choice. Since the normal portions of the glands may be atrophic, substitution therapy is needed in the postoperative period to prevent adrenal crisis. Cushing's syndrome due to pituitary adenoma resolves after surgical removal of the microadenomas. Initial results are good. Transphenoidal surgery is preferred in pituitary adenomas. Ten percent develop post-surgical complications. These include CSF rhinorrhea, diabetes insipidus and infection. Recurrence occurs in 15-25% of cases. They may require irradiation. An alternative is to do bilateral adrenalectomy and life-long hormone replacement.

Medical management: Symptomatic management of diabetes, hypertension and electrolyte disturbances is indicated as the conditions warrant. Specific drugs are rarely used. Metyrapone in a dose of 250-750 mg thrice daily blocks the synthesis of cortisol and abolishes the effects of hypercortisolism. Medical therapy is indicated if the primary cause is not correctable surgically.

Aminoglutethimide given orally in a total daily dose of 0.5-2 g daily, blocks the synthesis of aldosterone, cortisol, and other adrenal hormones. It may cause side effects such as ataxia, rashes, fever and drowsiness. **O, P'DDD [2,2-bis- (2-chlorophenyl-4 chlorophenyl-1, 1-dichloroethane – mitotane)]** given orally in divided doses to a total of 10-15 g/day causes atrophy and necrosis of the adrenal cortex and adrenal metastases. This drug may prolong life by a few months to years. **Ketoconazole** in a dose of 800-1000 mg/day inhibits cortisol secretion. Given on a long-term basis it controls the symptoms.

Irradiation: Pituitary tumour may respond to local irradiation with 40-50 Gy using a cobalt- 60 source or 90/Yttrium implantation. However the features of Cushing's syndrome take about one year to resolve even after successful therapy. Cushing's syndrome seen as a paraneoplastic manifestation of advanced malignancy does not generally respond to surgery. The improvements in pituitary surgery have resulted in far fewer patients being treated by irradiation, and hence irradiation is not recommended as the primary treatment.

Nelson's syndrome: Some patients who undergo bilateral adrenalectomy develop enlargement of the pituitary, pressure effects on the optic chiasma and raised intracranial tension. They also show increased pigmentation due to hypersecretion of melanocyte stimulating hormone (MSH). This syndrome follows after a few years of bilateral adrenalectomy.

Abnormalities of Sex Hormones Caused by Adrenocortical Lesions

Adrenal cortex may be the source of excessive androgen production if the lesion is a tumour or congenital enzyme defect interfering with the synthesis of cortisol. Excessive androgens influence the secondary sexual characters. The final clinical picture is determined by the sex of the patient, age of onset of the disorder, and its severity. The condition may remain unnoticed in adult males. Women develop virilization. Boys show precocious puberty. Girls develop clitoromegaly and other signs of hyperandrogenism. The classic example of this situation is congenital adrenal hyperplasia.

CONGENITAL ADRENAL HYPERPLASIA

This rare disorder is characterized by virilization in female and precocious puberty in male children (Fig. 100.7). The underlying defect is congenital deficiency of enzymes leading to metabolic block in hormone synthesis. This

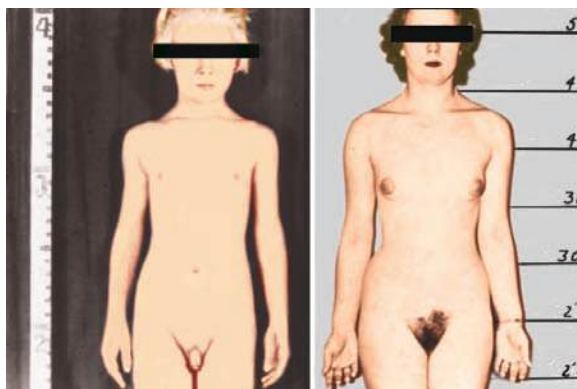


Fig. 100.7: Virilizing adrenal hyperplasia. Note: Enlarged clitoris in the girl on the left. Normal girl of same age—right (Fig. 100.8)



Fig. 100.8: Close up view of enlarged clitoris

results in the accumulation of intermediary metabolites with androgenic activity. Deficient synthesis of glucocorticoids and mineralocorticoids results in functional adrenocortical deficiency.

Etiology

The enzyme defect is transmitted as an autosomal recessive disorder, with clinical expression in the homozygous state. Females are affected more than males. The severity of enzyme defect determines the age of manifestation. Severe defects manifest earlier in life. At least six different enzyme defects are known, but five of these are more frequent. These are, C-21 hydroxylase defect, C-11,C-17 and C-18 hydroxylase defects and 3-beta dehydrogenase defect. Though the clinical effects are grossly similar, minor differences exist between them. C-21 hydroxylase defect accounts for 95% of the cases.

CLINICAL FEATURES

In some cases the newborn female infant shows pseudo-hermaphroditism due to androgen effect on the genitalia. Male infants show precocious sexual development after birth. Manifestations of adrenal insufficiency are failure to thrive, vomiting, hyponatremia, and hypotension. Death may occur due to adrenal insufficiency unless the condition is recognized and treated. Milder cases manifest as virilization in girls and sexual precocity in boys (Fig. 100.8). Due to the premature fusion of epiphyses, growth is retarded. Hyperandrogenism causes testicular atrophy and infertility in adult males.

Diagnosis

This disease should be considered in the differential diagnosis of all cases of hermaphroditism or ambiguous sexual development. Diagnosis is confirmed by estimation of the androgens in urine.

Treatment

Deficiency of glucocorticoids and mineralocorticoids should be corrected by supplementation. Liberal intake

of salt helps in mild cases. Fludrocortisone in a daily dose of 0.05-0.1 mg orally is given to correct mineralocorticoids deficiency. Prednisolone in a dose of 5 mg/day serves to overcome glucocorticoid deficiency. Surgery may be required for cosmetic correction of the genitalia. In those cases in which adrenal tumours or hyperplastic glands are demonstrable, surgical removal is indicated.

Adrenocortical Insufficiency

Hypofunction of the adrenal cortex may be due to a primary disorder of the gland or secondary to hyposecretion of the tropic hormone. The causes are listed in Table 100.5.

Majority of the cases are due to autoimmune adrenal atrophy. The classic features include hypotension, increased skin pigmentation, low levels of serum Na^+ and Chloride, high levels of HCO_3^- and K^+ and lower levels of plasma glucose.

TABLE 100.5

Causes of adrenal insufficiency

Primary adrenocortical insufficiency—Lesions in the adrenal cortex

1. Atrophy of the adrenal cortex due to autoimmune adrenalitis.
2. Tuberculosis, fungal infection, CMV infection, sarcoidosis and other granulomas
3. Infiltration by metastatic carcinoma
4. Hemochromatosis.
5. Amyloidosis
6. Post-surgical (total or subtotal adrenalectomy)

Secondary adrenocortical insufficiency

Hypothalamic causes: Tumours of the third ventricle, meningitis, encephalitis, injury to the base of the brain, corticosteroid therapy, sarcoidosis and histiocytosis

Pituitary causes: All causes of panhypopituitarism, especially tumours, basal meningitis, viperine snake bite, hypophysectomy or irradiation and empty sella syndrome.

Addison's Disease

Syn: Primary adrenocortical insufficiency

Thomas Addison described this condition first in 1855. It was due to tuberculosis of adrenal glands.

Among the diseases of the adrenal cortex this is the most treatable one. Autoimmune adrenal destruction (previously called idiopathic or primary atrophy) is more common in women. Antibodies against adrenal tissue may be demonstrable. Other autoimmune disorders like myxedema, type 1 diabetes, Hashimoto's disease, thyrotoxicosis, pernicious anemia, vitiligo, idiopathic ovarian failure and hypoparathyroidism may be associated.

There is association between Addison's disease and HLA-B38 and HLA-DR3 (Table 100.5).

Pathology

The adrenal glands show total cortical atrophy involving all three zones. The medulla is normal. In the primary form, histology shows lymphocytic infiltration and increase in fibrous tissue. In the other types, evidence of underlying disease may be demonstrable. In tuberculosis of the adrenals evidence of tuberculosis elsewhere in the body may or may not be present. Though tuberculosis used to be a major cause during the early part of the 20th century, primary adrenal atrophy, most commonly due to autoimmune adrenal damage, is more common at present. The major functional defect is marked reduction of glucocorticoids and mineralocorticoids. The main problem is inability to combat stress and the clinical features are determined by the severity of the stress and its nature. Sex hormones are also reduced, but the clinical presentation is less severe. Stress may include infections, injury, physical factors, mental stress and drugs which lead to hypoglycemia or hypotension and opioid narcotics.

Clinical Features

Generally, the onset is slow and may be unnoticed but many patients present for the first time in acute adrenal failure precipitated by stress. Initial symptoms may be vague such as weakness, tiredness, lethargy, weight loss, and gastrointestinal upset, especially vomiting. Sooner or later dark pigmentation develops. When fully developed, the pigmentation is characteristic and in most cases (Figs 100.9 and 100.10), diagnostic of primary adrenal failure.



Fig. 100.9: Male Addison's disease. Note: Dark pigmentation of the whole body—particularly palms, soles and face



Fig. 100.10: Female Addison's disease. Note pigmentation

Face, palms, soles extensor aspects of limbs, flexures, and mucous membranes of the mouth, tongue and genitalia show pigmentation. In severe cases the complexion becomes dark (Figs 100.9 and 100.10). Pigmentation is mediated by the melanocyte stimulating effect of ACTH and also secretion of melanocyte stimulating hormone (MSH). Unlike primary hypoadrenalism, in the secondary type, there is no hyperpigmentation. On the other hand, these subjects are pale and light coloured. Vitiligo is seen in some cases of Addison's disease. Premature graying of hair may occur which reverts to normal with treatment. Women develop amenorrhea and men develop impotence. Addison's disease confers abnormal sensitivity to drugs like morphine or pethidine. Hypoglycemia leads to extreme fatigue, sweating and coma.

Cardiovascular abnormalities include low blood pressure especially postural hypotension, and diminution of heart size.

Laboratory Investigations

1. Hypoglycemia is common. Blood glucose falls further during periods of stress.
2. Hyponatremia and hyperkalemia may occur.
3. Plasma cortisol levels are low and the diurnal rhythm is lost.
4. Stimulation test – There is no response to ACTH stimulation in primary adrenal insufficiency. In secondary types, prompt response occurs.
5. In Addison's disease plasma ACTH levels are high. In secondary hypoadrenocorticism ACTH levels are low.

6. Adrenal antibodies may be demonstrable in autoimmune adrenal damage.
7. X-ray of abdomen may show adrenal calcification. More often calcification is the sequel of tuberculosis of the gland.
8. CT/MRI of abdomen visualizes the anatomy quite clearly. Radionuclide imaging of adrenals gives information of morphology and function.

Diagnosis

Addison's disease should be suspected clinically and confirmed by investigations. Chronic malnutrition, malabsorption states, megaloblastic anemia, tuberculosis, disseminated malignancy, and psychiatric disorders should be considered in the differential diagnosis.

Diagnosis is established by estimating plasma cortisol level before and after ACTH injection.

The normal levels of plasma cortisol at 8 am is 5-25 µg/dL and ACTH is less than 80 pg/mL.

Secondary hypoadrenocorticism is a part of hypopituitarism.

Course and Prognosis

Severe Addison's disease is fatal if untreated. Adrenal crisis occurring during periods of stress causes death. Severe hyponatremia, shock, hypoglycemia or toxic reactions to drugs like morphine are common in them and these may prove fatal.

The prognosis has been completely changed with modern therapy. Apparent clinical and biochemical normalcy can be restored with adequate hormonal supplementation and fairly normal life with normal life span can be ensured. In many of them diabetes mellitus may develop on prolonged follow-up.

MANAGEMENT

The aim of therapy is to replace **glucocorticoids** and **mineralocorticoids** for life, with increase in dosage during periods of stress. Initially hydrocortisone is given in a dose of 100-200 mg/day intravenously in a crisis-like situation, the exact requirement is determined based on clinical and biochemical parameters. The optimum dosage required to keep the patient symptom-free with normal blood glucose and electrolyte levels is determined by trial and error. The treatment is started with 2.5 mg of prednisolone once or twice a day and the dose is increased till the patient becomes clinically normal and biochemical results also become normal.

Once a state of equilibrium is reached, long-term maintenance is by giving any one of the more potent preparations such as prednisolone, betamethasone or dexamethasone. Timing of the dosage is adjusted to

coincide with the normal diurnal variations, i.e. the equivalent of 20 mg cortisol at breakfast and 10 mg at about 6 pm. Peak serum levels are obtained 30-50 minutes after oral administration and the action lasts for 6-8 hours. In general the dose required for replacement therapy is much lower than that required for immunosuppression. Though glucocorticoids bring about considerable benefit, full health will be restored only with the replacement of mineralocorticoid preparations as well.

Mineralocorticoids: In all cases with moderate or severe adrenal deficiency mineralocorticoids have to be supplemented. Fludrocortisone is the most potent preparation in this class and it is given in a dose of 0.05-0.15 mg orally as a morning dose. Adequacy of therapy is assessed by the restoration of blood pressure to normal and corrected serum aldosterone levels. Side effects of overdose include hypertension, edema and hypokalemic alkalosis.

The importance of stress dosing: *During periods of stress and other medical or surgical emergencies the dose of corticosteroids should be stepped up to avoid the development of adrenal crisis. All subjects with hypoadrenocorticism should carry identity cards giving details of the disease, the treatment schedule and the doctor who treats him.*

ADRENAL CRISIS

Syn: Acute adrenal insufficiency (adrenal apoplexy)

Sudden development of adrenal cortical failure leads to adrenal crisis. It is a medical emergency, which is fatal if undiagnosed. Prompt recognition and replacement of glucocorticoids and mineralocorticoids, with other supportive measures gives prompt relief and saves life. Adrenal crisis may complicate chronic adrenal insufficiency or it may occur acutely in subjects who develop fulminant infections.

Causes

1. Sudden withdrawal of ACTH or glucocorticoid therapy.
2. Infections, trauma, surgery, drugs like morphine, diarrhea, vomiting, physical or psychological stress, and obstetric accidents precipitate acute adrenal failure in patients with chronic adrenal cortical insufficiency.
3. During meningococcal septicemia occurring in otherwise normal subjects, hemorrhagic necrosis of the adrenal may develop (Waterhouse-Friderichsen syndrome) leading to shock. Infarction of the adrenal, accidental destruction of the adrenal by trauma or surgery, and neonatal adrenogenital syndrome are rare causes.

Clinical Features

Severe vomiting, diarrhea, and profound shock are the prominent symptoms. Blotchy purpura develops in septicemia. If untreated, coma supervenes and death follows within hours.

Diagnosis

It is based mainly on clinical features. Estimation of serum sodium, potassium, chloride and bicarbonate give the electrolyte status. Estimation of plasma cortisol and aldosterone will help to assess the severity.

Management

Normal saline with 10% glucose should be started immediately. The rate is adjusted to maintain normal blood pressure, serum electrolytes and blood glucose level. Intravenous infusion may have to be continued for days. Drug of choice in an emergency is hydrocortisone hemisuccinate sodium in a dose of 100 mg given intravenously initially and repeated every 4-6 h. Parenteral medication is continued till the patient is fit for oral therapy. If the blood pressure does not come up promptly, or it tends to drop, fludrocortisone 0.1 mg oral is given in addition. After tiding over the crisis, long-term management for adrenal failure is instituted. When the condition is secondary to sepsis or other causes these should receive prompt attention.

Primary Hyperaldosteronism

Syn: Conn's syndrome

This is a rare disorder caused by a primary increase in the production of aldosterone. The condition is characterized by hypertension, unprovoked hypokalemia and low plasma renin activity. Only less than 2% of cases of hypertensive patients show hyperaldosteronism. Around 60-75% of cases are due to aldosterone producing adenoma of the adrenal cortex. In women aldosteronomas are more common. The second type called *idiopathic hyperaldosteronism* is probably due to bilateral adrenal hyperplasia. Idiopathic hyperaldosteronism is more common in men. There is a rare subgroup of idiopathic hyperaldosteronism that is suppressible by glucocorticoids. In normal subjects and hyperaldosteronism glucocorticoid administration does not suppress aldosterone levels.

The combination of low serum potassium, low plasma renin activity, alkalosis and a high non-suppressible plasma aldosterone confirms the diagnosis. *Conn's syndrome patients do not have edema. This phenomenon is called "mineralo corticoid escape".* It is probably due to increase in GFR and by the activity of both atrial and brain natriuretic peptides.

Demonstration of raised aldosterone levels in the adrenal venous blood obtained by selective catheterization helps to identify the side of lesion. CT scanning, MRI and isotopic imaging help to demonstrate the lesion.

Differential diagnosis includes malignant hypertension uni/or bilateral renal ischemia and potassium losing nephropathies.

Treatment

Adenomas have to be treated by surgery. Those with idiopathic hyperaldosteronism have to be treated medically with spironolactone 50-100 mg thrice daily. In intractable cases bilateral adrenalectomy can be done. The blood pressure returns to normal after several months in aldosteronomas, in the other types results are variable.

Secondary hyperaldosteronism can occur due to high renin production occurring in renal artery stenosis, congestive heart failure, prolonged use of diuretics and others.

Disorders of the Adrenal Medulla

PHEOCHROMOCYTOMA

Tumours arising from chromaffin tissue produce excess of catecholamines and give rise to hypertension and other effects. Tumours may occur at several sites. Common locations are the adrenal medulla (90%), Zuckerkandl's bodies adjacent to the abdominal aorta (8%), paraganglionic cells of the sympathetic nervous system, urinary bladder, aortic and carotid bodies, and the mediastinum. It is seen that 0.1-0.3% hypertensive patients may have a pheochromocytoma. The disease may be familial in 10% of cases and show autosomal dominant inheritance. The familial form may occur in association with the syndromes of multiple endocrine neoplasms (MEN) particularly MEN-2 in which primary hyperparathyroidism and medullary carcinoma of the thyroid may also occur. Pheochromocytomas secrete large amounts of adrenaline and noradrenaline. In pheochromocytomas at non-adrenal sites, noradrenaline is the major component constituting up to 80% of the total. Some tumours produce only one of these products. Of the pheochromocytomas, 90% are benign. 10% are malignant and these may metastasize. The secondary sites also produce catecholamines.

Clinical Features

The most prominent feature is hypertension, which is paroxysmal in the initial stages, but later becomes persistent. Headache, flushing, excessive sweating, tachycardia, fever, glycosuria, and postural hypotension accompany hypertensive paroxysms. Abdominal palpation, minor surgery, and parturition may precipitate

hypertensive attacks. The common hypotensive drugs like guanethidine, hydralazine, beta-adrenergic blockers, and methyl dopa lead to paradoxical elevation of blood pressure. Many develop malignant hypertension that may prove fatal. Hypertensive attacks triggered by micturition should suggest pheochromocytoma of urinary bladder.

For practical purposes the '*rule of tens*' is relevant in pheochromocytoma

- 10% extra adrenal
- 10% bilateral
- 10% malignant
- 10% familial
- 10% children

Diagnosis

Pheochromocytoma has to be clinically suspected in subjects developing paroxysmal hypertension associated with other manifestation of sympathetic over activity.

Investigations

Plasma free catecholamines as well as plasma metanephrines are the tests that offer the best diagnostic value, and a high value of either, strongly suggests the diagnosis. As these tests are not available routinely in India, the diagnosis may be established by demonstrating raised levels of **vanillylmandelic acid (VMA)** that is the excretory product of catecholamines present in urine or total or free urinary metanephrines. Normal value of VMA is up to 6 mg/day. Quantitative determinations are done in 24 hour collection of urine. Spot tests are also available for screening. Several drugs and articles of food such as bananas, chocolate, coffee, nuts and vanilla produce false-positive tests when urinary VMA or catecholamine determination are done and, therefore, these have to be avoided preferably for 5 days before doing the test. Plasma levels of catecholamines should be measured for diagnosis and follow-up.

Phentolamine, which blocks alpha-adrenergic system, causes a prompt drop in blood pressure. The basal blood pressure is recorded and 5 mg of phentolamine is given intravenously. Blood pressure is recorded at 30 sec. Intervals for 3 min and 60 sec intervals for 7 minutes. Fall in blood pressure above 35 mmHg systolic and 25 mmHg diastolic is suggestive. Adverse reaction include severe hypotensive crisis. False-positive results may occur. The test is positive only during the hypertensive phase.

Localization of the tumour is achieved by CT scanning, MRI, ultrasonography or radionuclide imaging using metaiodobenzyl guanidine (MIBG) and adrenal angiography. MRI is especially useful: a bright signal on T2-weighted image is highly suggestive of a neuroendocrine tumour like pheochromocytoma. Selective sampling of adrenal venous blood for estimating

catecholamines is a very useful confirmatory test. All these tests should be undertaken only in well-equipped centers since there is the risk of sudden hypertensive crisis.

Treatment

Once the diagnosis is established, treatment is to remove the tumour surgically. Rapid fluctuations in blood pressure occur during premedication, anesthesia, surgical manipulation, and postoperative period.

Preoperatively the blood pressure should be controlled by giving phenoxybenzamine or other alpha blockers like prazosin or doxazosin in doses of 1-4 mg/day. It is important to give adequate fluid intake during this preoperative phase. Beta blockers may be added a few days prior to surgery, especially if there is tachycardia. Intravenous diazoxide, sodium nitroprusside or phentolamine can control hypertensive episodes if judiciously administered IV.

THE ADRENAL INCIDENTALOMA: AN EMERGING DISEASE

There is an increasing trend to do abdominal imaging for diverse purposes, ranging from evaluation of abdominal pain to searches for occult or evident masses. This has resulted in the “incidental” detection of adrenal masses, aptly called adrenal “incidentalomas”. A patient with an incidentaloma needs careful evaluation to rule out a malignancy. A tumour size more than 4-6 cm and a heterogeneous consistency strongly suggests malignancy. However benign adenomas of this size can also occur as incidentalomas without hormonal abnormalities. In addition, in every case, hormonal abnormalities must be ruled out by biochemical tests. This should include tests to look for medullary tumours such as pheochromocytomas as well as cortical tumours that produce excess cortisol or androgens.

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Gonads and their Disorders

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General Considerations

Sexual reproduction requires three types of differentiation:

1. **Gonadal**- for production of gametes

2. **Genital**-for transfer of gametes to the site of fertilization and

3. **Behavioral**, for the urge to behave sexually.

The most important gene for gonadal differentiation is SRY gene situated in the short arm of the Y chromosome. This gene induces the gonad to differentiate into a testis.

The gonads and genital ducts intended for reproduction develop under the influence of genetic and hormonal factors. The sex chromosomes X or Y determine the genetic sex or gonadal sex of the offspring. Phenotypic sex (also called somatic sex) comprises the external genitalia and the secondary sex characters. The translation of gonadal sex into phenotypic sex is the direct consequence of the type of gonad formed and the endocrine secretion of the fetal gonads resulting in the formation of male or female urogenital tract. The development of the genitalia, breasts, body build, voice, facial and pubic hair, and other pubertal changes constitute secondary sexual development. The term ‘psychological

sex’ and the ‘gender role’ refers to the behavioural and psychosocial aspects of two sexes.

Gonadogenesis

The genetic composition XX or XY determines the morphological development of the gonads and other structures. The germ cells present in the intermediate mesoderm of the developing embryo transforms into the bipotential gonad, which can differentiate into testes and ovary under the control of sex hormones. In the presence of “Y” chromosome (SRY gene), the gonad differentiates into testes and starts secreting testosterone and mullerian inhibitory factor. Testosterone secreted by the testes directs the Wolffian ducts to differentiate into the male internal reproductive tract. The epididymis, vas deferens, and seminal vesicles develop from the Wolffian ducts. The Mullerian ducts degenerate under the influence of Mullerian duct inhibitor produced by the Sertoli cells of the testes (Fig. 101.1).

In the absence of the “Y” chromosome (SRY gene) the gonad differentiates into an ovary. In the female, the mullerian ducts give rise to the fallopian tube and the uterus. Figure 101.1 shows the schema of sex development. The development of external genitalia is controlled to a great extent by the hormonal profile in the individual. Sexual differentiation should be considered anomalous in any patient with ambiguous genitalia, cryptorchidism, inguinal masses in apparent females, inguinal hernia, clitoromegaly, or gynecomastia.

Pubertal changes: Puberty is the period of rapid physical and sexual development during which a sexually immature child is transformed into a mature adult. Pubertal development is preceded by adrenarche, which is characterized by the enhanced secretion of adrenal androgens- *dehydroepiandrosterone (DHEAS)* and *androstenedione*. The factors that determine the onset of puberty are poorly understood, but the sequence of events is well characterized. The earliest sign of puberty is the sleep-related pulses of LH secretion and episodic FSH secretion. Later on, a persistent and sustained secretion of gonadotropins ensues throughout the day resulting in elevated plasma levels of sex hormones that result in sexual maturation.

Sexual maturation in males and females occurs in stages and this has been divided into five grades. Changes in male include increase in testicular volume, growth of penis and glans, appearance of scrotal rugosity, and scrotal pigmentation. The pubic hair appears and spreads to the medial surface of the thighs and the linea Alba as an inverted triangle (pubarche). In girls, the breasts and areola enlarge and papillae project on the areola. The pubic hair appears and spreads. Mean age for menarche in girls is 12 years, and this is 1-2 years earlier than the age of puberty for boys. The gonadal hormones are essential for the maintenance of fertility, sexual behaviour and systemic effects in both sexes. In addition, in the female, ovulation, menstruation and nidation of ovum are maintained by gonadal steroids. Later axillary hair develops (adrenarche).

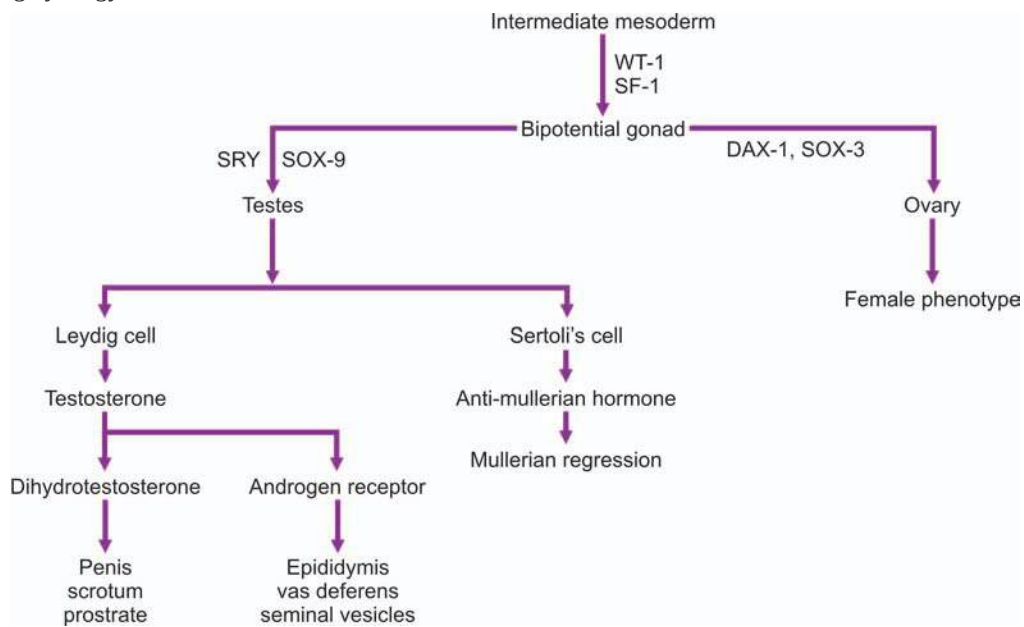


Fig. 101.1: The schema of sex differentiation

WT-1 Wilms' tumour gene
SF 1 steroidogenic factor
SRY Sex determining gene region of Y chromosome
DAY-1 Dosage sensitive adrenal hypoplastic gene 1 in X chromosome

Pubarche and adrenarche are under the influence of androgens.

Ovulation: The ovary increases in size after birth. In the years preceding menarche the medullary stroma hypertrophies. When puberty develops, cyclic gonadotropin rhythm is established and under the influence of gonadotrophins, a group of primary follicles are recruited and after the 6th to 8th day of menses one follicle becomes mature and dominant with accelerated growth of granulosa cells, and this results in ovulation. With the approach of menopause the ovary becomes less sensitive to gonadotropin stimulation. Maturation of follicles and ovulation stops. The levels of pituitary gonadotropin increase considerably and remain so for life.

REPRODUCTION IN MALES

The male reproductive system comprises testes, vas deferens, and accessory sex glands. The bulk of the testes is made up of seminiferous tubules embedded in a connective tissue matrix which also contains Leydig cells, blood vessels, and lymphatics. Spermatogenesis takes place in the epithelium of the seminiferous tubules and it takes about 74 days. Spermatozoa are stored in the epididymis. Sertoli cells present in the seminiferous epithelium secrete an androgen-binding protein under FSH control. Interstitial tissue of the testes contains the Leydig cells, which secrete the principal testicular hormone- testosterone.

Androgens are steroid hormones, which are responsible for conferring male characteristics. They are responsible for the development of male reproductive organs, secondary sexual characters and masculine behaviour. The testicular androgens include testosterone,

androstenedione and dehydropiandrosterone (DHE). Androgens are secreted by the testes under the influence of the luteinising hormone (LH) of the pituitary. Testosterone is converted into its active metabolite dihydrotestosterone (DHT) enzymically by 5-alfa reductase (Fig. 101.1). This conversion takes place both in blood and the target tissues.

The testicular hormones show variation with age. About 4-7 months after birth male infants show a substantial increase of circulating testosterone and LH levels. The levels of testosterone fall to low range by one year, so also FSH and LH. Puberty occur by the age of 10-15 years. The FSH reaches adults levels by the age of 15 years and LH reaches adult levels by the age 17 years. During puberty gonadotropin output occurs in spurts related to sleep. After completion of puberty, the gonadotropin levels become steady. After the age of 40 years marked changes in gonadal function occur in women but only to a lesser extent in men. Plasma levels of testosterone gradually decline in men. There is a gradual decline in libido and reduction in size of the testes.

Testicular function is essentially under a dual gonadotropin control. The LH stimulates the Leydig cells and FSH stimulates seminiferous tubules (Fig. 101.2).

Functions of Androgens

Androgens regulate gonadotropins secretion by the hypothalamo-pituitary axis, initiate and maintain spermatogenesis and are also responsible for the development of secondary sexual characters during puberty, and control of libido. Testosterone is necessary for linear growth and muscular development. It enlarges the larynx, including vocal cords, and is responsible for

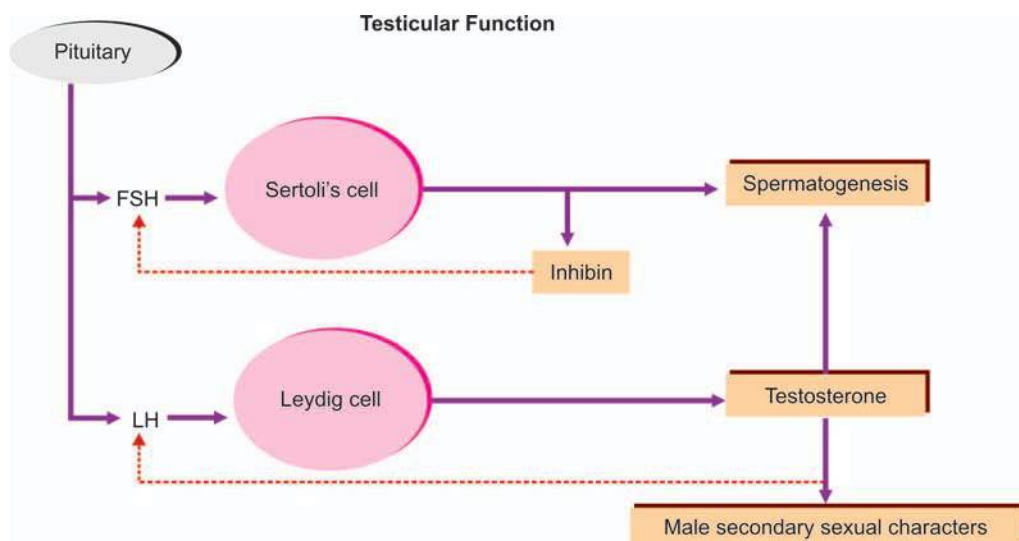


Fig. 101.2: Shows overview of testicular function. The gonadotropins, FSH and LH are secreted from the pituitary, and they control the Sertoli and Leydig cells respectively, which carry out testicular functions. Note that dotted arrows represent inhibitory pathways, while straight lines represent stimulatory pathways

change of voice in the male. Testosterone is converted to an active metabolite dihydrotestosterone (DHT) in target tissues by the action of 5- α reductase and DHT is responsible for the terminal hair growth of the beard, trunk, limbs, nostrils and external ears (Fig. 101.2).

Gonadal Disorders in Males

HYPOGONADISM

Testicular hypofunction at any age leads to functional and morphological abnormalities depending upon the age of onset and duration of the disorder. This may be primary or secondary depending upon whether the defect is in the gonads or it is in the endocrine glands controlling gonadal function (See below):

I. Causes of primary hypogonadism in males:

A. Disorders involving male sexual differentiation.

1. Chromosomal sex disorders:
 - a. Klinefelter's syndrome (XXY).
 - b. XX male.
 - c. Mixed gonadal dysgenesis (X/XY)
 - d. True hermaphroditism (XX/XY)
 - e. Ullrich-Turner syndrome (XO/XY) and
 - f. Heredofamilial disorders (e.g. Noonan's syndrome).
2. Developmental disorders occurring in normal genotypic males (46 XY):
 - a. Anorchism
 - b. Hypospadias
 - c. Cryptorchidism.
 - e. Germinal cell aplasia and
 - f. Abnormalities in the outflow tract for sperms.
3. Male pseudohermaphroditism:
 - a. Dyshormonogenesis (androgen biosynthetic defects).
 - b. Androgen insensitivity disorders, and
 - c. Persistent mullerian duct syndrome.

B. Adult testicular failure (acquired)

1. Idiopathic type.
2. Primary testicular disease.
3. Orchitis occurring in mumps, lepromatous leprosy and other infections.
4. Neurological diseases, e.g. paraplegia, dystrophia myotonica.
5. Acquired disorders like varicocele.
6. Drugs. e.g. cyclophosphamide, spironolactone, cyproterone, frusemide, cimetidine, heroin, medroxyprogesterone, phenothiazines, estrogens.
7. Hepatic and renal failure
8. Autoimmune disorders and
9. Accidental or surgical trauma, and irradiation.

II. Secondary hypogonadism

- A. Hypothalamic causes: tumour, trauma, radiation
- B. Pituitary causes: tumour, trauma, isolated gonadotropin deficiency.

III. Post-surgical, post-radiation

Testicular atrophy: The seminiferous tubules account for the size and volume of the testes. Normally the adult testes measures 15 to 25 mL in volume. In the prepubertal period, its volume is only 2-3 mL. Testicular size in adults does not depend upon age. Prepubertal damage to the testes manifests as small and firm testes. Damage in the post-pubertal period renders them small and soft. Testicular atrophy in adult may be due to hypopituitarism or due to primary testicular damage. In testicular atrophy, both spermatogenesis and testosterone production are affected to varying degrees.

Testicular atrophy with sterility may be part of liver failure, renal failure, spinal cord lesions, and dystrophia myotonica. Thermal or physical trauma and irradiation of the abdomen and scrotum may lead to testicular atrophy. In lepromatous leprosy direct invasion by the organisms results in panhypogonadism. Testicular atrophy may follow orchitis due to mumps, echovirus or group B arboviruses.

Anti cancer drugs like cyclophosphamide, chlorambucil and vincristine can damage testes especially in the prepubertal period.

The prominent clinical manifestations include small size of the penis, soft small testes, sparseness of facial and body hair, loss of libido and impotence. Testicular atrophy or mal-development occurring in childhood leads to the development of eunuchoidism.

Hypogonadotropic hypogonadism: Though secondary hypogonadism is usually secondary to panhypopituitarism, less commonly, isolated hypogonadotropic hypogonadism may occur. The main features are eunuchoidism, infertility, and impotence. **Kallmann's syndrome** is the combination of testicular failure, eunuchoidism, cryptorchidism and anosmia. Normally neurons secreting LHRH originate in the olfactory placode and migrate to the hypothalamus. When there is a defect in the KAL gene, this migration is affected, resulting in anosmia and hypogonadism of Kallmann's syndrome. When spermatogenesis is present in the absence of Leydig cell activity with under androgenisation, it is called **fertile-eunuch syndrome**.

Treatment of Hypogonadism

Removable causes if any, should be attended to. If this is not possible, symptomatic management should be instituted. The aim of therapy in such cases is to restore secondary sexual characters and the capacity to perform sexual intercourse. This is achieved by androgen

replacement therapy. Restoration of fertility is achieved in some cases by gonadotropin therapy. Gonadotropins have to be given by injection.

Androgen therapy: Orally administered testosterone is rapidly degraded in the liver, so that only a fraction of the administered dose reaches the systemic circulation. Similarly, injected testosterone is rapidly absorbed and metabolized. So for effective androgen therapy, the testosterone must be administered in a slowly absorbable form as e.g. transdermal or slow-release oral preparations or by injection of chemically modified testosterone preparations.

Oral preparations of testosterone include mesterolone acetate in doses of 25 mg/day and testosterone undecanoate. Of these the latter is absorbed through lymphatic systems into the circulation and physiological blood levels may be attained by a dose of 120 mg/day, given in divided doses. Transdermal preparations are also effective; a scrotal patch of testosterone is able to deliver 4-6 mg of testosterone over 24 hours. Of the injectable forms, testosterone propionate is short acting. It is given in doses of 20 mg IM injection. Testosterone caproate (60 mg IM) and enanthate are long acting. They have to be given once every 2-3 weeks. Troublesome side effects of androgens are the development of precocious puberty, premature fusion of the epiphyses in children, dyspepsia, polycythemia, suppression of endogenous androgens, and temporary cessation of spermatogenesis. Prostatic carcinomas may spread under the influence of androgens. Rarely androgens produce hepatic adenoma on prolonged therapy. Androgen withdrawal leads to tiredness, loss of libido, impotence, and hot flushes.

Gonadotropin therapy: This restores fertility in subjects with hypopituitarism. Since prolonged therapy can cause antibody production, this is reserved for inducing spermatogenesis. The commonly available preparations include human menopausal gonadotropins (HMG) which has 75 international units each of LH and FSH activity. Human chorionic gonadotropin (HCG) has got mainly LH activity and only slight FSH activity. HCG is supplied in vials containing 2000 to 10000 units. Usually, treatment is begun with HCG and later HMG is added on to stimulate the FSH-dependent phases of spermatogenesis. Human pituitary gonadotropin (HPG) has strong FSH and weak LH activity. 1mg is equivalent to 500-750 IU. It can also be used with HCG to promote spermatogenesis.

GnRH therapy: Usually GnRH stimulates gonadotropin release, and when given in a pulsatile manner every 90-120 minutes it is the ideal treatment for purely hypothalamic GnRH deficiency. Even though this condition is rare, some of the cases of isolated gonadotropin deficiency may be due to GnRH deficiency. Interestingly, if given continuously, GnRH can produce the opposite effect and suppress gonadotropin release.

The Sexual Act

The capacity for erection, emission, ejaculation of semen and orgasm are all together implied in the term sexual potency. The neural center for erection is situated in S2-S4 segments of the spinal cord. Tactile stimulation of erotogenic zone in the body activates this center. Penile erection is brought about by parasympathetic stimulation. Emission consists of ampullar emptying of semen into the posterior urethra. This is under control of the ejaculatory center of the spinal cord located in L2 and L3 segments. Ejaculation is under sympathetic control. During ejaculation jets of semen are expelled through the urethra. The total somatic and psychological experience accompanying ejaculation is called *orgasm*.

IMPOTENCE

Syn: Impotency

This condition constitutes inability to attain or maintain an erection of sufficient firmness to permit coitus to be initiated and completed.

1. Primary impotence- in this form the subjects have never been potent.
2. Secondary impotence- in this form the subjects experience impotence after a period of normal potency.

The term *apareunia* indicates inability to perform the sexual act.

Even in normal individuals transient episodes of impotence may occur as a result of fatigue, distraction, acute illnesses, or anxiety. These recover spontaneously.

Etiology

85-90% of cases are due to organic causes. In 10-15% cases the condition is psychogenic. In all types of impotence, it is common for psychological or behavioural abnormalities to supervene.

Organic Causes

1. All cases of primary and secondary hypogonadism.
2. Other endocrine disorders-acromegaly, hyper-and hypothyroidism, Cushing's syndrome, Addison's disease.
3. Neurological disorders involving the lumbosacral segments of the spinal cord, nervi erigentes and autonomic neuropathy occurring in diabetes mellitus.
4. Chronic systemic illnesses-diabetes mellitus, hepatic cirrhosis, chronic renal failure, obesity, starvation, disabling arthritis, connective tissue diseases, chronic obstructive airway disease, systemic malignancy.
5. Iatrogenic- antihypertensive drugs, estrogens, H2 receptor blockers, tranquillizers, sedatives, alcohol, psychedelic drugs and anticancer drugs.

TABLE 101.1

Differences between organic psychogenic impotence

Organic	Psychogenic
1. Impotence is always present.	Conditional and situational.
2. Begins insidiously and slowly progressive.	Usually sudden onset.
3. The onset of impotence coincides with any significant illness like myocardial infarction	There may be a temporal association to a stressful event as the death of a parent or child.
4. There is no reflex penile erection in the early hours of the morning	Morning erections are present (nocturnal tumescence).

Psychogenic Causes

1. Affective disorders like depression, mania, schizophrenia, hysteria, and antisocial personality.
2. Alcoholism and other drug addictions.
3. Organic brain syndromes.
4. Personality disorders.
5. Trans-sexualism (a strong desire to change to the opposite sex) (Table 101.1).

Diagnosis

It should be determined whether the impotence is primarily psychogenic or organic. The essential differences between the two are given below:

Treatment

Organic impotence must be managed according to its cause. In many cases the patient or his sexual partner may benefit from counseling or by psychotherapy. Drugs like androgens and replacement hormones are indicated only if the condition is secondary to an endocrine disorder.

Sildenafil

This is a selective inhibitor of cyclic guanosine monophosphate (cyclic GMP)- specific phosphodiesterase type 5, which is present in the cavernosa tissue. By selectively inhibiting this enzyme the catabolism of cyclic GMP is arrested and the normal erectile response of sexual stimulation is restored. Relaxation of smooth muscle allows inflow of blood into the corpora cavernosa and gives rise to penile erection, in response to sexual stimulation.

Sildenafil citrate is rapidly absorbed when given orally, blood levels peak at one hour and the mean half-life is 3-5 hours. Dose varies from 25-100 mg to be taken one hour before the desired sexual activity. The drug should not be used concurrently with nitrates or nitric – oxide donor drugs. Adverse effects include headache, flushing, dyspepsia, nasal congestion, diarrhea and impairment of platelet function.

Tadalafil is a newer drug with marginally better benefit and risk profile as compared with sildenafil.

Contraindications include advanced cardiac, hepatic and renal disease. In the Indian context since a good proportion of elderly women desire to avoid sexual intercourse, the drug should be given to elderly patients only after proper counseling of the sexual partners.

Sexual medicine has attained a high degree of specialization and several methods of treatments are in vogue to achieve penile erection and the sexual act. These include penile stimulation using stimulators, injection of papaverine into the corpora cavernosa and implantation of inflatable penile prosthesis which can be operated from outside.

Cryptorchism (syn: Cryptorchidism)

In male infants the testes are in the scrotum at birth. Descent of the testes into scrotum from the abdominal cavity occurs during the last month of pregnancy. Incomplete decent of testes in the scrotum is known as cryptorchism (**undescended testes**). Cryptorchism can be graded depending upon the extent of descent. Sometimes the testes may descend into the scrotum intermittently (**retractile testes**) or they may be retained at the upper part of the scrotum, groin or within the abdomen. Hereditary defects of testicular development may lead to cryptorchism. Even unilateral cryptorchism may be accompanied by infertility. Complications of cryptorchism include defective spermatogenesis and the development of testicular tumours.

Treatment

Success of therapy depends upon the initial position of testes and early institution of therapy. Treatment should be started before the age of 2 years. Human chorionic gonadotropin (hCG) and synthetic luteinizing hormone releasing hormone (LHRH) are used for this purpose. The hCG is given in a dose of 1500 units twice a week for 3-6 weeks. If the testes have descended into the inguinal canal, the prognosis is good. If there is no response to medical therapy, surgical correction has to be carried out.

Azoospermia

Absence of sperms from semen is called azoospermia. This is common in primary testicular disorders, which are developmental or endocrine in nature. In addition, several structural abnormalities also lead to this condition. These include congenital absence of vas deferens, acquired occlusion of the epididymis and vas deferens, and absence of seminal vesicles. Varicosity of the pampiniform plexus may lead to oligo/azoospermia in about 15% of cases.

Gonadal Disorders Affecting Both Sexes

DELAYED PUBERTY

When sexual maturation is delayed beyond 14 years in boys and 13 years in girls the condition should be fully investigated. Delayed puberty may be constitutional (idiopathic), or secondary to systemic diseases or hormonal disorders.

Causes of delay in puberty

1. Idiopathic delay of growth and development.
2. Neuroendocrine disorders.
 - Tumours of the central nervous system- craniopharyngioma, pinealoma.
 - Congenital malformations of the CNS
 - Hypopituitarism
 - Kallmann's syndrome
 - Laurence-Moon-Biedl syndrome
 - Prader-Willi syndrome
 - Functional gonadotropin deficiency.
3. Chronic systemic diseases
 - Malnutrition
 - Anorexia nervosa
 - Hypothyroidism
 - Debilitating illnesses like uncontrolled diabetes, renal failure, hepatic cirrhosis, thalassemia, malignancies and others.
4. Primary gonadal failure.
 - Chromosomal disorders-Klinefelter's and Turner's syndromes and their variants (Fig. 101.5).
 - Developmental agenesis- anorchia, cryptorchism
 - Other causes of primary gonadal failure.

Kallmann's syndrome: Isolated gonadotropin deficiency associated with partial or total loss of smell is known as Kallmann's syndrome. The olfactory bulb is not developed. There is failure of release of GnRH from the hypothalamus. Menstruation and fertility can be restored by treatment with GnRH or FSH and hCG.

Laurence-Moon-Biedl syndrome: In this rare congenital disorder which is characterized by obesity, dwarfism, hypogonadism, mental retardation, retinitis pigmentosa and polydactyly, a strong familial tendency is noticeable. It is inherited as autosomal recessive.

Prader-Willi syndrome: In this rare anomaly, intrauterine and postnatal hypotonia, obesity, mental deficiency, and hypogonadism are seen. The hands and feet are small. There may be mild retardation of growth. There will be feeding difficulty in the first few years of life followed by severe hyperphagia and uncontrolled obesity later on in life.

Sexual Precocity

The appearance of secondary sexual characters before 9 years of age in boys and 8 years in girls constitutes sexual

precocity. True precocious puberty is due to premature maturation of pituitary gonadal axis. Disorders of puberty may also result from increased secretion of testosterone or estrogen, independent of pituitary control. This leads to incomplete isosexual precocity.

Causes of sexual precocity

1. True precocious puberty (both sexes).
 - a. Idiopathic type
 - b. CNS tumours in the region of the hypothalamus.
 - c. Other CNS disorders, e.g. encephalitis, trauma, tuberculoma, hydrocephalus, neurofibromatosis.
 - d. Severe primary hypothyroidism.
2. Incomplete isosexual precocity in boys:
 - Ectopic hormone secretion, e.g. hepatomas, chorionepitheliomas, congenital adrenal hyperplasia (21 or 11 hydroxylase defects).
 - Adrenal carcinoma, Leydig cell adenoma, and drugs such as androgens, anabolic steroids.
3. Incomplete isosexual precocity in girls:
 - Ovarian diseases, e.g. follicular cysts, granulosa or theca cell tumours, gonadoblastoma, Albright's syndrome
 - Gonadotropin-producing tumours, e.g. teratoma, hepatoma, and drugs such as estrogens, gonadotropins.

Diagnosis

Cardinal feature is the appearance of secondary sexual characters and puberty before 9 years of age in boys and



Fig. 101.3: Sexual precocity girl aged 7 years



Fig. 101.4: Sexual precocity boy aged 8 years



Fig. 101.5: Girl of 18 with Turner's syndrome

8 years in girls. Precocious puberty also leads to increase in somatic growth and premature fusion of epiphysis before full growth is reached. This may result in shortness of stature. In contrast to somatic and sexual abnormalities the psychosexual and intellectual development corresponds only to the chronological age (Figs 101.3 and 101.4).

Differential diagnosis: Familial incidence of sexual precocity should suggest the possibility of true idiopathic precocious puberty, congenital adrenogenital syndrome or neurofibromatosis. Endocrine tumours lead to rapid development of sexual maturation.

Albright's syndrome (polyostotic fibrous dysplasia of bone): This is a rare disorder, which may be associated with precocious puberty due to inappropriate activation of the gonadotropins receptor. Other abnormalities include irregular pigmentation and dysplasia of several bones.

Treatment

Drugs inhibiting gonadotropins are partly successful in avoiding premature fusion of epiphyses and arresting sexual precocity. Drugs like medroxyprogesterone acetate 100 mg given IM once a week or 200-300 mg as depot injections, suppress gonadotropin secretion. For central or true precocity, GnRH agonists given continuously can delay puberty.

INFERTILITY

Definition: Infertility is defined as inability to achieve pregnancy after one year of normal married life. In primary infertility the woman fails to conceive, whereas in secondary infertility there is evidence of fertility occurring in the past such as abortion, ectopic gestation or successful childbirth. In general, the male partner is at fault in 40% and the female partner in 40%. The cause is obscure in 20% cases.

Ovum Transport

Normally the ovum with attached follicular cells passes through the fallopian tubes by ciliary action and reaches

the uterus in 60-70 hours after ovulation. Fertilization takes place in the ampulla of the tube. After fertilization and extrusion of the second polar body, the ovum becomes impervious to penetration by other sperms.

Sperm Transport

In normal adult men seminal ejaculate measures 3-7 mL and the sperm count is greater than 60 million/mL. More than 60% of sperms show progressive motility at 2 hours after ejaculation and more than 60% of the sperms have normal morphology. The ejaculated semen rapidly forms a gel and then liquefies. In the female genital tract the sperms acquire the capacity to penetrate the ovum (capacitation). About 200 sperms rapidly pass into the uterine cavity and the capacitated sperm penetrates the ovum and fertilizes it.

Causes of Male Infertility

To be fertile, a man has to have normal spermatogenesis, successful sperm maturation and storage, normal epididymal transport, proper functioning of the accessory glands and optimal timing of intercourse. Common causes of infertility include sperm counts below 20 million/mL; ejaculate volume below 1.0 mL, infections, failure of liquefaction, and sperm agglutination. Temporarily sperm counts may be suppressed by factors like fever, systemic illnesses, drug therapy and endocrine disorders.

Clinical evaluation comprises of a detailed history, physical examination of the genitalia and systemic examination, semen analysis, hormonal profiles, tests for sperm antibodies in the couple, testicular biopsy, karyotyping and other tests (Table 101.2).

TABLE 101.2

Causes of male infertility

<i>Pre-testicular causes:</i> 1. Hypothalamopituitary diseases Panhypopituitarism or selective FSH deficiency Hyperprolactinemia Drugs like phenytoin, androgens and estrogens Deletion of the long arm of Y chromosome and other subtle defects in the Y chromosome. 2. Testicular diseases: Testicular atrophy Cryptorchism Varicocele Spermatogenesis arrest Drugs like cyclophosphamide and other antimitotic drugs Autoimmune disorders giving rise to antibodies against testicular basement membrane and sperms. 3. Post testicular causes Infection of the genitourinary tract with bacteriospermia, congenital or acquired ductal obstruction, varicocele Disorders of ejaculation, e.g. retrograde ejaculation Anatomical defects such as hypospadias.

Treatment

The management of infertility in men involves effective correction of all treatable disorders like varicocele, endocrinopathies and ductal obstruction. Often specialized surgical interventions and prolonged management are necessary to ensure success. Though many cases respond favourably to therapeutic interventions, some remain intractable.

In vitro fertilization techniques especially intracytoplasmic sperm insertion (ICSI) are highly successful.

Causes of Female Infertility

Investigation and management of female infertility is generally done by the gynecologist. Women show maximal fertility from 24 to 35 years. The investigations include tests to detect defects in ovulation, transport of the ovum and sperms to the uterus, morphological abnormalities of the female genital tract, defects of facilitation of the sperms in the vagina, hormonal abnormalities and immunological causes. About 30-40% of cases have pelvic abnormalities like tubal occlusions, adhesions and endometriosis. Abnormalities of cervical secretions occur in 10-30%. Uterine abnormalities commonly cause recurrent abortions and are diagnosed by a full gynecological examination. Sometimes immunological abnormalities may develop leading to infertility. These are (1) ABO blood group incompatibility (2) circulating sperm agglutinating and sperm immobilization antibodies in women or (3) autoimmune disorders in men.

HERMAPHRODITISM

Syn: intersex

Intersex refers to the condition when the external genitalia are ambiguous; that is neither truly female nor truly male. It could be a male child whose genitalia are not adequately masculinised or a female child whose genitalia are virilised. Intersex is classified into the following categories.

True hermaphroditism: True hermaphroditism is characterized by the presence of both ovarian and testicular tissues in one or both gonads. Variable differentiation of the internal and external genitalia is seen. The external genitalia sometimes resembles that of a male or female, but mostly they are ambiguous. Chromosomal analysis reveals the common karyotypes as 46 XX.

Pseudohermaphroditism

In pseudohermaphroditism, the gonadal sex is at variance with the gender sex. The terms male or female denote the corresponding gonadal sex. Thus, in **male pseudohermaphroditism**, the gonads are exclusively testes with XY karyotype, but phenotypic characteristics are to varying

degrees female (failure of virilization). Causes include: defective testicular stimulation due to gonadotropin resistance or deficiency, sub-optimal testosterone and/or antimüllerian hormone secretion and failure of tissue response to androgens and/or antimüllerian hormone.

In female pseudohermaphroditism, the gonad is an ovary and the karyotype is XX. Varying degrees of virilization of external organs may be present. Ambiguity of external genitalia is usually caused by androgenic influences. Often there is no abnormality of internal genital development or functional capacity of the ovaries. The uterus, tubes and ovaries may be normally present and reproductive function may become possible after suitable correction of the external genitalia, which are masculine. Several causes may lead to female pseudohermaphroditism. The most common cause is congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Patients have impaired cortisol synthesis, high ACTH levels, and adrenal androgen hypersecretion. Steroid therapy can inhibit the ACTH drive and correct androgen excess.

It is preferable to investigate these cases in the first year of life so that the sex of the child can be assigned before the second year. Therapy is based on thorough clinical, psychological, and genetic analysis. In female pseudohermaphroditism the external genitalia should be surgically corrected during the first year of life. In male pseudohermaphroditism and intersexual genitalia, sex is assigned according to the state of external genitalia. Prolonged therapy may be necessary to achieve reasonably satisfactory results. Therapy includes hormone supplementation, surgical correction, and psychological rehabilitation.

Gonadal Disorders in the Female

Ovarian hormones: Estrogens stimulate sexual heat (estrus) in female animals. Major estrogens produced by the ovary are estradiol and estrone. The former is the main and more powerful hormone. Estrogens are inactivated by the liver and several metabolites are excreted in urine and bile as the conjugated products (Fig. 101.6).

Actions of Estrogens

Estrogens bring about pubertal changes occurring in females. They are responsible for the development of the breasts, formation of the feminine body contour, proliferation of uterine endometrium, vaginal keratinization and epiphyseal closure.

Progesterogens and their Action

These hormones prepare the uterus for reception and development of the fertilized ovum. The corpus luteum does this function normally and its main secretion is

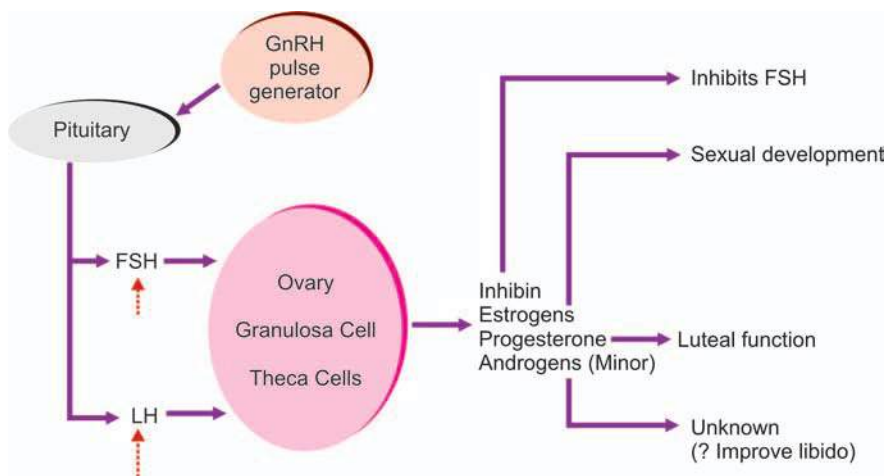


Fig. 101.6: Diagrammatic representation of ovarian function. This figure shows the GnRH Pulse generator in the hypothalamus that controls the pulsatile secretion of FSH and LH, which act on the ovarian cells to produce the sex hormones

progesterone which is under the control of LH of the pituitary. Synthetic progesterone with high potency is available for therapeutic uses. Progesterone makes the endometrial glands coiled and secretory (secretory phase). They are prepared for nidation of the ovum. The rise of temperature at ovulation is mediated by progesterone. Withdrawal of progesterone results in menstrual bleeding.

Assessment of ovarian function: Clinically, ovarian function can be assessed from the development and maintenance of the breasts and the internal and external genitalia. Hypofunction of the ovaries manifests as delay in sexual development, menstrual irregularities and disorders of ovulation. Several conditions give rise to such a clinical picture. These include primary ovarian disease, hypothalamopituitary abnormalities, unresponsiveness of the target organs, systemic diseases and gonadal dysfunction occurring in other endocrine diseases.

Investigations

These include: (1) Determination of levels of FSH/LH and ovarian hormones (2) Studies of the effect of ovarian hormones on vaginal epithelium such as cornification, cervical mucus and changes in the endometrium and (3) tests of ovulation such as measurement of basal body temperature which goes up at the time of ovulation, and serial ultrasound measurements of follicle maturation.

OVARIAN HORMONAL DISORDERS

Ovarian dysfunction manifests clinically as amenorrhea, infantilism or sexual precocity. In primary ovarian failure, the levels of pituitary gonadotropins are high. Ovarian failure may be due to primary disease of the ovaries in

60% and extra-ovarian causes in 40% of cases. For proper development and functioning of the ovaries, the essential requirements are:

1. Presence of two genetically active X-chromosomes.
2. Absence of Y- Chromosome.
3. Proper endowment of germ cells (oogonia).
4. Development of germ cells into primary oocytes and
5. Adequate gonadotropin stimulation in fetal life.

Abnormalities of any or all of these factors lead to ovarian failure.

OVARIAN FAILURE

Causes of ovarian failure are shown in the box below. When it occurs due to a disease of the ovary, it is called **primary ovarian failure** when it is secondary to gonadotropin deficiency is called **secondary ovarian failure**.

Primary Ovarian Failure

Causes

1. Dysgenesis or agenesis of the ovaries.
2. Resistant ovary syndrome- the ovaries are resistant to the action of pituitary gonadotropin even though they are morphologically and genetically normal.
3. Polycystic ovaries.
4. Prepubertal infections like tuberculosis and mumps, which give rise to oophoritis.
5. Systemic diseases like thalassemia, mucopolysaccharidoses, dystrophia myotonica, and autoimmune disorders such as primary Addison's disease
6. Female pseudohermaphroditism.
7. Isolated enzyme deficiencies such as 17 –alpha hydroxylase deficiency and 21- hydroxylase deficiency.
8. Genetic disorders, e.g. Turner's syndrome.

Secondary Ovarian Failure

1. Panhypopituitarism.
2. Prolactinomas- prolactin reduces ovarian response to FSH and LH and pituitary response to LHRH.
3. Acromegaly.
4. Isolated gonadotropin deficiency.

AMENORRHEA

Primary amenorrhea is delay of menarche beyond 18 years of age and secondary amenorrhea denotes cessation of menstruation for 6 months or more in normally menstruating women.

Gynecological causes:

1. Diseases of the endometrium
2. Obstruction to the outflow tract of the uterus
3. Imperforate hymen.

Endocrine causes:

1. Primary or secondary ovarian hypofunction and
2. Other endocrine disorders like Cushing's syndrome, adrenogenital syndrome, Addisons disease and thyrotoxicosis

Systemic disease

1. Disorders such as chronic liver disease, renal disease, diabetes mellitus and malnutrition

Drugs:

Several drugs which include hormonal and non-hormonal preparations are capable of producing amenorrhea, e.g. corticosteroids, androgens, estrogens, contraceptive pills, psychotropic drugs, anti-hypertension drugs and others

Hypothalamic causes

Anorexia nervosa, psychiatric disorders, hypothalamic tumours and developmental neurologic defects such as Kallmann's syndrome

Diagnosis

The most common physiological cause of secondary amenorrhea in the young is pregnancy. This should be excluded in all cases. Other common causes include menopause, drug therapy, systemic illnesses and psychiatric disturbances. Signs and symptoms of estrogen deficiency such as vasomotor instability and drying up of vaginal secretions should suggest the possibility of primary ovarian failure or menopause. The investigations and management of amenorrhea are the realm of the gynecologist.

Polycystic Ovary Syndrome (PCOS)

Syn: Stein-Leventhal syndrome,
Cystic disease of the ovary

This is a heterogeneous disorder, clinically characterized by ovulatory failure, hirsutism, obesity, glucose intolerance, resistance to insulin, dyslipidemia and infertility.

The ovaries are enlarged, multicystic, and show hyperplastic theca cells around the cysts. Only very small amounts of estradiol are produced by the immature follicles. Excessive amounts of androgens are produced by the hyperplastic theca cells and stromal cells. The enlarged cystic ovaries on both sides can be made out by bimanual examination, by ultrasonography or by diagnostic laparoscopy. Therapeutic measures are designed to restore fertility, normalize menstruation and reverse hirsutism. Signs of insulin resistance like acanthosis nigricans may be looked for in these patients.

The three key features of PCOS are

- a. oligomenorrhea
- b. hyperandrogenesis (clinical and laboratory parameters) and
- c. absence of other endocrinological disorders such as congenital adrenal hyperplasia, hyperprolactinemia, thyroid dysfunction and androgen secreting tumours.

The exact etiology is not known but the main biochemical abnormality in PCOS is hyperinsulinemia secondary to insulin resistance. This leads to ovarian overproduction of testosterone, and adrenal overproduction of DHEAS and androstenedione. Increased testosterone affects the pituitary ovarian axis leading to decrease in production of estrogen, abnormal production of progesterone, and overproduction of testosterone, LH and FSH.

Those with PCOS are at higher risk of diabetes and cardiovascular disease later in life. The diagnosis of PCOS is by demonstration of the cystic ovaries, exclusion of other hyper-androgenic disorders in women with chronic anovulation and androgen excess. PCOS is considered as a part of the metabolic syndrome.

Treatment of this condition depends on the patient's main concerns. Bilateral wedge section of ovaries were done previously to induce ovulation. Metformin is commonly used to reverse the endocrine abnormalities in PCOS by reducing the resistance to insulin, and correcting the other endocrine abnormalities. Dose of metformin is 500-750 mg bid. Metformin can be continued during pregnancy also especially the first two trimesters. Other treatment modalities include anti-androgens like spironolactone and finasteride for controlling virilizing signs, and cyclical estrogen and progesterone for regularizing the menstrual cycles. For inducing ovulation and fertility, clomiphene citrate can be used in doses of 50 mg daily for 5 days, preferably from the fifth to the ninth day of the menstrual cycle. Clomiphene increases the output of gonadotrophins from the pituitary. Cyproterone acetate which is an androgen antagonist relieves hirsutism. Application of hair removing preparations improves cosmetic results.

Dysfunctional Uterine Bleeding

Excessive or more frequent menstrual bleeding resulting from functional disturbances, but without other obvious pathological causes is called dysfunctional uterine bleeding. Hormonal imbalance and nutritional, psychological and hematologic factors play contributory roles. This is a common gynecological problem in women in the fourth and fifth decades of life, often requiring hysterectomy.

Medical Problems of Menopause

Women attain menopause usually between 40 and 47 years. Menopause is considered to be complete when a woman has not had periods for one year in the absence of any pathological condition or obvious features of ovarian deficiency.

Physiological changes: Menopause represents a form of primary ovarian failure. The number of ovarian follicles steadily decline with age and these follicles become less and less sensitive to the action of FSH as age advances. As women reach menopause the FSH/LH reach high levels and the estrogen levels fall. Because of diminishing number of follicles in the ovary production of estrogen is reduced. In many subjects the development of menopause may be quite uneventful and asymptomatic.

The following four groups of symptoms may develop in those who become symptomatic:

1. **General symptoms:** These include insomnia, nervousness, anxiety, depression, irritability, headache, dizziness, and joint pains. These affect the quality of life considerably.
2. **Vasomotor symptoms:** These consist of hot flushes, inappropriate perspiration, and palpitation, occurring frequently as sudden burning feeling all over the body followed by sweating, faintness, and palpitation. In 10-20% of women these symptoms are very frequent and disabling. Low body weight, sedentary habits and smoking increase the risk of developing these symptoms.
3. **Atrophic changes in the genitals:** The main symptoms are urinary stress incontinence, vaginal atrophy, vaginal discharge and irritation, dryness, dyspareunia, pruritus, and burning.
4. **Cosmetic effects:** Characteristics changes include the development of fine folds and marks radiating from the mouth, sagging of the infraorbital fold of skin on

the face, sagging and atrophy of the breasts, and generalized wasting of adipose tissue. Osteoporosis is common and this may lead to fractures of the vertebrae and limbs.

Management: Till five years ago hormonal replacement therapy (HRT) was widely used to counteract the failure of production of ovarian hormones —estrogen and progesterone. It was symptomatically very effective, but long term studies (Women's Health Initiative Study) revealed that the adverse effects included increase in cardiovascular events, venous thromboembolism, and a small, but significant increase in the incidence of endometrial and breast cancers. These findings have led to the avoidance of HRT as a routine. However, in troublesome symptomatic menopausal syndromes, estrogen supplementation is instituted for a short duration in the small doses. Short term indications for estrogen therapy are: a) hot flushes (b) dyspareunia (c) cosmetic disability. Estrogens are given orally in cycle of three weeks followed by a free interval for one week. In those cases with intact uterus, progestogens are employed in the third week. Estrogen therapy is absolutely contraindicated in those with cerebrovascular accidents, recent myocardial infarction, and carcinoma of breast, pancreatitis, cholecystitis, endometrial carcinoma, and recurrent venous thromboembolism. Designer estrogens (selective estrogen receptor modulators) have beneficial effects of estrogen without the disadvantages. An example is raloxifene in a dose of 60 mg once daily. These are emerging drugs for hormone replacement. Relative contraindications include cystic disease of the breasts, heavy smoking, hypertension, family history of carcinoma of the breast, liver diseases, cholelithiasis, diabetes mellitus, endometrial hyperplasia, gross obesity, and a single episode of thrombophlebitis. There has been an increasing focus on calcium and vitamin D supplementation to preserve bone health, and the judicious use of anti-resorptive agents acting on bone such as alendronate wherever appropriate for the management of osteoporosis. Clonidine in doses of 50 µg twice daily orally has been found useful in women who cannot tolerate estrogen. Clonidine may cause unacceptable side effects like sedation, dizziness and nocturnal restlessness. Drugs used in other systems of medicines such as plant products have been tried.

General measures include nutritional supplements and selective serotonin uptake inhibitors (SSRI) such as fluoxetine and sertraline which improve the mental state and reduce hot flushes.

102

Miscellaneous Endocrine Related Conditions

K.V. Krishna Das, R.V. Jayakumar,
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Chapter Summary

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Endocrine Disorders of the Breast

K.V. Krishna Das

GENERAL CONSIDERATIONS

The breasts develop from the mammary crest of the ectoderm called the milk line. Though the mammary gland is rudimentary at birth, sometimes the high prolactin levels derived from the mother may induce transient milk secretion in the newborn (*witch's milk*). The breasts grow and areolae enlarge with puberty depending on the influence of estrogens and progesterone.

The mammary glands develop fully with the formation of alveoli and they start functioning only during pregnancy. During early pregnancy the breasts enlarge and become nodular. The areolae become pigmented with the development of Montgomery's tubercles. Later, colostrum is secreted.

Hormonal interactions: Estradiol stimulates growth of mammary ducts and nipples and the formation of progesterone receptors. Cortisol and growth hormone potentiate the effects of estrogens. Further development of lobules and alveoli are mediated by four hormones—estradiol, progesterone, growth hormone, and prolactin. Progesterone inhibits the formation of estrogen receptors. Lactation is initiated by increase in prolactin and the sudden reduction in progesterone level on delivery of the placenta. Oxytocin facilitates ejection of milk by

contraction of myoepithelial cells of the alveoli. Regular suckling stimulates prolactin secretion by a neuro-endocrine reflex and this is responsible for maintenance of lactation. Other hormones like growth hormone, ACTH, thyroxine, human placental lactogen, and insulin also play their role in the maintenance of optimal milk secretion.

In health the size of the breasts varies. The two sides are not symmetrical. During menstrual cycles premenstrual pain and tenderness may develop even in normal women. Though generally mild, sometimes the pain and discomfort may be severe. These symptoms are promptly relieved by diuretics, progesterone or bromocriptine. Lactation can be suppressed by high doses of estrogens or bromocriptine.

ATROPHY OF BREASTS

This commonly occurs when the estrogen levels fall as in hypogonadism or menopause. Disorders occurring before puberty lead to abnormal breast development. Lesions occurring thereafter result in regression of the size of the breasts. Breast atrophy is also common in hyper-androgenism due to any cause—adrenal, ovarian or iatrogenic.

HYPERTROPHY OF BREASTS

Hyperprolactinemia may give rise to bilateral hypertrophy of breasts with galactorrhea. This may be idiopathic in some rare cases. Unilateral breast enlargement is usually due to juvenile fibroadenoma, malignant tumours, infections like tuberculosis or infiltrations as in acute leukemia. Bilateral fibroadenosis is associated with premenstrual pain and it commonly develops after puberty.

GYNECOMASTIA

The increase of glandular and stromal tissue of male breast is termed gynecomastia. True glandular enlargement has to be differentiated from adipose tissue deposition (pseudogynecomastia), carcinoma or neurofibromatosis by careful examination. Increased levels of estrogens with or without reduction of androgens lead to gynecomastia. If prolactin is also increased, galactorrhea follows.

Causes of Gynecomastia

1. About 50-70% of normal boys develop transient gynecomastia during puberty.
2. Primary testicular failure as in Klinefelter's syndrome, cryptorchism, leprosy.
3. Testicular tumours—seminoma or teratoma.
4. Hepatic cirrhosis.
5. Endocrine disorders like hyperthyroidism, hypothyroidism, adrenal cortical overactivity.
6. Paraneoplastic syndromes, e.g. bronchogenic carcinoma, renal carcinoma, Hodgkin's disease.
7. Drugs, e.g. estrogens, digitalis, spironolactone, reserpine, marijuana, metoclopramide, methyldopa, H₂-receptor antagonists, phenothiazines and others.
8. Trauma to chest wall.
9. Idiopathic.

The serum levels of testosterone, 17 estriol and gonadotropins are normal in idiopathic gynecomastia. High serum LH levels indicate primary testicular failure or HGH secreting choriocarcinoma of the testes. A very high level of serum 17 = estradiol should suggest a feminising adrenal carcinoma.

Treatment

Pubertal gynecomastia is often self-limiting and this may be left alone after assuring the individual of its benign nature. In others, the cause should be detected and treated. In some cases surgical excision is done for cosmetic reasons and to prevent neoplasia later.

GALACTORRHEA

Nonphysiological secretion of milk from the breast is known as galactorrhea. It is seen in both sexes, and the amount of milk may vary from a few drops to large volumes. Amenorrhea accompanying galactorrhea suggests a hypothalamo pituitary disorder.

Causes

1. Hypothalamo pituitary diseases.
 - a. Hypothalamic lesions, e.g. tumours, granulomas, histiocytosis X, postencephalitic sequelae, trauma, pituitary stalk section.
 - b. Pituitary disease, e.g. prolactinoma, acromegaly, empty sella syndrome, Cushing's syndrome.
2. Functional hyperprolactinemia
 - a. Drugs, e.g. oral contraceptives, digoxin, chlorpromazine, reserpine, methyldopa and several others.
 - b. Chest wall lesions, surgery, herpes zoster, burns.
3. Other endocrine disorders, e.g. myxedema, adrenal cortical disorders.
4. Ectopic prolactin secretion and paraneoplastic syndromes, e.g. bronchogenic carcinoma, hypernephroma, Hodgkin's disease.
5. Chronic renal failure.
6. Idiopathic.

Diagnosis

Galactorrhea may be an isolated symptom or this may be part of other endocrine manifestations. Many patients do not volunteer this symptom and, therefore, it is likely to be missed if not carefully looked for.

Management

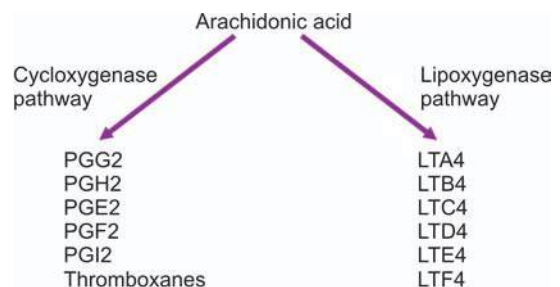
Therapy depends upon the cause. Endocrine disorders should be treated appropriately. Drug induced galactorrhea responds promptly to drug withdrawal. When the cause is obscure, bromocriptine in a dose of 5 mg/day may be tried. It stops galactorrhea within a few weeks. Adverse side effects of bromocriptine include nausea, vomiting, and hypotension.

Prostaglandins

R. V. Jayakumar, A.G. Unnikrishnan

Introduction

Von Euler of Sweden first discovered and isolated prostaglandins from human semen in the 1930s. Attributing their origin from the prostate gland, he termed them prostaglandins. Now it is known that prostaglandins are present and are synthesized in all tissues in the body. Prostaglandins are biologically synthesized from arachidonic acid. Essentially they are unsaturated carboxylic acids. They have a 20-carbon skeleton with a five-member ring. Like classic hormones, they act as chemical messengers, but with the difference that they act within the cells which produce them, without being transported to distant sites for their action. As per very rigid nomenclature systems, only the compounds produced by the cyclo-oxygenase pathway and prefixed as "PG" are termed prostaglandins, but all the other molecular derivatives of arachidonic acid which are called eicosanoids, belong to the prostaglandin family and they will be discussed together (Fig. 102.1).



Note : LT stands for Leukotrienes

Fig. 102.1: The eicosanoid family PG—prostaglandins
LT—Leukotrienes

Physiological Role

The most important role is in the modulation of the immune response. Leukocytes flock to areas of tissue destruction and release local prostaglandins that cause fever and even pain. In addition, prostaglandins have effects on vascular function. For instance thromboxane A₂, a potent prostaglandin, causes vascular constriction and aggregation of platelets. Another prostaglandin, PGI₂ has the opposite effect. Some prostaglandins stimulate smooth muscles contraction. For instance, leukotrienes cause bronchoconstriction and PGE₂ stimulates uterine contractions.

Clinical Applications

PGE₂, as mentioned earlier, can stimulate uterine contractions and it is used for inducing labour. Aspirin inhibits the action of cyclooxygenases COX₋₁ and COX₋₂ which can convert arachidonic acid to prostaglandins. By this effect aspirin suppresses prostaglandin-induced inflammation and pain. This is the main mechanism by which aspirin and non-steroidal anti-inflammatory agents (NSAIDs) act as anti-inflammatory and analgesic agents. Some prostaglandins that have beneficial effects on blood flow, like PGE₁ have been used to improve the microcirculation. Administration of PGE₁ helps to occlude a patent ductus arteriosus if administered to be baby in the perinatal and neonatal periods. In addition, leukotriene antagonists like monteleucast have been used in the therapy of bronchial asthma. Prostacyclin (PGI₂) reduces pulmonary artery pressure and therefore it is used in the treatment of pulmonary hypertension. Glucocorticoids exert their anti-inflammatory effects, by inhibiting the enzyme

phospholipase A, which converts phospholipids into arachidonic acid, thereby reducing prostaglandin and leukotriene production.

Aspirin exerts its anti-platelet effect by irreversibly inhibiting action of thromboxane which favours platelet aggregation and promotes thrombosis.

Endocrine Syndromes Produced by Cancer

R.V. Jayakumar, A.G. Unnikrishnan, K.P. Poulse

Introduction

Wherever a hormone is abnormally produced from a source that is different from the tissue of its usual origin, the production is called ectopic. Since most of the conditions are malignant, these are called *paraneoplastic syndromes*. An example of this is small cell lung cancer, which can produce ACTH in excess quantities. Usually ectopic hormones produce clinical syndromes because the hormones are produced in excess and in an unregulated manner. Some of the ectopic hormone producing states and the clinical conditions they produce are listed in Table 102.1. The common syndromes amongst them are discussed below. The appropriate therapy is to treat the hormonal abnormality and attend to the tumours which produce the hormones.

Ectopic Cushing's Syndrome

Ectopic ACTH production can stimulate the adrenal glands to produce excess cortisol and this results in

TABLE 102.1	
Common paraneoplastic hormonal abnormalities	
Hormone excess	Clinical syndrome
Chorionic gonadotropin	Gynecomastia
Vasopressin (ADH)	Syndrome of inappropriate ADH
Parathormone	Hypercalcemia
Growth hormone	Acromegaly
Growth hormone-releasing hormone	Acromegaly
Parathyroid hormone related protein	Hypercalcemia
Calcitonin	No known clinical effect
Somatostatin	Hyperglycemia, diarrhea
IGF-1	Hypoglycemia
ACTH,	Cushing Syndrome
Gastrin	Peptic Ulcer Disease
Erythropoietin	Polycythemia
Activated Vitamin D	
Hypercalcemia	

Cushing's syndrome. The most common neoplasms that result in ectopic Cushing's syndrome are carcinomas of the lung, thymus and pancreas. Rarely pheochromocytomas, medullary carcinoma thyroid, bronchial carcinoids and adenomas can cause this syndrome. The diagnosis should be suspected clinically if features which suggest underlying malignancy such as weight loss, severe pigmentation, muscle weakness, hypokalemia, alkalosis, lack of cortisol suppressibility to the high dose (8 mg) dexamethasone, and ACTH levels more than 1000 pg/mL occur. Recent studies have yielded an insight into the molecular basis of this syndrome. Usually ACTH is part of a larger precursor molecule called proopiomelanocortin (POMC). POMC gene is stimulated by 3 promoter genes: P1, P2 and P3. In the pituitary P2 is the promoter gene, while in all peripheral tissues, usually P3 (which results in a weak activity of the POMC gene) is the dominant one. In tumours resulting in ectopic ACTH syndromes, it has been shown that P1 replaces P3. P2 is a promoter that results in a large transcript with identical product as P2 of the normal pituitary. Thus while normal peripheral tissues have P3, a weak promoter, the ectopic peripheral tissue has P1, which is a strong promoter resulting in Cushing's syndrome.

The treatment of this syndrome is the excision of the tumour. Ketoconazole or adrenalectomy may be needed symptomatically if Cushing's syndrome is very severe.

Hypercalcemia

Hypercalcemia of malignancy may be either parathyroid hormone (PTH) dependent or independent. Usually there is release of PTH or PTH-like protein. PTH or PTH-like protein dependent syndromes result in hypercalcemia with hypophosphatemia, as this is the classic action of PTH. PTH-independent syndromes in malignancies can cause severe hypercalcemia and hyperphosphatemia through different mechanisms like extensive bony metastases, tumour lysis syndrome or overexpression of 1-alpha hydroxylase enzyme, which activates vitamin D at the 1-alpha position in an unregulated manner, resulting in extreme hypercalcemia with hyperphosphatemia.

Hematological malignancies like lymphoma and solid tumours like bronchogenic carcinoma may be associated with hypercalcemia.

Syndrome of Inappropriate ADH Production

ADH or vasopressin or anti-diuretic hormone decreases free water excretion and retains free water, resulting in a dilutional hyponatremia. Unregulated and excess production of ADH is called SIADH. Lung carcinoma, predominantly small or oat cell carcinoma is the most important cause of SIADH. Usually the patient appears euolemic, and hyponatremic. Plasma osmolality low and urine osmolality is high.

Rare Endocrine Syndromes due to Tumours

Growth hormone: There have been a few reported cases of acromegaly due to excess growth hormone or growth hormone releasing hormones from islet carcinoids.

Erythropoietin: Production of excessive quantity of erythropoietin by tumours can result in secondary polycythemia, as erythropoietin stimulates erythropoiesis.

RBC synthesis. Tumours of the kidney, liver, cerebellum and others organs may rarely produces erythropoietin - like substances.

Insulin like growth factors: Some carcinoids can produce insulin-like growth factors or even insulin, causing hypoglycemia. Rarely, large retroperitoneal tumours, especially sarcomas cause excess utilization of glucose resulting in hypoglycemia. Certain tumours like hemangiopericytomas can lead to phosphate depletion due to the elaboration of phosphaturic factors called "**phosphatonins**". In these situations, metabolic activation of vitamin D into its active form is also inhibited. This syndrome is rare. It results in a particular variety of osteomalacia known as "oncogenic osteomalacia".

Human chorionic gonadotropin (hCG): Production of hCG in dysgerminomas can lead to stimulation of the testes by hCG which, in turn produces estrogens and cause breast enlargement in boys.

Principles and Practice of Geriatric Medicine

B. Krishna Swamy, K.V. Krishna Das

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General Considerations

Changing demographic pattern worldwide, resulted in steep rise in elderly population both in developed and developing countries. The elderly population in India has risen from 12 million in 1901 to 70 million in 1999 (7% of the total population). India has the second largest elderly population, next only to China in the world. This phenomenal growth of geriatric population is the result of improved life expectancy, better socioeconomic environment, advances in the medical field and prevention and control of communicable diseases.

Along with this there is an exponential increase in disability, mental and physical morbidity of the elderly population, needing special health and social services. The manner in which persons age and the capacity to ward off disease are linked to socioeconomic factors the mental and physical activity patterns and the degree of fitness during life. Heredity and life-style patterns govern fitness and physiological reserve.

Regulated physical activity protects against obesity, type 2 diabetes mellitus, ischemic heart disease, hypertension, strokes and orthopedic disabilities. Regular employment protects against depressive illness.

Geriatric medicine is that branch of medicine concerned with preventive, curative and rehabilitative methods of management of medical, psychological and social problems of the aged. The term "Geriatrics" is

derived from the Greek word *Gerios* meaning old age and was coined by Ignatz L. Nascher in 1909.

Elderly people behave differently from others in respect to predisposition to disease, general resistance against infections, and response to drugs. The discipline of geriatrics deals with the diagnosis and treatment of persons aged 65 years and above. The age of 65 as the commencement of senescence has been accepted arbitrarily. During senescence all illnesses are accompanied by a higher mortality than when occurring in younger age groups. A better functional definition of senescence will be as the period when there is commencement of loss of vigor, skin changes of old age, slowed activity of the musculoskeletal system and onset of deterioration of mental functions. The life-span of man is increasing all over the world. In India over 7% of the population is above the age of 60 years. The maximum life-span has not changed despite increase in the average life-span.

Definition of aging: The changes in structure and function occurring in persons after the attainment of sexual maturity constitute aging. With advancing age the adaptability to overcome environmental or internal challenges decreases and the probability of death increases. Tissues differ in their behaviour during aging. Visual and auditory functions start deteriorating even in the third decade of life. The rate of deterioration in other organ systems depends to a great deal upon other factors like coexistent diseases, diet, physical exercise, and to a great deal on hereditary factors. The present explanations for aging process are not fully satisfactory though many have been put forward.

In dealing with problems in the elderly, it is essential to bear in mind that they may have (1) multiple problems, (2) atypical presentation of diseases, and (3) the response to drugs and other therapeutic measures may be unpredictable. Irrespective of the symptom, a full physical examination is absolutely necessary to make a complete diagnosis. Since the aged are very susceptible to adverse drug reactions, close monitoring is essential. As yet no drug is available to combat senescence. The aim of therapy is not just to prolong life but to make it useful and

enjoyable. General principles of therapeutics in the elderly are given in Chapter 4.

1. The term old is used to denote persons aged 75 years and above.
2. The term advanced age is used for persons aged above 85 years.

In older persons compensatory mechanisms are impaired either due to aging or due to disease. Therefore, even minor ailments tip the metabolic equilibrium. From a physiological stand point aging may be considered as a progressive diminution of function of each organ system so as to be unable to maintain homeostasis in the presence of a challenge. This graded decline of physiological reserve (homeostenosis) begins in the third decade and occurs in all organs systems independent of each other. This decline may be modified by heredity, environment, diet and personal habits.

Morphological Changes

Cellular changes: The total number of cells comes down in parenchymal organs such as brain, liver, and heart. Cell sizes and staining properties become irregular and many binucleate cells appear. The water content of collagen comes down and cross-linkages increase, rendering it increasingly rigid and inflexible. This affects mobility adversely. Elastin also shows degenerative changes. The proportion of body fat in males rises from 19% at 25 years to 35% at 70. In females, the change is from 33 to 49%. Serum albumin falls from 4g/dL in youth to 3.5g/dL in persons >80 years.

Alterations in Organs

Skin: The skin becomes hyperkeratotic, atrophic, and wrinkled. *Sweat glands* and sebaceous glands diminish.

Greying of hair occurs because of the progressively smaller amounts of dopa-oxidase and tyrosinase in hair follicles, both of which are required for the synthesis of melanin. Greying of the hair shows a strong genetic predisposition (autosomal dominant) and in the majority of people 50% of the hairs are grey above the age of 50 irrespective of the sex and hair colour.

Heart and Blood vessels: Ischemic and hypertensive diseases often supervene as age advances and, therefore, it is difficult to separate these changes from purely aging process. Above the age of 75 years, interstitial fibrosis and fatty infiltration of myocardium develop, even in the absence of any concomitant disease. Lipofuscin accumulates in the myocardium. Endocardium and valves are thickened. Amyloidosis may develop. Loss of elasticity leads to widening and tortuosity of the aorta. Atherosclerosis accelerates these changes.

Lymphatic organs: The spleen undergoes atrophy. There is increase in the number of plasma cells. Above the age of 70 years serum globulins are increased and amyloidosis may develop. This form of amyloidosis may affect the heart, islets of Langerhans, peripheral and autonomic nerves, and brain. There is generalized impairment of immune processes and, therefore, infections take a fatal turn.

Cancer: The risk of cancer increases with age and neoplasia accounts for 20% of the total deaths. Atherosclerosis, hypertension, and cancer together cause the majority of deaths. Invariably multiple diseases coexist in the elderly patients and diagnosis is often difficult. The symptomatology is atypical.

HEALTH PROBLEMS IN THE ELDERLY

Nutrition: The body weight tends to come down above the age of 70. Social neglect, loss of earning capacity, and intercurrent illnesses tend to precipitate malnutrition.

Infections: The general resistance against microbes is lowered by malnutrition and impairment of immune mechanisms. The local defence mechanisms of the respiratory, urinary, and alimentary tracts, mouth, skin, genitalia, and eyes are impaired and, therefore, bacterial infections are common. A common symptom occurring in the elderly subject is alteration in the level of consciousness, delirium, and coma, and these must raise suspicion of generalized infection. Fever may not be a prominent symptom in the early stages. Dehydration and electrolyte disturbances are common because of chronic renal impairment and endocrine deficiencies.

Cardiovascular changes: Ischemic heart disease is common. Above the age of 80 years presbycardia results in cardiac failure and arrhythmias. Recurrent thromboembolism leads to cerebrovascular occlusion, ischemia of limbs, and infarction of other vital organs. Varicosity of veins may develop. Dependent edema occurs as a result of exudation of fluid due to loss of elasticity of the skin and fall in tissue tension. Hypoproteinemia, cardiac failure, venous stasis, and immobility tend to perpetuate edema.

Respiratory system: Atrophic emphysema, chronic respiratory infection, and aspiration pneumonia are disabling problems of old age. Staphylococcal bronchopneumonia may follow influenza and it is a fatal complication. Acute respiratory infection is a common complication of severe illness and this causes death in many cases.

Neurological disorders: Atherosclerosis leads to gradual deterioration of higher functions ending up in dementia.

Cerebrovascular accidents accelerate this process. Subdural hematomas may develop following minor trauma, or even spontaneously. Cervical spondylosis, lumbodorsal osteoarthritis, and ischemia of the spinal cord contribute to pain and dysfunction of the extremities. Peripheral neuropathy occurs frequently. The sensory loss accounts for unsteadiness of gait and clumsiness of movements. Tremor occurring in them aggravates the disability and, therefore, feeding, writing, and other activities become difficult or impossible. Parkinsonism is common. This impairs speech and movements further. Cerebellar dysfunction may develop. Herpes zoster is more common in the elderly and post-herpetic neuralgia tends to be troublesome.

Autonomic dysfunction: Elderly individuals lose control over the bladder and bowel. There is incontinence of urine and feces. This gives rise to problems of nursing. Postural hypotension may contribute to syncope and falls are common in the elderly. The heat-regulating mechanisms are labile. Accidental hypothermia and hyperthermia may occur due to exposure to external environment.

Special senses: Loss of vision due to cataract, retinal degenerations or chronic iridocyclitis, and glaucoma is common. Diabetes and hypertension aggravate the disability. Loss of vision incapacitates them considerably and pastimes like reading, writing, and watching television become problematic.

Loss of hearing is common after the age of 50 years and it is a serious handicap. The diminution in hearing may be universal affecting all tones, or the higher frequencies may be selectively affected. Deafness impairs their ability to communicate with others and thus makes them isolated. Tinnitus and vertigo may be troublesome. Ageusia or parageusia may occur and these may aggravate their feeding problem.

Alimentary disorders: Loss of teeth makes ingestion of several articles of food difficult. Atrophy of the salivary glands, atrophic gastritis, peptic ulcers, colonic polyps, diverticulosis, and cholecystitis are common in the elderly. The poor food intake and immobility lead to constipation. If unattended, this may develop into inspissated feces syndrome in which constipation, alternating spurious diarrhea and fecal incontinence are seen. Malignant lesions in the hepatobiliary system, gall stones and drug-induced hepatotoxicity are more common.

Excretory system: Renal impairment occurs as a result of chronic pyelonephritis and benign nephrosclerosis. Obstructive uropathy due to enlargement of the prostate is an almost invariable accompaniment above the age of 80 years. The severity of symptoms vary. Several precipitating causes such as urinary infection, prolonged

recumbency, instrumentation or sympathomimetic drugs lead to acute obstruction. Elderly women develop senile vaginitis, rectocele, cystocele, and uterine prolapse, all predispose to recurrent urinary infections.

Bones and joints: Many weight-bearing joints such as knees, hips and spine, and small joints of the hands and feet develop osteoarthritis. This tends to make the patient immobile. *Phlebothrombosis and embolism* are common. Accidents and falls are frequent and these initiate the downhill course. Fracture neck of the femur, Colles' fracture, and vertebral compression fractures are brought about by osteoporosis. Movements of the shoulder may be restricted by shoulder-hand syndrome.

Muscles: There is generalized atrophy of muscles, myotonia, and loss of power. In many areas contractures, cramps or tetany, and claudication may develop.

Hematological disorders: Anemia may develop due to poor intake of proteins, iron and vitamins. This is further worsened by loss of blood from hemorrhoids, gastrointestinal blood losses, diverticulitis and malignancies. Incidence of lymphoma shows a peak in the elderly. Minor trauma in areas such as the dorsum of the hands, wrists, and lower parts of the legs and feet show senile purpura.

Endocrine system: The gonads, thyroid and adrenal cortex show generalized hypofunction. Myxedema is not uncommon. Since the presentation may be atypical, they may be initially mistaken for primary psychiatric disorders.

Skin: Atrophy of the skin makes it thin and inelastic. There is reduction in subcutaneous fat. These factors make the skin vulnerable to chronic decubitus ulcers. Paresthesiae and pruritus are common. The latter may become extremely distressing and intractable, leading to severe distress.

Psychological changes: The elderly become irritable and less adaptable to surroundings. Change in social behaviour, emotional instability, loss of self-confidence, mental depression, hallucinations and paranoid and persecutory fears result in social isolation.

Disease Pattern in Elderly

AGING CHANGES AND DISEASE STATES

There is often no clear distinction between changes due to aging and age-associated diseases. Often, medical problems are erroneously considered as aging changes and neglected. Many of the earlier cross-sectional studies on the aging population have created a wrong notion, that aging is always associated with declining function. However recent longitudinal studies in elderly have clearly

shown that physiological functions can be maintained or even improved in the absence of diseases.

The major physiological change associated with aging is the decline in reserve, resulting in a state of “homeostenosis” of every organ system. This decline is gradual and often progressive but variable in individuals. However, this decline in function causes no symptoms and possesses few restrictions in the activities of daily living. Loss of adaptability to an acute stress is the key problem in elderly, due to this functional decline.

Unlike in younger age group, multiple diseases are common in elderly. Numerous studies have shown that mean number of diseases per person, for those above the age of 70 years, is around 5. Chronic diseases like hypertension, coronary artery disease, diabetes mellitus, chronic obstructive pulmonary disease, degenerative joint diseases, cognitive decline, depressive illness, falls, incontinence and visual and hearing impairment may appear in varying combinations. Multiple symptoms and signs in elderly may be due to different diseases rather than a single disease and unitary disease model approach will lead to wrong diagnosis.

Clinical presentation of diseases also varies in elderly. Some diseases are silent and asymptomatic and many present with atypical symptoms. A disease affecting one organ system can precipitate decompensation in another due to age-related decline in reserve. For example, a respiratory infection can present as acute confusional state, mimicking a CNS problem. Whatever the underlying acute disease, the weakest areas like cardiovascular, CNS and musculoskeletal systems are often affected and symptoms pertaining to these systems dominate.

A classical presentation of a disease may totally be absent. For example pneumonia may present often without fever, cough, pleuritic pain and hemoptysis. Myocardial infarction and intra-abdominal emergency can present as shock or acute confusion.

Because of the decreased reserve, elderly persons develop symptoms at an early stage of the disease and if treated actively, the outcome is much better. Unfortunately, this advantage is set-off by the patients’ indifferent attitude toward these early symptoms. The elderly patients seek medical attention at a later stage, when the treatment becomes difficult and the outcome is poor.

At times a coexisting disease may alter the symptoms of another disease, leading to a delay in diagnosis, e.g. disabling old stroke may restrict physical activity, thereby masking an anginal pain of ischemic heart disease at an early stage. Secondary complications of an acute illness are common in elderly, especially if there is a delay in treatment. For instance, a simple gastroenteritis can lead to dehydration and acute renal failure. However, early diagnosis and prompt therapy result in good outcome.

TABLE 103.1

Morbidity pattern in Indian elderly—rural

Vision problems	88%	Skin problems	13.5%
Locomotor problems	40%	Nutrition problems	11.5%
CVS problems	18.7%	Abdominal problems	9.5%
CNS problems	17%	Psychiatric problems	8.5%
Respiratory problems	16%	Hearing problems	8%

Source:

1. ICMR study—1990, Venkoba Rao
2. VS Natarajan *et al*

TABLE 103.2

Morbidity pattern in Indian elderly—urban

CVS	44-48%	Hearing	20-24%
Vision	40%	Respiratory	19-23%
Locomotor	36-42%	Psychiatric	12%
CNS	28-32%	Healthy	2%

Sources:

1. Dept of Geriatric Medicine, Govt General Hospital, Chennai
2. Geriatric Clinics, AIIMS, New Delhi
3. KV Krishna Das, Trivandrum

Though there are no diseases peculiar to elderly, some ailments are more commonly seen in older persons. Sensory deprivation, degenerative joint disease, cardiovascular disorders, vascular and degenerative neurological diseases, diabetes mellitus malignancies and depression are the most common illnesses affecting the elderly. Immobility, instability (falls), incontinence and intellectual impairment (dementia) constitute the “geriatric giants”, posing management problems.

Tables 103.1 and 103.2 show the diseases pattern in Indian elderly.

MANAGEMENT APPROACH TO ELDERLY PATIENTS

Multidimensional Geriatric Assessment

Assessment of an elderly patient is always multidimensional and interdisciplinary. It is essential to determine the frail elderly person’s medical, psychosocial problems and functional capabilities, with the aim of immediate management, rehabilitation and long-term follow-up. The comprehensive geriatric assessment should include assessment of medical problems and cognitive functions by a physician, assessment of ADL and IADL by a physiatrist and social problems by a social worker. The aim of initial assessment is to set the realistic goal of improvement and to achieve maximum independence.

The term ADL denotes activities of daily living which includes self care activities such as eating, bathing, dressing, transferring and toilet, IADL denotes instrumental activities of daily living such as cooking, managing finance, using telephone, driving a car, etc. which demand better functional competence.

Barthel's index of activities of daily 'living' is a scoring system which helps to assess the functional capacity of the elderly, especially after a disabling illness.

Investigations in the Elderly

Since a coherent history is rarely possible and clinical presentation is often varied and atypical, investigations become essential to arrive at a clinical diagnosis. When an elderly person presents with an acute illness, basic biochemical and radiological tests should be done at the earliest. In asymptomatic patients safety and usefulness of the test should be considered. In general, non-invasive tests are preferred in elderly although age is not a bar for invasive procedures.

Drug Therapy in the Elderly

The problems associated with drug therapy include alteration in drug metabolism due to changes in body mass and composition, polypharmacy, drug interaction, self-medication, adverse drug reactions, compliance and cost of therapy. Worldwide data suggest that elderly are the major consumers of the drugs and adverse drug reactions (ADR) are more frequent in them. Sedatives, NSAIDs, diuretics, anticholinergics and antimicrobial drugs lead to adverse side effects frequently. The principle of "start slow and go low" is the practical method of preventing ADR, and one has to consider the age-related changes in absorption, distribution and metabolism of a drug before prescribing.

Pharmacotherapy in old age: Adverse drug reactions (ADRs) are more common. Most of them are dose related. Drug distribution changes with the changes in the proportion of fat in the body. Lipid and water soluble drugs show corresponding changes in distribution. Drugs such as cimetidine, digoxin and morphine have a smaller volume distribution, hence they show higher blood levels. Fall in the plasma albumin levels results in greater proportion of drugs to be in the free form and this leads to higher side effects e.g. warfarin, oral anti-diabetes drugs, NSAIDs and others. Drugs which depend upon hepatic metabolism may show vagaries in their concentration and actions. Glomerular filtration falls by 35% in the elderly, so too the renal tubular function. Drug dosage has to be adjusted depending upon the creatinine clearance.

Formula for calculating creatinine clearance (CrCl) in the elderly is given below

$$\text{CrCl (mL/minutes)} = \frac{(140 - \text{age}) \times \text{weight in kg}}{72 \times \text{serum creatinine mg/dL}}$$

Changes in hepatic functional impairment, autonomic nervous function and neuromuscular activity influence the actions of drugs. The best method is to individualize the dose on a trial and error basis. A simple prescription with clear instruction of dosage and duration of therapy is mandatory. Periodic review of medication and compliance will be beneficial. In addition to a definitive diagnosis and analysis of risk benefit of therapy, one has to consider the concomitant diseases before choosing a drug.

Common Geriatric Symptoms and their Management

There are a few symptoms which are more prevalent in elderly, requiring different approach and management. Pain, dizziness, constipation, dyspepsia, pruritis, memory disturbances, multiple somatic complaints falls and delirium are some of the common symptoms seen in geriatric clinics. A brief review of these symptoms will be useful. Many physicians adopt a syndromic approach while treating geriatric patients. This takes into consideration the functional disabilities such as restriction of movement, diminution of vision, falls and so on, irrespective of the exact pathology. Reduction of the ill effects of age-related phenomena and diseases is the main goal of geriatric medicine.

Constipation

Constipation is defined as less than three bowel movements per week and its prevalence varies from 40-60% in elderly. Dietary inadequacy, multiple medications, anorectal problems, reduced GI motility are often contributing factors for constipation. Acute constipation associated with acute medical problems often produce distressing symptoms like abdominal distension, confusion and urinary retention. Laxatives in the form of rectal suppositories and enema are useful and often digital evacuation has to be done. Dietary adjustments in the form of increased fluid and fiber in the diet, regular exercise, a fixed time of bowel evacuation are simple measures of preventing chronic constipation. Bulk and osmotic laxatives are the preferred form of therapy and reassurance that chronic constipation is age-related and benign, is quite useful.

Dyspepsia

Sedentary habits and reduced GI motility often leads to dyspeptic symptoms. Acid peptic disease, reflux esophagitis and upper GI malignancy and drugs are the common causes of dyspepsia. Upper GI endoscopy and barium studies are useful and safe in evaluation. Drugs that improve motility like domperidone and H₂ receptor blockers are widely used.

Memory Disturbances

Many elderly patients complain of declining memory function but often perform well during mental status examination. History obtained from the care-giver of declining memory is more reliable and needs evaluation. Age associated memory impairment (AAMI) has to be differentiated from early Alzheimer's disease. A thorough neurological examination and a regular follow-up can differentiate benign AAMI from progressive dementia. While memory loss is the lone disturbance of the higher function in AAMI, there is a diffuse and progressive alteration of mental functions in dementia. A treatable dementia is always to be considered in any dementing illness and a thorough evaluation is mandatory.

Pain

More than 50% of the elderly patients attending a geriatric clinic will present with pain as the primary complaint. Degenerative joint diseases, osteoporosis, muscular pain, neuritic pain, malignant and somatoform disorders are some of the underlying diseases producing pain. Nondrug method of physical therapy is the first line of management. When medication is required, paracetamol is safe and widely used. NSAIDs should be used with caution in elderly, but should not be withheld when required. Adjuvant pain therapy in the form of antidepressants and anticonvulsants is often useful in chronic and neuritic pain. Opioids should be reserved for intractable pain associated with malignancies. Referral to "pain clinics", where multimodal approach is provided, will be beneficial in chronic pain associated with malignancy and depressive illness.

Dizziness and Vertigo

Prevalence of these symptoms vary from 30-40% in elderly. Benign positional vertigo, vestibular dysfunction, age-related changes in the sensory system and drugs are some of the common causes of vertigo in the elderly. A thorough ENT and neurological evaluation is mandatory but often does not contribute in diagnosis or management. The major complication of dizziness includes a fall and fracture in a frail elderly, which should be prevented. Vestibular rehabilitative exercises are the main form of therapy, and vestibular sedatives should be used with caution. Walking aids in the form of walking sticks and walking frames are often useful in preventing a fall.

Multiple Somatic Complaints

Often multiple complaints are the presenting problems in elderly. A depressive illness is usually the cause of multiple somatic complaints and psychiatric counseling will be useful. A thorough clinical and diagnostic evaluation has to be performed in every case to rule out an organic basis and periodic re-evaluation is ideal.

Falls

Instability and frequent falling may be the presenting symptom in the frail elderly, the prevalence varying from 20-30% in the community. Multiple medical illnesses are often the cause for a fall rather than simple aging. Environmental hazards like poor lighting, uneven floor, slippery toilets, stairs without hand rails can lead to falls. Age-related changes in the nervous system, parkinsonism, cognitive decline, polypharmacy and cardiac arrhythmias are the intrinsic causes of recurrent falls. Physical injuries, fractures and psychological trauma and fear of fall can lead to invalidism. Identifying the basic disease and measures to improve the muscle strength and balance, especially of the lower limbs and physical training can prevent falls.

Delirium

Many a time elderly patients are brought in a state of acute confusion. Delirium involves altered consciousness with impaired attention and diminished arousability. Infection, dehydration, electrolyte disturbances, hypoxia, hypotension and drugs are the frequent causes of acute confusion in elderly. Since delirium is often a clinical manifestation of the underlying serious systemic disease, it has to be identified, evaluated and actively managed. Many times outcome of an acute confusional state is rewarding, provided it is treated early.

SOCIAL PROBLEMS IN THE ELDERLY

Elderly persons have several problems which cause hardship. These include health problems, financial problems, social alienation and possibly others. The elderly person tends to become uncooperative, withdrawn and cynical in behaviour. They are not accepted by the younger folk. Many of them are left alone due to death of the near relations or desertion by them. Helplessness is a real medical problem for those above the age of 65 years. Mortality among elderly persons living alone is 3.2% per annum. Mortality is higher in the months of extreme cold and heat. Social rehabilitation measures including living places, hostels, provision of the help at home and device such as emergency alarm for summoning help are available in developed countries. Ideal situation is one in which no elderly person has to live alone and to face death alone.

Socioeconomic problems add and aggravate medical, physical and psychological disabilities in the elderly. The changing demographic pattern has resulted in more number of elderly in the 'dependent population'. Psychosocial problems are the resultant of retirement, loss of occupation and income, housing problems and bereavement in the family. The joint family system which is the basic social support in the community, is unfortunately disintegrating because of the migration of children

for better opportunities. Neglect, loss of respect for elders and elder abuse are increasing in the community. It is vital to promote and protect joint family system to provide basic social and emotional support to the elders. Though old age homes are increasing in number in our country, they can never be a substitute for family care. Developing day care centers, senior citizen clubs and friendly visiting services would help to provide recreation, group activity and emotional outlet for the elders.

Development of Geriatric Health Services in India

At present, there are not many geriatric health units available in India. The few available are mostly placed in larger cities. Since most of elderly population lives in the rural area, geriatric health care should be included in the primary health care system. Multipurpose health workers can be trained to identify health problems of the elderly and to provide simple remedies and referral system whenever required. Taluk and headquarters hospitals should provide outpatient and inpatient geriatric services. Teaching hospitals should develop full-fledged geriatric units and provide geriatric training programs for primary care physicians. It is also vital to develop nursing homes or long stay hospitals with nursing and rehabilitative services for the elderly with chronic physical disabilities.

Appendix

Several indices have been designed to assess the pathological conditions in the elderly. Hachinski score distinguishes between dementia caused by ischaemic brain lesions and non-ischemic lesions. The *Barthel's index* is an assessment of functional capacity. It helps to assess the progress in the medical condition of elderly subjects objectively on follow-up:

Hachinski score-for ischemic versus non-ischemic dementia	
<i>Feature</i>	<i>Score</i>
Abrupt onset	2
Stepwise course	1
Somatic features	1
Emotional incontinence	1
Systemic hypertension	1
History of strokes	2
Focal neurological symptoms	2
Focal neurological signs	2

Interpretation

More than 4-Multi-infarct dementia
Less than 4-Non-vascular dementia

Barthel's Index of Activities of Daily Living	
<i>Feature</i>	<i>Score</i>
<i>Bowels</i>	
Continent	2
Occasional incontinence	1
Constant incontinence	0
<i>Bladder</i>	
Continent	2
Occasional incontinence	1
Incontinent	0
<i>Feeding</i>	
Independent	2
Needs some help	1
Dependent	0
<i>Combing hair, washing face, cleaning teeth and shaving</i>	
Independent	1
Needs help	0
<i>Dressing</i>	
Independent	2
Can do half	1
Dependent	0
<i>Transfer (mobility)</i>	
Independent	3
Minor help needed	2
Major help needed	1
Total inability	0
<i>Using the toilet</i>	
Independent	2
Needs some help	1
Dependent	0
<i>Walking</i>	
Independent	3
Walks with one stick	2
Wheel chair	1
Total inability	0
<i>Climbing stairs</i>	
Independent	2
Needs some help	1
Dependent	-
<i>Bathing</i>	
Independent	2
Needs some help	1
Dependent	0

The total score is ascertained immediately after the onset of illness. The total scores are recorded periodically during treatment. Improvement or deterioration can be assessed objectively thereby.

Rheumatology

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General Considerations

The term rheumatology denotes the branch of medicine which deals with the medical disorders of the musculoskeletal or locomotor system. The common disorders include:

1. Inflammatory lesions of joints, periarticular tissue, muscles, tendons, and fascia
2. Degenerative diseases produced by 'wear and tear'
3. Problems of the vertebral column produced by local pathological lesions, postural abnormalities and trauma
4. Generalised vasculitides and
5. Several others.

Rheumatic disorders are probably the most common ailments affecting mankind. In India at any period of time 8-9% of adults suffer from one or other of the rheumatic disorders. It is possible that about 50 million people suffer from these disorders at any one time. Among the rheumatic disorders 47% is constituted by inflammatory arthropathies, mainly rheumatoid disease, 18% by connective tissue disorders, 8.5% by seronegative spondyloarthritis, and 4% by crystal induced arthropathies. All other joint lesions make up the total.

Bones: The human body contains about 206 bones. Structurally, they can be divided into spongy and compact bones. In spongy bone the lamellae are stacked one above the other as trabeculae. In compact bone the lamellae are arranged closely in concentric circles around a central canal containing the osteocyte. Spongy bones house the bone marrow whereas compact bones do not. During bone formation and repair different cells such as osteocytes, osteoblasts and osteoclasts act in a coordinated and orderly

manner under the influence of several humoral factors. Periosteum covers bones. It has an outer fibrous layer and an inner cellular layer capable of producing bone—the osteogenic layer.

Trabecular bone has a greater turnover than cortical bone. Bone matrix consists of type I collagen which is laid down in lamellae. These give tensile strength to bones. Mineralisation of the bone matrix with deposition of hydroxy apatite ($\text{Ca}_{10}(\text{PO}_4)_6 \text{OH}_2$) between the collagen fibrils bestows rigidity to the bones.

Bone remodelling occurs throughout life and it replaces worn-out bone by new bone. About 10% of the skeleton participate in this process at any one time. It starts with the arrival to the site of osteoclasts which are derived from the monocyte macrophages system. These contain the enzyme tartrate resistant alkaline phosphatase. They reabsorb bone matrix and the minerals. At the end of this process osteoclasts undergo apoptosis. Then osteoblasts which are derived from marrow stromal cells arrive to lay down bone matrix which is subsequently mineralised. Osteoblasts are small cuboidal cells which actively lay down bone matrix. They are stimulated by parathormone, platelet derived growth factor and prostaglandins. They are inhibited by corticosteroids. Some osteoblasts remain embedded within bone matrix. They differentiate into osteocytes. They act as sensors of mechanical strain. They also secrete prostaglandins and nitric oxide which are signalling molecules concerned with the functions of neighbouring bone cells. **Osteoprotegerin** is a key regulator of osteoclast activity by inhibiting its action. The receptor activator of nuclear factor KB (RANK), its ligand RANKL and osteoprotegerin constitute a critical mechanism for signalling between osteoblasts and osteoclasts.

Cytokines participate in the process of bone remodelling. Parathormone, activated vitamin D ($1,25(\text{OH})_2 \text{D}_3$) thyroid hormone and growth hormone increase bone remodelling whereas it is suppressed by calcitonin, estrogens and androgens. In conditions like Paget's disease of bone where bone remodelling is very rapid, lamellae formation may be distorted and the resultant bone, though larger, may be brittle.

Long bones transmit body weight and act as levers for movement. The middle part of the tubular shaft is the diaphysis which is flanked on either end by the metaphyseal regions. The ends are expanded to form the articular areas, the epiphyses. Long bones derive their blood supply from diaphyseal, metaphyseal, epiphyseal and periosteal nutrient arteries. Short bones like the carpal bones function as points of absorption of pressure and distribution of shearing forces. They are made of compact bone.

Joints: Joints may be classified as fibrous, cartilaginous or synovial.

Type of joint	Range of movement	Examples
Fibrous	Nil	Cranial sutures, tibiofibular joint
Cartilagenous	Limited	Intervertebral joint, symphysis pubis
Synovial	Wide	Hip, knee, elbow

In a synovial joint the bone ends are capped by hyaline cartilage. At the osseochondrous junction, synovium is attached to bone and reflected from it to line the joint cavity. Outside the synovium is the tough fibrous capsule which is thickened in some areas to form ligaments. The capsule and ligaments prevent excess movement at the joint. In joints like the knee there are fibrocartilaginous pads or menisci which serve to appose the articulating surfaces properly. The synovial fluid and synovium reduce friction during movement. Bursae prevent friction between tissues around a moving joint. These are similar to synovium in structure, function and disease susceptibility. Synovium is highly vascular. Structurally, the synovium presents an ideal stage for humoral and cellular immune reactions. Synovium has only very few nerve endings, while cartilage has none. Articular cartilage is avascular. It derives its nutrition from materials passing into it from bone or synovial fluid. Articular branches of blood vessels enter at the joint margin.

The articular cartilage consists of chondrocytes, embedded in a matrix and it is provided with a framework of type II collagen which imparts its tensile strength. It does not contain nerves. It provides a low friction surface to the articular ends of bones.

Synovial membrane lines the inner surface of joint capsules. It consists of fibroblasts which secrete synovial fluid and macrophage-like cells with phagocytic activity. The synovial fluid is an ultrafiltrate of plasma, to which materials which increase its viscosity such as hyaluronan and lubricin are locally added. Hyaluronan is responsible for lubrication of the joint surface during movement, whereas lubricin acts as the lubricant during static stress.

In addition to its lubricating function synovial fluid provides nutrition to the avascular articular cartilage and helps to perform other metabolic functions. The synovium is supplied by unmyelinated nerve fibers which transmit pain.

The capsules, ligaments and periosteum around the joints are supplied with myelinated nerves for proprioception and unmyelinated nerves for conducting pain.

The points of attachment of tendons and ligaments to bone are called entheses. The joint capsule, entheses, ligaments and tendons are rich in nerve endings that perceive pain and proprioception. When a joint is inflamed, reflexogenic nerve endings cause reflex contractions of neighbouring muscles leading to painful stiffness.

The main function of all synovial joints is to allow stable, controlled movements. Muscles of the locomotor system are all striated muscles. They are all under voluntary control.

Symptomatology

Rheumatology is still a pre-eminently clinical discipline depending heavily on laboratory and other types of investigations. Since the joints and bones respond in a stereotyped clinical manner to different and multiple diseases processes, clinical distinction between the various rheumatological syndromes may not be perfect. So also the laboratory parameters usually undertaken in these diseases are of a more general character rather than being absolutely specific, so that considerable overlap occurs between health and disease. Many of the laboratory investigations such as ASO titre, rheumatoid factor, ESR and almost all others show prevalence in low titers even in apparently normal population, so that the interpretation of an equivocal laboratory value has to be made in the context of the clinical features and the characteristics in the general population.

Main symptoms pertaining to the locomotor system include pain in and around joints or other parts of the axial or appendicular skeleton, deformities of bones and joints, loss of functions of the joints and systemic manifestations such as fever, loss of weight, anemia and involvement of several organ systems. There may be considerable overlap in the clinical manifestations between the different rheumatic diseases. Therefore, it is very necessary to do investigations to pinpoint the diagnosis and follow-up the case.

The main clinical presentation of musculoskeletal disorders is with joint pains, stiffness of muscles, swelling, bone pains and muscle weakness. The source of the symptom can be clinically assessed by examination.

Symptomatology in articular and extra-articular lesions	
Joint tissues	Lesions around the joint or unconnected with the joint
Pain occurs during active and passive movements	Pain occurs during active movement, but not on passive movement
Swelling and tenderness limited to the anatomy of the joint	Not confined to the joint
Crepitus, instability and locking of joint in particular positions present	Not present

The distribution of joint lesions gives some clue. Predominant affection of the joints of the lower segment of the body occur in various spondyloarthropathies such as ankylosing spondylitis, Reiter’s syndrome, psoriatic arthropathy and early stages of polyarticular gout. In rheumatoid arthritis and systemic lupus the upper segment is more often affected. Morning stiffness is a frequent finding in many joint diseases. This term refers to pain on waking up from sleep or prolonged recumbency, felt especially in the lower limbs and spine, which takes 30-60 minutes to get maximum relief. This is a usual feature of inflammatory joint disease.

Disease Pattern Affecting the Locomotor System in India

Numerically, traumatic fractures, dislocations and other lesions head the list. These fall into the realm of orthopedics.

Rheumatological disorders contribute to the rest of the diseases of the musculoskeletal system and connective tissue. Among the connective tissue diseases rheumatoid arthritis tops the list. About a fifth of the rheumatological disorders may be related to allergic processes, e.g. *reactive arthritis*, *serum sickness like reactions*, *allergy to drugs* and so on. *Osteoarthritis* accounts for another fifth of the morbidity. *Osteoporosis*, *osteomalacia nonarticular rheumatism*, *low backache*, *sciatica* and problems related to defective posture and lack of exercise are common. In India, rheumatic fever merits a special mention since it is common in children and adolescents and it leads to life-long crippling cardiac sequelae. Osteoarticular tuberculosis is also common in children and adults, the osseous focus being in the metaphysis in children and in the epiphysis in adults. Tuberculosis can also cause an allergic reactive arthritis resembling rheumatoid arthritis. Arthritis associated with gut lesions such as *ulcerative colitis* and arthritis associated with *ankylosing spondylitis*, *psoriasis* and the *Reiter’s syndrome* are again common enough. Many systemic diseases may present with arthritis; these include *hypothyroidism*, *diabetes mellitus*, *acromegaly*, *bleeding disorders*, *myeloproliferative disorders*, *AIDS*

and other conditions. Finally we come to the diffuse connective tissue diseases (DCTD) under which umbrella come *systemic lupus erythematosus*, *scleroderma*, *inflammatory disease of muscle* and *rheumatoid arthritis*. Each of these may be associated with *Sjögren’s syndrome*. The DCTD’s can overlap with each other as in mixed connective tissue disease and progress on to other forms.

The pattern of rheumatological disorders differ in different age groups. In children the common problems seen are growing pains, hypermobility, hip pain due to several causes, traumatic lesions of knees, rheumatic fever, postviral arthritides, osteomyelitis, pyoarthrosis, juvenile rheumatoid arthritis (JRA), rickets and others. In the young adult male, seronegative spondyloarthritides are common. During the sexually active periods of life, arthritic complication of sexually transmitted diseases are more common. In pregnancy and the puerperium low back pain is nearly universal and sciatica is common enough. The postmenopausal age is associated with bone and joint symptoms. Osteoporosis proceeds rapidly after menopause. Hypothyroidism, depressive illness and osteoarthritis are common causes of rheumatic symptoms in this group. Degenerative joint diseases such as osteoarthritis of several joints, cervical spondylosis, sciatica and lumbar canal stenosis are more common in elderly. Those exposed to repeated occupational trauma during work develop osteoarthritic changes of particular joints early.

Occupation and environment can modify joint diseases, particularly osteoarthritis, e.g. *goal-keeper’s fingers*, *bass player’s thumb*, *Zulu dancer’s hip*, etc. Tenosynovitis like the Achilles tendonitis of long distance runners and prepatellar bursitis in housemaid’s knee are other examples of occupation-related rheumatism. Enthesopathies like lateral and medial epicondylitis of elbow (syn: tennis elbow and golfer’s elbow) are common in Indian housewives who do clothes washing, grain grinding, pounding, etc. Factory workers inhaling metal or polymer fumes can get fever associated with arthralgias. The WHO has categorized rheumatological disorders into four major categories

- 1. Back pain (48%)
- 2. Osteoarthritis (31%)
- 3. Soft tissue rheumatism (12%) and
- 4. Inflammatory rheumatic diseases (9%).

Immunological principles dominate the practice of present day rheumatologists. A sound understanding of immunology will go a long way in interpreting the evolution, course and management of rheumatological diseases (Table 104.1).

Investigations of Rheumatological Diseases

Laboratory Investigations

A. **Erythrocyte sedimentation rate (ESR):** It is common to find very high ESR, often exceeding 100 mm/hour in

TABLE 104.1

Shows the spectrum of cases seen in India

- A. Diffuse connective tissue diseases—rheumatoid arthritis and its variants, systemic lupus erythematosus, systemic sclerosis, polymyositis, dermatomyositis, Sjögren's syndrome, mixed connective tissue disease and various forms of generalised vasculitis
- B. Degenerative joint disease—osteoarthritis
- C. Spondyloarthropathies
- D. Infective arthropathies—by direct infection, e.g. tuberculosis or syphilis or indirectly by immunological mechanisms, e.g. rheumatic fever, Reiter's syndrome
- E. Crystal induced arthropathies gout, pseudogout, chondrocalcinosis
- F. Non-articular rheumatism, tendonitis, enthesitis, fibromyalgia and others
- G. Bone and joint manifestations associated with systemic diseases, e.g. osteomalacia, osteoporosis, Marfan's syndrome, endocrine disorders, psoriasis, fluorosis and others

Note: Almost all the varieties of bone and joint diseases are seen in India, in varying proportions in all age groups and in different geographical regions

active rheumatoid disease (RA), systemic lupus erythematosus (SLE) and infective arthritis. The ESR is generally normal or only mildly elevated in osteoarthritis and allergic arthropathies.

B. C-reactive protein (CRP): This is a beta globulin which is absent in normal plasma but appears in the presence of different types of inflammatory arthritis. CRP is an acute phase serum protein that is synthesized by hepatocytes. This protein is capable of reacting with the capsule of pneumococci, and hence this name. The CRP levels rise by up to 100 folds during infection, tissue injury and inflammation. Though the physiological role of CRP is not known, it may contribute to innate immunity and suppression of autoimmune processes. Estimation of CRP level is a reliable investigation to identify inflammatory processes and follow up their progress. The test can be quantitated. CRP is more expensive than ESR.

The advantages of CRP over ESR

- 1. More rapid procedure; only a few minutes.
- 2. CRP is positive even before ESR starts rising.
- 3. CRP can be quantified by serial dilution.
- 4. It helps to distinguish between rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). In RA it is elevated, whereas in uncomplicated SLE it is not.

Sjögren's syndrome, polymyositis, dermatomyositis, liver cirrhosis, sarcoidosis and several chronic infections including tuberculosis, leprosy, kala-azar and filariasis may lead to elevation of CRP. Tobacco smoking, obesity, diabetes mellitus and hypertension lead to mild elevation of CRP baseline. Higher levels of CRP have been associated with increased risk of myocardial infarction.

In experimental animals high levels of CRP have been associated with myocardial damage. The interpretation of borderline values of the test should be correlated with the clinical picture.

Both ESR and CRP are non-specific markers of joint inflammation and connective tissue diseases. In a case where diagnosis has been made, changes in ESR can be estimated for treatment and follow-up.

C. Serological markers

- 1. **Rheumatoid factor (RF):** This consists of different types of immunoglobulins and it is seen most frequently in rheumatoid arthritis. Their presence is detected by several tests such as sheep red cell agglutination test (Rose Waaler), latex fixation test and other slide agglutination tests. RF is present in a smaller proportion of patients with systemic lupus erythematosus (SLE), progressive systemic sclerosis (PSS), mixed connective tissue (MCT) disease and others. Based on the demonstrable presence of RF, arthritis can be broadly classified into seropositive and seronegative types.
- 2. **Antistreptolysin-O titer (ASO titer):** ASO is the antibody produced against streptolysin produced by *Streptococcus hemolyticus*. Presence of ASO titer in excess of 400 Todd units should suggest active or recent infection by *Streptococcus*.
- 3. **Antinuclear factors (ANF):** These are also known as antinuclear antibodies (ANA). Several components of the nucleus elicit antibody response in the host and detection of these components help to diagnose different rheumatic diseases.

ANAs are immunoglobulins, directed against nuclear components such as DNA, RNA, histones centromere and others. Identification and estimation of levels of ANA are of great diagnostic help. Only in a few diseases their detection is of absolute diagnostic help since several diseases are associated with their presence, at least in low-titers. Methods employed to detect them include radioimmunoassay, ELISA and immunofluorescence microscopy. The pattern of immunofluorescence gives additional information. Some of the antinuclear antibodies are listed below.

Anti DNA antibodies

High levels of anti-double-strand DNA antibodies (anti-dsDNA) are suggestive of active SLE. They are also present in low levels in RA. Anti-single-stranded DNA (anti-ss DNA) is non-specific, seen in SLE, drug induced lupus, chronic active hepatitis, infectious mononucleosis and others.

Antiribonucleoprotein (anti-RNP) is elevated in mixed connective tissue diseases.

Antibodies to histones are elevated in SLE, Felty's syndrome, Juvenile rheumatoid arthritis and primary biliary

cirrhosis. Several other antibodies against various nuclear components have been identified. For example, anti-Smith, and U₃ (fibrillarin) JO-1, Mi, SS-A, SS-B, anti-RO, anti-Ka, Sn RNP, PM sal, Scl 70 and others. Their detection is of help in the specific diagnosis of some of the connective tissue diseases. All these tests are highly expensive for routine use.

Antibody	Diseases association
Anti-dsDNA	SLE
Anti-RNP	MCTD, SLE
Anti-sm	SLE
Anti-histones	
H1, H2, H3	SLE
Anti-histone	
H2A, H2B	Drug induced lupus
Anti-SSA (anti-RO)	Sjögren's syndrome (SS)
	SLE, neonatal lupus
Anti-SSB (anti-La)	SS, SLE
Anti-centromere	Limited systemic sclerosis (CREST syndrome)
Anti-JO-1	Polymyositis-dermatomyositis with lung involvement

4. **Serum complement levels:** Components of the complement system such as C3 and C4 are consumed during antigen-antibody reaction and so levels of C3 and C4 may be reduced generally or selectively.
5. **Lupus erythematosus (LE) cell phenomenon:** This is a test to detect phagocytosis of nuclear material by neutrophils seen in active SLE. Rarely the test is positive in RA and allergic states.
6. **Antineutrophil cytoplasmic antibodies (ANCA's)**
These are antibodies directed against the granules present in the cytoplasm of neutrophils and monocytes. Based upon their pattern and immunofluorescence they have been classified into three types.
1. Cytoplasmic—cANCA—directed against proteinase 3
 2. Perinuclear—pANCA—directed against myeloperoxidase
 3. Atypical—xANCA—antigen specificity not clear

Frequency of ANCA positivity

cANCA- 90% in active diffuse Wegener's granulomatosis (WG) and 70% in limited WG
pANCA- typical of microscopic polyangiitis 50-60%, Churg-Strauss syndrome-25-30%

False positive tests for ANCA are very common. Presence of low levels of ANCA are relevant only if supported by clinical and other investigational parameters.

7. **Anti-phospholipid antibodies (APLA):** These are acquired antibodies which are heterogeneous, directed against plasma proteins bound to phospholipids. APLAs are a family of about 20 antibodies that are directed against phospholipid binding plasma proteins. The target proteins include beta-2 glycoprotein, prothrombin, annexin which is a phospholipid binding

protein with anticoagulant activity, protein C, protein S and others. APLA may belong to IgG or IgM classes. These include circulating anticardiolipin antibodies and circulating lupus anticoagulant. The latter is directed against coagulation factors X and V and platelet phospholipids. The presence of these antibodies is seen in the syndrome known as antiphospholipid antibody syndrome. Lupus anticoagulant is detectable only in 30% of cases of SLE and this name is a misnomer. Lupus anticoagulant is detected by performing rapid Russel viper venom time or kaolin clotting time. Though in the laboratory it behaves like an anticoagulant, in the clinical situation presence of these antibodies leads to thrombo-occlusive phenomena. Anticardiolipin antibodies are demonstrable by ELISA test. Presence of these antibodies also gives rise to false-positive VDRL test.

8. **Serological test for syphilis:** False-positive VDRL may be obtained in SLE, especially in those cases showing the presence of anticardiolipin antibody.

D. **Biochemical tests:** Serum uric acid is elevated in gout. **Blood glucose examination:** It is important to exclude diabetes mellitus since it is a very common cause of nonarticular rheumatism.

E. **Synovial fluid examination:** Synovial fluid should be examined for its mucus content, cells, crystals and viscosity. Diagnostic findings are obtained in different types of arthritis.

F. **Arthroscopy and synovial biopsy:** Several joints can be inspected by direct arthroscopy. Diagnostic findings are present in many cases. Biopsy and several surgical procedures can be done through the arthroscope.

G. **Determination of HLA status:** Several rheumatological disorders show strong HLA associations, e.g. ankylosing spondylitis (AS) and other seronegative spondyloarthropathies show high prevalence of HLA B27. Except HLAB27, which is present in over 75% of cases of AS no other laboratory test is diagnostic of the condition.

Rheumatoid arthritis shows association with HLA DR4.

In addition to the specific investigations in rheumatic diseases, investigations for systemic diseases presenting predominantly with rheumatological symptoms are also to be done when indicated e.g. brucellosis, Lyme borreliosis, rickets, osteomalacia and others.

H. **Imaging procedures:** X-ray examination of the bones and joints gives very important diagnostic information in most of the rheumatological disorders. In conditions like ankylosing spondylitis and gout, the skiagram is pathognomonic.

Other imaging procedures which are available include:
Scintigraphy — Using isotopes the presence of inflammatory and neoplastic lesions

can be delineated and their progress can be assessed periodically. Depending upon the nature of the lesion the appropriate isotope and technique have to be chosen.

Arthrography — Imaging after instilling a radiopaque contrast into the joint.

Tenography — Imaging tendons.

High frequency ultrasound (20MHZ) can be employed to detect muscle inflammation and fascial involvement **Doppler studies** can reveal increased blood flow to inflamed muscles. Calcinosis can be picked up much earlier before radiological evidence develops.

CT Scanning and MRI

CT scanning and MRI have become very specific investigations in rheumatological disorders. CT scan can reveal the anatomical details particularly in the vertebral column, skull bones and in joints. MRI is very useful to bring out the details of cartilage inside joints, especially the semilunar cartilages inside the knees. MRI also brings out details of bone marrow and intraosseous structures. MRI of muscle can be very useful to demonstrate the severity, distribution and extent of muscle inflammation, atrophy, fibrosis and fat infiltration. Involvement of nerves and other soft tissues by bony lesions will be brought out vividly. With the advent of CT and MRI other invasive investigations have gone out of vogue.

Bone densitometry: This imaging procedure aims to measure the bone mass or bone mineral density (BMD) which is the most reliable parameter to diagnose osteoporosis and predict the chances of fragility fractures in future. The two types of bone mineral densitometers available in India are the ultrasound densitometers and dual energy **X-ray absorption (DEXA) densitometers**. This is a very reliable investigation to detect bone mass and the changes in osteoporosis and osteomalacia.

Metastases in bones The skeletal system is a common site for metastases from malignant tumours. The axial skeleton such as vertebrae, skull bones, pelvis, ribs and the long bones of the limbs are commonly affected.

These may be *osteolytic* or *osteoblastic (osteosclerotic)*.

Factors favouring bone as a common site for metastases.

1. High blood flow in areas of red marrow
2. Tumour cells produce adhesive molecules which bind them to marrow stromal cells and bone matrix. These adhesive molecules stimulate the production of angiogenic factors and bone resorbing factors that further enhance tumour growth in bone. The tumour cells establish a parasitic relation on the bone leading to progressive growth.

In osteolytic metastases, the bone destruction is effected by increasing osteoclastic activity. In myeloma, the bone response is purely lytic. Tumour cells stimulate the proliferation of osteoclasts.

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Rheumatoid Arthritis and its Variants

K.V. Krishna Das

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Rheumatoid Arthritis: General Considerations

This is perhaps the most common form of inflammatory arthropathy seen in India. Among adult population below the age of 50 years this is the most common form of arthritis. There are several reports on the frequency of rheumatoid arthritis (RA) in different population groups. A study from West Bengal (1997) gave the prevalence rate as 4.48 to 4.63 per 1000 population. Seropositive disease occurred in two-thirds among them. The country wide general prevalence of RA is 0.5% of the population. In the rural parts it is 0.7%. Among the connective tissue diseases, RA is by far the commonest.

In western countries rheumatoid arthritis occur in 1% of the population. Above the age of 50 years osteoarthritis exceeds in number. Often it presents as symmetrical polyarthritis affecting the distal joints more commonly. In the majority it presents as a chronic fluctuating disorder, but less commonly it may have an acute presentation. The disease process may also involve several other tissues such as the skin, lungs, liver, heart, nerves and eyes during the course. Hence, many authors refer to this disease as rheumatoid state.

The exact cause and triggering factor are not fully known. Several evidences point to autoimmune mechanisms as the basic pathological processes and viral infections as triggering factors. There is increased frequency of HLA DRW4, DR4 and DR1 in these subjects. HLA DR4 is also correlated with the severity of the disease. Genetically predisposed individuals produce IgM or IgG antibodies on microbial or other forms of challenge. These antiglobulin antibodies which are known as rheumatoid factor (RF), combine with native IgG and activate complement to release lysosomal enzymes from synovial leukocytes. These elicit a type III immune response. Presence of RF is associated with higher morbidity and amplification of the rheumatoid process.

Pathology

Articular lesions: Most marked changes are seen in the joints. The earliest change is in the synovial membrane which shows congestion, infiltration by mainly CD4+ lymphocytes, plasma cells and macrophages. Synovial effusion occurs. Muscles around the joint also show mononuclear cell infiltration. Synovium shows fibrinoid degeneration surrounded by infiltration with fibroblasts and mononuclear cells. The synovial membrane is thickened, hyperemic, and edematous. It proliferates to form villi which fill the joint. Later, vascular proliferation invades the articular cartilage to form a pannus. Irreversible destruction of cartilage occurs in the later stages of the disease. The proliferated synovial membrane which invades cartilage, ligaments and subchondral bone centripetally liberates proteolytic enzymes which aggravate the destructive process.

Several cytokines participate in the inflammatory process. Among these TNF- α plays the major part. Antigen activated CD4+T cells lead to the production of several cytokines such as 1L-1, 1L-6, and TNF α . TNF α is a soluble 17 kd protein with three identical subunits. It is a potent cytokine involved in normal inflammatory and immune responses. It is an autocrine and paracrine inducer of several other cytokines, such as 1L-1, 1L-6, 1L-8, PDG F- β , eicosanoids, platelet activating factors, and granulocyte monocyte colony-stimulating factor (GM-CSF). TNF α is present in high levels in the synovial fluid and it plays an important role in inflammation and joint destruction which are the hallmarks of RA. Modern biological therapeutic agents target TNF α to block its action in causing inflammation.

The articular cartilage is eventually destroyed with loss of joint space. Fibrosis develops across the joint space to produce ankylosis. The joint is deformed and secondary degenerative changes develop. Infection may supervene in these joints to convert them into pyoarthroses.

Extra-articular lesions: Other tissues are affected to varying degrees. Basic pathology is the same as in the synovium. Lesions are seen in the skin, lungs, heart, liver, nervous system, and eyes. The small blood vessels may be affected. They show intimal hyperplasia, perivascular round cell infiltration, and occasionally necrotizing panarteritis. Subcutaneous nodules consist of a central areas of fibrinoid necrosis surrounded by mononuclear cells arranged in a palisade manner.

Clinical Features

Females are affected more than males in a ratio of 4:1. The disease is more common in the fourth and fifth decades. The disease passes through different stages (Fig. 105.1):

1. Onset to 6 months -early disease
2. 6 months to 3 years -established disease
3. Above 3 years -advanced disease.



Fig. 105.1: Typical rheumatoid arthritis hands, moderately advanced. Note: (1) swelling of finger joints, (2) deformity of fingers, (3) wasting of small muscles of the hands (arrow head)

Early symptoms are non-specific and they include undue fatigability, weight loss, poor appetite, transient myalgias, and paresthesia.

Articular involvement: The onset is generally insidious and the disease presents as a chronic symmetrical poly-arthritis. Less common presentations include: (1) acute polyarthritis, (2) oligoarthritis, (3) acute monoarticular arthritis, (4) chronic monoarticular arthritis, and (5) systemic disease with fever, sweating, leukocytosis and pleural effusion in addition to arthritis.

Any diarthrodial joint may be inflamed. Arthralgia, arthritis, muscle wasting, tendonitis, tendon rupture, and deformities constitute the main lesions. The affected joints are warm, painful, and swollen. Movements are restricted, especially in the morning after sleep (morning stiffness) and after periods of resting. Classic lesions are in the joints of the hands and feet. Metacarpophalangeal, metatarsophalangeal, and proximal interphalangeal joints are inflamed most frequently. Wasting of the small muscles of hand may develop due to disuse and direct muscle involvement (Figs 105.2 to 105.5).

In the hands, there is the typical ulnar deviation of the metacarpophalangeal joints. Sometimes, there is anterior subluxation of metacarpal heads and medial dislocation of the extensor tendons. Swan neck deformity of the fingers consists of hyperextension of the proximal interphalangeal joints and flexion of the distal interphalangeal joints. This deformity impairs effective hand grip. Sometimes, the extensor expansion overlying the proximal interphalangeal joint ruptures resulting in the dorsal protrusion of the head of the proximal phalanx. This leads to flexion of the proximal interphalangeal joint and hyperextension of the distal interphalangeal joint (*boutonnière or button hole*) deformity.

The extensor tendons may undergo attrition, these result in loss of extension of the *fingers (dropped fingers)*. The thumb may show a 'Z'-shaped deformity (*Hitch-hiker's thumb*). Large joints like the knees, wrists, ankles, elbows, and shoulders may also be involved. Tense synovial effusions may develop in the knees. **Baker's cysts** are tense cysts developing in the popliteal fossae as a result of collection of synovial fluid. These may occasionally rupture giving rise to a painful and tender swelling on the calf. Lateral subluxation of the knee joint is also very common. Chronic arthritis develops which leads to permanent deformities. Deformities are also common in the feet. **Hammer toe** is flexion at the proximal interphalangeal joint and hyperextension at the metatarsophalangeal joint. **Hallux valgus** (lateral deviation of the big toe) may develop. The arches of the feet may be lost due to affection of the joints and ligaments. Callosities develop over prominent bony points.

Less commonly, the cervical spine and temporomandibular joints are affected, but when they occur, the lesions

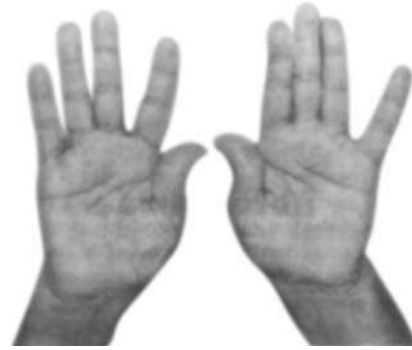


Fig. 105.2: Rheumatoid hand



Fig. 105.3: Rheumatoid hand: swan-neck deformity left index finger



Fig. 105.4: Hitch-hiker's thumb



Fig. 105.5: Dropped fingers

are characteristic. At the atlantoaxial joint the transverse ligament of the atlas may be weakened leading to **atlantoaxial subluxation**. This leads to pain in the neck and pain referred to the temporal and retro-orbital regions. There may also be a “clunking sound” in the neck on flexion. It is dangerous to manipulate the neck to elicit this sign. Atlantoaxial subluxation produces a host of neurological manifestations. The risk of sudden compression of the spinal cord is high in such subjects. Hence, tracheal intubation and similar procedures which require manipulation of the neck should be done only with caution. **Temporomandibular arthritis** leads to pain on mastication. Other portions of the spine such as the dorsolumbar regions and sacroiliac joints are usually not affected.

Tissue Involvement in Rheumatoid Arthritis

<i>Number of joints affected</i>		
Monoarticular (Only one joint affected)	-	3%
Oligoarticular, pauciarticular (less than 4 joints affected)	-	34%
Polyarticular	-	63%
<i>Joints affected</i>		
Proximal interphalangeal joints (PIP)	-	85%
Metacarpophalangeal joints (MCP)	-	70%
Wrists	-	70%
Elbows	-	50%
Knees	-	80%
Ankles	-	65%
Metatarsophalangeal joints (MTP)	-	30%
<i>Nonarticular involvement</i>		
Pulmonary interstitial fibrosis	-	3%
Episcleritis	-	1%
Sjögren’s syndrome	-	2%
Pleural effusion	-	1%
(As reported from Chennai, India)		

Systemic Involvement

Extra-articular Manifestations

Skin: Painless and nontender subcutaneous nodules ranging in size from a few millimeters to a few centimeters develop around the extensor aspects of the elbow and other subcutaneous bony surfaces and over tendons in 20-30 percent of cases. They are almost always associated with a positive serology. They persist for considerable periods (Fig. 105.6). Involvement of blood vessels gives rise to Raynaud’s phenomenon, vasculitis of the nailbeds and finger pulps, nonhealing ulcers of the finger, palmar erythema, and hyperhydrosis of the extremities (Fig. 105.7).

Eyes: Ocular lesions develop in a few cases and these may become disabling. Scleritis is common. In some cases



Fig. 105.6: Rheumatoid nodules elbow



Fig. 105.7: Rheumatoid disease with chronic ulcer ankle vasculitis

it becomes nodular. In necrotizing scleritis the nodules degenerate and the underlying dark uvea imparts a blue colour. Sometimes the sclera may be thickened due to granuloma formation. Perforation of the sclera leads to prolapse of the uvea and eventual rupture of the globe (**scleromalacia perforans**).

In the cornea, band keratopathy may develop. This is more frequent in Still’s disease. Though the sclera is affected, it is rare to involve the iris. Lesions of the iris are more frequent in seronegative arthropathies.

Respiratory system: **Cricoarytenoid** arthritis manifests as dysphonia, stridor, or dyspnea. Recurrent pleural effusion may occur which is usually unilateral. Rheumatoid nodules may develop in the lungs and these may cavitate. Interstitial fibrosis may develop and this may be indistinguishable from the idiopathic type.

Caplan’s syndrome is a special phenomenon occurring in subjects with rheumatoid disease who develop pneumoconiosis. Large coalescing nodules develop in the lungs. These are demonstrable by X-rays (Fig. 105.8).

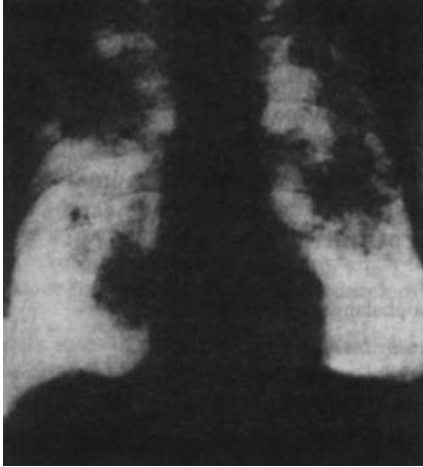


Fig. 105.8: X-ray of lung—Caplan's syndrome

Cardiovascular system: It is only rarely involved. Lesions include pericarditis, aortic regurgitation, and conduction defects.

Nervous system: Neurological involvement is not uncommon in chronic cases.

1. **Entrapment neuropathy** such as carpal tunnel syndrome and tarsal tunnel syndrome may be the presenting lesions or they may develop during the course.
2. **Symmetrical polyneuropathy** develops which improves with treatment. *Mononeuritis multiplex* develops in some cases.
3. In severe cases of rheumatoid disease (**malignant rheumatoid arthritis**) foot drop and wrist drop may develop. These are generally resistant to treatment.

Cervical cord compression due to atlanto-axial subluxation is a less common complication in long-standing RA. Mild cases present with transient neck pain radiating to the back of the head. It can rarely lead to subluxation of the odontoid process with compression of the cord which may end fatally.

Progressive clinical *myelopathy* at a lower level may develop insidiously. This is characterized by gradual onset of limb weakness, inability to hold the head erect and quadriparesis. The lesion is due to subluxation at lower levels of the cervical cord.

Renal Lesions

Type 1 renal tubular acidosis, drug induced renal lesions.

Secondary amyloidosis is a late complication in some cases of generalized rheumatoid disease (see also Chapter 174).

Laboratory Investigations

Erythrocyte sedimentation rate is markedly raised in the active disease and may exceed 100 mm/hour in the

majority. Normochromic normocytic anemia, iron deficiency anemia or rarely hemolytic anemia may be present in the acute phase. Serum protein electrophoresis may show elevation of alpha-2 gammaglobulins.

Serology: Markers of disease activity

Rheumatoid factor: Antibodies in rheumatoid disease, especially the IgM, can be demonstrated by the *Rose Waaler test*, *latex fixation test* or *bentonite flocculation*. Rheumatoid factor is positive in 80% of adults with rheumatoid arthritis. A differential agglutination titer of 16 and above is diagnostic. In 20% of cases LE cells and antinuclear antibodies may be demonstrable. To establish seropositivity the test should be positive at least on two occasions separated by 3-6 months. If negative, it should be repeated at least once more after 6-12 months. During DMARD treatment quantitative estimation of rheumatoid factor can be used as a marker of disease activity and progression. 5-10% of normal individuals may show RF positivity in low titers.

Synovial fluid aspiration: This reveals a turbid fluid with low viscosity and poor mucin clot. The white cell count in the fluid exceeds 1500/cmm. The cells are mostly neutrophils even though the synovial membrane is not infiltrated by them. Complement levels are low. The protein content is high and the electrophoretic pattern approaches that of serum.

Radiology: Characteristic lesions which have been graded from I to IV are seen on radiological study.

Grade I: Soft tissue swelling which indicates synovitis with or without juxta-articular osteoporosis which indicates active inflammation.

Grade II: Narrowing of joint space due to cartilage destruction.

Grade III: Erosions which may be of 2 types:
i. Surface erosion at joint margins,
ii. Cystic erosion of the bone shaft.

Grade IV: Marked irregularity of articular surfaces with subluxation and secondary degenerative changes. Bony ankylosis occurs only very rarely. (Figs 105.9 to 105.11).

Diagnosis

The diagnosis is to be made on clinical examination and laboratory criteria. Since, clinically several conditions resemble rheumatoid arthritis, diagnostic criteria have been laid down.

Differential diagnosis: Rheumatoid arthritis has to be distinguished from **rheumatic arthritis** in which children are more affected, the joint lesions are migratory, large joints are affected, effusion is prominent and ASO titer is high (more than 1/200).



Fig. 105.9: X-ray wrist-early rheumatoid arthritis. Note: loss of clear margins, haziness of inter carpal joints and juxta articular osteoporosis more so on the right side



Fig. 105.10: Advanced lesion—elbow. Note loss of joint space ankylosis



Fig. 105.11: X-ray of rheumatoid hand. Note the juxta-articular rarefaction of bone

Diagnostic criteria for rheumatoid arthritis (RA)

1. Morning stiffness extending for 1 hour or more.
 2. Arthritis of three or more joints.
 3. Arthritis of hand joints.
 4. Symmetrical arthritis.
 5. Rheumatoid nodules.
 6. Positive rheumatoid factor test: significant titer in India is $>20 \mu\text{U/mL}$
 7. Radiological abnormalities.
- Four or more of these criteria occurring for more than six weeks should make the diagnosis probable.

In **psoriatic arthritis** there is invariably evidence of psoriasis of the skin or nails and the arthritis involves the small joints of the hands (especially distal interphalangeal joints) and feet more. The hand may be severely mutilated (**arthritis mutilans**). Involvement of the sacroiliac joints and spine is not uncommon.

Gout Several joints may be affected in gout. The metatarsophalangeal joint of the big toe is characteristically affected more frequently, though any joint may be involved. In chronic tophaceous gout tophi may be seen as nodules around the joints, especially the elbow.

Osteoarthritis affects elderly subjects. Most common joints affected are the spine, hips, knees, and distal interphalangeal joints. **Heberden's nodes** may be seen at the base of the distal phalanges. The condition is progressive. The ESR is generally normal or only moderately elevated. In many cases rheumatoid and osteoarthritis may coexist in different joints.

Allergic arthritis manifests as arthralgia and arthritis involving several joints, both proximal and distal. Permanent deformity does not occur. Other manifestations of allergy may be evident. The ESR is only moderately elevated and not to the high levels seen in rheumatoid disease.

Other conditions which may mimic rheumatoid arthritis are **syphilitic arthritis**, **gonococcal arthritis**, **Reiter's syndrome** and **ankylosing spondylitis**. In ankylosing spondylitis the sacroiliac joints and spine are maximally affected. Peripheral joint involvement is less common.

In India several other conditions should be considered when the clinical presentation and investigation are not helpful straight away. These include allergy to tuberculosis (**Poncet's syndrome**), serum sickness-like reactions, reactions in leprosy, drug induced arthralgias, infections such as brucellosis and borreliosis, joint tuberculosis, AIDS and others.

PROGNOSIS

In general the disease tends to become recurrent and chronic and in many cases it leads to considerable disability and deformity. Severe rheumatoid arthritis shortens life. It leads to severe impairment of the quality

of life. A third of the patients with RA deteriorate clinically by consumption of food articles such as trout, fishes, peas, carrots, bottled mineral water, sea salt, milk, dairy products, wheat, coffee, chocolate, citrous fruits, corn and others. Free amino acids and oligopeptides contained in some of them are weakly antigenic and they may be responsible for this adverse effect.

Favourable criteria are:

1. Acute onset.
2. Male sex.
3. Onset at late age.
4. Asymmetrical or monoarticular involvement.
5. Negative rheumatoid factor.
6. Absence of subcutaneous nodules,
7. Absence of vasculitis, and
8. Prompt response to therapy early in the disease.

Unfavourable prognostic factors:

1. High titers of rheumatoid factor.
2. Insidious onset and failure to achieve remission even after 12 months of treatment.
3. Early development of nodules and bony erosions.
4. Extra-articular lesions.
5. Female gender.
6. HLADR₄ and DR₁ especially if homozygous.

Management

The aims of therapy are:

- a. Relief of pain
- b. Control of disease activity
- c. Prevention of joint damage and disability
- d. Maintenance and recovery of function
- e. Improvement in the quality of life

The modalities employed include:

- a. Patient education
- b. Physiotherapy and occupational therapy
- c. Drug therapy
- d. Surgical measures
- e. Improvement in nutrition and
- f. Supportive measures.

General Measures

Bed rest is essential during the acute phase of the disease. Local rest is ensured by splints which reduce muscle spasm and deformities. In the stage of deformity, splints are used as corrective measures. Physiotherapy to relieve muscle spasm and maintain joint mobility is an essential component of management during all stages of the disease.

Articles of diet such as fish or fish-oils which are rich in eicosapentanoic acid and docosahexaenoic acid are reported to give relief of inflammation and clinical symptoms, when combined with other modalities of

treatment. These polyunsaturated fatty acids suppress the inflammatory response and platelet activation. They may be tried in suitable cases. The dose of fish oils required for the beneficial effects varies from 10-20 g daily.

Drugs: There is no curative drug. Hence several groups of drugs are used symptomatically. Some also suppress inflammation and bring about resolution of the disease process.

1. *Analgesics*, e.g., aspirin, paracetamol, dextropropoxyphene.
2. *Analgesic anti-inflammatory drugs*, e.g. indomethacin, phenylbutazone, naproxen, ibuprofen, ketoprofen, fentiazac, mefenamic acid, flufenamic acid, diclofenac, nimuselide and the newer selective cyclooxygenase inhibitors (COX2 inhibitors) such as celecoxib, valdecoxib, rofecoxib, etoricoxib and others.
3. *Disease modifying drugs* such as gold salts, chloroquine, hydroxyl chloroquine, penicillamine and salazopyrine.
4. *Anti-inflammatory and immunosuppressant drugs*—corticosteroids and *biological agents* such as infliximab, adalimumab and etanercept, anakinra.
5. *Immunosuppressants* like methotrexate cyclosporin, cyclophosphamide, azathioprine and others.

Aspirin: Aspirin being very effective and cheap used to be the drug of first choice in all cases. This is given as calcium aspirin or the other preparations in doses of 3-6 g/day and an antacid is prescribed concurrently to reduce gastric upset. Troublesome side effects include abdominal pain, upper gastrointestinal bleeding, allergic rashes, tinnitus and vertigo. Due to weaker action and availability of more potent drugs, aspirin is rarely used as the drug of first choice at present.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

These are the most widely used drugs in view of their analgesic and anti-inflammatory action and free availability. The analgesic effect of NSAIDs is prompt within hours, whereas the anti-inflammatory effects manifest only after two weeks of therapy.

1. Indomethacin	25-50 g three times daily
2. Naproxen	200 mg two times daily
3. Ibuprofen	100-800 mg three times daily
4. Ketoprofen	100 mg two or three times daily
5. Fentiazac	200 mg two times daily
6. Mefenamic acid	250 mg four times daily
7. Flufenamic acid	100 mg four times daily
8.. Diclofenac sodium	50 mg thrice daily
	also the potassium salt and several others.
9. Nimesulide	100 mg twice daily

All of them share the same gastrointestinal side effects of aspirin but to a lesser degree and these are indicated when adequate relief is not obtained with rest, splinting and use of disease modifying drugs. They are several times more expensive than aspirin. NSAIDs are effective in relieving pain and acute manifestations. As a maintenance therapy they help to suppress symptoms and make the patient ambulant. They have only little effect in modifying the course of the disease, so that the disease flares up on withdrawing the NSAID. Therefore, they have to be combined with disease-modifying antirheumatic drugs (DMARDs).

Gastrointestinal complications induced by the ingestion of NSAIDs have assumed importance in recent times since hematemesis and melena occurring in day-to-day practice are commonly induced by these drugs. 1-3% of patients consuming NSAIDs develop a major gastrointestinal problem annually. The manifestations include overt or occult gastrointestinal bleeding, acute and chronic gastritis and progressive anemia. *H. pylori* infection is an independent risk factor which also aggravates hematemesis. NSAID related hematemesis has a mortality of 5-10% if not treated promptly, NSAIDs inhibit the synthesis of prostaglandins. Prostaglandins are protective to the mucosa. Even as small a dose as 30 mg of aspirin can inhibit gastric prostaglandin synthesis. The spectrum of lesions includes subepithelial hemorrhage, erosions and ulcers in the stomach and duodenum. NSAIDs should not be taken on an empty stomach since this favours gastrointestinal complications especially pain and bleeding. These can be prevented to some extent by the concurrent use of a H₂ receptor blocker such as ranitidine 150 mg b.d or a proton pump inhibitor such as omeprazole 40 mg o.d or b.d. Antacids and mucosal protective agents like sucralfate and prostaglandins augment the benefit partially.

The different NSAIDs vary in their propensity to cause gastrointestinal bleeding. Aspirin is highly ulcerogenic to the gastroduodenal mucosa. None of the NSAIDs is totally safe. All NSAIDs cause serious impairment of renal function in those with underlying kidney lesion.

COX-2 inhibitor drugs have been introduced with the claim that they do not produce gastrointestinal bleeding, e.g. celecoxib 100 mg b.d., valdecoxib, rofecoxib, etoricoxib and others. The average dose is 100 to 120 mg b.d. They are more expensive. They are effective pain relievers but, long term use has revealed serious adverse effects including the precipitation of cardiac failure and sudden death. Some of the COX-2 inhibitors such as rofecoxib have been withdrawn from the market due to their adverse effects on the cardiovascular system.

Disease-modifying Antirheumatic Drugs (DMARDs)

Even though DMARDs used to be administrated as the second line drugs when the analgesics and NSAIDs proved inadequate, the present trend is to employ them early in the course of the disease in order to modify the disease activity and prevent progression and permanent disability. The drugs included in this class are chloroquine, hydroxychloroquine, sulfasalazine, glucocorticoids, methotrexate and immunosuppressants and biological disease modifiers. DMARDs should be introduced early during therapy. They are effective in >80% of cases.

Chloroquine diphosphate 250 mg twice daily or once at bed time orally is effective in controlling pain, swelling, and stiffness in chronic cases. The drug is to be used over long periods. It helps to suppress the inflammatory process and prevent further deterioration. Serious side effects include retinopathy and deposition of the drug in the cornea. These are indications for stopping the drug.

Hydroxy chloroquine is more effective and it is to be preferred. The dose is 200 mg b.d orally. This is more expensive than chloroquine.

Salazopyrine and its analogues which are used for ulcerative colitis are excellent drugs to bring about relief and modify the progression of the disease. The dose is 0.5 g thrice a day orally. The effect is manifested after a week or two of starting the drug. It may have to be continued for several months or even years. The common adverse side effects include gastrointestinal upsets, allergic manifestations and blood dyscrasias. The drug is expensive, but widely used.

Systemic corticosteroids: These are very helpful in bringing about dramatic relief in acute cases and during exacerbations. Due to their undesirable side-effects, they should be employed only when other drugs fail and that too for short periods if higher doses are employed.

Indications for systemic corticosteroids are:

- Active and progressive vasculitic disease.
- Severe incapacitation—corticosteroids give temporary relief and make the patient suitable for physiotherapy.
- In severe and progressive radiological joint damage, use of corticosteroids helps to arrest the lesion and salvage the joint.
- Special situations like pregnancy and lactation.

When systemic therapy is unsuccessful intra-articular injections of cortisone acetate or triamcinolone hexacetonide or methylprednisolone acetate may be given. In uni-articular disease this may be advantageous. Intra-articular dose is 50-100 mg of cortisone acetate for large joints and

5-10 mg for small joints. After the acute symptoms are controlled, systemic therapy should be resumed in the minimum dose required. Corticosteroids should be withdrawn as early as possible since they do not modify the course of the disease in chronic cases. They induce steroid-dependence and also confer the adverse effects of corticosteroid therapy if given in doses equivalent to 5 mg prednisolone or above. Still a few patients do require small doses of corticosteroids for symptom free relief (steroid dependent cases), in addition to other drugs.

Immunosuppressant drugs: Cyclophosphamide, azathioprine, cyclosporin A, chlorambucil and low dose methotrexate are potent drugs which suppress the immunological injury and help to arrest the disease process. All these drugs have been tried with benefit. At present methotrexate given orally in a dose of 5-15 mg twice weekly is the most widely used drug in this group.

Biological Therapies

Blocking the action of $TNF\alpha$ is highly effective in the treatment of early and advanced RA. The available biologicals are:

1. **Infliximab:** Is a monoclonal antibody that binds $TNF\alpha$ with high affinity. The dose is 3-10 mg/kg b.w IV at 0, 2 and 6 weeks followed by maintenance infusion once in 8 weeks. It predisposes to reactivation of tuberculosis.
2. **Adalimumab:** It is a fully humanized antibody that binds $TNF\alpha$, made by rDNA technology. It is given in doses of 20-80 mg SC weekly. Adverse side effects include severe infections, neurological defects and lymphoid malignancies.
3. **Etanercept:** This is a recombinant fusion protein which binds 2 $TNF\alpha$ molecules. It is given in a dose of 25 mg SC twice a week or 50 mg once in two weeks. Adverse effects include local irritation at injection sites and predisposition to infection. Other drugs in this group are *lanercept*, *atlizumab*, *abatacept*.
4. **Anakinra:** It is a recombinant form of nonglycosylated human interleukin-1 receptor antagonist, expressed in *E.coli*. The dose is 1-2 mg/kg/SC. Adverse side effects include leukopenia, cardiac arrest, flu-like symptoms and infections like tuberculosis.
5. **Leflunomide** is a new drug which is an isoxazole derivative. Leflunomide is a pro-drug which is converted into its active metabolite in the system. It blocks the enzyme dihydro-orotate dehydrogenase which is needed for the synthesis of pyrimidines. It blocks proliferative activity. Its DMARD activity is comparable to that of sulfasalazine and methotrexate. The dose is 100 mg/day/oral for 3 days and adjusted thereafter. It is contraindicated in pregnancy due to

fetotoxicity. Serious side effects include hepatic damage and others.

TNF inhibitors are indicated in patients with active rheumatoid arthritis who have had no response to conventional DMARDs. TNF inhibitors should not be combined due to risk of infections. Vaccination using live vaccines should be avoided during TNF inhibitor therapy. Pregnancy should be avoided during therapy. If TNF inhibitors are found to be ineffective within 3-6 months of therapy or if they produce severe toxic effects they should be withdrawn. TNF inhibitors increase the incidence of lymphomas.

Indian experience on these biologicals is limited, though a few studies are available. Effect on RA is good, but all authors report the risk of exacerbation of tuberculosis. These drugs are very expensive Rs. 33500 for 100 mg of infliximab and Rs. 16500 for 25 mg of etanercept.

Further reading: Mahajan A. Biological therapy in rheumatoid arthritis, current status Indian J Rheim 2006; 1(1):13-9.

Pregnancy and Antirheumatic Drugs

NSAIDs should not be given during the last four weeks of pregnancy since they may give rise to bleeding complications and delay in labour. During lactation, a short acting NSAID such as ibuprofen is preferable, taken just before feeding the baby. The feeding interval should be four hours or more. Prednisolone, sulfasalazine, paracetamol and azathioprine are safe during pregnancy. Chloroquine is contraindicated. Methotrexate is absolutely contraindicated since it causes fetal death.

General Principles of Therapy

It is now established that use of disease modifying agents which will arrest progress of the disease and prevent joint damage should be introduced from the start of therapy. DMARDs can be used singly or in combination determined by trial and error and the experience of the physician. The effects produced by these drugs are slow. Therefore, analgesics and NSAIDs have to be given for immediate symptomatic relief of acute cases and those who are steroid-dependent, corticosteroid preparations have to be given systemically or intra-articularly.

The present approach is as follows:

Step 1. Early cases	Combination therapy with NSAIDs, DMARDs, and physical modalities.
Step 2. Moderately advanced cases	Combination therapy with immunosuppressants or immunomodulators.
Step 3. Disabling deformities	Drug combinations, surgical correction of deformities and rehabilitation.

Physical Modalities of Treatment

These play a major role in the total management of all cases of moderately advanced and advanced rheumatoid disease. The aims of physiotherapy are:

1. To provide comfort, relieve pain and aid in recovery,
2. To prevent deformities and loss of function of joints, and
3. To help in functional and corrective rehabilitation.

Physical modalities of treatment include various forms of superficial and deep heating devices, ultrasound, short-wave, exercises, manipulation of joints, splinting and several others. During the acute and subacute stages of the disease, rest, splinting and various forms of heat give relief. As the pain subsides, exercises are started with a view to maintain normal range of movement in all joints and prevent wasting of muscles. These have to be accepted as a life-style by the patient. Surgical measures and rehabilitatory procedures are to be instituted in crippled patients.

In Ayurveda and several types of herbal medicine prevalent in India there are modalities of treatment which are preferred by many patients. Their role in the management of rheumatoid arthritis has to be evaluated by modern methods.

Surgical correction: When permanent joint deformities develop, surgical measures have to be employed. These help to relieve morbidity and hasten recovery. Occupational therapy, social rehabilitation and re-education constitute the remedial measures necessary in bringing the cripple back to the stream of almost normal day-to-day activities.

Medical synovectomy: Synovial obliteration can be achieved by the instillation of osmic acid, or a variety of radioactive colloids into the synovial cavity.

Surgical measures include surgical decompression of the joint and synovectomy, especially at the wrists and carpal tunnel, reconstructive tendon surgery, osteotomies, excision arthroplasty, arthrodesis and joint replacement.

Further reading: Indian guidelines for the management of rheumatoid arthritis JAPI 2002;50:1201-18.

Variants of Rheumatoid Arthritis

Several arthritic syndromes occur which show some resemblance to rheumatoid arthritis, but also show distinguishing features with overlap into other conditions. These include:

1. *Juvenile idiopathic arthritis (JIA)*
2. *Felty's syndrome.*
3. *Sjögren's syndrome,* and
4. *Palindromic rheumatism.*

Juvenile Idiopathic Arthritis (JIA)

It is the most common cause of chronic arthritis in childhood. This term encompasses all idiopathic arthritis affecting children below 16 years of age and lasting for more than 6 weeks. This may be oligo- or polyarticular. In the oligoarticular types lower limb joints-knees, hips, ankles and tarsal joints are affected asymmetrically. In the polyarticular type both small and large joints are affected, usually in a symmetrical manner. The clinical features may be confined to the skeletal system, but in 10% the onset and course are characterized by systemic manifestations such as high fever ($>38.5^{\circ}\text{C}$) transient erythematous rash, generalized lymphadenopathy, hepatosplenomegaly, anemia and weight loss. Fever is intermittent with periods of normal temperature in between, during which the child appear to be normal. The serious complications include *macrophage activation syndrome* characterized by onset of thrombocytopenia, anemia, liver dysfunction and rapid downhill course which may end fatally.

Treatment

In addition to all general measures required for poly-arthritis, specific medications include methotrexate in relatively high doses, cytotoxic immunosuppressant drugs, IV IG, and biological therapies such as etanercept. Aspirin, NSAIDs and corticosteroids relive symptoms and may even modify the course of the disease.

About 50-60% of children recover by the time they reach adulthood, where as 40% continue to have active disease even after 10 years.

Further reading: Angello Revelli, Alberto Martine. Juvenile idiopathic arthritis. The Lancet 2007;369:767-78.

Aggarwal A, Grover S. Juvenile idiopathic arthritis, classification, diagnosis and treatment. In Sukumar Mukherjee (Ed): Recent-Trends in Connective Tissue Disorders. Indian college of physicians publication 2005;209-21.

Macrophage Activation Syndrome (MAS)

This is a complication which can develop in chronic rheumatic disorders, particularly in systemic onset juvenile idiopathic arthritis. It is a hemophagocytic syndrome characterized by excessive activation of well differentiated macrophages, clinically manifesting as fever, hepatosplenomegaly, lymphadenopathy, peripheral blood cytopenias, liver involvement, intravascular coagulation and neurological lesions. This entity has been described from India, mostly associated with other connective tissue diseases or malignancy. Untreated, the mortality is high reaching up to 40%.

Ref: Pinto L, et al. Macrophage activation syndrome: experiences from a tertiary referral centre. JAPI 2007; 55:185-7.

Classification

1. Familial MAS—caused by gene mutations
2. Secondary or acquired—seen in viral infections and malignancy
3. Reactive—it is also secondary to rheumatic diseases

Pathogenesis

Macrophage activation occurs as a result of Th-1, T cell activity. The T cells augment the phagocytic capacity of the macrophages and also recruit the macrophages to the site of inflammation or infection. Bone marrow is stimulated to produce macrophages. Th-2 cells inhibit the processes.

Strong immunological activation may result from infection, malignancy or autoimmune disease. The viruses particularly incriminated include herpes viruses—especially Epstein-Barr virus, cytomegalovirus and adenoviruses.

The pathological findings in infection-associated histiocytosis include

1. Infiltration of all organs by benign-looking lymphocytes and histiocytes and
2. Atrophy of the germinal centres of lymph nodes and spleen.

The immunological abnormalities include hyperstimulation by infective agents, immunosuppression by drugs or HIV or immune dysregulation as in autoimmunity and malignancy.

Clinical features include fever, cutaneous rash, lymphadenopathy, hepatosplenomegaly and a downhill course. Failure of the liver and central nervous system, disseminated intravascular coagulation (DIC) and overwhelming infections may supervene. If untreated, the disease is fatal in about two weeks.

Investigations reveal cytopenias, rise in liver enzymes such as transaminases, at times alkaline phosphatase, LDH and high serum ferritin levels often exceeding 10000 ng/dL. Blood picture is one of normocytic normochromic anemia, low reticulocyte counts and sometimes, atypical lymphocytes. The ESR is characteristically low due to hypofibrinogenemia.

Bone marrow shows varying cellularity, with normo- or at times, megaloblastic erythropoiesis. There is infiltration by histiocytes accounting for > 2% of the cells. Many show hemophagocytosis (i.e.) phagocytosis of erythrocytes.

Treatment

This includes supportive care and attention to the underlying disease. Two lines of treatment are available.

1. Interruption of function of the activated macrophages and histiocytes by drugs such as etoposide, glucocorticoids and IV immunoglobulin (IVIG).
2. Interruption of function of the activated lymphocytes by glucocorticoids, cyclosporine, antithymocyte globulin (ATG) and biological drugs against TNF α .

Further reading: Joshi VR, Kaushik Bhyani. Macrophage. Activation syndrome. In Mukerjee S (Ed): Recent Trends in Connective Tissue Disorders. Indian College of Physicians Publication 2005;161-9.

Still's Disease (Chronic Juvenile Polyarthritis)

This disorder occurs before the age of 16 years. Girls are affected more than boys. It differs from adult rheumatoid disease in that the disease is more often pauciarticular. Rash, fever, lymphadenopathy, and splenomegaly are characteristic. Subcutaneous nodules are rare and rheumatoid factor is negative. Eye involvement with uveitis and keratopathy is more common. The treatment is along the same lines as for adult rheumatoid arthritis.

Felty's Syndrome

This is seen in older age groups. In addition to the classic features of seropositive rheumatoid arthritis, splenomegaly and neutropenia also occur. Splenomegaly may lead to hypersplenism. Splenectomy may have to be considered to correct hypersplenism, in addition to treatment for the rheumatoid state.

SJÖGREN'S SYNDROME (SS)

This is a chronic inflammatory autoimmune disease characterized by mixed cellular infiltration of the exocrine glands, particularly the lachrymal and salivary glands— a form of autoimmune exocrinopathy (autoimmune epithelitis). This results in dryness of the eyes (xerophthalmia), dryness of the mouth (xerostomia) and frequently, dryness of the nose, throat and vagina. This condition predisposes to increased risk of **mucosa-associated lymphoid tissue lymphoma (MALT lymphoma)**.

SS may be primary in which it is the only demonstrable abnormality. Secondary SS, known also as sicca complex may be associated with any of the other autoimmune diseases. Radiation therapy of the head and neck for Hodgkin's disease, sarcoidosis, amyloidosis and tuberculosis may lead on to SS.

Epidemiology: The disease is rare. 2% of cases of rheumatoid arthritis and 0.73% of SLE may have associated S S. Almost all patients are females. They show association with HLA (DW3) (DR3) and DR52.

Immunology: At least one of the following autoantibodies will be present in the serum. These are-antibodies to Ro/SS-A in 40-60% or LA/SS-B, ANAs or rheumatoid factor. Levels of these antibodies correlate with the degree of cellular infiltration of the salivary and other glands. B-cell activation is the consistent immunoregulatory aberration. Viral infections may trigger off the condition.

Clinical features: A wide spectrum of clinical features may be present. These are:

1. Ocular dryness and consequent symptoms
2. Oral dryness with consequent symptoms
3. Arthralgias in 75%, arthritis in 10%
4. Skin manifestations- annular erythema on the face and trunk
5. Vascular involvement- leading to Raynaud's phenomenon in 35-50%
6. Gastrointestinal symptoms -dysphagia, atrophic gastritis
7. Renal tubular acidosis
8. Hypothyroidism in 10-15%
9. MALT lymphoma (Table 105.1)

Diagnosis

Schirmer's test is positive. This test is based on the wetting of a piece of filter paper by tears when applied to the palpebral conjunctiva. It is positive if the length of the wetting is < 5 mm in 5 minutes. Biopsy of the parotid gland, salivary scintigraphy and parotid sialography are helpful in diagnosis.

Course: The disease follows a benign prolonged course over 10-12 years or more.

Treatment: The conjunctival sac and mouth are kept moist. Hydromellose (hydroxy methyl cellulose) helps to moisten the conjunctival sac.

Strict oral hygiene is advised. Bromhexine 40 mg/day oral in divided doses and pilocarpine hydrochloride 5 mg tds helps the dryness of the mucous membranes. Drugs such as hydroxychloroquine 200 mg oral daily, corticosteroids, cyclosporin and interferon have been tried with modest benefit. High dose IVIG and plasma exchange may produce limited benefit.

TABLE 105.1

Showing clinical features in SS

Glandular features	Extra glandular features
Xerostomia dry eyes parotid enlargement	Arthralgia/arthritis Raynaud's affection of organs—lungs, kidneys, liver peripheral nerves, muscles, CNS and vasculitis and lymphoma

Secondary SS occurs as a complication of RA, PSS, SLE, MCD, and primary biliary cirrhosis, (polymyositis/ dermatomyositis, (PM/DM) chronic active hepatitis (CAH) and mixed cryoglobulinemia. The underlying disease generally manifests earlier.

Prognosis: The condition is generally benign. Purpura, glomerulonephritis, decrease in complement levels and mixed monoclonal cryoglobulinemia are adverse prognostic factors.

Treatment: Eye care, sugar free lozenges for xerostomia and lubricating jellies for vaginal dryness give symptomatic relief. Hydroxychloroquine 200 mg is effective to relieve arthralgia and myalgia. Systemic corticosteroids and immunosuppressants may be required for the treatment of systemic manifestations.

Further reading: Lata Bichile. Sjögren's syndrome. In Mukherjee S (Ed): Recent Trends in Connective Tissue Disorders) ICP publication 2005;113-25.

Palindromic Rheumatism

In this condition repeated attacks of joint pains, redness and swelling occur. The attacks occur suddenly within hours and may affect one joint usually. The affected joint shows signs of inflammation. These last for a few days and subside without any residual lesions. The ESR is raised during the attacks and remains high even during the intervals. After varying periods of time, typical rheumatoid arthritis supervenes in many cases, whereas spontaneous remission occurs in some.

Further reading: Indian guidelines for the management of rheumatoid arthritis. JAPI 2002;50:1201-18.

Systemic Lupus Erythematosus, Antiphospholipid Antibody Syndrome

K.V. Krishna Das

Chapter Summary

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General Considerations

Definition: It is an inflammatory disease of autoimmune nature involving the connective tissue of several organ systems and associated with a variable course.

SLE is worldwide in distribution. In India it constitutes 1-2% of the major rheumatological problems. Females predominate and the male to female proportion being 1:18. The disease is rare below the age of 5 years, but children account for 20%. More than 60% of cases are between the ages of 30 and 60. SLE results from a gross disturbance of immune mechanisms. Normal body constituents are rendered immunogenic by various damaging factors such as exposure to sunlight, infection, tissue injury, drugs or others. Among these, viral infection and drugs top the list. Several autoantibodies are produced against the host's own tissues. There is suppression of T-lymphocyte function and overactivity of B-lymphocytes, leading to formation of autoantibodies, mainly belonging to IgG and IgM classes. Antigen antibody complexes are formed, with the utilization of complement factors. Deposition of immune complexes on tissues stimulates further inflammatory processes and this accounts for most of the lesions. C3 and C4 components of complement are mainly used up and, therefore, their levels fall.

Genetic factors: These probably play an important role in many. This is evidenced by the simultaneous occurrence of the disease in monozygotic twins, higher incidence of SLE and other connective tissue disorders in the relatives of SLE patients and the presence of several autoantibodies

and low serum complement levels in many of them. HLA types B8 and DR3 and inherited deficiency of C1, C4 and C2 complements are known to be associated with a higher incidence of SLE.

Pathogenesis

Traditionally SLE has been considered to be a disease of hyperactive immune system. Recent work reveals that the disease process is set in motion by insufficiency of immune regulatory cells and factors. Once the process is triggered off, it proceeds stepwise to produce the florid disease. SLE is an autoimmune disease characterized by insufficiency of immune regulation by T cells and regulatory factors which starts the process. Hyperactive and self-reactive T and B cells produce autoantibodies against several self-components. Activated T and B cells infiltrate several tissues and produce auto-antibodies and immune complexes. Immune complex deposition leads to further inflammation and tissue damage. The progression of the disease occurs in distinct stages.

- Stage: 1 Immune insufficiency stage in which there is lack of immune regulation
- Stage: 2 Hyperactivation stage in which self reactive T and B cells are activated.
- Stage: 3 Invasion of tissues by the hyperactive T and B cells, autoantibodies and immune complexes formed locally and systemically.
- Stage: 4 Active disease: SLE with inflammation of tissues.
- Stage: 5 Organ destruction, fibrosis and progress to end stage.

Further reading: Ram Raj Singh. Pathogenesis of SLE: the author's perspective: Review article. Indian J. Rheumatol 2006;14(1):19-29.

Pathology

The lesions of SLE are widespread and all tissues may be affected. Basically four types of histological pictures are seen. These are fibrinoid change, collagen sclerosis, formation of hematoxylin bodies and inflammatory changes in arterioles and capillaries. Tissue damage occurs

in two different ways. These are: (1) *Direct cytotoxicity (type II reaction) caused by antibody and complement*, e.g. brain damage and abortion, and (2) *type III immune reaction caused by immune complexes and complement*, e.g. renal and vascular lesions. Though the full spectrum of autoimmunity in SLE is not clear, several abnormalities have been observed. Among the tissues which become antigenic, nuclear components, especially nucleosomal histone complex are important. Antinuclear antibodies (ANA) are important demonstrable diagnostic markers occurring in over 95% of cases.

Clinical Features

SLE presents a wide spectrum of clinical presentation depending upon the system affected maximally. Data collected from Indian literature gives the following picture.

Presentation of SLE	Frequency (%)
Arthralgia/arthritis	70-90%
Fever	50%
Cutaneous rashes	50-80%
Malar rash	40%
Lymph node involvement	40%
Renal lesions	45-65%
Neuropsychiatric symptoms	35-40%
Cardiac lesions	30%
Pleuropulmonary lesions	20-25%
Hepatosplenomegaly	20-25%
Discoid lupus	10%
Ocular lesions	10%

In many cases the presenting symptom is fever which may take several forms, from mild subacute illness to severe hectic fever.

Arthritis and arthralgia: Joint manifestations occur in 90% of subjects with SLE in the early stages. Large joints are affected more than others. Severity of joint involvement varies widely. Permanent deformities do not occur. Jaccoud’s arthropathy may affect the hand in upto 50% of cases. It is characterized by reducible, non-erosive joint deformities with preservation of hand function. The pathogenesis of this condition is probably extra-articular secondary to inflammation and shortening of the tendons.

Hip pain may suggest the development of avascular necrosis and is usually a complication of corticosteroid therapy. It may be a manifestation of SLE in which case it is associated with the presence of antiphospholipid antibodies.

Skin lesions: These occur in 65 percent of patients at some stage or other. The classic lesion is the erythematous, photosensitive, butterfly rash affecting the cheeks and nose and this is diagnostic (Fig. 106.1). Discoid lupus, maculopapular rashes and purpura may occur in some. Frontal baldness may develop. Alopecia occurs due to breaking up of the hair. Painful ulcers may develop in the mouth and pharynx.



Fig. 106.1: Facial rash in SLE

Discoid lupus is the form in which the only manifestation of the disease is confined to the skin for a few years. The lesions show scaling, atrophy, telangiectasia and keratotic plugging. They heal with considerable scarring. Some patients develop systemic lupus.

Cardiovascular system: Cardiovascular lesions develop in 25-40% of cases. Cardiac lesions include pericarditis, pericardial effusion, myocarditis with cardiac failure, and valvulitis involving the mitral valve. **Libman-Sacks endocarditis** is a nonbacterial verrucous endocarditis affecting the mitral valve which is occasionally seen. It results in mitral incompetence. Cardiac abnormalities in the form of valvular thickening, vegetations and stenosis develop in decreasing order of frequency. Cardiac involvement does correlate with either the duration or the presence of other clinical manifestations, and their presence increases the morbidity. Vasculitis leads to **Raynaud’s phenomenon**, necrotic ulcers of the finger pulp and chronic ulcers. Patients with SLE have increased risk of ischemic heart disease and major cardiac events apart from the risk factors posed by the disease and its treatment. Proper control of SLE brings down the cardiovascular risk as well.

Respiratory system: Thirty percent of cases manifest lesions in the respiratory system. Common lesions are dry pleurisy, pleural effusion, fibrosing alveolitis, and lupus pneumonitis. A **syndrome of shrinking lung** is uncommon but virtually pathognomonic of SLE. It is characterized by progressive reduction in lung volume with evidence of diaphragmatic weakness.

Kidney: This organ is affected in about 60% of cases. Renal involvement used to be the most important lesion deciding the prognosis. Renal involvement may remain asymptomatic with only proteinuria for long intervals or may manifest as nephrotic syndrome, hematuria, acute nephritic syndrome or renal failure. The histological pattern is that of focal glomerulonephritis, diffuse glomerulonephritis or membranous glomerulonephritis. The wire loop lesions which are produced by thickening of the glomerular walls are characteristic on histology. The



Fig. 106.2: 16 years female suffering from SLE with nephritic syndrome

international society of nephrology renal pathology group proposed a new classification of lupus nephritis by revising the WHO classification in 2003. It has classified the renal lesions into six classes 1-VI (Fig. 106.2).

(Ref: Gupta RK. Current classification of lupus nephritis. J Indian Rheumatol Assoc 2005;13:156-61).

Sm antibodies are associated with membranous nephritis. Renal tubular acidosis is occasionally seen, particularly when Sjögren's syndrome coexists with SLE and it is due to tubulointerstitial disease. Antiphospholipid antibodies may be associated with renal vein thrombosis. Treatment instituted early in the disease helps to avert renal involvement. Indian experience is that 66% of adults and 80% of children develop renal lesions. Among them 14.3% had class II lesions, 22.8% had class III, 17.2% had class IV. Compared to the west, the progress of renal lesions appear to be more severe in Indian subjects. 50% of class IV develop renal failure and 25% develop end stage renal disease (ESRD). There was no significant difference in those treated with cyclophosphamide and azathioprine (see also Chapter 174).

(Ref: Jacob George-management of lupus nephritis. JAPI 2003;51:1489-94).

Nervous system is affected in about 40% of cases. Neurological involvement is generally a later manifestation, even though psychiatric symptoms may occur early. Lesions are caused by vasculitis and occlusive vascular phenomena. Patients with antiphospholipid antibodies are more prone to develop stroke. Other manifestations include psychosis, convulsions, cranial nerve palsies, peripheral neuropathy, mononeuritis multiplex, chorea and cerebellar disturbances. Involvement may be the result of primary CNS lupus or the secondary effects of complications, or drugs. Infection, uremia and malignant hypertension are not uncommon.

Muscle involvement manifests as myalgia, rarely polymyositis and muscle wasting. Patients with neurological involvement have a poor prognosis.

Hematology: Most of the cases show normocytic normochromic anemia. Other abnormalities include *Coombs' positive autoimmune hemolytic anemia*, *leukopenia*, and *thrombocytopenia*. *Lupus erythematosus (LE) cells* are demonstrable by suitable techniques. These are polymorphonuclear leukocytes which have phagocytosed nuclear material under the influence of antibodies. Their number increases with the activity of the disease. Their presence and numbers generally correlate with the activity of the disease. In a marginally positive case their diagnostic value is not absolute since a few other conditions such as rheumatoid arthritis, drug allergy, and drug induced lupus may also show this phenomenon.

SLE may be the primary lesion in at least 10% of cases of immune thrombocytopenic purpura (ITP). For considerable periods of time the diagnosis may masquerade as ITP till other features of SLE manifest. *Antiphospholipid antibody syndrome* gives rise to additional features such as strokes, portal vein thrombosis, thrombophlebitis, pulmonary embolism and abortions in the later part of the second trimester or in the third trimester. Recurrent abortions with or without phlebothrombotic episodes should raise the possibility of this syndrome. Antiphospholipid antibodies (APLAB), lupus anticoagulant (LA) and/or anticardiolipin (ACL) antibodies are demonstrable in over 30% of cases of SLE. Those that show ACL also give false-positive VDRL test.

Presence of LA imposes 30% life time risk of venous thromboembolism. Other features of this syndrome include thrombocytopenia and immune hemolytic anemia. 1-2% of young and 2-12% of elderly among the general population show low levels of antiphospholipid antibodies (APLAB) without any other demonstrable disease.

The liver is enlarged in 60%, spleen in 60% and lymph nodes in 25% of cases. Abdominal emergencies may be produced by the development of acute peritonitis, perisplenitis, or pancreatitis.

Eyes: These may be affected in a few cases, lesions include dryness of the conjunctiva and retinal abnormalities such as hemorrhage and exudates known as cytooid bodies.

Laboratory Investigations

SLE gives rise to an array of abnormalities, some being specific and the other non-specific. The non-specific features include, markedly elevated ESR (above 100 mm), moderate anemia, leukopenia, thrombocytopenia, and moderate to severe proteinuria. The specific tests depend upon the immunological abnormalities and they are described as follows.

Serological Abnormalities in SLE

The antinuclear antibodies (ANA): They occur in over 95% of cases. Though the ANA are not specific for SLE, presence of three or more components is almost diagnostic of this disease. The titer is high during exacerbation and

TABLE 106.1

Showing the frequency of antibodies

ANA	95%
Anti ds. DNA	60%
Anti-Sm	35%
False-positive VDRL	15%
Low level of C3	60%
Low level of C4	70%
Anticytoplasmic antibodies	41%

low during remission. Low levels of ANA occur in rheumatoid arthritis (20%), Sjögren's syndrome (60%), scleroderma (40%) dermatomyositis (30%), and drug reactions in a variable number (Table 106.1).

Lupus erythematosus (LE) cell phenomenon: The phenomenon is due to antinuclear antibodies. Since the titer required for LE cell formation is high, the positivity for LE cells is less than that for ANA (Fig. 106.3).

Other immunological markers which are non-specific are anticytoplasmic antibodies, lymphocytotoxins, antibodies against RBC, WBC and platelets, circulating anticoagulants, antithyroid and other organ specific antibodies, rheumatoid factor, false-positive Wassermann reaction and VDRL, cryoglobulins and circulating immune complexes. Levels of complements C3 and C4 are reduced. Cryoglobulins are IgG and IgM proteins which precipitate when cooled and redissolved when warmed. They get deposited on the walls of blood vessels. They may be monoclonal, polyclonal or both.

Presence of antinuclear antibodies and demonstration of LE cells should make the diagnosis reasonably certain.

Diagnosis

The diagnosis of SLE should be suspected if there are febrile episodes with multisystem involvement and high ESR not responding to general lines of treatment. The American Rheumatism Association (ARA) has laid down

criteria for diagnosis of SLE. These help to distinguish SLE from the other rheumatic disorders. The important criteria are malar rash, discoid lupus, Raynaud's phenomenon, alopecia, photosensitivity, oral and nasopharyngeal ulceration, arthritis, neuropsychiatric manifestations, and the laboratory features. Presence of four or more of these features is highly suggestive of the diagnosis.

Course and Prognosis

The course is variable, but in general the prognosis is grave, if untreated. Treatment improves the outlook for morbidity and mortality considerably. At present the majority of cases are detected early and they respond to treatment. More than 60 to 80% survive over 10 years. The main causes of death are renal failure, hypertension secondary to proliferative or membranous glomerulonephritis, cardiovascular events and central nervous system complications leading to strokes, coma or seizures. With modern therapy the renal lesions can be arrested to a great extent, but neurological complications pose a major threat to life.

SLE and Pregnancy

SLE does not affect fertility. SLE may flare up during pregnancy and this may cause deterioration of renal function. During pregnancy there is increased risk of pre-eclampsia (5-38%). Presence of pre-existing hypertension, nephritis and antiphospholipid antibody syndrome (APAS) increases the risk further. It may be difficult to distinguish between the renal-flare of SLE from pre-eclampsia; since both conditions are associated with hypertension, proteinuria, edema and deterioration of renal function. Complement C3 and C4 levels fall in SLE flare up, whereas they remain unchanged in pre-eclampsia. Anti-ds DNA levels increase in SLE, whereas they are unaffected in pre-eclampsia.

Abortion rates are high 6-35% and still births, 0-22%. Active SLE, presence of antiphospholipid antibodies and history of previous fetal deaths are worse prognostic factors. Both lupus anticoagulant and a ACL are associated with higher rates of fetal loss.

Neonatal lupus erythematosus (NLE) may develop in the baby; caused by maternal antibodies to the 52KD SSA/RO, 60KD SSA/RO or 48 KD, SSB/La ribonucleoproteins. The baby may present with skin rash and congenital complete heart block. Except the heart block the other features disappear in a few days.

Aspirin and NSAIDs should be avoided during the last weeks of pregnancy due to risk of hemorrhage.

Hydroxychloroquine, NSAIDs, prednisolone and azathioprine can be continued during pregnancy if the mother's condition warrants. Breast feeding is safe for the baby if the mother is taking prednisolone and hydroxychloroquine. Breast feeding is contraindicated if the mother is on azathioprine, cyclophosphamide, methotrexate or cyclosporine A.

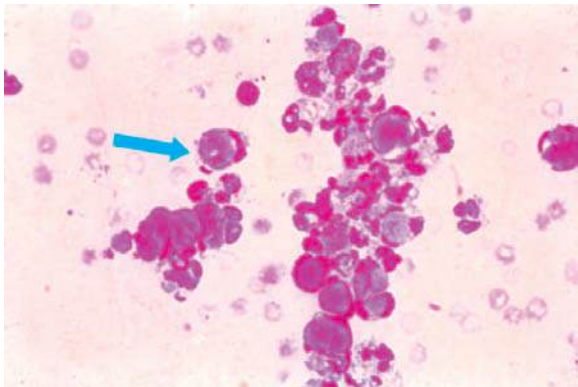


Fig. 106.3: LE cell—a neutrophilic leukocyte engulfing amorphous eosinophilic material—its own nucleus pushed to the periphery—arrow)

The chance of SLE being transmitted to the offspring is low ($\pm 10\%$). Contraceptive pills do not flare up SLE.

Management

Since there are no curative measures, the main aim is to induce remission and prevent relapses. General management consists of avoidance of direct sunlight and offending drugs and prompt attention to complications.

Drug treatment depends upon the stage and severity of the disease. Mild SLE with only cutaneous and joint involvement without constitutional symptoms respond to chloroquine 250 mg o.d or b.d given orally. An alternate drug is dapsone given in doses of 50-100 mg/day oral. In moderately severe SLE in which organ systems are affected, but there is no general constitutional symptoms, steroids are used as the mainstay of treatment with immunosuppressants as add on drugs. In severe SLE there is gross affection of vital organs, particularly the heart, kidneys, lungs and brain. In them immunosuppressants are almost always required.

Specific drugs used are corticosteroids and immunosuppressants. Corticosteroids are indicated as the first line drugs. On an average the dose is 1 mg prednisolone per kg. body weight given orally daily. Once the symptoms are controlled, alternate day regime with 40-100 mg prednisolone given as a single dose is started. This serves to minimize the unwanted side effects without reducing effectiveness.

The dose is gradually reduced and finally withdrawn over a period of months or years. The activity of the disease is assessed clinically and by the fall in ESR. However, many cases will require maintenance dose for several years.

Symptomatic relief can be provided by the use of NSAIDs and analgesics.

Immunosuppressant drugs: The commonly used drugs are cyclophosphamide and azathioprine. They are indicated in severe life-threatening disease, failure to respond to steroids or intolerance to steroids. However, infections, severe anemia, and leukopenia are relative contraindications. The usual daily dose of cyclophosphamide is 2-3 mg/kg and that of azathioprine is 1-4 mg/kg given in divided dosage. Several dosage schedules of cyclophosphamide have been advocated. High doses such as 0.5-1 g/m² given once a month for 6 months, followed by smaller doses at longer intervals for 2 years have been found to be beneficial in severe cases. Some individuals have genetic defects which lead to severe marrow suppression following exposure to azathioprine. Therefore, persons receiving this drug should be monitored by regular blood tests.

General supportive measures include maintenance of nutrition, management of infection, analgesics, and hematinics. Specific clinical symptoms like convulsions, psychosis, pericardial effusion, and cardiac failure require appropriate management,

Vasculitis: Antiplatelet drugs like aspirin 150 mg daily, and anti-sludging agents like low molecular weight dextran are found to be very useful, in addition to corticosteroids and immunosuppressants.

For maintenance therapy in mild cases, especially with localized skin lesions, chloroquine in a dose of 250-500 mg given oral daily is effective. Long-term therapy may lead to ocular complications which should be looked for.

In severe cases with rapid deterioration of renal function or neuropsychiatric manifestations large doses of methyl prednisolone 1 g given IV daily with pulse doses of cyclophosphamide 0.5-1 g daily IV may be required to tide over the crisis. Newer modalities of treatment include cyclosporin, mycophenolate mofetil, cladribine, fludarabine and others. Supportive treatment for advanced renal failure may be necessary as per indications.

Drug-induced SLE

Several drugs like hydralazine, procainamide, dilantin, mesantoin, oral contraceptives, phenothiazines, INH, PAS, methyl dopa, levodopa, penicillin, and sulfa drugs lead to a syndrome of fever, arthritis, skin rashes, and lymphadenopathy which closely resembles SLE. The clinical and biochemical profile are identical with natural SLE but the course is mild and renal and CNS manifestations are rare. Withdrawal of the offending drug leads to resolution. If resolution is delayed, short course of corticosteroids—20-30 mg prednisolone oral daily will accelerate remission. The patient should be informed about drug toxicity in future.

Antiphospholipid Antibody Syndrome (APAS)

Syn: Hughes syndrome

This condition is seen not uncommonly in all parts of India and several case reports and studies are available.

APAS is characterized by the presence of a family of autoantibodies termed anti-phospholipid antibodies (APAs). These are a family of 20 antibodies that are directed against phospholipid binding plasma proteins. These include **anticardiolipin antibodies (aCL)**, **lupus anticoagulant (LAC)** and others. These antibodies are directed against anionic phospholipids participating in the coagulation cascade. These antibodies are detected by RIA and ELISA tests. APAS shows overlap between systemic autoimmune connective tissue diseases and coagulopathies, particularly thrombophilic states.

APAS may be primary or secondary. In primary APAS there is no evidence of underlying connective tissue disease. Secondary APAS occurs in association with other connective tissue diseases, particularly, SLE in which 15-34% have LAC and 12-30% have aCL.

Several surveys done worldwide show the presence of APAs in small quantities in 2-5% of the general population. LAC and aCL may occur together in the same individual or only either of them may be present. Persons with aCL also show the presence of LAC in 20%. On the other hand the presence of aCL in those with LAC is 80%.

Causes of secondary APS

- A. Connective tissue diseases – SLE, MCTD, PSS, primary SS, discoid lupus, RA and AS
- B. Other immunological disorders
Crohn's disease, systemic vasculitis, immune thrombocytopenic purpura, Behcet's syndrome and others
- C. Malignancy: Lymphomas, cancers of kidney, lung and ovary
- D. Drug induced: Oral contraceptives, quinine, quinidine, phenytoin, hydralazine, procainamide, beta adrenergic blockers, biologics like and alpha interferon.

These antibodies predispose to venous and arterial thrombosis and consequent complications. They also lead to fetal loss in pregnancy. The hallmark of APS is the presence of the antibodies aCL and LAC, false positive Venereal Disease Reference Laboratory (VDRL) and Wasserman reaction (WR) and other antibodies against cofactors associated with anionic phospholipids.

Common Presenting Features

- 1. Deep vein thrombosis 32%
- 2. Thrombocytopenia which is mild and subclinical 22%
- 3. Livedo reticularis 20%
- 4. Stroke 13%
- 5. Superficial thrombophlebitis 9%
- 6. Fetal loss 8%
- 7. Transient ischemic attacks (TIA) 7%
- 8. Autoimmune hemolytic anemia 7%
- 9. Arterial thrombosis in limbs and several organs. This may lead to gangrene of the limbs and superficial structures or infarcts in deep organs. Others include osteonecrosis, pulmonary hypertension, renal lesions and catastrophic anti-phospholipid antibody syndrome (CAPS).

APAS and Pregnancy

Fetal loss occurs around the 10th week of pregnancy. Placental venous thrombosis is a contributory factor. Presence of LAC antibodies or IgG class of aCL antibodies confer a risk of 50% for fetal loss. Proper management leads to successful outcome in over 75% of such cases.

Criteria for the Diagnosis of APAS in Pregnancy

- 1. 3 or more consecutive unexplained miscarriages before the 10th week of gestation
- 2. One or more unexplained deaths of a morphologically normal fetus at 10 weeks of gestation or older
- 3. One or more premature births of a morphologically normal fetus at 34 weeks gestation or younger associated with severe pre-eclampsia or placental insufficiency.

Prevalence of APAS in women with recurrent miscarriages is 15%. Women with APAS has 90% chance of recurrent miscarriages in subsequent untreated pregnancies.

Causes of Miscarriage in APAS

- 1. Thrombosis and infarction of the uteroplacental vasculature
- 2. Other possible effects of antiphospholipid antibodies include interference with signal induction mechanisms which control endometrial cell decidualisation, promotion of trophoblast apoptosis, decrease in trophoblast fusion and impairment of trophoblast invasion.

Management

LMW heparin and low dose aspirin improve the fetal survival in 80 to 85% of cases. Heparin should be given when pregnancy is confirmed or when the cardiac activity of the fetus is demonstrable. Heparin dose should be individualized. Heparin, in addition to its anticoagulant effect, can bind to APAS and antagonize the action of Th-1 cytokine interferon gamma, thereby protecting the fetus from injury.

Aspirin is also given to prevent thrombotic events.

Catastrophic Anti-phospholipid Antibody Syndrome (CAPAS)

In APS widespread vascular occlusions in multiple vital organs may develop. Vascular occlusion occurs in 3 or more organs simultaneously within a period of 1 week. Antiphospholipid antibodies are present. Histology of the organs reveals non-inflammatory thrombotic lesions.

Infections, pregnancy or surgery may trigger off this syndrome. If untreated, mortality exceeds 50%, usually due to cardiopulmonary failure. CAPAS has to be distinguished from disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP), other forms of systemic vasculitis and severe infections. Haematology helps to distinguish between them

Condition	Diagnostic feature
Systemic vasculitis	Thrombocytosis
DIC	thrombocytopenia and low fibrinogen levels
TTP	Low platelets and presence of schistocytes

Coexistence of APAS with SLE worsens the clinical features of the latter

Management of APAS 1. Elective long-term anti-coagulant therapy with heparin and later on, coumarin drugs to keep INR at 2-3 to 3-4, depending on the severity and frequency of thrombotic episodes is effective in preventing thrombotic complications.

Normalization of LAC or aCL is not an indication for stopping therapy. Treatment has to be continued indefinitely. There is no firm indication for using glucocorticoids or immunosuppressant drugs unless the APS is secondary to immunological diseases.

Thrombocytopenia: Corticosteroids and/or IVIG should be considered.

Management of catastrophic APS: It is a life-threatening emergency. A combination of high intensity anticoagulation, corticosteroids, plasma exchange and IVIG form the therapeutic modality

Treatment of Symptomatic aPL Positivity

There is no consensus of opinion on this matter. Prophylactic low dose aspirin is recommended by some workers.

At times clinical features of APS occur, without demonstrable antibodies. Anticoagulation therapy, given on presumptive grounds has helped such patients.

Further reading: Raj Rai, Lesley Regan. Recurrent miscarriage. The Lancet 2006;368:601-11.

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Progressive Systemic Sclerosis (PSS)

Syn: Scleroderma

K.V. Krishna Das

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General Considerations

In this generalized disorder of connective tissue, fibrosis and degenerative changes predominate. The skin, synovium, digital arteries, gastrointestinal tract, lungs, heart, kidneys and other organs may be affected. The most conspicuous feature is thickening and hardening of the skin which becomes "hide-bound". The term scleroderma is derived from the Greek word 'scleros', which means 'hard' and 'derma' which means skin. The two major categories are (1) limited cutaneous scleroderma where sclerosis is confined to the extremities distal to the elbows and knees with or without facial involvement and (2) diffuse cutaneous systemic sclerosis.

The extent of skin involvement and presence of lesions in internal organs form the basis of classification into diffuse and limited diseases.

1. **Localized scleroderma (morphea):** The lesion is restricted to a localized area on the skin.
2. **Linear scleroderma:** The skin involvement is linear. It leads to atrophy of underlying tissues. In the face it gives a characteristic appearance.
3. **Disseminated morphea:** There are multiple skin lesions, but systemic involvement is minimal or absent.
4. **CREST syndrome:** This consists of calcification of subcutaneous tissues, Raynaud's phenomenon, esophageal hypomotility, sclerodactyly, and telangiectasia.
5. **Progressive systemic sclerosis:** There is progressive involvement of skin and other internal organs leading to systemic manifestations. This carries the worst prognosis.

Even in the limited cutaneous disease occlusive vascular lesions, gastrointestinal lesions, interstitial pulmonary fibrosis and pulmonary hypertension may

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occur. Scleroderma occurs all over the world and is occasionally seen in Indian subjects.

Pathology

The three cardinal features are excessive collagen production and deposition, vascular damage and inflammation or autoimmunity. There is suggestion that human parvovirus B19 may trigger the disease process.

The prominent pathological abnormality is overproduction and cross-linking of collagen and vasculitis. HLA DR1, DR2, DR3, DR5 and DRWS2 class II alleles show association and glycosaminoglycans are produced by fibroblasts. The vascular lesion consists of structural damage to small vessels occurring extensively, resulting in proliferative changes and luminal narrowing. The humoral arm also shows abnormalities. The presence of antinuclear antibodies (ANAs), inflammatory lesions in the skin and lung and increased amounts of pro-fibrotic chemokines in circulation and in tissues are the consequences of immune activation. ANA is positive in 50% of cases, antibodies to single stranded RNA develop. Scl-70, also known as anti-topoisomerase is an antibody against an extracellular nuclear antigen. It may be detectable in 20% of cases. Its presence is a predictive marker for pulmonary involvement. There is activation of T lymphocytes and complement. Advanced lesions show atrophy of the dermis, loss of hair follicles and sweat glands, depigmentation and calcinosis.

Skin: The dermal collagen is increased leading to fibrosis. Endarteritis and calcinosis supervene in some cases. Collagen types 1 and 3 are increased, the former being more abundant.

Joints: Synovium shows infiltration with lymphocytes and plasma cells and deposition of fibrin. The changes may resemble those of rheumatoid disease, but pannus formation is unusual.

Kidneys: Changes occur in the interlobular arteries. These comprise intimal hyperplasia, fibrinoid necrosis of afferent arterioles and glomerular tufts, and thickening of glomerular basement membrane. These changes lead to cortical infarctions and glomerulosclerosis. The lesions may resemble those seen in malignant hypertension.

Muscles: The histological lesions resemble those seen in myopathy such as fragmentation and loss of striation of muscle fibers and nuclear changes. Affected muscles are replaced by fibrosis.

Vasculitis: Affection of small arteries leads to intimal thickening and narrowing of lumen. The lesions are particularly demonstrable in the digital arteries of patients showing Raynaud's phenomenon.

Clinical Features

The disease is seen more in the fourth and fifth decades and male to female ratio is 1:4. Onset is insidious. The initial symptoms are variable. These include Raynaud's phenomenon, tightness of the extremities, arthralgia, and vague manifestations.

Cutaneous manifestations: Three stages can be distinguished during the evolution of the disease. These are edematous, indurative, and atrophic stages. Initial manifestations are edema of the hands and feet, which may extend more proximally. The edema is followed by thickening and tightening of the skin. Skin loses its normal pliability and ultimately becomes "hide bound" and non-pinchable. Appendages are lost over the affected areas. Affection of the face gives rise to the "mouse head" appearance with microstomia, beaked nose, mask like expression, and difficulty in opening the mouth (Figs 107.1 and 107.2).

Pigmentary changes develop over the extremities and anterior chest wall. These consist of hyperpigmentation or a combination of spotty hyper- and hypopigmentation (salt and pepper skin), and telangiectasia over the fingers, palms, face, lips, and tongue. The tight atrophic skin is particularly vulnerable to trauma. Painful, nonhealing, chronic, indolent ulcers are common over the fingers and toe tips. When the extremities are predominantly affected, the condition is called acrosclerosis. Over the palmar aspect of the terminal phalanges subcutaneous calcification occurs. These ulcerate and extrude calcareous material. Ischemia aggravates this tendency. Paroxysmal vasospasm of digital blood vessels leads to Raynaud's phenomenon, which is present in 25% of cases, when exposed to cold environment. Raynaud's phenomenon may also occur during emotional disturbances or even spontaneously.

Raynaud's Phenomenon

Raynaud's phenomenon is the term used to describe the episodic events of vasoconstriction of the digital arteries, pre-capillary arterioles and cutaneous arteriovenous shunts. Raynaud's phenomenon may be primary or secondary. Primary Raynaud's phenomenon shows the following features;

- vasospasm is precipitated by cold or emotional stress.
- symmetrical in distribution
- absence of necrosis and gangrene
- normal nail fold capillaries
- normal ESR and negative tests for dyscollagenoses

Secondary Raynaud's phenomenon is characterized by;

- age over 30 years
- presence of tissue necrosis
- evidence of dyscollagenoses
- abnormal nail fold capillaries and presence of auto-antibodies.



Fig. 107.1: Progressive systemic sclerosis. Note: pinched face, difficulty to open the mouth, swelling of finger joints, painful flexion



Fig. 107.2: Progressive systemic sclerosis. Note: depigmentation of arm and tight skin

Systemic manifestations: The pattern of involvement reported in Indian series is acrosclerosis (53%), arthralgia (83%), arthritis (20%), upper GI lesion (66%), lower GI lesion (33%), lungs (20%), and kidneys (25%).

Progressive systemic sclerosis overlaps with other connective tissue disorders such as systemic lupus erythematosus (14%), rheumatoid arthritis (8.4%), and mixed connective tissue disease (2.8%).

Bones and joints: Mobility is restricted due to fibrosis of soft tissue. Primary articular involvement can occur in many. Crepitus can be palpated over major joints and tendons and 50% develop deformities. Long standing cases show erosion and absorption of the terminal phalanges.

Gastrointestinal tract: Affection of the GI tract can be demonstrated by investigations even in the asymptomatic cases. Esophagus and intestines are affected most frequently. Common symptom is dysphagia, which is initially due to esophageal spasm and later fibrosis. Barium swallow reveals dilated esophagus resembling achalasia cardia. The small and large intestines show dilatation, impaired peristalsis, and malabsorption.

Involvement of the lungs results in progressive interstitial fibrosis and alveolocapillary block syndromes. Cystic changes are seen occasionally. Secondary pulmonary hypertension and cor pulmonale develop in long-standing cases.

Cardiovascular system: Heart is enlarged with myocardial dysfunction and rarely conduction defects. Malignant hypertension is more common.

Renal involvement: Secondary hypertension and renal failure may follow. Scleroderma renal crisis is the rapid development of malignant hypertension and oliguric renal failure during the course of systemic sclerosis.

Limited cutaneous forms, often confined to the skin may be seen at times. These include morphea, linear scleroderma and limited cutaneous systemic sclerosis syndrome, also known as **CREST syndrome**. This consists of *calcinosis*, *Raynaud's phenomenon*, *esophageal involvement*, *sclerodactily* and *telangiectasia*. Morphea and linear scleroderma give rise to well demarcated pale, indurated lesions of the skin and subcutaneous connective tissue. Even in the absence of systemic involvement, the serological markers may be present.

In patients with Raynaud's phenomenon, two markers viz abnormal cutaneous capillaries in the nailfold (detectable by an ophthalmoscope) and presence of antinuclear antibodies predict the subsequent development of scleroderma.

Raynaud's phenomenon may be part of systemic sclerosis, without evidence of cutaneous scleroderma (*scleroderma sine scleroderma*) but with only systemic lesions. In this form the humoral markers such as ANF and Scl-70 are detectable and these help in diagnosis.

Nervous system involvement: This manifests as cranial or peripheral neuropathy at times.

Diagnosis

This is mainly clinical; the most important finding is the hard skin, which is not pinchable and is also devoid of hair. Laboratory investigations help to rule out other conditions. Skin biopsy helps to confirm the diagnosis and rule out other conditions like eosinophilic fasciitis and scleredema.

Laboratory Investigations

Erythrocyte sedimentation rate is moderately raised but it may be normal in early cases and in cases where only the skin is affected. During the active phase IgG may be elevated. Muscle enzymes are elevated when myopathy occurs. Rheumatoid factor is positive in 20-25% and antinuclear factor (ANF) in about 40% cases in low titers Scl-70 are detectable and these help in diagnosis.

Differential Diagnosis

Progressive systemic sclerosis must be distinguished from other collagen disorders such as dermatomyositis and mixed connective tissue disease. Thickening and tightness of the skin may occur in other disorders like eosinophilic fasciitis, scleredema adultorum Buschke, myxedema, and acromegaly.

Scleredema adultorum Buschke: This condition is characterized by painless edematous induration with an abrupt onset over a short period of time occurring in young subjects. Face, scalp, trunk, and proximal parts of the extremities are extensively affected. Though the exact cause is not clear, some cases are seen to follow streptococcal infection. There is accumulation of mucopolysaccharides in the dermis and in the underlying muscles. The condition resolves spontaneously over a period of 6-12 months even without specific treatment. Systemic manifestations of PSS are not present.

In eosinophilic fasciitis which starts in the form of painful and tender swellings over the extremities, there is fasciitis, myositis, eosinophilia, and hypergammaglobulinemia. The skin is indurated and tight. Etiology is unknown. Onset is acute or subacute starting as symmetrical swelling and pain of the extremities followed by induration and joint contractures. Forearms, legs, hands and feet are affected. These parts become shiny and erythematous, which later become taut and woody. The skin is restricted by the subcutaneous tissue. Systemic involvement may develop at times. There is no evidence of autoimmunity.

Biopsy reveals perivascular infiltration by eosinophils, histiocytes, lymphocytes, and plasma cells in the skin, fat and even underlying muscles. These lesions are self-

limiting. Raynaud's syndrome does not occur. Carpal tunnel syndrome may develop. Histology shows inflammatory exudate consisting mainly of eosinophils. Fibrosis is prominent. The condition is self-limiting. Excessive consumption of L. tryptophan in health foods has been associated with the development of eosinophilic fasciitis. Corticosteroids bring about remission promptly.

Myxedema and acromegaly are conditions which may show skin changes mistaken for scleroderma. They are associated with other endocrine abnormalities as well.

Course and Prognosis

Progressive systemic sclerosis is a slowly progressive disease. Widespread skin involvement, lesions of the kidneys, lungs and heart, and onset earlier in life are unfavourable factors. More than 70% survive 5 years or more.

Treatment

At present there is no drug which will arrest the progression of the disease. The use of corticosteroids is controversial. The renal lesions may even be aggravated by corticosteroids. Nonsteroidal anti-inflammatory drugs like indomethacin or ibuprofen may help to relieve arthralgia and arthritis. D-penicillamine may help in the early stages on account of its ability to inhibit cross-linking of collagen. Blood flow in the digital arteries can be improved by the infusion of low molecular weight dextran. This may prevent ischemic ulcers and help in their recovery. Early use of ACE inhibitors helps to allay the progress of renal lesions and hypertensive complications. Calcium channel blockers have found use in complications such as pulmonary hypertension, Raynaud's phenomenon and calcinosis. Nifedipine in usual dosage relieves Raynaud's phenomenon. Severe and disabling Raynaud's phenomenon may respond to infusion of prostacyclin. Epoprostanol 0.5-0.6 ng/kg bw is infused IV for 6-24 hours for 2-5 days. The drug is expensive. Intractable Raynaud's syndrome is relieved by cervical sympathectomy.

Since the potential role of cells, cytokines, paracrine signalling and role of immunity have been known; treatment targeted against these processes is possible. Best results are obtained in the case of vascular complications.

ACE inhibitors prevent renal crisis and these drugs are the preferred choice in the treatment of renal crisis.

The following drugs have been approved by the FDA for the treatment of pulmonary artery hypertension (PAH). These include

1. Epoprostanol, treptostinil, iloprost – They supply prostacyclin to the vascular endothelium
2. Sildenafil - It is a vasodilator. In addition it can generate nitric oxide (NO) which leads to vasodilation.
3. Bosentan - This inhibits endothelin.

These drugs reduce vasospasm and increase the walking distance and quality of life. Epoprostenol and bosentan may prolong survival. Nifedipine is given orally, iloprost and epoprostanol are given IV and nitroglycerine is given as an ointment. Bosentan which is given orally is a receptor antagonist for endothelium. It reduces the frequency of new digital ulcers and necrosis.

Drugs targeted against immune activation include fluorouracil, methotrexate and cyclophosphamide. They improve skin lesion and a few other manifestations, but not the visceral lesions. Cyclophosphamide given in doses of 3-5 mg/kg or higher doses IV monthly for 6 months with prednisolone 20 mg on alternate days showed improvement.

Azathioprine is also effective.

Interferon- γ has shown mild benefit in pulmonary fibrosis but not on the skin lesions. Future strategies aim to modulate transforming growth factor (TGF β) and connective tissue growth factor (CTGF) which also promotes fibrosis

Further reading: Christina Charles, et al. Systemic Sclerosis; hypothesis driven treatment strategies. The Lancet 2006; 367:1683-91.

Overlap Syndrome

Multisystem diseases of varied pathogenesis and clinical features are difficult to be compartmentalized precisely.

This is particularly true of the connective tissue diseases (CTD). Some distinct entities include systemic lupus erythematosus (SLE), systemic sclerosis (SSC), polymyositis dermatomyositis (PM-DM), rheumatoid arthritis (RA), giant cell arteritis and others. Some patients show overlapping features of more than one CTD and these are included under the terms overlap CTD (OCTD) or undifferentiated CTD (UCTD).

Mixed Connective Tissue Disease

A set of patients show features combining the manifestations of SLE, SSC, PM-DM and RA. This combination is termed mixed connective tissue disease (MCTD).

Presenting symptoms are given below.

1. Raynaud's phenomenon.
2. Sausage like swellings of fingers.
3. Skin changes of dermatomyositis or scleroderma.
4. Arthralgias.
5. Prolonged fever.
6. Esophageal achalasia.

Symptomatic measures to relieve Raynaud's phenomenon and arthralgia give relief. Chloroquine given in a dose of 250-500 mg oral daily is beneficial in mild and moderate cases. Corticosteroids and immunosuppressants are indicated in severe cases.

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General Considerations

Population data on vasculitides is not available in India. They are seen at times, though not very frequently. Primary vasculitis disorders constitute 1% of the material in Rheumatology Clinics.

Necrotising vasculitic disorders include polyarteritis nodosa (PAN) Wegener's granulomatosis (WG), microscopic polyangiitis (MPA) and Churg-Strauss Syndrome (CSS).

Vasculitis which is defined as inflammation of blood vessels (arterioles, veins and capillaries) is a common

TABLE 108.1

Classification of the primary vasculitis

Size of vessel	Sites	Clinical entity
Large vessels	1. Temporal arteritis	Giant cell arteritis syn: temporal arteritis polymyalgia rheumatica
	2. Aorta and main arteries to head and limbs. Occasionally pulmonary arteries	Takayasu's arteritis
Medium size vessel	1. Diffuse lesions in several arteries 2. Coronary arteries	Polyarteritis nodosa Kawasaki disease
Small vessels—arterioles capillaries or venules	Kidneys, lungs	Microscopic polyangiitis, Goodpasture's syndrome
	Upper and lower respiratory tract	Wegener's granulomatosis, Churg-Strauss syndrome
	Skin, mucous membrane, genitalia, joints	Behcet's syndrome
	Skin, joints, abdominal viscera, kidneys	Henoch-Schönlein purpura
Cutaneous vessels	Isolated angiitis without systemic lesion	Isolated cutaneous leucoclastic vasculitis

The frequency distribution of vasculitic disorders in India

Disease	%
Aortoarteritis	20.2
Henoch-Schönlein purpura (HSP)	22
Giant cell arteritis	3.4
Polyarteritis nodosa	8.8
Small vessel vasculitis	5.7
Wegener's granulomatosis	13.8
Behcet's disease (BD)	13.6
Microscopic polyangiitis	3.9
Kawasaki disease miscellaneous conditions	0.5
Churg-Strauss syndrome	1.8
Not properly diagnosed	5.9

Ref: Joshi VR, Gayatri Mittal. Vasculitis. Indian perspective supplement to JAPI, 2006;12:5.

manifestation of several different immunological processes which may occur as primary manifestations, or secondary to other established entities such as the discollagenoses. In many of the primary vasculitis syndromes the exact pathogenesis is not clearly known. They lead to multisystem manifestations as a result of vascular occlusion in addition to the primary pathological processes specific to them. The vessels show infiltration by leucocytes, secondary changes in the vessel walls and occlusion. Since many of them lead to systemic symptoms such as fever, skin manifestations, arthralgias, vague pains and tenderness they can be included under the rheumatological syndrome. The classification takes into account the size of the vessel that is affected (Table 108.1).

General Clinical Features of Small Vessel Vasculitis

1. Constitutional symptoms and signs: Fever, malaise, arthralgia, myalgia.

2. Skin lesions: Localized purpuras, focal necrosis, ulceration—particularly seen in the lower limbs.
 3. Nervous system: Peripheral neuropathy, mononeuritis multiplex.
 4. Intestines: Ischemic ulceration, bleeding, perforation, intussusception.
 5. Respiratory tract: Infections, often hemoptysis
- Vasculitis may be secondary to several other classes of diseases which are given below:
- Infections—immune-complex vasculitis
- Neoplasms— Paraneoplastic syndromes
Lymphomas
Myeloproliferative disorders
Carcinoma.

Polyarteritis Nodosa

General Considerations

Polyarteritis nodosa (PAN) is characterized by the formation of multiple nodules along blood vessels, mainly affecting the smaller arteries, arterioles, and adjacent veins. Capillaries are spared. Pathologically the lesion consists of polymorphonuclear infiltration, necrosis and aneurysmal dilatation of the arterial wall. Thrombotic occlusions may occur. The lesions are widespread and all tissues may be involved. Main impact is on the arteries of the muscles, kidneys, heart, mesentery, and vasa nervorum. The disease is more common in people who are infected with hepatitis B virus. Circulating immune complexes containing hepatitis B surface antigen may be present in them. In view of this finding PAN may be classified as hepatitis-B-related and hepatitis B-unrelated.



Fig. 108.1: Polyarteritis nodosa: gangrene of fingers, discolouration of hands

Clinical Features

Polyarteritis is rare compared to the other connective tissue disorders. Though all ages may be affected, adults suffer more frequently. Males predominate. The onset is variable. The condition may be precipitated by drugs or upper respiratory infections.

The onset is with general symptoms like fever, muscle pains, arthralgia, rash and anorexia. Inflammatory nodules ranging in size from 5-10 mm may be palpable over the superficial arteries. These nodules are tender. Symptoms referable to organ systems develop depending on the lesions. In about 50% cases the kidneys are affected leading to the clinical picture of acute nephritic syndrome or glomerulosclerosis with secondary hypertension and renal failure. Vascular occlusion leads to distal gangrene of extremities. Occlusion of vasa nervorum leads to mononeuritis multiplex. Retina may show hemorrhages and exudates. Pericarditis, pleurisy, myocardial infarction, ulceration, and bleeding from intestines and necrosis of the liver and gallbladder may be encountered at times (Fig. 108.1).

Diagnosis

The condition has to be suspected clinically. There are no specific laboratory tests. The ESR is markedly elevated. Neutrophil leukocytosis is common. Diagnosis is confirmed by demonstrating the lesions on biopsy specimens. Muscle, kidney or liver is selected for biopsy depending on the presentation. Tests for infection by hepatitis B and C are indicated in all cases.

Differential Diagnosis

Polyarteritis nodosa has to be differentiated from allergic vasculitis and Goodpasture’s syndrome and microscopic polyangiitis.

PAN has to be differentiated from microscopic polyangiitis (MPA).

Difference between microscopic polyangiitis and PAN	
PAN	MPA
Lesions: medium arteries and arterioles-necrotizing vasculitis	Small vessels—capillaries, venules and arterioles necrotizing vasculitis
Renal involvement leads to hypertension	Mainly rapidly progressive glomerulonephritis
Pulmonary hemorrhage—rare	Common
Relapse—rare	Frequent
HBV- HCV association—frequent	Indefinite
C-ANCA—Positive	Negative

Prognosis

Polyarteritis nodosa is a serious illness with a mortality ranging from 50-60% in one year. Common causes of death are renal failure, myocardial infarction, infections, congestive heart failure, and gastrointestinal bleeding.

Treatment

Corticosteroids may cause symptomatic improvement. Immunosuppressants are of benefit if used judiciously. With proper treatment mortality and morbidity can be brought down considerably. Patients who show evidence of hepatitis B infection improve better if the infection is also treated simultaneously.

Giant Cell Arteritis

Syn: Temporal arteritis, Cranial arteritis

Definition

This form of systemic connective tissue disease occurs in the elderly, in the sixth and seventh decades.

It is characterized by panarteritis with giant cell infiltration, predominantly affecting the cranial vessels. The etiology is not established.

Pathology

The arterial wall normally contains dendritic cells in the adventitia. The inflammation is T-cell mediated. The activation of the dendritic cells sets in motion a complex cascade consisting of cytokine activation, intimal proliferation supported by neo-angiogenesis, oxidative injury to smooth muscles and effects of systemic inflammation. The larger arteries such as the internal and external carotids, temporal, occipital, and ophthalmic arteries are usually involved, though any other artery may show lesions. The lesions are segmental with intervening

normal areas. The media of the artery is infiltrated by round cells and giant cells. The vessels may be occluded by thrombi which recanalize later.

Clinical Features

Both sexes are equally affected. Onset is with severe, unilateral or bilateral headache in the temporal or less commonly in the occipital regions, associated with vomiting. Diagnostic feature is the palpably thickened, tender and nonpulsatile temporal arteries.

Loss of vision due to occlusion of the ophthalmic artery is a dreaded complication. Rarely patients present as facial neuralgia with jaw claudication on chewing, deafness, necrosis of the tongue, or an associated widespread necrotizing arteritis of small vessels which presents as peripheral neuropathy.

Laboratory Diagnosis

ESR often exceeds 100 mm and all immunoglobulin fractions are elevated. Temporal artery biopsy which reveals the characteristic histology is diagnostic. However, a negative biopsy does not rule out the diagnosis, since the lesions may occur segmentally.

Treatment

Corticosteroids are indicated in high doses. Prednisolone (50-60 mg/day) may be started initially and tapered off slowly to the minimum maintenance dose required to keep the ESR down. This treatment must be continued for at least one year. Once blindness occurs it is irreversible and it has to be prevented by early diagnosis and institution of steroid treatment. Relapse occurs in 20-30% on stopping treatment. This is an indication for restarting treatment with addition of immunosuppressants such as azathioprine or methotrexate. Low dose aspirin is useful in long-term management.

Polymyalgia Rheumatica

This is a syndrome rarely only seen in India, characterised by severe pain and stiffness in the neck, back, shoulder, upper arms and thighs, particularly worse in the morning.

This condition may be associated with giant cell arteritis which may coexist, or in some cases, develop later. The ESR is elevated, muscle enzymes are normal and this finding helps to differentiate this condition from polymyositis. Treatment with corticosteroids gives prompt improvement.

Takayasu's Arteritis

This is described in Section 13 along with diseases of the aorta.

Kawasaki Disease

Syn: Mucocutaneous lymph node syndrome. The disease is mainly described from Japan. This disease has been reported from Chennai and Chandigarh. Probably there is under-reporting of cases from India.

Kawasaki disease- Indian data M:F ratio 83:17

Age group	Total no. of cases	%
< 1 year	5	14
1-5 years	26	72
>5 years	5	14

Affection of organs

Incomplete or atypical 17%, Conjunctiva 81%, Oral mucosa 94%, Lymph nodes 83%, Skin lesions 92%, Arthritis 19%

Ref: Nutan Kamath, et al. Kawasaki disease in India. J Indian Rheumatic Assoc 2005;13:113-20.

This is an acute or subacute exanthema-like disease, often affecting children, characterised by onset of abrupt fever, erythematous rash over the face, mouth, palms and soles, nonsuppurating cervical lymphadenopathy, conjunctival congestion and vasculitis affecting particularly the coronary arteries. The arterial lesion leads to aneurysms in the coronary arteries. The coronary arterial lesion can be demonstrated by 2D echocardiography and the lesion can be quantified. Treatment during the acute febrile phase consists of aspirin given in a dose of 80-100 mg/kg bw/day to be tapered off later and IVIG given as IV infusion in a dose of 2 g/kg bw over 10 hours. 5% of children who develop Kawasaki disease develop coronary aneurysms.

Churg-Strauss Syndrome

This is characterised by vasculitis and granuloma formation. There is previous history of asthma and eosinophilia antedating the vasculitic manifestations by 3-4 years. Pulmonary infiltrates with eosinophilia may be present. Necrotising vasculitis occurs in several organs leading to skin nodules or rashes, mononeuritis multiplex, myocarditis, cardiac infarction, and pericarditis. Cause of Churg-Strauss syndrome is not known.

American College of Rheumatology criteria for diagnosis of Churg Strauss syndrome

- 1. Asthma
- 2. Eosnophilia > 10%
- 3. Neuropathy mono or polyneuropathy
- 4. Pulmonary infiltrates
- 5. Paranasal sinus lesions and
- 6. Extravascular eosinophil infiltration on biopsy.

Note: Four out of six criteria should be present

Antineutrophil cytoplasmic antibodies ANCA are present in high titers in 70-80% of cases. These antibodies act

against neutrophil granules and the lysosomes of monocytes. The antibodies show further specificities. ANCA is positive also in Wegener's granulomatosis and microscopic polyangiitis which all are together grouped as ANCA associated vasculitis.

Treatment is with high doses of corticosteroids. Immunosuppressants are only rarely indicated.

Behçet's Disease (Behçet's Syndrome)

It is an inflammatory disease of unknown cause characterised by recurrent aphthous ulceration in the mouth, genital ulcers, uveitis and skin lesions. The uveitis tends to recur and leads to blindness, whereas the other manifestations are self-limiting.

Pathologically it is a recurrent acute inflammatory disease rather than a chronic inflammatory process. Persons with HLA B1 have a strong predilection to develop Behçet's disease. This disease is present in India rarely and it may masquerade as other multisystem diseases.

The basic pathophysiological process is small vessel vasculitis, autoimmune responses and hyperfunction of neutrophils. The neutrophils are overactive with increased lysosome production and chemotaxis.

Clinically this can be demonstrated by the pathergy tests in which a needle prick area is infiltrated by neutrophils to produce a visible papule or pustule seen at 48 hours. Lymphocyte function is also abnormal. Diagnosis is almost certain if in addition to oral ulceration, any two of the following criteria are present.

Clinical Features

Recurrent genital ulcers, eye lesions, skin lesion especially erythema nodosum, folliculitis, pustules or acneiform lesions.

Skin lesions: Erythema nodosum, pseudofolliculitis, papular pustular or acneiform lesions.

Recurrent ulcers over the scrotum, penis or vulva.

Ocular lesions: Uveitis and retinal vascular occlusions.

Joint lesions: Mono- or polyarthritis—major joints are affected.

Gastrointestinal features include recurrent oral ulcerations. Abdominal pain, hematemesis, melena and perforation of viscera.

Neurological manifestations include meningitis, meningoencephalitis, motor disturbances, brainstem symptoms and psychiatric disturbances.

Treatment

Mainstay of treatment is corticosteroids. Immunosuppressants such as azathioprine and cyclosporine and cytotoxic drugs such as cyclophosphamide and chlorbucil are required in cases resistant to corticosteroids. Ocular lesions are treated with local corticosteroid drops and colchicine 0.5-1.5 mg/day orally. In intractable cases interferon alpha is being used with success.

Arteritis is treated with a combination of corticosteroids and immunosuppressants. Thrombotic complications are treated with anticoagulants and antiplatelet drugs. Hemoptysis is a dangerous symptom occurring in patients with pulmonary vasculitis. Fifty percent of patients die within 3 years of onset of hemoptysis. In spite of recent modalities of treatment, functional recovery is unsatisfactory.

Mixed Essential Cryoglobulinemia

Cryoglobulinemia is a systemic vasculitic disorder secondary to the deposition in small and medium sized blood vessels of circulating immune complexes and complement, which precipitate at reduced temperatures. Serological classification defines type I as isolated monoclonal immunoglobulin without rheumatoid factor (RF), predominantly associated with malignant conditions of the immune system such as multiple myeloma. Types II and III are polyclonal containing IgG and rheumatoid factor. The manifestations include mild vasculitis, arthralgia, mild Raynaud's syndrome and palpable cutaneous purpura. More severe vasculitis involving renal and neurological systems may be seen. Treatment consists of corticosteroids, alkylating agents and in selected cases, interferon.

Henoch-Schönlein Syndrome

See Chapter 163.

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General Considerations

Idiopathic Inflammatory Myositis (IIM)

Inflammatory muscle diseases, currently referred to as idiopathic inflammatory myositis (IIM) are a group of acquired and potentially treatable muscle disorders.

These can be separated into 3 subsets:

1. Dermatomyositis
2. Polymyositis and
3. Inclusion body myositis

In addition, myositis may occur in association with malignancy and connective tissue diseases. Crucial investigations in IIM include elevated muscle enzymes, typical EMG changes and muscle biopsy findings.

POLYMYOSITIS

Polymyositis is a diffuse immune-mediated connective tissue disease in which predominantly muscles show nonsuppurative inflammatory lesions associated with weakness, atrophy and later calcification. Some are associated with changes in the skin manifesting as rash, pigmentation or others. These are included under the term dermatomyositis. In India this disease may be seen in skin clinics, rheumatology services, neurology clinics or internal medicine departments. Majority of them are primary without any underlying disease. Secondary form occurs in the course of other connective tissue diseases or as a paraneoplastic manifestation of malignancy.

Analysis of 87 patients with inflammatory myositis seen over a 10 year period at the Madras Medical College gave the following break up.

- Adult polymyositis 24,
Adult dermatomyositis 26,

Juvenile myositis 5,
Carcinomatous myositis 1,
Amyopathic dermatomyositis 1
Overlap connective lesions 30
Male to female distribution was 1.2: 3.5

Ref: Porkodi R, et al. Clinical Spectrum of Inflammatory Myositis in South India. JAPI 2002;50:1255-8.

DERMATOMYOSITIS

Dermatomyositis is the least common among the connective tissue disorders. It consists of inflammatory and degenerative lesions involving the striated muscles, skin, and other connective tissues in varying combinations.

The *clinical types* are:

- Type I *Typical polymyositis.*
Type II *Typical dermatomyositis.*
Type III *Dermatomyositis associated with malignancy.*
Type IV *Childhood dermatomyositis.*
Type V *Dermatomyositis or polymyositis associated with other collagen diseases as part of an overlap syndrome.*

Pathology

The muscles show fragmentation, loss of cross-striation, cellular infiltration of interstitial connective tissue, increase in sarcolemmal nuclei, and rarely calcification. Perivascular inflammatory changes are present. Skin shows swelling and edema of dermal collagen, atrophy of epidermis, and flattening of rete pegs.

Clinical Features

Dermatomyositis is more common in the second, fifth, and sixth decades. Women are more affected than men. A wide spectrum of clinical severity ranging from an acute, extensive rapidly fatal paralytic syndrome to a very slowly progressive muscle disease closely resembling a muscular dystrophy may be seen. Proximal muscles are affected more than others in the early stages. Muscle tenderness is prominent in the acute stages. Eventually fibrosis and

contractures occur. The muscles are hyperreflexic. Though in a third, the esophageal and pharyngeal muscles are affected, the ocular muscles are spared. Muscle enzymes are increased. The EMG shows myopathic pattern.

The diagnostic skin lesion is a heliotrope eruption on the face associated with periorbital edema. Skin lesions may precede, coexist, or follow the muscular involvement. Cutaneous lesions may ulcerate and leave behind depressed scars. Subcutaneous and periarticular calcification may be seen. Around 35% of cases show a non-erosive arthritis particularly small joints of the hands.

Diagnosis

The diagnosis is made on clinical grounds, electromyography, raised levels of creatine phosphokinase, aldolase, SGOT and lactic dehydrogenase. *Rheumatoid factor* is present in many cases and antinuclear factor in 30%. Muscle biopsy confirms the diagnosis.

The course is variable. In some it is rapidly progressive and fatal due to cardiac (myocarditis), renal or pulmonary complications (interstitial lung disease). Many follow a slowly progressive course extending over 10-15 years leading to muscle weakness, contractures, and

deformities. Spontaneous remission is seen in some cases. In the course of other connective tissue disorders like rheumatic fever, rheumatoid disease, Sjögren's syndrome, scleroderma or lupus erythematosus, a picture of dermatomyositis may occur. In such cases the occurrence of muscle weakness out of proportion to the primary condition should suggest the possibility of superadded dermatomyositis. Death in dermatomyositis is mainly due to respiratory complications.

Management

Prednisolone in a dosage of 1-2 mg/kg/day to start with and subsequently tapered off is effective in majority of cases. Immunosuppressive agents are indicated when the response to corticosteroids is unsatisfactory. Physiotherapy is indicated to prevent disuse atrophy and contractures.

Since dermatomyositis may occur as a paraneoplastic phenomenon, an underlying malignancy should be excluded in all cases. The usual primaries are the breasts, lungs, ovaries, prostate and stomach. Removal of the tumour brings about remission.

Drugs such as hydroxyurea, NSAIDs, quinidine, penicillamine and others may cause dermatomyositis as side effects.

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Miscellaneous Rheumatic Syndromes

12

K.V. Krishna Das

Chapter Summary

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In many musculoskeletal syndromes no definite disorders of bone, cartilage or connective tissue may be demonstrable. These present with pain and varying grades

of disability due to local inflammatory changes but follow a self-limiting course. *Precipitating factors* include exposure to inclement weather, unaccustomed exercise, infections, faulty postures, and mild trauma. These disorders are more common in the older age groups. In many cases underlying diseases such as diabetes may be present, which have to be specially looked for.

Lumbago-sciatica Syndrome

Pain is vaguely located in the low back, it may radiate to the lower limbs. Signs of nerve root compression do not occur.

Frozen Shoulder

This is a condition of painful limitation of movement of the shoulder. In the initial stages the shoulder is tender and painful, but later on it becomes painless. It is most probably caused by lesions of the rotator cuff. Myocardial infarction, hemiplegia, herpes zoster or surgery on the chest wall may be followed by the syndrome of “frozen shoulder”.

Shoulder-hand Syndrome

This is a condition in which shoulder movements are restricted and it is associated with pain and swelling of the hand. Conditions which lead to frozen shoulder also may give rise to this syndrome. The incidence is more in epileptics and those on barbiturates and anti-tuberculosis drugs. Treatment consists of judicious administration of analgesics, anti-inflammatory drugs, corticosteroids, local short wave diathermy and manipulation, in some cases sympathetic nerve block may be required. In many cases shoulder-hand syndrome may be the first manifestation of diabetes mellitus or impaired glucose tolerance.

Tennis Elbow

This condition is caused by the traumatic rupture of the common origin of the extensor tendons at the lateral epicondyle.

Golfer's Elbow

This condition is caused by the rupture of the common flexor tendon from the medial epicondyle.

Other Painful Conditions Around the Shoulder

These include *supraspinatus tendinitis*, *subacromial bursitis*, *bicipital tendinitis* and *periarthritis* of the shoulder joint. These result from over-use of the joints or faulty positions. They are more common in diabetics and elderly persons.

Management

Though these various rheumatic syndromes are not serious, they can lead to painful limitation of movement, prolonged morbidity and atrophy of shoulder muscles. Treatment consists of nonsteroidal anti-inflammatory drugs, local physiotherapy and manipulation of the joint to restore mobility. Local injection of cortisone acetate into the affected tissue gives immediate relief.

Fibromyalgia

Pain and stiffness arising in muscles or other soft tissues may occur in the absence of any definable musculoskeletal pathology. It is a syndrome of widespread chronic muscular pain and tender points. Widespread pain is defined as pain on the axial spine together with pain at least in two contralateral quadrants of the body; ‘chronic’ is defined as more than three months of pain; high tender count was defined as 11 or more tender points out of a specified set of 18 points to be examined. These tender points may have physical humps of all sizes ranging from the size of wheat grain to that of an apple. Associated symptoms such as fatigue, poor sleep and stiffness are also recognized as common. They were also more likely to report depressive symptoms, anxiety and difficulty with sleep. There are other associations with diseases such as irritable bowel syndrome and chronic fatigue.

The etiology of this condition is unclear. The relationship with psychological factors suggest an abnormal sensitivity to pain. Analgesic therapy is of questionable benefit. Cognitive therapies are being assessed.

Whether we label patients as having fibromyalgia or not, there is no doubt that many patients have diffuse pain, sleep disturbances, fatigue and tender points. There is no specific treatment and the prognosis is poor, but individual patients may be helped by an adequate explanation of the condition, to learn to live with it and avoid further unnecessary investigations and drug treatment.

111

Seronegative Spondyloarthropathies

K.V. Krishna Das

Chapter Summary

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The term seronegative inflammatory arthropathy includes ankylosing spondylitis, enteropathic arthritis, psoriatic arthropathy and Reiter's syndrome. These diseases are characterized by chronic inflammatory arthritis, major affection of the axial skeleton, strong HLA association, varying grades of multisystem involvement and absence of the serological markers characteristic of the connective tissue diseases. The common factor is HLA B27. In the general population HLA B27 positivity is below 5%.

The positivity rates for HLA B27 in the different forms of arthritis.

- Ankylosing spondylitis—above 90%
- Reiter's syndrome—75%
- Psoriatic arthropathy—50-75%
- Enteropathic arthritis—30-70%

Association with HLA B27 is one of predispositions to the disease. The genetic markers for these diseases are probably on chromosomes 2,6 and 10. The HLA B27 group consists of at least 14 subtypes which differ in their amino acid substitutions-B 2701 to B 2714. The subtype 2704 is probably more common in Indians.

HLA B27 shows weaker association with anterior uveitis, reactive arthritis, sacroiliitis, late onset juvenile chronic arthritis in boys and inflammatory bowel disease with axial joint involvement.

Ankylosing Spondylitis

Syn: Marie-Strümpell disease, Bamboo spine, Poker back

This is an inflammatory arthropathy predominantly involving the axial skeleton, and in the advanced stages

the entire vertebral column undergoes bony ankylosis. This disease entity belongs to the group of seronegative spondyloarthritides (SSA).

Prevalence and epidemiology: This disease is rare compared to rheumatoid arthritis. It is not an uncommon disease in India. Male to female ratio is 7:3.

Genetic factors: The histocompatibility antigen type HLA B27 is positive in over 90% of patients and 53% of their first degree relatives. The presence of the HLA B27 antigen predisposes such individuals to develop arthritis in response to several environmental factors. The triggering event is probably an infection. In many cases the organism is *Klebsiella pneumoniae*. Maximal lesions are in the entheses which show edema and infiltration by lymphocytes, plasma cells and polymorphonuclear leucocytes. The adjacent bone marrow also shows edema and inflammation.

Pathology

The sacroiliac joints and vertebral joints are maximally affected, but the manubriosternal joints, symphysis pubis, costovertebral and sternocostal joints, shoulders, hips, and rarely the joints of the hands and feet may also be affected. The joints show mild synovitis. Periarticular fibrous tissue, ligaments, and articular cartilage also show inflammation. Extra-articular lesions develop in various ligaments, tenoperiosteal junctions (entheses), the ascending aorta, uveal tract and the upper lobes of the lungs. Ankylosis develops in the joints on account of the tendency for calcification and ossification. The new bones formed are known as syndesmophytes which form the characteristic feature of the disease. Calcification and ossification of the annulus fibrosus and proliferative bony outgrowths from the vertebral borders result in ankylosis of the spine. The spinal column becomes a rigid pillar giving the radiological appearance of *bamboo spine*.

CLINICAL FEATURES

The clinical severity ranges from partial forms (formes frustes) to the classic picture of severe ankylosis of the

spine and other joints. The disease is more common in the second, third, and fourth decades. Bouts of low backache, felt mostly in the morning and aggravated by periods of rest are the early manifestations. Later, the pain becomes constant. At this stage the obliteration of lumbar lordosis and generalized limitation of movements of the lumbar spine due to muscular spasm are detectable. Later, ankylosis of spinal joints (*poker back*) occur. The whole spine becomes a single rigid column.

Tenderness over the sacroiliac joints is elicitable by deep palpation. Pain from the sacroiliac joints is elicited by the *pump handle test*, the pelvic compression test and hyperextension test.

Other joints may be involved in 50% of cases, the most common being the root joints, viz. hips and shoulders, and hence the term *rhizomelic spondylitis*. It is rare to get affection of the peripheral small joints. When it occurs, it is asymmetrical and milder compared to rheumatoid arthritis. Later on they also may be ankylosed.

The patient with advanced ankylosing spondylitis develops forward craning of the neck, high dorsal kyphosis, rounding of the shoulders, obliteration of the normal lumbar lordosis, wasting of the glutei, flattening of the chest, and ballooning of the abdomen. Forward vision is impaired due to the stooping posture.

A simple but reliable test to diagnose ankylosing spondylitis is the *modified Shober test*. A 10 cm long line is drawn perpendicularly up from the midpoint of a line joining the posterior superior iliac spines. In normal persons this line stretches to 16 to 22 cm when the patient fully bends forwards. In established ankylosing spondylitis this line does not stretch more than 1 or 2 cm (Fig. 111.1).

Extra-articular Features

These include unilateral iritis (20%), aortic incompetence, heart block, pericarditis and fibrosis of the upper lobes of the lung.



Fig. 111.1: Ankylosing spondylitis. Note: the kyphosis and fixed flexion deformity of the neck and upper thoracic spine in two patients, almost similar

Enthesopathy occurs in many cases. This manifests as plantar fasciitis, costochondritis or Achilles tendonitis.

Complications

Fracture dislocations of the spine and other bones and secondary amyloidosis constitute the main complications.

Though in the majority of cases the picture of ankylosing spondylitis is typical, less commonly the presentation may be atypical. These are: (i) isolated sacroiliitis, (ii) asymmetrical peripheral polyarthritis or (iii) uveitis.

Laboratory Data

The ESR is elevated in the early phases of inflammation, but it returns to normal levels in the later stage when ankylosis is complete.

Radiology

Early abnormality is in the sacroiliac joints which show an appearance of widening (*pseudowidening*) and erosions. As the disease progresses, the adjacent zones become sclerosed and the joint space is obliterated by bony fusion. The vertebrae appear square due to a combination of osteitis of the borders and filling up of the anterior concavity. The fully developed stage gives the typical picture of *bamboo spine* (Figs 111.2 and 111.3).

Diagnosis

Clinical diagnosis has to be confirmed by radiology and the diagnosis is strengthened by the demonstration of HLA

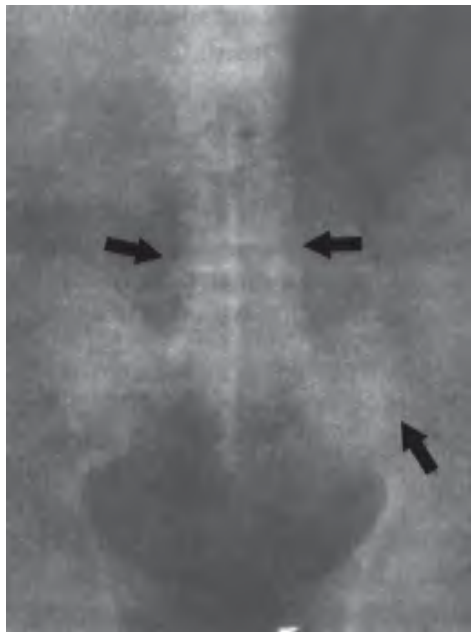


Fig. 111.2: X-ray spine PA view—ankylosing spondylitis
Note: sclerosis of sacro-iliac joints



Fig. 111.3: X-ray spine lateral view—ankylosing spondylitis
Note: calcification of anterior and posterior regiments leads to the appearance of bamboo spine

B27. When the age of onset is below 20 years, other forms of arthritis which involve this age group have to be distinguished. The diagnosis is likely to be delayed in such cases.

The New York criteria for diagnosis include

- Limitation of movements of spine in all planes
- Pain in lumbar spine or dorsolumbar junction
- Chest expansion less than 2.5 cm
- Radiological features of unilateral sacroiliitis grade III-IV or bilateral sacroiliitis grade I-II.

Differential Diagnosis

This includes osteoarthritis, cervical spondylosis, other causes of sacroiliac arthritis, and endemic fluorosis. In endemic fluorosis radiology may show lesions of the spine resembling ankylosing spondylitis but the sacro-iliac joints are normal (Fig. 111.4).

Management

Treatment is aimed at improving spinal mobility, preventing ankylosis and giving symptomatic relief. The modalities of treatment include physical measures and appliances, medications, irradiation or surgery.

Physical Measures and Appliances

Regular spinal exercises help to correct postural abnormalities and strengthen the spinal ligaments and paraspinal muscles. Prolonged immobility tends to accelerate ankylosis and this should be avoided. Spinal braces help to correct postural defects partly. Prismatic spectacles enable the patient with severe kyphosis to see objects in front.



Fig. 111.4: X-ray spine—fluorosis
Note: that SI joints are free

Drugs

Commonly used drugs are indomethacin, aspirin, and the nonsteroidal anti-inflammatory agents. Corticosteroids are not widely used except for limited indications. Salazopyrin in doses of 500 mg 6 h orally, given over prolonged periods help to relieve pain of peripheral arthritis and possibly of the axial lesion too. Anti rheumatic biologicals have been used in the treatment of intractable spondylarthropathies. Infliximab given in a dose of 5 mg/kg IV at weeks 0, 2 and 6 produced remarkable improvement when followed up to 1 year. Reactivation of tuberculosis was seen in 50% of patients. In resistant cases combination of sulfasalazine, weekly subcutaneous injections of 20-25 mg of methotrexate and monthly cycles of 3 injections of 500 mg of IV methyl prednisolone give relief. Pamidronate 60 mg given IV as slow infusion has been tried with encouraging results.

Ref: Grover R, et al. Clinical experience with infliximab on spondylarthropathy: an open label study in fourteen patients. J Ind Rheumatol Assoc 2005;13:78-82.

Malaviya AN, et al. JAPI 2007;55:193-7.

Surgery

Permanent deformities of the spine, hip and other joints can be corrected by orthopedic procedures. The disability has been considerably reduced by total hip replacement which has improved the outlook for patients with ankylosing spondylitis.

ENTEROPATHIC ARTHRITIS

A heterogenous group of arthritic syndromes develop secondary to primary lesions in the gastrointestinal tract.

The primary gastrointestinal disorders leading to arthritis are: (i) Chronic inflammatory bowel diseases such as ulcerative colitis, Crohn's disease (regional ileitis) and Whipple's disease (intestinal lipodystrophy); (ii) acute infective disorders such as salmonellosis, bacterial dysenteries, and *Yersinia enterocolitica* infection; (iii) intestinal bypass surgery; and (iv) gut associated neoplasms which produce arthritis as paraneoplastic manifestations.

Arthritis associated with chronic inflammatory disease of bowel: Even though ulcerative colitis, Crohn's disease, and Whipple's disease are separate entities, arthritis produced by all the three are similar clinically. Two types are seen: (i) A *peripheral polyarthritis*, and (ii) *ankylosing spondylitis* with sacroiliitis.

The peripheral arthropathy manifests as asymmetric affection of the major joints of the lower limbs. Distal interphalangeal joints may be affected. The arthritis is self-limiting and residual damage is unusual. With subsidence of the intestinal lesion, the arthritis also subsides.

A clinical picture identical with idiopathic ankylosing spondylitis may develop in some cases but there is no male preponderance. Unlike the peripheral arthritic syndrome, the spondylitic variety does not bear any relation to the severity or extent of the bowel disease.

Investigations

Neither the synovial fluid nor the synovial biopsy shows diagnostic features. Radiology of the joints remains essentially normal except for the soft tissue swelling and minimal osteoporosis. The diagnosis is based on the clinical picture, temporal relation with bowel disease and exclusion of other forms of arthritis.

Management

Since the peripheral type of arthritis is self-limiting only symptomatic and supportive measures are required for the joint disease. Treatment is directed toward the bowel disorder.

In the spondylitic type, line of management is similar to that of idiopathic ankylosing spondylitis.

Arthritis Associated with Other Forms of Intestinal Disease

Infective disorders of the intestines: A migratory polyarthritis may develop up to three weeks after the occurrence of bacillary dysentery, *Salmonella* infections and *Yersinia enterocolitica* infection. This is an immunologically-mediated reactive arthropathy.

Gastrointestinal bypass surgery: Jejunocolic or jejunoleal anastomosis done as a therapeutic measure for severe obesity may be followed by a polyarthritic syndrome 2-3 months later. Restoration of normal bowel anatomy clears the arthropathy.

Arthritis associated with malignancies of the gastrointestinal tract may precede or accompany the neoplasm. Removal of the tumour clears the joint lesions also.

Psoriatic Arthropathy

Joints may be affected in psoriasis in one of the following four ways:

1. Predominantly distal arthritis involving the interphalangeal joints.
2. Classic arthritis mutilans with digital telescoping and sacroiliac involvement.
3. Arthritis closely resembling rheumatoid arthritis but with asymmetrical involvement and negative serology, and
4. Spondylitis with or without peripheral arthritis.

Clinical Features

Pain and disability are less severe than in rheumatoid arthritis. Psoriatic lesions may be demonstrable in the skin or nails along with the arthritis. Rarely the joint lesion may precede or follow the skin lesion and in such cases diagnosis may be presumptive for long periods. Involvement of the distal interphalangeal joint has to be distinguished from rheumatoid arthritis, osteoarthritis, hypertrophic osteoarthropathy and enteropathic arthropathy.

Management

Psoriatic arthropathy is managed on the same lines as rheumatoid arthritis. Chloroquine and gold are seldom used due to risk of exacerbating the skin lesion. Corticosteroids bring about dramatic relief in an acute case. For long-term use, NSAIDs, salazopyrin and methotrexate are all useful. The retinoid—*etretinate*-20 mg daily is an effective adjuvant to treat the joint as well as the skin condition. A newer analogue is *acitretin* which is cleared faster from the system the dose is 25 to 50 mg/day, to be given for several months. It should be avoided in young women due to risk of teratogenicity.

The primary treatment for psoriasis, i.e. photochemotherapy with methoxy psoralen and long wave ultraviolet light (PUVA), while relieving the skin condition may benefit the arthritis as well. Biological antirheumatic drugs such as infliximab are being used in intractable cases.

For further details see Section 18, Chapter 196 Psoriasis.

Reiter's Syndrome

This is one among the reactive arthritis.

The triad of symptoms—non-specific urethritis, conjunctivitis, and arthritis—which follows an attack of dysentery or urethritis is termed Reiter's syndrome. The etiology is unknown. Reiter's syndrome develops as a complication of nongonococcal or postgonococcal

urethritis and dysenteries. Over 80% of subjects have HLA B27.

Age and Sex

Young adult males are considerably more affected in Reiter's syndrome following nongonococcal urethritis but this phenomenon is less striking in the post-dysenteric group.

Clinical Features

The clinical spectrum may vary from the fully developed picture of urethritis, arthritis, and conjunctivitis to less complete forms with only urethritis and arthritis. The clinical spectrum includes recurrent episodes of tenosynovitis, plantar fasciitis, enthesopathies and frank arthritis. 20% may develop lesions of the sacroiliac joints and secondary spondylitis. Other common features include stomatitis, circinate balanitis, and *keratoderma blennorrhagica* (hyperkeratotic lesions of the palms, soles, and other regions) which may proceed to pustulation and scaling. The oral and cutaneous lesions are painless. The ESR is elevated upto 100 mm and this is a common finding. Uveitis may develop which may lead to blindness. Cardiac lesions similar to those that occur in ankylosing spondylitis may develop. In many cases the disease tends to become chronic and progressive leading to considerable disability.

Diagnosis

Clinical features and the presence of the precipitating cause should suggest the diagnosis. Rheumatoid factor is negative. X-ray changes are unusual except in chronic or recurrent cases. Presence of primary infection supports the diagnosis.

Management

Management is symptomatic since there is no specific curative treatment. Tetracycline is employed to treat the urethritis. Nonsteroidal anti-inflammatory drugs give symptomatic relief. Immunosuppressive therapy is indicated for severe progressive arthritis and keratoderma blennorrhagia. Intra-articular corticosteroids have been tried with temporary benefit.

Whipple's Disease

This is a rare disorder affecting several systems characterized predominantly by diarrhea, steatorrhea, malabsorption, fever, anemia, pigmentary disturbances and joint lesions.

The causative agent is most probably a gram-positive bacillus belonging to the *Actinobacter* group and designated *Tropheryma whipelli*. Histologically the small intestine shows characteristic lesions. Large macrophages containing glycoprotein-rich lysosomes are seen to

infiltrate the lamina propria and submucosa. The bacilli are seen within the macrophages. The mucosal and submucosal lymphatics are dilated and obstructed. Other tissues may be involved. These include mesenteric and peripheral lymph nodes, liver, spleen, heart, lung and central nervous system.

Clinical features are protean, depending upon the predominant pathological process. Joint symptoms occur in about 60% of cases. These may pre-date the intestinal symptoms, or coexist with them. Joint symptoms include episodic inflammatory arthritis of abrupt onset involving large joints mainly, but also the joints of the hands at times. Diagnosis is established by demonstrating the intestinal lesion by mucosal biopsy. The joint fluid shows only signs of non-specific inflammation.

Treatment

Whipple's disease responds to antibiotics such as cotrimoxazole, chloramphenicol or tetracyclines. Symptomatic measures are instituted for joint symptoms.

Joint Involvement in Sarcoidosis

Joint manifestations develop in 25% of cases with systemic sarcoidosis, especially in the pulmonary form. Two types of joint manifestations may occur.

1. An acute transient polyarthropathy, associated with erythema nodosum. Usually this affects the large joints.
2. A chronic persistent polyarthropathy, usually affecting the small joints of the fingers. Larger joints may be affected less commonly. The synovium shows granulomatous changes. Joint destruction may follow. Treatment is symptomatic with NSAIDs. Improvement may result from chloroquine, other DMARDs, colchicine and corticosteroids. Immunosuppressant drugs act as adjuvants to glucocorticoids. (Refer Section 14 chapter 143).

Joint Symptoms in Infective Conditions

Several infections give rise to joint symptoms either as allergic manifestations or due to direct involvement. Polyarthritis occurring in systemic tuberculosis (**Poncet's syndrome**) and reactions in leprosy fall in the former group. Joints may be directly involved by pyogenic organisms, *M. tuberculosis*, *T. pallidum*, gonococci, meningococci, *S. typhi*, *brucella*, *Lyme borreliosis*, rubella, hepatitis B virus, mumps, chickenpox, smallpox, AIDS and several others.

Several drugs give rise to arthralgia and possibly arthritis as adverse side effects. These include immune sera and vaccines, penicillin and other antibiotics, antihypertensive drugs, parenteral iron, iron chelators, interferons and others. Detailed drug history is important to diagnose these conditions.

Metabolic Arthropathies

Osteoporosis, Gout and Other Forms of Crystal Induced Arthropathies

K.V. Krishna Das

Chapter Summary

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Other forms of Crystal Induced Arthropathy 731

Osteoporosis

Osteoporosis is defined at a consensus conference, as a systemic skeletal disease characterised by lowered bone mass and microarchitectural deterioration of bone tissue with consequent increase in fragility and susceptibility to fractures. The WHO has defined osteoporosis based on bone mineral content (BMC) and bone mineral density (BMD). In simple terms osteoporosis can be described as a reduction in bone mass without gross alteration in its chemical composition. Osteopenia is reduction in bone mass or disruption of bone architecture leading to increased risk of fractures. Osteoporosis can also be defined in terms of bone mineral density (BMD) studies as a dual energy X-ray absorptiometry (DEXA) score of – 2.5 or less at the spine, hip and forearms. BMD studies of the hips are the most reliable parameters to predict fracture risk.

The bone matrix itself is deficient but osteoid that is present is normally mineralised. Bone formation and resorption are in equilibrium in adults upto the age of 50 years and, therefore, upto this age the bone mass is fairly constant. The bone mass declines steadily but slightly after the age of 50. Osteoporosis results from excessive resorption compared to formation. The precise mechanism leading to osteoporosis is not clear. In the majority an etiological factor is demonstrable while in a few this is not so. Genetic factors play a role. Several potential candidate genes have been described especially the one for vitamin D receptor.

Pathogenesis

The resorption rate is high in osteoporosis, even though bone formation proceeds normally. Particular areas of the

Common Causes

Generalised Osteoporosis

- A. *Idiopathic osteoporosis*: Two types of idiopathic osteoporosis are seen—the adult type and the juvenile type (8-12 years).
- B. *Secondary osteoporosis*:
 1. Senile osteoporosis.
 2. Prolonged bed rest, especially in the elderly subjects.
 3. Endocrine abnormalities:
Postmenopausal osteoporosis,
Diabetes mellitus,
Cushing's syndrome and corticosteroid therapy
Hypogonadism,
Hypopituitarism,
Thyrotoxicosis, and
Hyperparathyroidism.
 4. *Nutritional causes*:
Protein malnutrition,
Malabsorption syndrome,
Scurvy, and
Alcoholism.
 5. *Hereditary connective tissue diseases*:
Ehlers-Danlos syndrome,
Marfan's syndrome,
Homocystinuria, and
Osteogenesis imperfecta.

Localised Osteoporosis

- i. Localized immobilization following fractures.
- ii. Inflammatory arthropathy, e.g. rheumatoid arthritis.
- iii. Reflex bone dystrophy, e.g. shoulder-hand syndrome, and
- iv. Secondary to irradiation therapy.

skeleton such as the metacarpals, femoral neck and vertebral bodies show higher rates of resorption. Maximum impact is on the axial skeleton. The peripheral bones are affected to a varying extent.

Two types of bone loss are seen

Type I and type II which are due to different mechanisms occurring after menopause.

Type I is seen mainly in women in the age group 51-75. It is due to accelerated bone loss with fracture sites mainly in the vertebrae and distal part of the radius. In type II trabecular bone is not affected. Cortical loss of



Fig. 112.1: X-ray osteoporosis spine. Note: 1. Kyphosis, 2. Loss of density of vertebrae compression fracture—arrow, cod fish vertebrae—arrow head

bone occurs above the age of 70 years. It presents with multiple wedge fractures of the vertebrae and fracture of hip.

CLINICAL FEATURES

Osteoporosis remains asymptomatic for considerable periods till bone loss has become advanced. The vertebral bodies become soft and compressed. The intervertebral discs herniate into the vertebral bodies and this results in shortening of the vertebral column. The terms *dowager’s hump* or *widow’s hump* are used to denote the dorsal kyphosis with exaggerated cervical lordosis brought about by vertebral compression. When symptoms occur, they include vague muscular aches and pains, loss of height of the spine, and kyphoscoliosis. Vertebral collapse, fracture neck of the femur, and Colles’ fracture (fracture distal end of the radius) develop as a result of trivial trauma or even spontaneously. In general the fractures heal within 4-6 weeks with simple treatment (Figs 112.1 and 112.2).

These sites may become painful and even tender for varying periods before demonstrable fractures develop. Early institution of treatment of this stage may relieve this symptom.

Skiagram reveals reduction in density of the vertebral bodies in the early stages, and the vertical trabeculations appear more prominent. The vertebra becomes biconcave and this is referred to as *cod fish vertebra*. The inter-vertebral discs herniate into the vertebral bodies. Vertebral



Fig. 112.2: Osteoporosis wrists. Note: haziness and translucency of carpal bones

collapse in the late stages results in anterior wedging of the vertebral bodies. The medullary cavities of long bones are expanded with thinning of the cortex. Sometimes differentiation from osteomalacia can be extremely difficult but pseudofractures are not seen in osteoporosis.

The most reliable investigation is to measure bone mineral density by DEXA. Quantitative values of BMD are given, expressed in two forms—T score and Z score. T score compares the BMD of the patient with the mean peak BMD of the normal young adult population and expressed in terms of standard deviation (SD). Z score compares the BMD of the patients of the same age.

WHO criteria for osteoporosis in adult women using T-scores by DEXA	
Normal	: BMD is within 1.0 SD of the young adult reference mean
Osteopenia	: BMD 1 to 2.5 SD below the young adult mean
Osteoporosis	: BMD more than 2.5 SD below the young adult mean
Severe osteoporosis	: Osteoporosis with the presence of one or two fragility fractures.
BMD values of 0.72 suggests fracture threshold in South Indian elderly person	

The sites commonly measured are the lumbar spine (L1-L4) including the intervertebral discs, hips and forearms. BMD of any other part of the skeleton or that of the whole skeleton can also be determined.

Workers at the KJ Hospital, Chennai have evolved a formula for diagnosing post-menopausal osteoporosis. The KJ Hospital Amburajan’s *empirical formula* is based on the radiographic features of the clavicle in plain radiographs of the chest.

Ref: Amburajan MM 1999. Evaluation of osteoporosis using conventional radiographic methods and dual energy X-ray absorptiometry PhD thesis, Anna University, Chennai.

Before accepting the diagnosis as osteoporosis a careful search for primary bone malignancies such as

multiple myeloma and malignant secondaries from the female genital organs, breasts and other sites should be excluded by appropriate investigations.

Laboratory Findings

The serum calcium, phosphorus, and alkaline phosphatase are normal and this distinguishes osteoporosis from osteomalacia in which calcium and phosphorus are low and alkaline phosphatase is elevated. As a result of excessive resorption of bone, urinary hydroxyproline is elevated above normal range (6.42 mg/g of creatinine up to 55 years of age), during the active phase of the disease.

Treatment

Acute episodes of fracture should be managed in the usual orthopedic lines.

General measures: Adequate nutrition should be ensured, especially with supplements of calcium, vitamin D and proteins. Calcium supplementation given as calcium gluconate, lactate or carbonate 500-1000 mg/oral/day helps to improve bone mineralization. Active vitamin D₃ analogues such as calcitriol and alfa calcidol stimulate the formation and action of osteoblasts. A small but definite risk of urolithiasis occurs. Supplementation of vitamin D 800 units/day reduces the risk of fracture. Calcitonin, given intranasally in a dose of 200 IU/day reduces the risk of fracture. This drug is available in India, but is expensive. Vertebral collapse usually heals satisfactorily with bed rest and analgesics. Early ambulation and exercise help to improve muscle tone. Provision of weight-bearing appliances or corsets helps to relieve pain and prevent further damage in the acute phase.

Bisphosphonates: Bisphosphonates are synthetic analogues of inorganic pyrophosphate. They are deposited on bone surfaces. When ingested by osteoclasts during bone turnover their main action is anti-resorptive.

These are excellent drugs which help to restore bone mineral density in both sexes, relieve bone pains and possibly reduce the progression of osteoporosis. They are indicated for the treatment of the established cases with demonstrable X-ray or DEXA criteria, on a short-term (a few months) or a long-term basis depending on the individual case. Though several preparations available, one acceptable drug is **alendronate sodium** which is an aminophosphate. It inhibits osteoclastic activity. Given over periods up to three years in daily doses of 10 mg, it relieves the symptoms of postmenopausal osteoporosis and restores bone density. An alternative is to give 75 mg orally on an empty stomach once a week. Since the drug causes esophageal ulceration by local contact, the patient should maintain the erect posture for 15-30 minutes after taking the tablet. Side effects include heartburn, nausea,

abdominal pain and vomiting. The drug is freely available in India. Other drugs in this class include etidronate, pamidronate, clodronate, tiludronate and others. These can be employed under special indications. Follow-up studies exceeding 10 years in osteoporosis have shown continued benefit. On stopping bisphosphonates the bone density falls gradually. In a trial of glucocorticoid induced osteoporosis alendronate in a dose of 10 mg/oral daily was more effective than alpha calcidol.

Other than for osteoporosis bisphosphonates have been used for the treatment of hypercalcemia, malignant secondaries in bones and multiple myeloma.

Calcitonin: Though it is an excellent drug to relieve osteoporosis, it is seldom used due to its high cost.

Parathyroid hormone (PTH) given intermittently over short courses in doses of 100 µg/day by injection increases bone strength primarily by stimulating bone formation, especially of trabecular bone like the vertebrae and other sites. Both intact PTH as well as the 34- aminoacid peptide, known as *teriparatide* are effective in reducing fracture risk, as long as the drugs are continued. The risk for fracture in postmenopausal women is also reduced. Continued elevation of parathyroid hormones, as is seen in hyperparathyroidism gives rise to bone demineralization and bone loss.

Hormone replacement therapy (HRT): This is an accepted regimen for prevention of osteoporosis and fragility fractures in postmenopausal women. Menopause before the age of 45 years, surgical menopause, lean body mass, presence of nutritional inadequacy, lack of aerobic exercise and concurrent use of drugs such as corticosteroids (for asthma) aggravate the tendency and prepone the onset of osteoporosis. Benefits of HRT are several including the feeling of well-being, reduction in progression of ischemic heart disease and cosmetic effects. In postmenopausal osteoporosis administration of 0.625-1.25 mg of conjugated estrogen daily for 3 weeks every month helps to arrest the progression of bone loss. Since estrogens may increase the tendency to develop endometrial cancer, it is advisable to give intermittent therapy with estrogens and progesterone. A popular regimen is 0.625 mg conjugated estrogen and 2.5-5 mg medroxy progesterone daily. Withdrawal bleeding may be a troublesome side-effect in some.

The possible adverse effects include slight, but statistically significant increase in cancer of the breast and endometrium, increase in venous thrombosis, especially in these with thrombophilia. Persons on HRT should have regular gynecological check-up once a year and also self palpation of the breasts. In males the situation is less clear.

With the availability of evidence that female hormones will increase the risk of cancers of the endometrium and

breasts and venous thrombosis, their use has come down markedly.

Androgens or anabolic steroids may be tried in particular situations. Stanozolol in a dose of 2.5-5 mg oral o.d, or nandrolone in a dose of 50 mg I.M once a week are available for use. Attention to the primary cause is necessary to relieve secondary osteoporosis.

Newer Anti-osteoporotic Drugs

These include (1) strontium ranelate and (2) biological agents such as monoclonal antibody with high affinity to RANKL, thereby preventing its action in promoting osteoclast differentiation and survival. These drugs are under trial.

Ref: Philip Sambrook, Cyrus Cooper. Osteoporosis. The Lancet 2006;2010-8.

Prevention

Incidence of generalised osteoporosis can be reduced by ensuring regular exercises and proper intake of proteins, vitamins, and calcium in persons above the age of 65 years.

Pharmacological interventions for osteoporosis			
Intervention	Dosing regimen	Route of administration	Licensed indication
Alendronate	70 mg once weekly, or 5 mg or 10 mg once daily	Oral	Postmenopausal osteoporosis; glucocorticoid-induced osteoporosis; osteoporosis in men
Etidronate	400 mg daily for 2 weeks every 3 months	Oral	Postmenopausal osteoporosis; glucocorticoid-induced osteoporosis
Ibandronate	150 mg once monthly	Oral	Postmenopausal osteoporosis
	3 mg once every 3 months	Inter-venous injection	Postmenopausal osteoporosis
Risedronate	35 mg once weekly, or 5 mg once daily	Oral	Postmenopausal osteoporosis; glucocorticoid-induced osteoporosis
Raloxifene	60 mg once daily	Oral	Postmenopausal osteoporosis
Strontium ranelate	2 g once daily	Oral	Postmenopausal osteoporosis

Teriparatide	20 µg once daily	Subcutaneous injection	Postmenopausal osteoporosis
Parathyroid hormone 1-84	100 µg daily	Subcutaneous injection	Postmenopausal osteoporosis

Gout

Gout is a metabolic disorder of purine metabolism clinically characterized by recurrent attacks of acute arthritis progressing to chronic deforming arthropathy, formation of tophi and development of systemic complications like renal failure. Gout causes elevation of uric acid levels in blood and leads to deposition of urate crystals in tissues. Hyperuricemia is the cardinal abnormality leading to gout. Chronic hyperuricemia caused by any lesion, whether primary or secondary, may lead to gout. Gout is present in India, though primary gout is less common.

The term “gout” includes a heterogenous group of diseases characterized by hyperuricemia. This can be the result of several metabolic errors operating singly or in combination. Plasma levels of uric acid vary from 2 to 7 mg/dL (0.12-0.42 mmol/L) in health. The term hyperuricemia denotes values above 7 mg/dL (0.42 mmol/L) in men and 6 mg/dL (0.36 mmol/L) in women.

Uric acid metabolism follows different pathways. Uric acid is the end product of purine metabolism. Purines are derived partly from the diet and partly from endogenous metabolism. In the liver nucleic acids and purine nucleotides are degraded to form the purine bases xanthine and hypoxanthine. These are oxidised to form uric acid by the enzyme xanthine oxidase. The urates circulate in the plasma to be excreted mainly by the kidneys. A smaller amount is secreted into the gut.

Precursors of uric acid can be utilised by endogenous metabolism to synthesize purine nucleotides, through pathways involving several enzymes, including 5 phosphoribosyl-l pyrophosphate (PRPP) synthetase and hypoxanthine-guanine phosphoribosyl transferase (HGPRT).

In normal men taking purine-free diets the daily urinary excretion of uric acid is 350-500 mg. Increased production of uric acid, reduced urinary elimination or a combination of both these processes lead to hyperuricemia.

Causes

1. **Primary or genetic gout:** This accounts for 95% of the total cases and is either due to primary overproduction or underexcretion of uric acid. The underlying metabolic error is complex.

2. **Secondary gout (5%):** Hyperuricemia results from a demonstrable disorder, leading either to overproduction or defective excretion of uric acid.

Causes of Overproduction of Uric Acid

1. **Increased breakdown of cellular nuclei** occurs in malignant disease, especially when treated by anticancer drugs, e.g. chronic and acute leukemias, myeloma, polycythemia and others.
2. **Several inborn errors of metabolism lead to overproduction of uric acid:**
 - i. **Lesch-Nyhan syndrome** where there is congenital deficiency of hypoxanthine-guanine phosphoribosyl transferase (HGPRT). This syndrome is characterised by spasticity, choreoathetosis, mental retardation and compulsive self-mutilation.
 - ii. **Type I glycogen storage disease** where there is glucose 6-phosphatase deficiency, and
 - iii. **Phosphoribosyl pyrophosphate synthetase overactivity.**

Impairment of excretion of uric acid: The excretion of uric acid is impaired (i) in chronic renal failure; (ii) during intake of drugs like thiazides and other diuretics, low doses of aspirin and salicylates, pyrazinamide, sulfonamides, alcohol, in lead poisoning (*saturnine gout*); (iii) in lactic acidosis; and (iv) in miscellaneous conditions like hypertension, hyperparathyroidism, myxedema, Down's syndrome, toxemia of pregnancy, starvation and exercise.

Pathogenesis

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Hyperuricemia is the central abnormality in gout but this may not lead to gout in all cases.

Arthritis is caused by the deposition of monosodium urate crystals in the synovium. Polymorphonuclear leucocytes ingest the crystals. They release lysosomal enzymes which cause inflammation. Kinins and related cytokines lead to increased vascular permeability. Crystals are demonstrable in the synovium and articular cartilage in the stage of acute arthritis. In the chronic stage, erosion of articular cartilage, proliferation of synovial membrane, pannus formation, cystic erosions of bones and secondary osteoarthritic changes develop. **Tophi** are nodular urate deposits found in and around the joints and in the articular cartilage. Histologically these consist of monosodium urate crystals surrounded by mononuclear cell infiltration and foreign-body giant cells. These lead to osteoarthritic changes, ankylosis of joints and tissue destruction.

Urate deposition and inflammatory reaction in the parenchyma of the kidneys lead to hyalinization or fibrosis of glomeruli. Multiple urate calculi, chronic pyelonephritis, and arteriolosclerosis are other changes seen in long-standing gout.

Clinical Features

Gout passes through three clinical stages, namely, asymptomatic hyperuricemia, acute gouty arthritis and chronic tophaceous gout. Gout is seen predominantly in men during middle life. The M: F ratio is 7:1 to 9:1. Onset of gout in the second or third decade of life should raise the possibility of other metabolic disorders of purine metabolism such as *hypoxanthine guanine phosphoribosyl transferase* deficiency.

Acute gout: Classically intensely painful monoarticular arthritis of the metatarsophalangeal joint of the big toe develops within minutes to hours. The joint is red and swollen and this may be mistaken for septic arthritis. The term **podagra** denotes painful affection of the foot occurring as a result of metatarsophalangeal arthritis. Later other joints are involved. This may be associated with fever and other constitutional disturbances.

The initial attack subsides with treatment or spontaneously to recur periodically, due to precipitating factors like dietary excess, alcoholic bouts, infections, trauma, undue physical exercise, surgery or withdrawal of drugs.

Chronic tophaceous gout: The acute attacks do not remit completely and the joints become constantly painful and swollen. Tophi develop as subcutaneous nodular masses around the joints and on tendons. They are soft and small initially but later on become hard and may reach up to 7 cm in diameter. They may ulcerate discharging chalky material. Most common sites for tophi are around the olecranon, ankles, tendo-Achilles, helix of the ear, and over other joints. Osteoarthritis and ankylosis supervene.

Atypical forms may develop in addition to the typical gouty arthritis. Subacute polyarthritis similar to rheumatoid disease or isolated joint lesions may occur. Sometimes the initial presentation may be with soft tissue involvement such as Achilles tendonitis or olecranon bursitis. Tophi may be seen in organs such as the cornea, heart, tongue, bronchi, and pleura.

Complications

1. **Renal damage:** This may occur in two forms. Acute hyperuricemic nephropathy is due to obstruction of renal tubules by urate crystals or uric acid calculi. Chronic hyperuricemic nephropathy is due to urate deposition in the renal parenchyma. It presents as chronic renal disease. Renal failure is the major cause of death in gout.
2. **Cardiovascular system:** There is higher incidence of hypertension and ischemic heart disease in gouty subjects (see Section 13, Chapter 124).
3. Gout is associated with insulin resistance.

Diagnosis

Strong clinical suspicion is essential to make prompt diagnosis. Gout should be considered in all cases of obscure

mono- or polyarticular disease. Presence of positive family history, tophi, and radiological findings strengthen the diagnosis. Serum uric acid levels above 7 mg/dL are diagnostic. Often serum uric acid may be normal in acute gout. Urate crystals can be demonstrated in synovial fluid by their birefringence under polarized light.

Radiological changes: Radiological changes occur in chronic recurrent gout. In well developed chronic gout periarticular bone shows small punched out erosions due to urate deposits, with superadded osteoarthritic changes.

Treatment

Emergency management of the acute attack: The affected part is immobilized in a splint. Indomethacin 25 mg twice daily initially and then reduced to a maintenance dose is very effective in relieving pain and arthritis. Other NSAIDs are also effective. Colchicine in a dose of 1 mg initially followed by 0.5 mg 2 h is specific in relieving the acute attack but sometimes the response may be delayed. Colchicine is given orally. Troublesome diarrhea limits its use. The mechanism of action of this drug is not clear. This drug is not freely available in India. In resistant monoarticular involvement intra-articular hydrocortisone is highly useful. All precipitating factors should be meticulously avoided.

Interval Therapy

1. **Diet:** Acute attacks can be avoided by omitting purine-rich diets like red meat, liver, pancreas, testes, peas, and alcohol. Though vegetable articles of diet such as lentils, peas, beans, spinach, mushrooms, cauliflower and oatmeal are rich in purines they generally do not provoke acute attacks. Obese individuals should lose weight gradually.
2. **Uric acid lowering agents:** When the attacks are frequent, or serum uric acid level is high and in the presence of tophi, drugs are indicated to lower serum uric acid. **Allopurinol** inhibits xanthine oxidase which is required for the conversion of xanthine and hypoxanthine to uric acid and is a very effective drug to lower serum uric acid. In addition, allopurinol also helps in elimination of urates. The advantages of this drug are its low toxicity and sustained therapeutic effect even in the presence of renal disease or diuretic therapy. The starting dose is 100 mg thrice daily, to be increased upto 500 mg/day if required, to achieve the effect. Later the dose is reduced to a maintenance level. Diarrhea, dyspepsia, and skin rashes are untoward side effects. Dose dependent toxic effects consisting of hypersensitivity reactions such as fever, eosinophilia, dermatitis, hepatic dysfunction, renal failure and vasculitis may develop in persons taking more than 400 mg/day. If allowed to proceed, the condition can be fatal. Treatment is to desensitize the patient and use lower doses of the drug.

Febuxostat is a newer non-purine selective inhibitor of xanthine oxidase, effective in gout, in a dose of 80-120mg/day. It reduces serum urate levels. Adverse side effects include hepatic and renal toxicity. The drug is still under trial.

Uricosuric agents such as probenecid 0.5-1 g twice daily and sulphinpyrazone 100 mg thrice daily help to eliminate uric acid in urine and lead to reduction of attacks and disappearance of tophi. They are indicated in conditions where production of uric acid is normal but elimination is impaired. They are contraindicated in conditions with overproduction of uric acid, renal failure, and urate calculi.

Asymptomatic hyperuricemia: This warrants treatment if there is:

- i. previous history of gout,
- ii. presence of tophi,
- iii. family history of gout,
- iv. presence of uric acid stones,
- v. presence of renal damage, and
- vi. serum uric acid greater than 9 mg/dL.

Other Forms of Crystal Induced Arthropathy

Calcium pyrophosphate dihydrate crystals may be deposited in joint tissues and this leads to acute gout like attacks. This is known as **pseudogout**. Basic calcium phosphates (hydroxy apatite and octacalcium phosphate) may be deposited in joint tissues mainly affecting shoulders and knees. Calcium oxalate crystals may be deposited in cartilage, synovium, bone and other tissues in renal failure patients treated with dialysis regimen and those with primary oxalosis.

Calcium Pyrophosphate Crystal Deposition Disease (CPPD)

Syn: Pseudogout

CPP crystals are seen in synovial fluid and these are derived from articular cartilage. Processes that lower solubility of the CPP crystals lead to their precipitation. The condition may be familial, sporadic or caused by metabolic disorders such as hyperparathyroidism, hemochromatosis, hypothyroidism, hypomagnesemia, hypophosphatasia and others. CPP crystals deposit in hyaline cartilage and fibrocartilage, the latter is affected more. The menisci of the knees, articular discs of distal radioulnar joints, acetabulum, symphysis pubis and annulus fibrosus of lumbar and dorsal intervertebral discs are sites of predilection. Men above 50 years are more affected though both sexes are susceptible. The patients may fall into one of three categories.

1. Familial,
2. Those associated with metabolic disease, trauma or joint surgery, and
3. Sporadic.

Though many cases may be silent, some present with recurrent attacks of subacute inflammation and progressive degeneration of joints. Once the degenerative process starts, it proceeds relentlessly, despite treatment.

The presentation may resemble gout, rheumatoid arthritis, osteoarthritis or neuropathic joints.

Differential diagnosis includes all other types of mono- or polyarthritis, depending upon the presentation. X-ray of the joints reveals calcification in distinctive locations and this is diagnostic. Microscopy of the synovial fluid is confirmatory.

Management

During acute attacks NSAIDs may be tried. Colchicine given IV in a dose of 1 mg is very effective. Aspiration of synovial fluid and injection of microcrystalline cortisone (cortisone acetate) gives rapid relief.

Basic Calcium Phosphate (BCP)

Crystal Arthropathy

Syn: Milwaukee shoulder/knee syndrome

This condition affects elderly persons, mostly women. The shoulder or knee may be affected. Many cases may be asymptomatic despite the deposition of crystals. Symptoms include pain in the shoulders or knees after exertion and at night. Progressive destruction of joints occurs. Treatment is symptomatic.

Calcium Oxalate Arthropathy

This is a complication occurring in renal failure when the serum creatinine levels exceed 8 mg/dL, especially so in patients undergoing dialysis regimen. Crystals of calcium oxalate may be deposited in joints, skin, blood vessels and other tissues. Joint manifestations include subacute, chronic or acute painful episodes. Several other substances may get deposited in joints and lead to crystal-induced arthropathy. These include xanthine, cholesterol, cystine, aluminium phosphate, Charcot-Leyden crystals and possibly others

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Osteoarthritis

K.V. Krishna Das

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General Considerations

Syn: Osteoarthritis, Degenerative joint disease

Osteoarthritis (OA) is predominantly a disease of the elderly but no age is exempt. It is caused mainly by wear and tear of the joints. It may be primary or secondary. Presence or absence of Heberden's nodes on the distal interphalangeal joints helps to distinguish two forms of primary osteoarthritis—the nodal and non-nodal types.

The former indicates the presence of generalized disease. Osteoarthritis forms about 25-35% of the joint lesions seen in clinical practice.

Etiology

The most regular association of osteoarthritis is with aging. Beyond the age of 50 years osteoarthritis is demonstrable in one or more joints invariably, but it may be asymptomatic. Several factors predispose to the disease and accelerate its progression. These include pre-existing joint disease, obesity, hypermobility, orthopedic deformities, endocrine disorders like diabetes mellitus, acromegaly and hyperparathyroidism, and sensory neuropathies which impair joint sensations. Overuse of any joint and adoption of unusual postures for long



Fig. 113.1: X-ray spine PA view—osteoarthritis vertebrae



Fig. 113.2: X-ray spine lateral view—osteoarthritis vertebrae

periods predispose to the condition e.g. OA of the knees of obese subjects and long distance walkers and OA of the neck in computer professionals.

Pathogenesis and Pathology (Fig. 113.3)

The basic pathology can be defined as a loss of focal areas of hyaline cartilage with increased activity in marginal and subchondral bones in synovial joints. Primary lesion starts in the articular cartilage. Due to mechanical stress the collagen fiber network of the articular cartilage is disrupted. This leads to alteration in the composition of the ground substance with resultant loss of resilience. The chondrocyte function and number change. Bone turnover is less in OA, but cartilage turnover is more. Crystals may be present in synovial fluid, especially in the knee. These include hydroxyapatite, octacalcium phosphate and

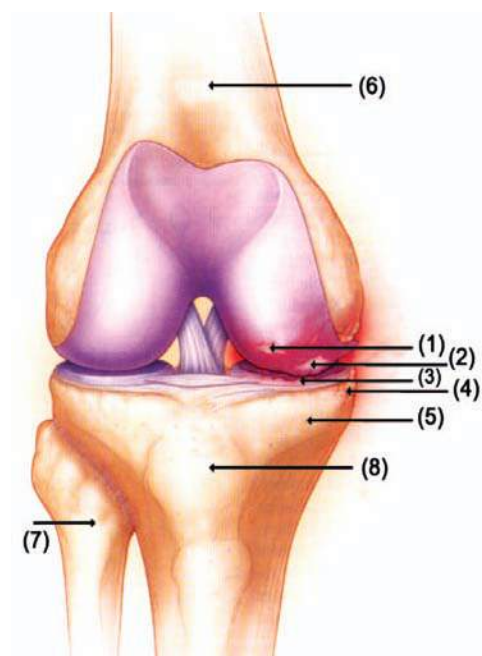


Fig. 113.3: Pathogenesis of osteoarthritis knee—diagram

1. Worn articular cartilage
2. Damaged medial meniscus
3. Narrowed joint space
4. Osteophytes
5. Bony sclerosis and cysts
6. Femur
7. Fibula
8. Tibia

tricalcium phosphate (BCP) and calcium pyrophosphate dihydrate (CPPD). Presence of crystals in synovial fluid is strongly associated with cartilage degeneration.

Wear and tear leads to further disruption of collagen fibers. The lubricating mechanism of the joint is impaired. The normal surface matrix is lost, resulting in exposure and fibrillation of the cartilage fibers and later cleft formation. Synovial fluid gains access to the deeper layers of the cartilage. This leads to further destruction of load-bearing cartilage. The cartilage undergoes calcification. The exposed weight-bearing bones undergo eburnation. Osteophytes grow at the margins of articular bones. Still later subchondral bone may fracture to form cysts. Crystals are liberated into the synovial cavity. These add to the inflammatory process. Though synovial inflammation and effusion occur, these processes are generally mild compared to the primary inflammatory arthropathies.

Clinical Features

Many cases are asymptomatic though abnormalities are detectable radiologically. Knees, cervical spine, lumbar spine, hips, shoulder, and distal interphalangeal joints are affected most frequently. Figures 113.1, 113.2, 113.4A and



Fig. 113.4A: X-ray knees—osteoarthritis
Note: osteophytes—arrow



Fig. 113.4B: Osteoarthritis knees lateral view
Note: reduction of joint space and osteophytes



Fig. 113.5: Osteoarthritis hand—Heberden's nodes



Fig. 113.6: Osteoarthritis knees



Fig. 113.7: Osteoarthritis cervical spine. Note: the osteophytes in front and back of the vertebral bodies, narrowing of disks spaces and loss of cervical lordosis

sideways causes pain. Vague pain and stiffness in the knee especially after getting up from the sitting posture are the early symptoms. Cartilage is aneural and therefore it does not contribute to pain. The tissues from which pain arises are (1). osteophyte growths (2). localized areas of increased intra-osseous pressure (3). synovitis and (4). periarticular structures. Subchondral bone and synovium may be responsible for nociceptive stimuli. Sensitization of peripheral neuronal elements aggravates the pain response. The processes of attempted joint repair lead to osteophyte growth as well as subchondral bone changes

B, 113.5 and 113.7 weight bearing joints such as the knees develop deformities (Fig. 113.6).

Osteophyte formation at the distal interphalangeal joints leads to the formation of **Heberden's nodes** which may become painful. In the knees movement of the patella

which are nociceptive. Production of secondary particles and chemical mediators from the cartilage give rise to secondary synovitis. In addition altered mechanics of the joints give rise to periarticular phenomena such as strain on muscles and ligaments, and inflammation of bursae which are all painful. These lesions which cause pain lower the pain threshold centrally either at the spinal cord level or cortical level, or both.

The patients experience disability while walking down the stairs or slopes. The quadriceps undergoes atrophy. Transient effusions may occur even in asymptomatic cases. Osteophytes may be palpated around the joints. Crepitus may be elicited on movement. Deformities develop. Later osteoarthritis of the cervical spine leads to a group of clinical manifestations. These are described along with cervical spondylosis (section 17 chapter 199). Affection of the lumbar spine leads to low backache and sciatica.

Radiology

The bones show subchondral sclerosis, narrowing of joint spaces, osteophyte formation, joint destruction, cyst formation in the cortical bone, and loose bodies (joint mice) within the joints.

Laboratory Investigations

These are not diagnostic. They help to exclude other forms of inflammatory arthropathies. The acute phase reactants are not elevated. The leucocyte pattern is not altered. Synovial fluid shows normal viscosity, normal mucus content and cell count below 2000/cmm. Fragments of cartilage or bone and crystals of hydroxyapatite and calcium pyrophosphate dihydrate may be seen.

Arthroscopy

Using appropriate arthroscopes the interior of many of the peripheral joints can be directly inspected and this helps to confirm the diagnosis. Arthroscopic surgery is also practiced widely. Arthroscopy is available in many centers in India.

Course and Prognosis

Osteoarthritis is a slowly progressive disease which leads to considerable morbidity with passage of time, if allowed to proceed unchecked. The rate of progress and morbidity

can be considerably retarded by lifestyle changes such as weight reduction, use of appropriate footwear on walking and regular exercises for 1) strengthening the weight bearing muscles in and around the joints and 2) for preserving the range of movements. Any postural or orthopedic deformity should be corrected to prevent progress of the arthritis.

Management

The principles of management include prevention of overuse of the affected joint, limitation of activity to reduce pain, and physiotherapy to strengthen the muscles. Application of heat and graded movements help to reduce pain.

Medical treatment is symptomatic. Nonsteroidal anti-inflammatory drugs relieve pain and inflammation. Reduction of weight and management of metabolic and endocrine disorders may serve to arrest the progress of the joint lesions.

Intra-articular cortisone acetate or triamcinolone may be given as temporary measures to relieve acute pain and disability. Intra-articular corticosteroids may accelerate degenerative changes in the joint if given repeatedly.

Drugs have been introduced with the claim that they protect cartilage from degeneration. These include glycosaminoglycan polysulfate ester (arteperon), glycosaminoglycan peptide complex—rumalon pentosan polysulfate and hyaluron. Their role in prevention and treatment of degenerative joint disease is to be evaluated, even though they give relief of pain.

Joint replacement should be considered for osteoarthritis of the hip and knee if medical measures fail to relieve pain and disability and to restore mobility. The mechanical impairment caused by OA lesions in the knees can be properly assessed by simple tools such as pedometers and the 'GAIT rite' gait analysis system. The results of knee and hip replacement are excellent in most of the cases. Therefore replacement surgery should be advised without undue delay. In good centers the success rate is high. The average life for a prosthetic knee is more than 10 years and that for a hip is 10-15 years. Second operations can be undertaken. The cost for surgery varies between Rs. 40-50 thousands.

Further reading: Paul Dippe. Osteoarthritis: Some recent trends J. Indian Rheumatol Assoc 2005;13:107-12.

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HYPERTROPHIC OSTEOARTHROPATHY

Syn: Hypertrophic pulmonary osteoarthropathy, Marie-Bamberger's syndrome

This is an acquired disorder characterized by clubbing of the fingers and toes, painful thickening of the ends of long bones such as the tibia and radius, and varying degrees of arthritis. In most cases it is secondary to other underlying disorders, rarely it may be idiopathic and at times it runs in families. The exact mechanism of development of the lesions is not clear.

Causes

Pulmonary lesions: Chronic suppuration such as bronchiectasis, lung abscess and empyema, carcinoma lung, pleural mesothelioma, alveolocapillary block syndromes, fungal infections, and chronic fibroid tuberculosis.

Cardiovascular lesions: Cyanotic congenital heart disease, infective endocarditis, aneurysm of the aorta or its branches.

Other conditions: Chronic malabsorption states, ulcerative colitis, Crohn's disease, cirrhosis liver, hepatic abscess, and thyrotoxicosis.

Clinical Features

Onset is very insidious in the vast majority of cases, but it is rapid in malignancy of the lung or pleura and infective

endocarditis. It is usually bilateral but unilateral clubbing may develop in aneurysm of the subclavian artery.

The manifestations include clubbing of the fingers and toes, symmetrical painful enlargement of distal ends of bones at the wrist and ankle and intermittent swelling and painful limitation of joint movements. In a few cases true arthritis, fibrous ankylosis, and deformity may result (Figs 114.1A and B).

When hypertrophic osteoarthropathy is associated with marked thickening of the skin of the limbs and face, this is called *pachydermoperiostosis*.

Management

In all secondary cases the primary cause should be detected and corrected. This leads to resolution of the bone changes. Nonsteroidal anti-inflammatory drugs relieve pain.

PAGET'S DISEASE OF BONE

Syn: Osteitis deformans

This is a rare disease of unknown etiology, characterized by enlargement, softening, and deformity of several bones, seen after the age of 40 years, more commonly in men. Though this disease is common in the west, it is seen only rarely in Indians. The involvement is localized in the majority of cases but may be widespread, involving several bones.

Pathology

There is increased and disorderly formation and destruction of bone. This results in a high rate of bone turnover. There is increase in the number and activity of osteoclasts. The osteoblasts try to compensate by adding more bone, but osteoclastic activity preponderates. The bone is highly vascular and functional arteriovenous shunts develop, resulting in a high cardiac output state. The marrow is replaced by highly vascular fibrous tissue. Pelvis, femur, skull, tibia, and vertebrae are affected in the order of frequency.



Figs 114.1A and B: (A) Hypertrophic pulmonary osteoarthropathy male 52 years. Note: Clubbing of fingers. (B) X-ray chest of the same patient showing cancer left lung arrow

CLINICAL FEATURES

Many cases are asymptomatic and detected on routine radiological examination. Symptoms include pain on weight-bearing, progressive enlargement of the skull, deformities of the affected bones, pressure on the nerves which pass through bony canals (cranial nerves, spinal nerves and spinal cord) and rarely the development of high output cardiac failure state. Though the bones are thickened, they are weaker than normal. The femur and tibia undergo bowing and other deformities due to weight-bearing. The overlying skin is warm due to increased vascularity. Deafness, optic atrophy, and paraplegia are rare neurological complications. **Serum alkaline phosphatase is grossly elevated. Bone specific alkaline phosphatase is the iso-enzyme that is diagnostic.** Serum calcium and phosphorus are normal. Urinary hydroxyproline is increased during the active phase of the disease.

Complications

These include fractures, progressive deformity, cranial nerve palsies (especially deafness), spinal cord compression, degenerative joint disease, high output cardiac failure if the disease is extensive and in long-standing cases, osteogenic sarcoma (Figs 114.2 and 114.3).

Diagnosis

The diagnosis is based on clinical features and is confirmed by radiography. The bone appears larger, chalky white and nonhomogenous in the skiagram. Localised enlargement and hyperdensity of bones is suggestive. This feature helps to differentiate from multiple osteosclerotic secondaries and other osteosclerotic conditions such as myelosclerosis and endemic fluorosis.

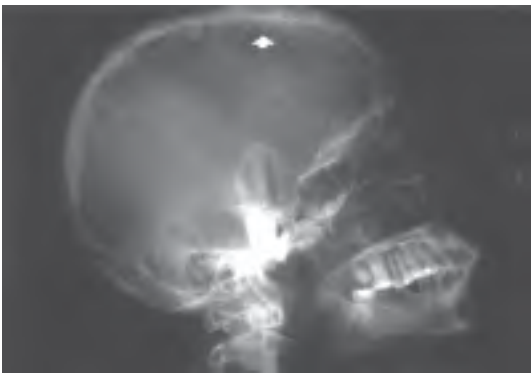


Fig. 114.2: X-ray Paget's disease of bone Skull. Note: Non-homogenous moth eaten appearance arrow head



Fig. 114.3: X-ray Paget's disease of bone Note: Dense enlarged deformed lower end of femur normal tibia

Treatment

Asymptomatic localised lesions have to be left alone. Symptomatic relief of pain is achieved by aspirin, indomethacin or corticosteroids. Human calcitonin in a daily dose of 0.5 mg subcutaneously for six months (or salmon calcitonin 100 MRC units/day) promptly relieves bone pains and helps to reduce the turnover of bone with improvement in the condition, the serum level of alkaline phosphatase also comes down. Mithramycin (Now called plicamycin) in a dose of 25-50 µg/ kg given intravenously for 10-14 days is effective. This drug inhibits bone resorption. It produces myelosuppression and a hemorrhagic tendency. Bisphosphonates (disodium etidronate) in a dose of 5-10 mg/kg/day also reduce bone turnover and bring about clinical relief in some cases. Bisphosphonates correct the chaotic bone formation by inhibiting the osteoclasts and inducing the formation of lamellar bone. Alendronate, 10 mg may be given orally daily on a long term basis. Pamidronate may be given by slow IV infusion. Newer bisphosphonates include zoledronic acid 5 mg given IV as infusion over 15 minutes or at longer intervals. The effect may last even as long as 6 months.

Schedule of pamidronate dose

- < 2 years of age : 0.5 mg/kg bw/day for 3 days every 2 months
- 2-3 years : 0.75 mg/kg bw/day for 3 days every 3 months
- > 3 years : 1mg/kg bw/day (maximum 60 mg) for 3 days every 4 months

The rate of infusion is 0.1 mg/minute. Total time for infusion is 3-4 hours.

Treatment improves bone strength and reduces fracture risk. In severe cases not amenable to medications bone marrow transplantation is curative. However, they are less effective than calcitonin. Calcitonin and etidronate can be combined. Other bisphosphonates that are available include alendronate, pamidronate, clodronate, tiludronate and others. The bone formed during the therapy with these drugs is usually normal.

Immobilization should be avoided since it leads to hypercalcemia and hypercalciuria. The onset of osteogenic sarcoma should be looked for in long-standing cases.

Juvenile Paget's Disease of Bone

Syn: Hyperostosis corticalis deformans

This is a rare autosomal recessive disorder causing bony deformities. Nerve deafness may occur due to compression of the 8th nerve in the petrous temporal bone. It usually starts in infancy or early childhood. It is characterized by painful debilitating fractures and deformities. Accelerated bone remodeling occurs throughout the skeleton. Juvenile Paget's disease is different from the adult form of the disease.

Treatment

Recombinant osteoprotegerin is effective in treating Juvenile Paget's disease.

Achondroplasia

This is the most common inherited disorder of bone and cartilage. It is transmitted as autosomal dominant. Some cases arise as mutations. It presents as disproportionate dwarfism characterized by normal trunk and short limbs (*circus dwarfs*). Face appears small, the skull vault is normal but the base is shortened. Other features are lordosis, waddling gait, large and flat feet, and diverging fingers of equal length (trident hands). In general, the muscles are well developed and some of the joints appear stiff, but are not painful. Complications include premature osteoarthritis involving the weight-bearing joints, spinal stenosis and hydrocephalus. Apart from the cosmetic disabilities they lead normal lives, enjoy family life and rear children. The condition does not warrant any treatment unless complications develop.

Osteogenesis Imperfecta

Syn: Fragilitas ossium, Brittle bone disease

This is a generalised connective tissue abnormality inherited as an autosomal dominant, manifesting as a peculiar brittleness of the bones, making them vulnerable to recurrent pathological fractures. This disease is occasionally seen in India. There is either reduction in the production of type I collagen or formation of abnormal collagen due to mutations in the type I collagen genes. There is defective formation of osteoid with associated osteoporosis but the process of calcification is essentially normal. Two groups have been recognized.

In some cases the disease manifests *in utero* with the birth of a severely affected baby with multiple fractures. The baby may die *in utero* or soon after birth. The other group manifests later in life—*osteogenesis imperfecta*



Fig. 114.4: Osteogenesis imperfecta: bowing of leg bones

tarda. Severe skeletal deformities result from the softening and bending of bones under stress or following repeated fractures with excessive callus formation. Bowing of long bones, kyphoscoliosis, pectus excavatum, and bulging of the calvarium are some of the common deformities (Fig. 114.4). Fractures may remain without union and give rise to pseudojoints. The sclerae show a characteristic blue colour due to thinning. Bruising of the skin and laxity of ligaments and joints are common. Wound healing and scar formation are imperfect.

The clinical severity varies widely. Severity can be graded as follows.

- Type I Mild form—occasional fracture before puberty. The stature is normal.
- Type II Most severe form—fractures *in-utero*, pulmonary insufficiency and perinatal death.
- Type III High frequency of fractures in postnatal life leading to severe deformities and short stature.
- Type IV Less severe form—deformities and fractures occur.

Types I and IV are autosomal dominant, the others are autosomal recessive. Bisphosphonates, especially pamidronate given intravenously in short courses with intervals in between, may produce clinical improvement and also reduce the frequency of fractures.

Bone and Joint Tuberculosis

This is common in India. Bone tuberculosis is generally secondary to established tuberculosis in other parts such as lungs, lymph nodes or kidneys. The organisms reach the synovium or subchondral bone by hematogenous or lymphatic spread. In the vast majority of cases a single large joint like the hip or knee is affected. Involvement of the vertebrae is common. In addition to the general symptoms of tuberculosis, severe local pain and restriction of movement of the affected region occur. If left untreated, the joint may be destroyed. Tuberculosis of the vertebrae leads to cold abscess formation and compression of the spinal cord. This used to be frequent cause of paraplegia in India.

Diagnosis

Strong clinical suspicion is necessary for making early diagnosis. X-rays show periarticular osteoporosis and soft tissue swelling in the early stages. Later, there is narrowing and irregularity of joint space and erosion of the cartilage and subchondral bone. Cold abscess may be seen (Figs 114.5 and 114.6).

The Mantoux test is often strongly positive. X-ray of the affected joint and synovial biopsy help in confirming the diagnosis.

Treatment

Standard systemic anti-tuberculous therapy is indicated for durations ranging from 9-12 months. Local measures

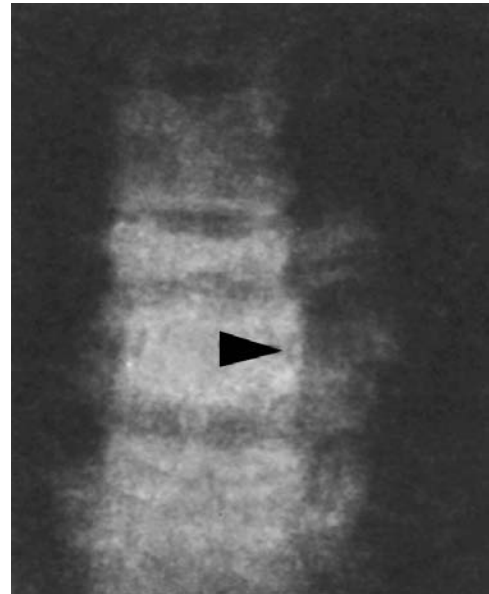


Fig. 114.5: X-ray-PA view—tuberculosis spine
(See cold abscess: arrow)

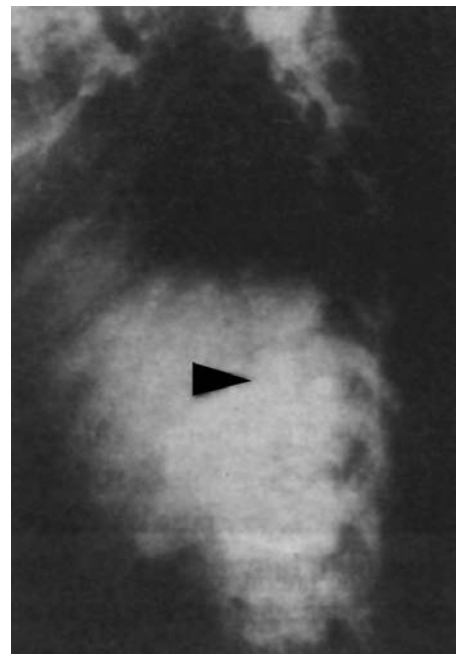


Fig. 114.6: X-ray lateral view—tuberculosis spine
Note: Compression of vertebra: arrow

include immobilization of the spine to reduce pain and spinal compression. Surgery may be indicated to relieve spinal cord compression.

Bone and Joint Involvement in Hematological Disorders

Several hematological disorders may present with bone and joint symptoms. Unless these are borne in mind, the primary condition may be missed.

Leukemias: In acute lymphatic leukemia, arthralgia, arthritis, and bone pains are common. These may be mistaken for rheumatic fever or rheumatoid arthritis.

Secondary gout is common in all forms of leukemias either in the florid stage or this may be precipitated by treatment.

Allergic purpura: Joint manifestations are characteristically seen in Henoch-Schönlein purpura. Large or small joints may be affected.

Sickle cell anemia: Involvement of finger joints and other periarticular tissues and severe bone pains are common during crises.

Hemophilia and other coagulation defects: Bleeding into weight-bearing joints is common. The knees, ankles and elbows are frequently affected. In the early stages a primary joint disease may be suspected. Later, due to recurrent bleeding the joint is damaged and ankylosis results.

Multiple myeloma: This disorder commonly presents with bone pain, and fractures, especially in the axial skeleton. It may also lead to secondary gout.

Malignant lymphoma: This disorder may involve bones directly or indirectly by giving rise to secondary gout.

Sports Injuries

In modern times several children take to sporting activities which expose them to repeated injuries. These include growth plate fractures, epiphyseal fractures, osteochondrosis dessicans and traction apophysitis. Sports injuries are becoming increasingly common. Most of them are soft tissue lesions and are often managed inadequately. Many of them are preventable. There are two major mechanisms of injury—trauma and overuse. Overuse may be due to intrinsic factors like malalignment of joints or limbs. Extrinsic factors are related to equipment and environment.

Excessively strenuous training, especially for competitive sports leads to injuries associated with overuse and growth problems. Negligence on the part of the children, such as failure to wear protective equipment like helmet, knee guards face shields predispose to injury. They may also not care to follow proper techniques which will minimize injuries to themselves and others. Evidence based preventive measures are available which have to be followed by those in training.

Principles of General Management

Prevention is by addressing the contributory factors like malalignment of joints which should be corrected and the equipment used should be reviewed. Management of acute

phase involves treatment of inflammation, the NICER approach.

NSAID is used to reduce pain and inflammation.

ICE is an analgesic and it limits excessive inflammation.

Compression and

Elevation of the injured area reduces swelling.

Rest for 24 hours and supportive protective strapping may be helpful to relieve muscle spasm and pain.

This may be followed by exercise which is the corner stone of the rehabilitation of soft tissue injury. This prevents muscle weakness and wasting. It includes strength training and flexibility training. Local steroids have no role in acute soft tissue injury even though they may be useful and needed in chronic tendon insertion injury unresponsive to conservative management. Arthroscopic surgery procedures may have to be performed with minimal invasiveness for faster rehabilitation.

Specific structural injuries to tendon, ligament, muscle and bone may require special management. Commonly affected tendons are the Achilles tendon and supraspinatus. The most common ligament injury in sport is the sprained lateral ligament of the ankle. Muscle injury results from trauma or overstretching. Rupture is uncommon and hematoma may be complicated by myositis ossificans. Stress fracture of bone may be missed unless a high degree of suspicion is maintained.

In many countries athletes in training for major sports events are subjected to appropriate investigations to rule out the known causative factors.

SUDDEN DEATH IN YOUNG ATHLETES

The frequency is 1/100000 annually. The male to female ratio is 10:1. Probably this is due to the higher prevalence of cardiological abnormalities in males.

Causes

Cardiac lesions account for the majority of sports related sudden death

Atherosclerotic heart disease in athletes aged > 35 and congenital and inherited disorders – in those who are younger

Hypertrophic cardiomyopathy – This accounts for over 30% of deaths

Congenital coronary anomalies

Other causes include arrhythmogenic right ventricular cardiomyopathy, myocaditis, mitral valve prolapse, conduction defects, W PW syndrome, aortic rupture in Marfan's syndrome, bronchial asthma, subarachnoid hemorrhage and non penetrating strike to the chest wall.

Sudden death in sports may be the only evidence of underlying heart disease. There may be no previous history or any familial predisposition.

Diagnosis can be made by making a careful history and physical examination. Plain radiography, bone scanning, CT or MRI all have a role in selected cases.

Cardiology

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Cardiology: General Considerations

C.G. Bahuleyan

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Cardiac Physiology

The normal adult human heart weighs 250-350 g. The left ventricle is two to three times the thickness of the right ventricle. The former constitutes 60% of the total weight. Histologically the cardiac muscle forms a syncytium though the myocardial cells are electrically isolated by high resistance membranes. Cardiac muscle possesses intrinsic properties such as excitability, contractility, rhythmicity, conductivity, and distensibility. As the cardiac muscle is stretched within physiological limits the force of contraction increases (*Starling's law*). Though the sinoatrial node (S-A node), atrioventricular node (A-V node), the conducting tissues and cardiac muscle are all capable of impulse production, in health, the heart beat is initiated by impulses from the S-A node. Vagal impulses depress the rate of the S-A node and increase the refractory period of the cardiac muscle. Sympathetic fibers arising from the cervical and upper thoracic ganglia supply the heart and they accelerate the S-A node and decrease the refractory period of the myocardium. Atrial contraction is followed by ventricular contraction. Atrial contraction helps in pumping blood remaining in the atria towards the end of diastole and this helps to augment ventricular filling, thus preparing the ventricles for more effective contraction. Atrial contraction gives rise to the a-wave in the jugular veins. With the onset of ventricular systole, A-V valves close and the A-V valve apparatus bulges towards the atria giving rise to the c-wave in the jugular veins. As the ventricular pressure increases rapidly, the semilunar valves open and blood is ejected into the aorta and the pulmonary artery. The ventricles eject 60-70% of their contents during each systole. Initial phase is one of rapid ejection. This is

followed by the period of slowed ejection. During each contraction the ventricles eject 70 mL of blood which is the stroke volume. The atrial filling continues during ventricular systole and the rise of pressure in the right atria gives rise to the v-wave of the jugular venous tracing. At the end of ejection the semilunar valves close and the isometric relaxation follows. Though, in a broad sense, the ventricular contraction occurs synchronously on the right and left sides of the heart, closer examination will reveal that the right ventricular ejection starts earlier and is completed slightly later than left ventricular ejection. Atrioventricular valves (A-V valves) open when the ventricular pressure falls below that of the atria during diastole. Atrial blood flows into the ventricle rapidly in the early part of diastole and this may give rise to the third heart sound (S_3).

Heart sounds: These are produced by deceleration of blood impinging on elastic structures in the heart, giving rise to vibration. More rapid deceleration gives rise to louder sounds and *vice versa*. The pitch of the sound (frequency) is determined by the relative contribution of the mass of blood and the elastic properties of the structures which are responsible for producing the sounds.

First heart sound (S_1) occurs at the commencement of systole and coincides with the closure of the A-V valves. **Second heart sound (S_2)** marks the onset of diastole and indicates closure of the semilunar valves. **The third heart sound (S_3)** occurs in the earlier part of diastole and it coincides with rapid ventricular filling. **The fourth heart sound (S_4)** is produced by atrial contraction and this is a late diastolic sound. When S_3 or S_4 becomes pathologically accentuated giving rise to a characteristic cadence resembling the canter of a horse, it is termed "*gallop rhythm*". The terms "*protodiastolic gallop*" and "*presystolic gallop*" were used to denote S_3 or S_4 respectively. When both these are audible, and the diastolic interval is shortened due to rapid heart rate, these may merge (summate) and such a phenomenon is called *summation gallop*.

Cardiac output: This is the volume of blood pumped by the left ventricle in one minute. Normal average is 5-6

liters in healthy adults. It is also expressed as the cardiac index, when related to the surface area of the individual. *Normal cardiac index* is 2.8-4.2 (mean 3.4) liters/min/m². Cardiac output is controlled by several factors such as heart rate, effective filling pressures of the ventricles, compliance of the chambers, contractile force of the ventricles and the blood pressure. Generally, the increase in cardiac output is achieved by increasing the heart rate and stroke volume. Exercise and emotion normally increase the cardiac output, whereas extreme tachycardia, extreme bradycardia, atrial fibrillation, myocardial dysfunction and anatomical or functional obstruction to the outflow of blood reduce it.

Heart receives its oxygen supply and nutrition from the coronary arterial blood flow which is 72-85 mL/100 g of cardiac muscle/min in the resting phase. The heart utilises 8-10 mL of oxygen/100 g every minute. The oxygen demand during systole is thrice that during diastole. Diastole is also an active energy-consuming process. Proper diastolic function is essential to accommodate the optimum quantity of blood before the onset of systole.

Right ventricular physiology: Right ventricle has the same output as the left. It has only 1/6 the muscle mass and performs only 1/4 the stroke work as the left ventricle. This is due to the fact that the pulmonary vascular resistance is only 1/10 that of systemic resistance. The two ventricles differ in shape but their function is made interdependent through the mechanism of action of the interventricular septum and surrounding pericardium. The systolic pressure wave caused by LV septal contraction augments the systolic force of the RV and promotes pulmonary perfusion.

Arterial blood pressure: The arterial blood pressure is influenced by several factors such as the cardiac output, peripheral resistance in the arterial system, blood volume in the arterial system, viscosity of blood, and elasticity of the arteries. The control of blood pressure is achieved mainly by alteration in the cardiac output and peripheral resistance. Normally, arterial blood pressure fluctuates widely depending on exercise and emotional stress, time of the day and posture. The systolic blood pressure falls by 15-30 mm Hg during sleep. In the erect posture diastolic blood pressure is greater than during recumbency.

Average systolic blood pressure readings are:

1. Neonates—40 mm Hg,
2. Infants aged 2 weeks—70 mm Hg,
3. Children upto 12 years—105 mm Hg, and
4. Above 17 years—120 mm Hg.

In adults, for a considerable period of life (up to the sixth or seventh decade) the blood pressure remains more or less steady, but with old age, due to reduction in elasticity of the arterial wall, the systolic pressure may tend to rise.

Symptomatology in Cardiovascular Diseases

Dyspnea is the most common symptom which brings the patient to the doctor in most instances. This is the uncomfortable awareness of breathing. Several factors may contribute to dyspnea. Dyspnea has been quantitated for assessing the severity and for helping in follow-up.

Grade I (slight)—symptoms are provoked by more than ordinary activity like running, climbing uphill.

Grade II (moderate)—symptoms occur in ordinary activity like walking briskly, going two flights of stairs.

Grade III (considerable)—symptoms develop with less than ordinary activity like walking on level ground, light household work.

Grade IV (gross)—total incapacity and dyspnea at rest and recumbency.

Orthopnea (dyspnea on recumbency) is common in left-sided heart failure. **Paroxysmal nocturnal dyspnea** is the occurrence of sudden onset of dyspnea which abruptly wakes the patient up in the early hours of sleep. The patient jumps up for breath with cough and frothy sputum. Assuming the erect attitude relieves the distress in many cases. Paroxysmal nocturnal dyspnea (also known as *cardiac asthma*) is an early symptom of left-sided heart failure. Pulmonary congestion and edema account for this phenomenon. Cheyne-Stokes respiration is the periodic alteration in the rate and depth of breathing. The respiratory rate waxes and wanes alternately with apneic pause in between. Cheyne-Stokes respiration occurs in several conditions, left-sided heart failure being a common cause.

In the presence of other evidences of heart disease, dyspnea is a strong pointer of cardiac failure.

Edema: Subcutaneous edema is demonstrated by the phenomenon of pitting on pressure. Considerable amount of fluid (more than 2 liters) should accumulate in the body before manifesting as generalized edema. Abnormal increase in weight (0.5-1 kg/day) associated with oliguria occurs early. When edema is manifest, the skin is stretched and shiny and pitting can be demonstrated.

The factors which help in retaining sodium and fluid are:

1. Reduction in the cardiac output
2. Increased venous pressure, transudation of fluid into the interstitium, and
3. Overactivity of aldosterone and antidiuretic hormone.

These hormones acting together reduce the renal output of sodium and water. The edema is '*dependent*', i.e. it is more prominent in the most dependent parts of the body. In those who are ambulant the edema is maximal

on the feet, and that too in the evening. In bed ridden patients, the edema is localized to the back and sacral region.

Precordial pain: Among the several causes of precordial pain, cardiac disease is the most important. Pain sensitive structures in the heart are the pericardium which gives rise to pain due to inflammation (pericarditis) or stretching as in pericardial effusion, and the myocardium in which severe pain may occur as a result of ischemia. Pain arising from the pericardium and myocardium are distinguishable in many cases, but sometimes they are identical.

Ischemic pain is vague, felt over the precordium or retrosternal region and may be described as crushing, bursting, lancinating, burning or otherwise. Anginal pain comes on with exertion or emotional stress and is relieved with rest. In myocardial infarction the pain is of longer duration and is experienced usually at rest. The pain shows characteristic radiation. The classical sites of radiation are: (1) along the inner aspect of the left arm to the little finger, (2) left or both sides of neck and jaw, (3) left scapular region, (4) right shoulder and arm, (5) epigastrium and at times, to any other part of the body. Patients with cardiac neurosis and hypochondriasis may complain of chest pain. This pain is localized to the cardiac apex and may be described as catching or pricking. Such pain may not have an organic basis.

Palpitation: This is awareness of the heart beat. Though normal individuals can experience the heart beat during exercise or emotional stress, under pathological states this symptom may be troublesome. Palpitation may be due to tachycardia, extreme bradycardia, irregularity of rhythm or increase in stroke volume. In anxious individuals this is a common symptom.

Syncope (Faint): Loss of consciousness occurs when the cardiac output is not sufficient to maintain cerebral blood flow. The patient loses consciousness rapidly over seconds, unlike epilepsy in which the loss of consciousness is more abrupt. As the patient sinks into the flat position, consciousness is regained. If cerebral ischemia continues the patient may develop convulsions (*Stokes-Adams attacks*). Syncope is common in Fallot's tetralogy, aortic, pulmonary and mitral stenosis, intermittent heart block and at the onset of acute myocardial infarction.

Other causes of syncope include pooling of blood in the lower limbs as seen in persons standing still for a long time (e.g. parade or drill), sudden rise in intrathoracic pressure resulting in diminution of venous return to the heart (e.g. cough syncope), or hyperreactivity of the carotid sinus in which sudden neck movements or pressure over the carotid sinus leads to severe bradycardia and syncope.

Apart from these specific symptoms, general symptoms such as extreme fatigue may be the result of

low cardiac output states. Anemia and fever occur in infective endocarditis. Clubbing of fingers is a common symptom of cyanotic congenital heart disease and infective endocarditis.

Physical Examination

Before proceeding to the examination of the cardiovascular system, a full general examination should be performed. Findings that may point to disease of the cardiovascular system are cyanosis, digital clubbing and dependent edema. Other general findings like anemia, skin rashes, pyrexia, and obesity may have relevance in the final analysis.

Cyanosis: Congenital heart disease gives rise to central cyanosis due to mixing of arterial and venous blood within the heart or outside it. In central cyanosis due to cardiac cause the extremities and tongue are all cyanosed, the periphery is warm and the cyanosis is not abolished by breathing 100% oxygen (Fig. 115.1).

Low cardiac output states may give rise to peripheral cyanosis in which there is stagnation of blood in the capillaries and overextraction of oxygen by tissues resulting in cyanosis. The limbs are cold to feel and only the periphery is affected, the central parts like tongue are not cyanosed.

Edema: Careful search for edema and its distribution is essential in all cases.

Temperature of the limbs: This depends on the state of arterial circulation. In low cardiac output states peripheral vasoconstriction gives rise to coldness of the palms and feet.

In high cardiac output states (e.g. thyrotoxicosis), the limbs are warm and the arterial pulsations may become prominent.



Fig. 115.1: Central cyanosis

Arterial pulse: The radial artery is generally taken up for examining the pulse. The rate, rhythm, volume and character of the pulse and nature of the arterial wall are noted. Pulse is of large volume in high cardiac output states such as thyrotoxicosis and anemia and in conditions where the stroke volume is high as in aortic incompetence. Small volume pulse (*pulsus parvus*) occurs in low cardiac output states such as mitral stenosis. When there is anatomical obstruction to the outward flow of blood as in aortic stenosis, the pulse is small in volume and slow rising (*slow rising pulse* or *pulsus parvus et tardus*). The pulse is jerky in hypertrophic subaortic stenosis. When the stroke volume is large and there is vasodilatation. The pulse is of high volume and low tension, such a pulse is called “*collapsing pulse*” or “*Corrigan’s pulse*”. This occurs classically in aortic incompetence and some cases of patent ductus arteriosus. The term “*bisferiens pulse*” is used, when the pulse wave shows two upstrokes. This is seen when there is a combination of aortic stenosis and incompetence or sometimes even in pure aortic incompetence. Pulsus bisferiens may be more clearly identified over the carotid artery.

In normal subjects, during inspiration the pulse volume falls slightly, but this is often not noticeable. Marked fall of pulse volume and pulse pressure during inspiration is called “*pulsus paradoxus*”. This is seen in pericardial effusion and constrictive pericarditis. “*Pulsus alternans*” is the condition in which alternate beats are weak. This difference may be palpable in most cases. When in doubt, this abnormality can be brought out using the sphygmomanometer. The difference between the stronger and weaker beats may be up to 40 mm Hg. Presence of pulsus alternans signifies gross impairment of left ventricular function.

Examination of the arterial wall for thickening, nodularity, and calcification reveals several abnormalities. When the medium-sized arteries like the radials are nodular and thickened, it suggests medial sclerosis (*Mönckeberg’s sclerosis*), which is generally seen with advancing age.

All the major arteries should be palpated to assess whether they are patent or occluded. Generally the carotid, axillary, brachial, radial, femoral, popliteal, dorsalis pedis, and posterior tibial are examined. Simultaneous palpation of the radial and ipsilateral femoral artery helps to detect occlusion of the aorta. Normally the femoral pulse precedes the radial pulse by 0.005 sec. The femoral pulse is delayed in coarctation of the aorta and aortoarteritis. Auscultation over the arteries may reveal bruit. Bruit may be the result of narrowing of the lumen (e.g. carotid stenosis and renal artery stenosis) or may arise from increased blood flow through the artery (e.g. carotid artery opposite to the side of carotid occlusion, thyroid arteries in Graves’ disease).

Jugular venous pulse: It is ideal to examine the internal jugular vein with the patient resting comfortably at an angle of 45°. The jugular vein closely reflects the pressure changes within the right atrium. In health, at 45° incline the upper limit of the venous column lies just behind the right sternoclavicular joint, which is at the same horizontal level as the sternal angle. When right atrial pressure is increased as in right-sided heart failure, the venous column is seen above the right sternoclavicular joint and the vertical height of this column is measured to express the increase in venous pressure. The waves a, c and v and the troughs x and y are studied. The jugular vein is a low pressure system and, therefore, the waves are occluded easily by palpation.

‘a’—wave is caused by atrial contraction and is presystolic. It is more prominent when the right atrium is contracting against increased resistance. It disappears in atrial fibrillation.

‘c’—wave is recordable but not usually visible as a separate wave. It reflects the bulging motion of the closed tricuspid valve during isovolumic systole.

‘v’—wave is systolic and is due to passive filling of RV during systole when tricuspid valve is closed.

‘x’—wave is the trough caused by atrial relaxation.

‘y’—wave is caused by opening of the tricuspid valve and rapid inflow of blood into the right ventricle (Fig. 115.2).

In the ordinary case it is easy to distinguish carotid artery pulse from jugular venous pulse, but sometimes

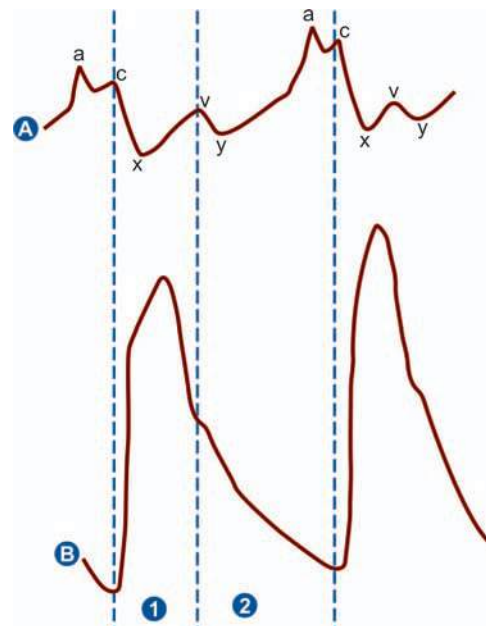


Fig. 115.2: Jugular venous tracing and arterial pulse: (A) Jugular venous pulse (B) Carotid arterial pulse (1) Systole (2) Diastole

TABLE 115.1

Differences between the jugular venous pulse and carotid artery pulse

Jugular vein	Carotid artery
1. Better seen than felt	Seen and felt well
2. Wavy column with 2-3 waves	Jerky, only one wave
3. During inspiration the vein becomes empty	Not much change with the phase of respiration
4. Vein becomes more prominent when the patient lies flat	No change
5. Hepatojugular reflux present	No change

when the former is very prominent or when both coexist, difficulty may arise (Table 115.1).

The hepatojugular reflux: While observing the jugular vein, the abdominal wall is pressed. Rise in intra-abdominal pressure drives blood from the liver to the inferior vena cava, thus increasing the venous return to the heart. This results in rise of the jugular venous pressure. Release of abdominal pressure promptly brings back jugular venous pressure also to the normal level. In early right-sided heart failure, abdominal pressure raises the jugular venous pressure, but release of the pressure is not followed by prompt fall of the jugular venous column.

Proper examination of the jugular venous pulse is a simple and very reliable bedside method to assess the hemodynamic events in the right atrium and it is absolutely essential that the clinical student spends time to learn this technique fully.

JVP is increased in right-sided heart failure, in which this is the earliest sign. Hypervolemic states (over-hydration) lead to engorgement of the jugular (e.g., acute nephritic syndrome). Study of the wave pattern helps in diagnosing arrhythmias such as atrial fibrillation and A-V dissociation. *Cannon waves* are jugular venous waves occurring in conditions such as complete heart block or extrasystoles when the atrium contracts against a closed tricuspid valve. Regular cannon waves may occur in junctional rhythm and in ventricular rhythms with 1:1 retrograde conduction. Irregular cannon waves are more common and occur in complete heart block and ectopic beats (ventricular or junctional) and ventricular tachycardia without retrograde atrial activation.

Examination of the Chest

Inspection: Cardiomegaly occurring in early life gives rise to precordial bulge. This is true of congenital heart disease and juvenile rheumatic heart disease. In the majority of these cases right ventricle is enlarged. Displacement of the apex beat and abnormal pulsations occurring in ventricular aneurysm or aortic aneurysm can be made out.

The epigastrium pulsates in right ventricular hypertrophy. Liver pulsates in tricuspid incompetence.

Palpation: This is the method to locate the apical impulse. Other valuable informations obtained by palpation are the presence of ventricular hypertrophy, expansile pulsation of aneurysms, abnormally loud heart sounds, and thrills produced by loud murmurs.

Normal apex beat is palpable in thin and moderately built individuals. It just lifts the palpating finger. Normally the apex beat is felt in the fifth left intercostal space 1 cm inside the midclavicular line. It may be impalpable if the chest wall is thick or if it is behind a rib. Pathological causes include emphysema and pericardial effusion. When the apex beat is not located in the normal position, the right side should be palpated, so as not to miss dextrocardia. *When there is volume overload of a ventricle, the impulse is more forcible (also called hyperdynamic), but not sustained. Forcible and sustained impulse (heave) is suggestive of pressure overload.* Left ventricular hypertrophy is manifested by heaving apex beat, whereas right ventricular hypertrophy manifests as left parasternal heave. Normal pulmonary artery pulsation may be visible in the second and third left intercostal spaces in thin individuals. If this is prominent, it suggests abnormal pulsation and pulmonary hypertension.

Thrills are caused by vibrations imparted to the palpating hand by turbulent blood flow.

Percussion: The precordial dullness is increased in cardiomegaly due to various causes and in pericardial effusion. The cardiac dullness is obliterated in emphysema, and left sided pneumothorax. Enlargement of the pulmonary artery, occurring in atrial septal defect or gross pulmonary hypertension can be detected by extension of the dullness outside the normal in the left second intercostal space. Normal pulmonary artery does not extend beyond 1 cm outside the left sternal edge. Since assessment by percussion can at best be only approximate, more accurate estimation by radiography or ultrasonography has to be resorted to in all cases when facilities permit (Fig. 115.3).

Auscultation: Rene Theophile Hyacinthe Laennec (1781-1826 French Physician) invented the stethoscope between 1816 and 1819 AD and introduced auscultation in cardiology. The original instrument was made of cedar wood or ebony. It was 30 cm long, 3.7 cm thick and with a central lumen of 0.6 cm in diameter. He named it stethoscope ('stethos' – chest, scopein- to observe (GK)). The modern stethoscope has undergone many changes.

The chest piece of many stethoscopes has the bell and the diaphragm. The former picks up low-pitched sounds better, whereas the latter is more useful to receive high-pitched sounds. Newer stethoscopes have only one chest piece. The sensitivity of the diaphragm to different pitches of the sound can be altered by the pressure exerted with



Fig. 115.3: Skiagram of normal chest

Note: Lungs are translucent and bronchial and vascular markings are traceable to the chest wall. The cardiothoracic ratio is less than 50%. The blood vessels at the hilum and major bronchi are visible.

the chest piece. The mitral, tricuspid, pulmonary and aortic areas are auscultated in sequence and then the third left intercostal space (second aortic area) is auscultated. Several additional areas of the chest or body have also to be auscultated, when there are indications. These include the interscapular area, neck, first and second left intercostal spaces, apices of lungs, abdomen, spine, and head. Normal heart sounds, additional sounds such as (third and fourth heart sounds), clicks and murmurs, and pericardial rub are specially looked for. In general, the events occurring at the different valves are heard best over the corresponding areas.

The second sound in the pulmonary area shows two components—the aortic and the pulmonary (A_2 and P_2). Normally, during inspiration the pulmonary component becomes delayed whereas the aortic component occurs slightly earlier and S_2 becomes split. In expiration, both the components merge and S_2 becomes single. Splitting of the second sound is called “fixed”, if it does not show a variation between inspiration and expiration. This happens in atrial septal defect and right ventricular failure. In atrial septal defect the phasic changes in venous return during respiration are associated with reciprocal changes in the volume of left to right shunt. Inability to vary its stroke volume by the failing right ventricle accounts for the fixed splitting of S_2 in right ventricular failure. If the splitting of the second sound becomes narrow during inspiration, it is called *reversed split (paradoxical split)*. This occurs in aortic stenosis and left ventricular failure.

Gallops are diastolic events and appear to be related to filling of the ventricles. The ventricular diastolic gallop also known as third heart sound occur during the rapid filling phase. This is an early sign of ventricular

dysfunction, although it can occur physiologically in normal children and young adults. The atrial gallop also known as fourth heart sound occurs during the presystolic filling phase due to atrial systole. It is abolished in atrial fibrillation.

Murmurs: These are produced by turbulence of blood flow at or near the valves or through abnormal communications. If a murmur occurs as a result of abnormally large amount of blood flowing through a normal valve or artery, this is termed flow *murmur* (previously known as functional murmurs). This disappears when the hemodynamic abnormality is corrected. On the other hand organic murmurs are produced by structural abnormality in the heart or blood vessels and these murmurs tend to persist. In addition, murmurs may occur without intrinsic structural or functional abnormalities in the heart valves and blood vessels. These are generally benign, without any hemodynamic abnormality. In addition to the location of the murmur several other characteristics help to identify its source. These are: (1) the timing, (2) duration, (3) character (high-pitched or low-pitched), (4) change with respiration and position of the patient (5) conduction, and (6) response to maneuvers like hand grip, Valsalva and squatting.

Extra-cardiac adventitious sounds are venous hum, bruit over arteries, pericardial rub and pleuropericardial rub.

Recording the blood pressure: The appropriate sized cuff for adults and children has to be used, otherwise the values will be altered. It is ideal to use mercury sphygmomanometers. If aneroid instruments are used, their accuracy should be verified periodically. Generally the blood pressure is recorded in one of the arms. If there is any abnormality in the blood pressure or if arterial occlusion in the arm is suspected, the blood pressure should be recorded in both arms and legs. Normally the systolic blood pressure recorded in both the arms does not vary more than 10-15 mm Hg. The systolic pressure in the lower limb is 20-30 mm higher than in the upper limb. Though the point of muffling of *Korotkoff's sounds* denotes the diastolic blood pressure, to achieve consistency in recording, the point of disappearance of these sounds can be accepted to represent the diastolic blood pressure for clinical purposes.

Special Investigations

Radiology: The size and shape of the heart can be assessed from chest radiographs. Posteroanterior views, lateral views and oblique views are used to assess abnormalities of the different chambers. Normally the cardiothoracic ratio is less than 50%. Enlargement of different chambers gives characteristic configuration in the X-ray. The contraction of the chambers can be seen

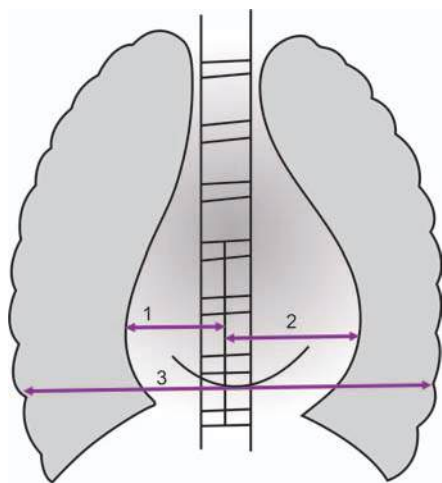


Fig. 115.4: Line drawing of chest X-ray
Note: Transverse diameter of the heart is 1 + 2
Cardiothoracic ratio (CTR) $\frac{1 + 2}{3}$

by fluoroscopy. Pulsation of the aorta and pulmonary artery can be observed. Pulmonary congestion, pulmonary oligemia and pulmonary edema can be diagnosed. Serially taken chest radiographs also help in assessing the progress of cardiac disease (Figs 115.3 to 115.5C). Chest radiographs taken in different views bring out the different chambers clearly.

Electrocardiography: The electrical changes that take place in the heart during different phases of the cardiac cycle are recorded in the electrocardiogram (ECG). The standard 12 lead ECG consists of three standard bipolar limb leads (L_1 , L_2 and L_3), three augmented unipolar limb leads (aVR, aVL and aVF) and six precordial unipolar leads (V_1 - V_6) (Fig. 115.6). When required, further additional leads such as right-sided chest leads, high anterior chest leads or left posterior leads are also taken. Normal ECG shows the P-wave which is caused by electrical activation of the atria, QRS which represents ventricular depolarization, and T-wave which is caused by ventricular repolarization. The amplitude of these waves, their configuration, their duration, and the time interval between various deflections (P-R, QRS and QT, P-P and R-R intervals) are all studied to derive diagnostic information (Fig. 115.7).

Clinical applications: Following are the clinical applications of electrocardiography:

1. determining the heart rate and rhythm;
2. to detect atrial or ventricular enlargement;
3. diagnosis of all arrhythmias and disorders of impulse production and conduction;
4. detection, localization, and semiquantitation of myocardial ischemia (reversible and irreversible);
5. diagnosis of myocardial diseases (myocarditis or cardiomyopathy);
6. diagnosis of pericardial diseases (pericarditis, effusion);

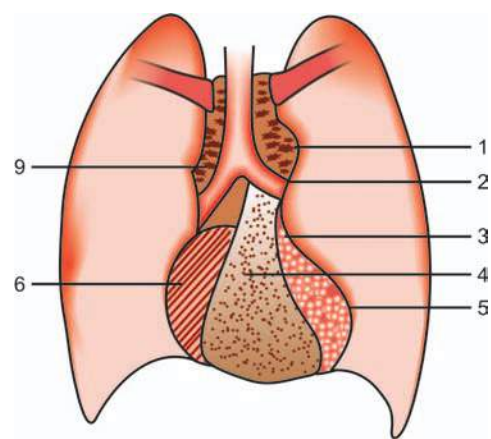


Fig. 115.5A: X-ray—PA view of the chest

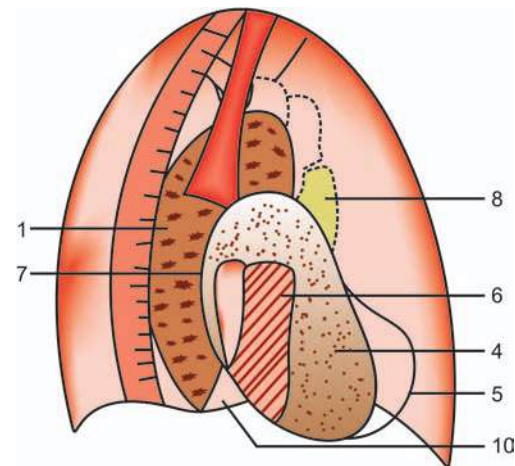


Fig. 115.5B: X-ray—right oblique view

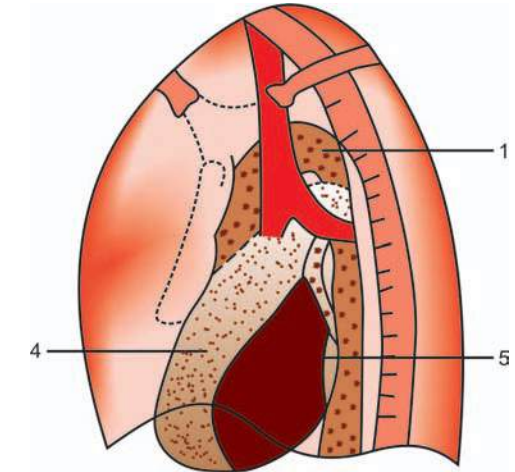


Fig. 115.5C: X-ray—left oblique view

Figs 115.5A to C

1. Aorta
2. Pulmonary artery behind left bronchus
3. Left atrial appendage
4. Right ventricle
5. Left ventricle
6. Right atrium
7. Left atrium
8. Pulmonary conus
9. Superior vena cava
10. Inferior vena cava

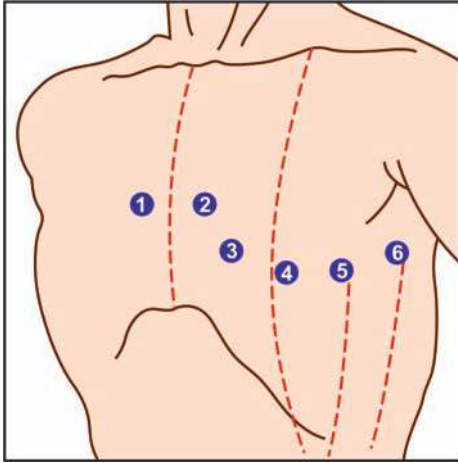


Fig. 115.6: Position of chest leads—V₁-V₆

7. monitor toxicity of drugs like digoxin; and other ingested toxins such as cerebra odollum
8. diagnosis of the cardiac involvement in metabolic diseases like myxedema, thyrotoxicosis and others
9. determining the cardiac effects of electrolyte disturbances, especially hyper- and hypokalemia.

The ECG has been employed in several varied clinical situations so that recording the ECG is a routine basal investigation to look for evidence of heart disease.

The following modifications have been made over the conventional ECG.

1. **Stress test:** Treadmill test is the most commonly used type of stress test. This can be used to assess the likelihood and extent of coronary artery disease, prognosis of coronary artery disease, functional capacity and effects of therapy. Stress test is positive for inducible ischemia when ECG shows ≥ 0.1 mV horizontal or down sloping ST depression or ≥ 0.15 mV slow upsloping ST depression or a ST segment elevation of ≥ 0.1 mV in a noninfarct territory. This is a highly reliable test.
2. **Holter monitoring:** ECG is recorded continuously for long periods on audio tapes in ambulant subjects. This is very useful for evaluation of arrhythmias and silent ischemia.
3. **His bundle electrography:** Electrical activity of the bundle of His may be recorded by an electrode catheter placed near the tricuspid valve under fluoroscopy. This technique known as His Bundle electrography permits division of the P-R interval into two subintervals, namely, the A-H interval (an approximation of A-V nodal conduction time) and H-V interval (representing conduction time within the His Purkinje system). Thus, more precise localisation

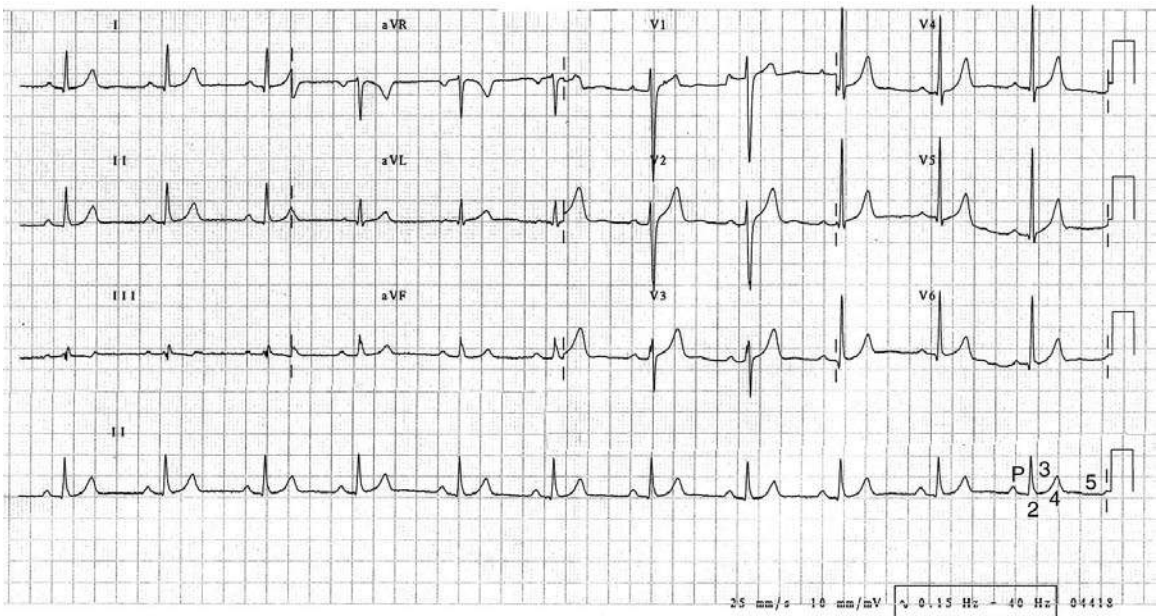


Fig. 115.7: Normal ECG. ECG shows sinus rhythm. Each QRS complex is preceded by a P wave. PR interval in this ECG is 0.16 sec. (Normal PR interval is upto 0.21 sec). QRS duration is also normal, i.e. 0.08 sec (Normal upto 0.1 sec). No ST segment of T wave changes

I, II, III, limb leads	
aVR, aVL, aVF augmented unipolar leads	
V ₁ -V ₆ unipolar chest leads	
2. QRS segment	5. Position of U wave
3. ST segment	
4. T wave	

of the site of atrioventricular block and distinction between supraventricular and ventricular beats become possible.

Signal Averaged ECG (or) High Resolution Electrocardiography

This technique is used to identify the different frequencies and voltage components that constitute the QRS complex. Late potentials (delayed low-voltage signals) detected by this technique serve as predictors for the development of ventricular arrhythmias especially in ischemic heart disease.

Echocardiography

In principle this method records the reflection of pulsed ultrasound from various parts of the heart studied in different directions. Ultrasound of 1-7 megahertz frequency is generally used. The earlier machines used time-motion mode display, but later versions permitted two-dimensional imaging. Color coding has also been introduced for specialised investigations. The echocardiogram can be visualized on a fluorescent screen, photographed or recorded on tapes to be examined on a video screen for future use. In the echocardiogram the anterior right ventricular wall, both sides of the interventricular septum, mitral valve, posterior left ventricular wall, pericardium, walls of the aorta, aortic valve, pulmonary artery and valve, pulmonary veins, posterior left atrial wall, both atria, and the tricuspid valve can be identified distinctly. Incorporation of Doppler echography in echocardiography helps to assess abnormal flow of blood as occurring in septal defects and valvular incompetence. Being a simple easily available and non-invasive procedure the use of echocardiography has become an integral part of cardiological studies. With its use, invasive investigations such as catheterization and angiocardiology can be avoided in many cases (Figs 115.8 to 115.9B).

One of the drawbacks of conventional transthoracic echocardiography has been the difficulty to get proper images of the posterior aspect of the heart and finer details such as valvular vegetations and intra-atrial thrombi. This has been overcome by the introduction of *trans-esophageal echocardiography* in which the probe is introduced into the esophagus and images are recorded. Better visualization of the intracardiac structures is possible. Coupling this method with *Doppler imaging and colour-coding* of the images helps to assess the dynamics of blood flow and its abnormalities. Another application is the intraoperative use of this method to get continuous recording of cardiac events during procedures such as mitral valve reconstructive surgery.

Stress echocardiography is a very useful technique in the evaluation of coronary artery disease and valvular heart disease. This is done by evaluating the cardiac chambers by echocardiography at rest and during and

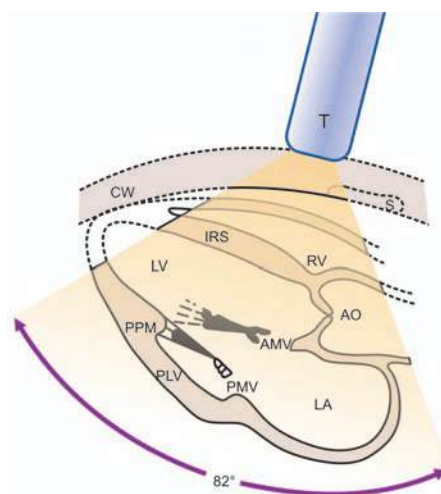


Fig. 115.8: Schematic drawing showing a sagittal section of the heart through the long axis of the left ventricle. The path of the ultrasound beam emitted by the transducer (T) placed over the chest wall, as it is swept through an arc of 82° is illustrated. This diagram serves as a reference for the normal cardiac anatomy as visualized by ultrasound in the time motion mode display (M-mode) schematically illustrated in Figure 115.9B along with simultaneous ECG record.

T—Transducer; CW—Chest wall; S—Sternum; RV—Right ventricle; IVS—Interventricular septum, RV—Right ventricular wall; AMV—Anterior leaflet of mitral valve; PMV—Posterior leaflet of mitral valve; LV—Left ventricle; PPM—Papillary muscle; PLV—Posterior left ventricular wall; AO—Aorta; LA—Left atrium

immediately after applying some forms of stress. Commonly used modalities of stress are exercise, atrial pacing and pharmacologic methods (dobutamine, adenosine).

Intravascular ultrasound uses crystals mounted on arterial catheter. This probe can be passed through small arteries like the coronary arteries. This technique is employed in the assessment of arterial lesions such as atherosclerosis and thrombus and utilized in the treatment of coronary artery disease (CAD) by angioplasty and stenting.

Uses of Echocardiography

- Assessment of cardiac function
- Diagnosis of valvular heart disease
- Diagnosis of congenital heart disease
- Evaluation of coronary artery disease
- Diagnosis of pericardial disease, cardiomyopathy and tumours.
- Demonstration of the vegetations of infective endocarditis.

From its original introduction, the ultrasound scanners and the techniques have undergone steady improvement in machine design, probe specifications and probe positioning. Whereas the early studies are conducted with the

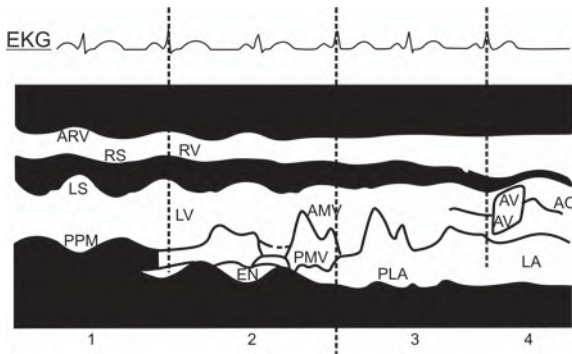


Fig. 115.9A: Schematic drawing—normal echocardiogram
PLA—Posterior left atrial wall Ao—Aorta
AV—Aortic valve LA—Left atrium
EKG—Electrocardiogram

1. At papillary muscle level,
2. At the level of chordae tendinae, 3 and 4-further up. The ventricular internal dimensions and ventricular and septal thickness are measured at this level. Slight superior angulation of the transducer brings into view the anterior and posterior leaflets of the mitral valve. The normal leaflet motion pattern has a characteristic appearance of M and W for the anterior and posterior leaflets respectively. The normal aortic valve (AV) echogram has a box like configuration in systole. The left atrium is immediately posterior to the aorta.

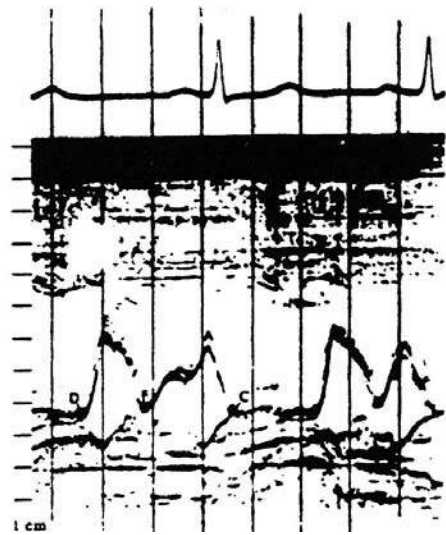


Fig. 115.9B: Normal echocardiogram

Note the pattern of motion of the anterior and posterior mitral leaflets. Anterior leaflet motion pattern resembles the letter 'M' (DEFAC) point D marks the beginning of mitral valve opening it is completed at E. F denotes mid-diastolic closure. A denotes valvular opening at the beginning of atrial systole. Point C marks the beginning of systole. Motion pattern of posterior leaflet resembles the letter 'W' (mirror image of M).

transducer probe positioned outside the body, at present probes which can be attached to endoscopes and arterial or venous percutaneous catheters are available. These permit real time events inside the chambers and vascular lumen.

In many conditions such as valvular lesions, congenital heart disease, cardiac failure, ischemic heart disease, cardiomyopathy, pericardial disease and others accurate measurement of the structural and hemodynamic abnormalities is possible. Being non-invasive and repeatable, the echocardiogram has established its place in preoperative and postoperative assessment. In the follow up of patients with diseases of the cardiac muscle, this investigation is invaluable.

Isotopic investigations: Availability of radionuclides such as ^{99m}Tc (half-life 6 h) and ^{201}Tl (half-life 73 h) and sestamibi has enabled isotopic studies to assess blood flow and myocardial perfusion. Isotopic studies are also non-invasive.

Flow studies: ^{99m}Tc compounds are used for dynamic flow studies. These include: (i) delineation of the various cardiac chambers during systole and diastole (*nuclear angiocardigraphy*); (ii) calculation of ejection fraction; (iii) evaluation of congenital cyanotic heart disease; (iv) demonstration of akinetic segments of the ventricular wall following myocardial infarction; and (v) quantitation of intracardiac shunts.

Myocardial scanning: For this purpose ^{201}Tl which is concentrated in the myocardium is employed. This isotope behaves similar to potassium and its concentration in the myocardium depends on the myocardial blood flow. Areas of diminished perfusion can be detected as "cold" areas in ischemic heart disease. Appearance of cold areas during exercise is an indication of stress induced ischemia. Sestamibi is another isotope used for myocardial imaging. It is not taken up by necrotic myocardium. Isotope studies are employed for the following conditions.

- i. for assessing myocardial perfusion during rest and exercise;
- ii. studying the configuration of the myocardium, especially hypertrophy;
- iii. to detect the presence of myocardial infarct, its extent, and viability of the ischemic myocardium
- iv. for the evaluation of post-bypass surgery patients.
- v. for the identification of hibernating myocardium.
- vi. for the assessment of the prognosis in myocardial infarction.

MRI in Clinical Cardiology

Magnetic resonance imaging (MRI) has established its place in cardiology, over the past ten years. It is a useful investigation in various situations for the assessment of (1) cardiac structure (2) function (3) perfusion and

(4) myocardial viability. MRI is accurate and reproducible. Images of cardiac chambers and the great vessels help to assess morphological and functional changes in these locations. MRI is being increasingly used for imaging the coronary circulation, myocardial perfusion, study of intravascular plaques and for the delineation of heart valves. Hypertrophic cardiomyopathy and cardiac tumours are well demonstrated. Next to skiagram of the chest, MRI is the investigation of choice in the study of pericardial lesions. More sophisticated and dedicated machines are being introduced into this branch of investigative cardiology. Cardiac MRI studies show promise as non-invasive investigative tools to assess coronary artery occlusions. Unlike the contrast agents used in conventional angiocardiology, gadolinium used in MRI is not nephrotoxic.

Single photon emission computed tomography (SPECT) and positron emission tomography (PET) can be employed to study the myocardium in greater detail. These studies are available in India only in a few centers, since the equipment is expensive. Studies employing these methods help to identify potentially salvageable myocardium in ischemic heart disease. Using appropriate radiolabelled isotopes the metabolic activity of the myocardium can be assessed.

Cardiac catheterization: The right and left sides of the heart can be catheterized, using special catheters. Pressures in the different chambers can be recorded during catheterization and this helps in identifying anatomical abnormalities.

Blood can be sampled from different locations for estimation of oxygen (*oximetry*) and this helps to quantitate left-to-right or right-to-left shunts. Cardiac output and cardiac index can be calculated by oximetric studies in the aortic and pulmonary arterial blood. Normal cardiac index is 2.8-4.2 liters/min/m². Reduction below 2.4 indicates abnormality. Pressure tracing of the ventricles enables detection of obstruction to ventricular filling, outflow obstruction, intactness of interventricular septum, and the presence of large septal defects, and also permits the calculation of the *systolic ejection time*. Systolic ejection time is the interval between the end of isometric contraction and the end of ejection.

A suitable catheter can be passed into the right side of the heart and manipulated into the pulmonary artery and advanced till it gets impacted in a small branch. Measurement of the pressure at this site (*pulmonary wedge pressure*) reflects the left atrial pressure.

Upper limit of normal pulmonary artery pressure is 30/14 mm Hg. Rise in right ventricular end diastolic pressure above 8 mm Hg and left ventricular end diastolic pressure above 12 mm Hg is indicative of ventricular failure or restriction to ventricular filling due to pericardial disease or myocardial fibrosis.

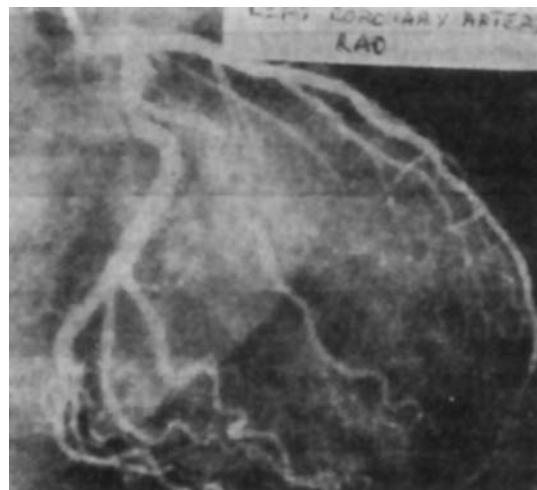


Fig. 115.10: Normal coronary angiogram showing the various branches filling normally

Selective angiocardiology is the imaging of the different cardiac chambers after injecting contrast material into them. This method helps to visualize the cardiac chambers and sequential flow of the dye during the different phases of the cardiac cycle. Angiocardiology clearly demonstrates the anatomical and functional abnormalities in the heart. Mitral incompetence, mitral stenosis, aortic stenosis, aortic incompetence, tricuspid and pulmonary valve lesions, cardiac aneurysms, and complex congenital malformations can be fully visualized.

Coronary angiography is the method of demonstrating the right and left coronary arteries after selective catheterization using special catheters (Fig. 115.10).

Angiocardigraphic studies provide invaluable information in several disorders where other non-invasive methods fail. Therefore, angiocardiology has to be resorted to particularly in the preoperative assessment of some of the cardiac lesions.

Interventional Cardiology—Catheter Laboratory (CATH lab) Procedures

This term is used for the therapeutic procedures done by an interventional cardiologist in a catheter laboratory. This specialty has expanded rapidly during the last two decades. The procedures include primary angioplasty for acute myocardial infarction, coronary angioplasty and stent for CAD, renal angioplasties, peripheral angioplasties, closure of PDA by coil or device, device closure of ASD and VSD and balloon valvuloplasties for mitral stenosis, pulmonary valve stenosis and aortic stenosis.

Coronary angioplasty is widely used for management of single vessel disease and 2 vessel disease. For three vessel disease with normal LV function and suitable lesions for angioplasty the results are comparable to bypass surgery except for the greater need for repeat revascularization. However complex 3 vessel disease,

especially in diabetics is preferably managed by bypass surgery.

Balloon valvuloplasty is employed for definitive treatment of mitral stenosis and pulmonary valve stenosis. Balloon pulmonary valvuloplasty is the treatment of choice for pulmonary valve stenosis. Mitral stenosis with suitable valve morphology treated by balloon mitral valvuloplasty has excellent short-term and long-term outcome which is comparable to open surgical commissurotomy. Balloon aortic valvuloplasty still remains largely as a palliative measure.

Routine stenting during angioplasty helps to keep vascular patency over long period.

Conventional stents have given place to drug eluting stents. These stents are coated with drugs such as

tacrolimus, paclitaxel and others. The initial studies over a few years have shown that the rate of re-occlusion of the coronary arteries is lower and the patency of the lumen is maintained for longer periods. Drug eluting stents are considerably more expensive than the plain stents.

Digital subtraction angiography: In this technique the bony cage and soft tissue shadows are eliminated by computer-aided subtraction which makes the vascular anatomy stand out prominently. Enhancement of vascular image obtained by elimination of other shadows enables one to visualize lesions in the major arteries (cerebral, thoracic, visceral or peripheral) by venous injection of small doses of contrast media, thereby avoiding arterial puncture.

116

Heart Failure (Syn: Cardiac Failure)

C.G. Bahuleyan

Chapter Summary

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General Considerations

Definition: Heart failure is a pathophysiological state in which the heart is unable to pump at a rate commensurate with the requirement of the metabolizing tissues (systolic failure) or can do so only with elevated filling pressures (diastolic failure).

Heart failure manifests as a complex clinical syndrome characterized by circulatory congestion, impaired systolic function, impaired diastolic function or both, and progressive activation of the neuroendocrine system. ***In all forms of cardiac disease, if the abnormality is allowed to progress without treatment, heart failure sets in, invariably after varying periods of time.***

Though there have been significant advances in the treatment and prevention of heart failure, it is still

increasing in incidence and prevalence. Approximately 1.5-2% of the population has some form of cardiac failure and the prevalence increases to 6-10% in patients >65 years old.

Heart failure should be distinguished from circulatory failure, in which an abnormality of any of the components of circulation—the heart, the blood volume, concentration of oxygenated hemoglobin in the arterial blood or vascular bed is responsible for the deficiency in cardiac output.

PATHOPHYSIOLOGY

During the past 4 decades there has been a progressive evolution in the concept and understanding of heart failure (Table 116.1).

In 1940-60s, heart failure was considered as a 'cardio-renal' disorder where it was thought that impaired ventricular function led to reduced cardiac output, and renal perfusion leading on to salt and water retention. Later on in 1960-80s, heart failure was considered as 'cardio-circulatory' disorders where the 'hemodynamic abnormality' was given more emphasis. Now it is known that heart failure cannot be simply defined in

TABLE 116.1

Pathophysiology of CHF

a. Hemodynamic alterations
1. Increased EDP; EDV
2. Reduced cardiac output
b. Neurohumoral alterations
1. Alterations in autonomic nervous system
a. Increased norepinephrine
b. Altered baroreceptor control
2. Alterations in beta adrenergic receptors
a. Down regulation of beta receptors
b. Increased beta-adrenergic receptor kinase
3. Alterations in renin-angiotensin system
a. Increased renin
b. Increased angiotensin II
c. Increased aldosterone
d. Down regulation of angiotensin I and II receptors
4. Others
a. Elevated atrial and brain natriuretic peptide (ANP)
b. Elevated endothelin
c. Role of cytokines
c. Cellular and molecular alterations
1. Calcium kinetics
a. Reduced Ca++ cycling
b. Reduced SERCA 2 enzyme level
c. Reduction in calcium release channels
2. Changes in contractile apparatus
a. Re-expression of genes
3. Free radicals and apoptosis

hemodynamic terms and the role of neurohumoral, cellular and molecular mechanisms are all important.

A. Hemodynamic Alterations

In the early stages of heart failure (HF), the hemodynamic abnormalities occur only during exercise. As the HF progresses they occur at rest as well. Reduction in cardiac output is associated with a rise in end-diastolic pressures (EDP) in the ventricle and increased venous pressure. Increase in end-diastolic pressure is accompanied by increase in end-diastolic volume (EDV) generally. The end-diastolic pressure and volume determine the extent to which myocardial fibers are stretched prior to acute active contraction, this is termed **preload**. The load the ventricle has to move once it starts contracting is called **afterload**. As the preload and afterload increase venous congestion develops behind the failing chamber to manifest as pulmonary or systemic venous congestion in left sided and right sided heart failure respectively. Reduction in cardiac output leads to reduction in tissue perfusion. Blood flow to the vital organs like brain and heart is maintained by diverting the flow from less vital organs.

B. Neurohumoral Alterations

Consequent to the two principal hemodynamic alterations viz reduced cardiac output and atrial hypertension—a complex series of neurohumoral alterations occurs. In

early stages, these alterations act as compensatory mechanisms, but later on they lead to undesirable effects and injury.

1. Alterations in Autonomic Nervous System

These include increased sympathetic activity and elevation of plasma norepinephrine (NE) levels. Extent of elevation of plasma NE correlates directly with the severity of heart failure. Augmented, sympathetic activity and elevated NE causes vasoconstriction and arrhythmias and may cause sudden cardiac heart death. The increase in adrenergic activity is mainly due to altered control of adrenergic outflow from the CNS.

2. Alterations in the Beta-adrenergic Receptor Pathway

Increased levels of local NE concentration cause down regulation of beta-I adrenergic receptors in the ventricles. In addition there is increase in beta-adrenergic receptor kinase (BARK) enzyme level, which leads to uncoupling of beta receptors. Down regulation of beta-receptors can be reversed by beta blockers.

3. Alteration in Renin Angiotensin System (RAS)

Increased adrenergic activity stimulates the $\beta 1$ receptor in juxtaglomerular apparatus of the kidneys. Also, decreased blood flow to kidney activates the baro-receptors. Both these lead to release of renin. Renin acts on *angiotensinogen* to form *Angiotensin I* which is acted upon by angiotensin converting enzyme (ACE) to form *angiotensin II*. Angiotensin II is a potent vasoconstrictor and leads to elevated systemic vascular resistance, which in turn leads to a vicious cycle. Angiotensin II also stimulates production of aldosterone and NE.

Only 1-10% of ACE is found in circulation. 90-99% is present in tissues such as vasculature, heart and kidneys. Angiotensin has 2 receptor subtypes AT1 and AT2. In patients with severe heart failure there occurs a down regulation of these receptors. Angiotensin acts on these receptors and causes cell growth and altered gene expression.

4. Role of Arginine Vasopressin (AVP)

In CHF, circulating AVP is elevated. This leads to salt and water retention and systemic vasoconstriction.

5. Role of Natriuretic Peptides

3 Natriuretic peptides—atrial natriuretic peptide (ANP); brain natriuretic peptide (BNP) and C-natriuretic peptide (CNP) have been identified. ANP is stored mainly in the right atrium. BNP is stored mainly in the ventricles. They cause vasodilatation and natriuresis and diuresis and counteracts the effects of adrenergic, RAS and AVP

systems. CNP is located primarily in the vasculature and it is produced by vascular endothelium as a response to shear stress, primarily in the vasculature. In addition, these peptides inhibit myocytes and vascular smooth muscle hypertrophy. They improve functions of the failing myocardium. Circulating levels of ANP and BNP are increased in heart failure and they confer beneficial effects. Levels of BNP and ANP have been utilized as diagnostic test in ventricular failure. Normal level is < 100 pg/mL. In CHF the levels go above 675 ± 450 pg/mL. This estimation supports the diagnosis of CHF in doubtful cases.

6. Role of Endothelin

It is a potent vasoconstrictor released by endothelial cells. 3 types of endothelins 1, 2 and 3; and 2 subtypes of receptors, A and B have been recognized in CHF. Circulating endothelin levels are increased.

7. Role of Cytokines

Cytokines implicated in the pathogenesis of CHF include tumour necrosis factor α , transforming growth factor β , peptide growth factors and interleukin-1 beta. They have crucial roles in mediating the changes in myocardial structure and function in CHF.

C. Cellular and Molecular Mechanisms

1. Role of Calcium

Calcium plays a central role in myocardial contraction and relaxation. In CHF, there is prolonged elevation of intracellular calcium during relaxation and calcium cycling is reduced by 50%. Calcium reuptake by sarcoplasmic reticulum is mediated by ATP-dependent enzyme Ca^{++} -ATPase (SERCA-2). SERCA 2 activity is inhibited by phospholamban. In CHF, SERCA 2 activity is reduced.

Calcium release channel (CRC) located on the sarcoplasmic reticulum (SR) mediates release of Ca^{++} from the SR into the myoplasm during systole. In CHF, MRNA level for CRC is decreased.

2. Changes in the Contractile Apparatus

There occurs a qualitative and quantitative change of the contractile proteins. Myosin ATPase activity is reduced in CHF. Also there occurs a re-expression of genes coding for fetal and neonatal isoforms of myosin, rather than adult isoforms. In addition, there is alteration in the regulatory protein-expression of troponin T. In normal myocardium 98% of the regulatory protein is troponin T. In CHF, there is a change to troponin T-2.

3. Role of Free Radicals and Apoptosis

In CHF, altered mitochondrial oxygen metabolism results in formation of free radicals, i.e. molecules with unpaired electrons. These molecules cause cell damage.

Apoptosis is programmed cell death. Free radicals produced by various mechanisms have been shown to result in apoptosis of cardiac myocytes in CHF.

4. Diastolic Heart Dysfunction and Failure (DHF)

Nearly 50% of patients with congestive heart failure have diastolic dysfunction – often referred to as diastolic heart failure. The LV function and ejection fraction may be normal. DHF is more common in older age groups, more in women. Hypertension is more common and IHD less common in them. Some show impairment of active ventricular relaxation and compliance of the ventricles. Ventricular diastolic pressures rise. This results in increase of pulmonary venous pressure. Stroke volume does not increase with exercise. When effort intolerance, dyspnea, venous congestion and pulmonary edema develop, it is termed diastolic heart failure.

Ref: A. Radfield MM. Understanding diastolic heart failure. N Eng J Med 2004;350:1930-1.

Forms of Heart Failure (HF) (Table 116.2)

1. Forward vs Backward HF

In backward failure hypothesis, when the ventricles fail to discharge the content, blood accumulates and pressure rises in the atria and venous systems emptying to it.

In forward failure hypothesis, manifestations of CHF are due to reduction in cardiac output. In most cases, both these mechanisms operate simultaneously.

2. Right Sided vs Left Sided Failure

In right sided failure, systolic output of right ventricle and/or right atrium falls. Common causes include pulmonary artery hypertension (PAH) in mitral stenosis, ASD and cor pulmonale; pericardial diseases, pulmonary stenosis, right sided cardiomyopathy, massive pulmonary embolism and tricuspid stenosis. This manifests as elevated right atrial pressure, elevated JVP, and systemic venous congestion leading to edema and hepatomegaly.

Left sided failure is caused by dysfunction of left ventricle and left atrium, chronic ischemic heart disease, systemic hypertension, and aortic and mitral valve disease. This manifests as dyspnea, orthopnea and paroxysmal nocturnal dyspnea. Persistent left heart failure gives rise to pulmonary hypertension which results in right heart failure as well.

3. Low Output vs High Output Failure

In the former, the cardiac output is reduced resulting in inadequate tissue perfusion, e.g. mitral stenosis, ischemic heart disease and hypertensive heart disease.

In the latter, cardiac output is above the normal range, but it falls from the original levels as heart failure sets in, e.g. thyrotoxicosis, anemia, beriberi.

TABLE 116.2

Causes of cardiac failure

1. Myocardial causes which reduce the contractile force of the myocardium	
a. Myocarditis	Infective (e.g. rheumatism, typhoid, Coxsackie infection) Toxins-diphtheria, scorpion stings, drugs like emetine, adriamycin Nutritional causes—beri beri Dyscollagenosis—lupus erythematosus Other miscellaneous causes—alcohol, diabetes myxedema
b. Coronary artery disease	Acute myocardial infarction Chronic ischemic myocardial damage
c. Cardiomyopathy	Primary and secondary
d. Infiltrations	Amyloidosis, hemochromatosis, leukemia, malignant deposits, iron
2. Structural abnormalities in the heart or great vessels arteriosclerotic which reduce the cardiac output	Valvular heart disease (rheumatic, syphilitic, and congenital) Infective endocarditis, traumatic lesions (injury or post-surgical) congenital heart diseases
3. Pericardial disease which leads to interference with diastolic filling of the ventricles especially the right ventricle	Pericardial effusion, constrictive pericarditis
4. Arrhythmias	
Tachycardias which lead to reduction in the diastolic interval, thereby reducing the end diastolic volume	Paroxysmal tachycardias, atrial flutter and fibrillation
Extreme bradycardia	Heart block in which the ventricular rate goes below 30/min.
5. Increased demand on cardiac output. Normal heart is able to cope up with even extremes of demand within physiological limits, since the reserve capacity is great. In the majority of pathological states increased demand is associated with impairment of cardiac function as well	Pregnancy, fever, thyrotoxicosis, severe exercise, arteriovenous fistula, chronic respiratory failure, hepatic failure
6. Cor pulmonale	Acute cor pulmonale as in pulmonary embolism or chronic cor pulmonale as in obstructive airway disease
7. Increased resistance to ventricular emptying	Systemic arterial hypertension leads to left ventricular failure, and pulmonary hypertension leads to right ventricular failure

4. Acute vs Chronic Heart Failure

In acute heart failure, there is insufficient time for compensatory mechanisms to become operative and hence clinical manifestations are marked, e.g. acute myocardial infarctions, tachyarrhythmias, acute pulmonary embolism.

In chronic heart failure, there is time for adaptive mechanisms to develop and hence patients are able to tolerate the reduction in cardiac output better.

5. Systolic vs Diastolic Heart Failure

When the abnormality is in systolic function leading to defect in ejection of blood, it is systolic heart failure whereas if the abnormality is in diastolic function leading to defect in ventricular filling, it is diastolic heart failure. More often both coexist, but in a third of the cases of heart failure, it may be purely diastolic.

Pathology: At autopsy the heart may be dilated in cases of chronic congestive cardiac failure. The underlying cardiac lesions may be evident. The lungs are heavy, congested, and edematous. In chronic cases the pulmonary

vessels show medial hypertrophy and intimal hyperplasia. Liver is enlarged, firm, and edematous. The central hepatic veins and sinusoids are congested. Cardiac cirrhosis is histologically characterised by centrilobular necrosis, atrophy, and extensive fibrosis.

The spleen may be enlarged and congested. Pancreas may show venous congestion. Intestines may reveal infarction and hemorrhagic necrosis. Kidneys and brain show chronic venous congestion.

Clinical Features

Symptoms: Most common symptom is dyspnea, which is more marked in left-sided heart disease. Orthopnea, paroxysmal nocturnal dyspnea and Cheyne-Stokes respiration are seen in left-sided heart failure.

Weakness, fatigue, and apathy are suggestive of low cardiac output states. Oliguria and nocturia may develop even before dependent edema manifests. Nocturia occurs in the early stages of heart failure. During daytime when the patient is ambulant cardiac function is impaired and fluid accumulates. At night, with recumbency edema fluid



Fig. 116.1: Cardiac cachexia

Note: Feature of cardiac failure and emaciation

is reabsorbed into the circulation, cardiac function improves with rest, and the excess fluid is eliminated.

Edema is the most prominent symptom in right-sided heart failure. Initially the edema is dependent, later it becomes generalized. In the early stages the edema readily pits on pressure but in long-standing cases the part becomes indurated and pigmented. Hepatic congestion manifests with upper abdominal pain and tender hepatomegaly. In long-standing congestive heart failure, weight loss and emaciation develop as a result of inadequate intake of food and wasting of tissues. This picture is termed “**cardiac cachexia**”. Alterations in the cytokine system, especially increase in levels of tumour necrosis factor, interferon gamma and interleukin III also play a part in the production of cardiac cachexia (Fig. 116.1).

Physical Examination

Pulse and blood pressure: The pulse becomes rapid as a result of compensatory adrenergic activity. *Pulsus alternans* is suggestive of left ventricular failure. The blood pressure is not generally affected in mild and moderately severe cases. But in severe heart failure the systolic pressure may fall due to reduction in cardiac output. The diastolic pressure is maintained by increase in the peripheral resistance.

Engorgement of the jugular vein: This is seen characteristically in right-sided and combined heart failure. Abnormality of the hepatojugular reflux can be demonstrated even before the jugular venous pressure is elevated.

Examination of the precordium: In the majority of cases the heart is dilated, though in many cases (e.g. mitral

stenosis, acute myocardial infarction, myocarditis, and constrictive pericarditis) it may not be so. Evidence of the underlying heart disease may be found. In left ventricular failure a protodiastolic gallop (S_3) may be heard over the apex beat, and it is better heard during expiration. In right ventricular failure S_3 gallop is heard over the lower left sternal border and it is better heard during inspiration. Rise in pulmonary arterial pressure gives rise to accentuation of the pulmonary second sound. Dilatation of the ventricle gives rise to valvular incompetence. Functional pansystolic murmurs arising from the mitral or tricuspid valves may be audible, which disappear when the heart size returns to normal.

Abdomen: The liver is enlarged, soft and tender and this may be evident even before overt edema manifests. Hepatic enlargement persists for varying periods after edema clears up with treatment, but with intensive therapy it recedes completely. Mild jaundice and impairment of hepatic function may occur. In long-standing right-sided heart failure with **cardiac cirrhosis**, the liver is firm and nontender. It does not recede with treatment at this stage. Mild to moderate splenomegaly occurs in some cases initially due to passive venous congestion, later the organ may become fibrotic. Significant splenomegaly should suggest the possibility of infective endocarditis. Ascites may develop as a result of passive venous congestion. Prominent ascites occurs in organic tricuspid valve disease, constrictive pericarditis, and right ventricular endomyocardial fibrosis (Fig. 116.2).

Lungs: Physical signs in the lungs are more pronounced in left-sided heart failure. These are the presence of rales over the infrascapular regions, bronchospasm, uni- or



Fig. 116.2: Female 35 cardiac cirrhosis

Note: Cachexia and prominent abdomen—arrow

bilateral hydrothorax, frequent respiratory infections (pneumonia, bronchopneumonia or bronchitis) and pulmonary infarcts.

DIAGNOSIS (TABLE 116.3)

TABLE 116.3
Framingham criteria for diagnosis of congestive heart failure (CHF)
Major criteria
1. Paroxysmal nocturnal dyspnea
2. Neck veins distension
3. Rales (crackles) over the lower portions of the lung
4. Cardiomegaly
5. Acute pulmonary edema
6. S3 gallop
7. Increased venous pressure > 16 mm Hg
8. Circulation time >25 sec
9. Hepatojugular reflux
Minor criteria
1. Ankle edema
2. Night cough
3. Dyspnea on exertion
4. Hepatomegaly
5. Pleural effusion
6. Decrease of vital capacity exceeding 1/3
7. Tachycardia > 120/mt
Major or minor criteria
1. Weight loss > 4.5 kg in 5 days in response to treatment.
2. Major +2 minor criteria if present concurrently establishes the diagnosis of CHF

Note: Framingham is a township in the USA where a cohort of persons have been followed up meticulously over a long period of time and several biological parameters have been recorded continuously. This study has become a classic prospective study, for several disorders, especially for cardiovascular disorders. The follow up and observation are still continuing.

Investigations

Based on the American College of Cardiology/American Heart Association Task Force Guidelines.

Class I: Investigations (usually indicated and always acceptable)

- 1. Blood counts—helpful to exclude infections
- 2. Urinalysis—proteinuria may occur due to renal congestion
- 3. Blood biochemistry:
 - i. Serum Na⁺, K⁺. In severe CHF, dilutional hyponatremia occurs. Diuretics may cause hypokalemia.
 - ii. Blood urea nitrogen and creatinine are moderately elevated. Severe elevation indicates reduction in renal blood flow.



Fig. 116.3: Acute aortic regurgitation with pulmonary edema
Note: Cardiomegaly with left ventricular contour, filled up pulmonary artery segment, enlarged left atrium and “bat-wing” type of pulmonary opacity

- iii. Blood glucose, phosphorus, magnesium, calcium and albumin levels are helpful in etiological diagnosis.
- iv. TSH levels help to point to thyroid function.
- 4. ECG: Though not directly diagnostic of CHF, underlying diseases like ischemia, ventricular hypertrophy, arrhythmias and conduction defects can be diagnosed.
- 5. X-ray chest: This may show cardiomegaly, and features of pulmonary venous or arterial hypertension. Acute pulmonary edema gives characteristic butterfly-shaped opacity extending on both sides from the hilum. A normal chest radiograph does not rule out systolic or diastolic dysfunction (Fig. 116.3).
- 6. Echo-Doppler evaluation: This is very useful in evaluating both RV and LV functions and identifying causes like ischemic heart disease, valvular abnormalities, ventricular hypertrophy, congenital heart disease, infiltrative myocardial and pericardial diseases and thrombi. Quantitative measurement of systolic function like ejection fraction, fractional shortening, stroke volume, cardiac output and rate of changes of ventricular pressure (dp/dt) can be obtained with accuracy.

Doppler echocardiography is the corner stone for evaluation of diastolic heart failure. Measurements like isovolumic relaxation time (IVRT), mitral inflow pattern, deceleration time; and pulmonary and hepatic venous flow patterns are very helpful in the diagnosis and quantification of diastolic dysfunction.
- 7. Non-invasive stress testing (treadmill test; stress echocardiography and nuclear perfusion studies): These tests can detect ischemia in patients with and without angina, but with a high probability of coronary artery

disease who could be candidates for revascularization and in patients with previous coronary artery disease.

8. **Assessment of myocardial viability:** In patients with ischemic heart disease it is necessary to determine the amount of viable myocardium which is the important determinant for assessing prognosis and formulating therapy. This can be done using dobutamine or dipyridamole stress echocardiography, myocardial contrast echocardiography, nuclear imaging using thallium or sestamibi and positron emission tomography.
9. **Cardiac catheterization and coronary angiography:** This is indicated in patients with angina or large areas of ischemic viable myocardium and those at risk of coronary artery disease who require surgical coronary revascularization and those who have to undergo surgery for noncardiac conditions.

Right and left heart catheterization can determine the cardiac output, filling pressures, pulmonary artery pressure, pulmonary and systemic vascular resistance, shunts and parameters of diastolic function.

Class II: Investigation (acceptable but of uncertain efficacy)

These include:

1. **Serum iron and ferritin** to exclude iron overload states.
2. **Endomyocardial biopsy:** This is indicated in patients with clinical indication of myocarditis and systemic disease with possible cardiac involvement such as hemochromatosis, amyloidosis, sarcoidosis, subendocardial fibroelastosis and those who have received adriamycin chemotherapy.

Complications of Cardiac Failure

Cardiac failure on its own can produce many complications. These include:

1. Arrhythmias and sudden death
2. Venous thrombosis and pulmonary embolism
3. Intracardiac thrombi and related problems
4. Pulmonary infections due to venous congestion
5. Cardiac cirrhosis in long-standing cases
6. Renal failure.

Course and prognosis: The prognosis depends upon the type of heart failure and the nature of underlying disease. In the majority of cardiac disorders, cardiac failure is a major cause of death. Acute pulmonary edema occurring in myocardial infarction, systemic hypertension, mitral stenosis, and myocarditis may prove fatal, if emergency treatment is not instituted. In systemic hypertension, ischemic heart disease, aortic valvular disease and chronic cor pulmonale, onset of cardiac failure marks a steady downhill course and the majority die within two years, if not properly managed. On the other hand, in mitral stenosis, tricuspid valve disease, pericardial diseases and right ventricular endomyocardial fibrosis, chronic right-

sided heart failure may become established and these cases progress to cardiac cirrhosis with ascites, or **cardiac cachexia**. They show waxing and waning of cardiac function from time to time (Fig. 116.1).

In the Framingham heart study, the median survival was 3.2 years. The risk for death in mild CHF is 5-10% annually which increases to levels as high as 30-40% annually in patients with advanced CHF (NYHA class II and IV). Many factors affect the prognosis adversely (Table 116.4).

TABLE 116.4

Poor prognosticators in CHF
1. Diabetes mellitus
2. Hypertension
3. Tobacco use
4. ECG abnormalities—left ventricular conduction abnormalities
5. Ejection fraction < 25%
6. Peak exercise capacity < 14 mL/kg/mt of oxygen consumption
7. Pulmonary capillary wedge pressure >18 mm Hg
8. Poor socioeconomic factors
9. Age > 65 yrs
10. Male sex
11. Serum sodium < 135 mmol/L
12. Arrhythmias—esp. ventricular
13. Plasma norepinephrine levels >400 microgram/dL

Management

The principles of management include: (1) *restoration of cardiac function*; (2) *removal of the precipitating factors*, and (3) *elective correction of all remediable lesions after controlling the heart failure*.

Based on these guidelines, the broad components of management may be considered as under (Table 116.5):

Principles of management of HF

- A. General measures
- B. Pharmacologic therapy
- C. Devices
- D. Surgery
- E. Newer evolving therapies

TABLE 116.5

Management outline
1. Establish that patient has heart failure
2. Ascertain presenting features—acute pulmonary edema, exertional breathlessness/fatigue, edema
3. Determine etiology
4. Identify relevant concomitant disease
5. Assess severity
6. Estimate prognosis
7. Anticipate complications
8. Counsel patients and relatives
9. Choose appropriate management strategy
10. Monitor progress and manage accordingly

General Measures

1. **Rest:** During periods of acute decompensation bed rest is recommended. Since restriction of activity promotes physical deconditioning on prolonged immobilization, bed rest should not be prolonged indefinitely. Activities leading to exhaustion should not be undertaken. Aerobic training may improve symptoms and exercise capacity. Ambulation reduces the incidence of venous thrombosis and pulmonary embolism.
2. Tobacco smoking should be stopped forthwith and alcohol discontinued. There are reports that tobacco produces systemic effects also when chewed. Therefore, it is better to stop this form of tobacco as well.
3. Co-morbidities like hypertension, dyslipidemia and diabetes should be controlled.
4. Weight reduction is advised in obese patients.
5. Factors aggravating or precipitating CHF such as anemia and systemic infections should be corrected.
6. Salt restriction—sodium intake should be limited to < 2 g/day.
7. Fluid restriction—to 1-2 L/day is advisable in patients with dilutional hyponatremia.
8. Daily weight measurement helps to detect early occurrence of fluid retention.
9. Regular follow-up to monitor progress.
10. The patient and his family members should be informed regarding the disease, treatment and prognosis in order to enlist their cooperation.
11. Specific interventions for treatable causes, e.g. revascularization in patients with ischemic heart disease.

Pharmacologic Therapy (Table 116.6)

TABLE 116.6

Drugs used in treatment of CHF

Indicated and acceptable drugs

1. ACE inhibitors
2. Digoxin
3. Diuretics
4. Beta blockers
5. Anticoagulants
6. Hydralazine and isosorbide dinitrate

Acceptable; as alternate drugs or add- on drugs

1. Angiotensin receptor blockers
2. Aldosterone antagonists
3. Calcium antagonists
4. Antiarrhythmics
5. Positive inotropes

1. ACE INHIBITORS (ACEI)

ACEI have shown definite benefit in all classes of CHF, due to their actions on the heart as well as vasodilatory effect on blood vessels.

Indication

All patients with heart failure and systolic dysfunction benefit from ACEI; and these are indicated, unless otherwise contraindicated.

Mechanism of Action

ACE inhibitors act by reducing the formation of angiotensin II. In addition they block kininase II, which is responsible for degradation of kinin, thereby augmenting effects of kinins. By these actions ACEI suppress the neurohumoral mechanisms, reduce the afterload and improve the hemodynamic parameters such as cardiac output.

Drugs: The ACE inhibitors (ACEI) approved for the CHF treatment include captopril, enalapril, lisinopril, quinapril, fosinopril and ramipril.

Adverse Effects

- i. **Hypotension:** Patients with hyponatremia or on diuretics experience hypotension more frequently. This can be avoided by correcting hyponatremia, decreasing the dose and frequency of diuretics, and by initiating ACEI therapy with smaller doses.
- ii. **Renal failure:** This is seen more in patients with concurrent use of diuretics, hyponatremia and in NYHA class 4 patients. Renal failure has been reported in 5-15% of patients.
- iii. **Hyperkalemia:** This can be severe enough to cause cardiac arrhythmias. Patients at risk include those taking potassium supplements, potassium sparing diuretics or those having renal failure.
- iv. **Cough:** This is characteristically a non-productive and irritating cough which can be very distressing. It is seen in 5-15% of patients and this is the most common reason for withdrawing ACEI.
- v. **Angioedema:** This is seen in 1% of patients and this can be life-threatening at times.

Contraindications to ACEI

1. Hypotension; SBP < 80 mm Hg
2. Serum creatinine > 3 mg/dL
3. Bilateral renal artery stenosis
4. Hyperkalemia (K^+ > 5.5 mmol/L)
5. History of angioedema

Benefits of ACEI

Alleviation of symptoms

1. Improves ejection fraction
2. Improves NYHA class
3. Decreases need for hospitalisation
4. Reduces mortality

2. ANGIOTENSIN RECEPTOR BLOCKERS (ARBs)

These drugs include losartan, valsartan, irbesartan, candesartan and eprosartan. These are as effective as and others. They are not substitutes for ACEI in patients who are tolerating ACEI. They are useful in patients who are intolerant to ACEI, due to disturbing cough or angioedema. Like ACEI they can also cause hypotension, worsen renal failure and cause hyperkalemia. At present there is no indication to replace ACEI with these drugs in patients well controlled by the former. ACEIs and ARBs can be combined for better results in resistant cases.

3. DIURETICS

Diuretics inhibit the reabsorption of sodium and chloride at specific sites in the renal tubules and thereby prevent sodium retention. Commonly used agents include furosemide, torsemide and bumetanide which act at the loop of Henle (loop diuretics) and thiazides, metolazone and potassium sparing agents which act at the distal tubule. Loop diuretics are more powerful. They increase sodium excretion by 20-25% whereas thiazides increase sodium excretion only by 5-10% in moderately impaired renal function.

Indications

Diuretics should be prescribed for all patients with symptoms of CHF who have fluid retention. Goal of diuretic therapy is to eliminate symptoms and signs of fluid retention. Diuretics produce symptomatic benefit more rapidly than any other drug. Appropriate use of diuretics is complementary for the successes of other drugs. Under-dosing of diuretics may lead to fluid retention, and decrease the efficacy of ACEI. Overdosing can lead on to volume depletion, and increase the risk of hypotension and renal failure with ACEI.

Risks of Diuretic Therapy

1. **Electrolyte depletion:** Hypokalemia and hypomagnesemia can occur which may cause serious arrhythmias particularly those caused by digitalis therapy. Concomitant administration of ACEI or combination with potassium sparing agents such as spironolactone can prevent potassium depletion.
2. **Neurohumoral activation:** Diuretics increase the activation of endogenous neurohumoral systems particularly renin angiotensin system. In the long-term this can increase the risk of disease progression. Hence, neurohumoral antagonists are combined.
3. **Hypotension and azotemia:** Excessive use of diuretics can cause hypotension and azotemia. Other problems include allergic rashes and damage to the auditory nerves.

Dose: Therapy is initiated with low doses such as 20-40 mg furosemide/day. The dose is increased till the symptoms or signs of fluid retention are abolished. The dose is 20-120 mg per day. Wherever possible the drug is given orally. The action starts within 2 hours and lasts for 6-8 hours or more. In emergencies such as acute pulmonary edema furosemide is given IV as slow injection not exceeding 4 mg/minute, to a dose of 40 mg, increased if necessary upto 120 mg. Action starts within 15-30 minutes. Other diuretics such as thiazides and potassium sparing diuretics such as spironolactone or amiloride can be given as per indications, once the emergency is tided over. Some patients develop diuretic resistance, which can be overcome by use of diuretic combinations or by using IV diuretics.

NSAIDs can inhibit the therapeutic effect of diuretics and may precipitate the development of azotemia.

Benefits of Diuretics

1. Alleviate symptoms and signs of CHF
2. Improve cardiac function and NYHA class
3. Improves effort tolerance

4. BETA ADRENERGIC BLOCKERS

Beta adrenergic blockers have shown definite beneficial role in the management of CHF, since adrenergic overactivity plays a role in the pathogenesis of CHF.

Indications

1. All patients with class II or III, CHF unless otherwise contraindicated benefit by beta blockers.
2. Recent data has shown definite benefit in class IV patients also.

Mechanism of Action

The effects on sympathetic nervous system helps to prevent progression of CHF. Risk of fatal arrhythmia is reduced. Ventricular volumes and peripheral vasoconstriction are reduced. Cardiac hypertrophy and apoptosis of cardiac muscle are reduced.

Initiation and Maintenance

Beta blockers that have been found most beneficial in CHF include carvedilol, metoprolol, bisoprolol and bucindolol. Treatment is initiated with small doses such as carvedilol 3.125 mg twice daily; bisoprolol 1.25 mg once daily or metoprolol sustained release tablet 12.5 mg once daily. The dose is increased every 2-4 weeks till the target dose is achieved. In clinical trials optimal dose of carvedilol was 50-100 mg/day and that of metoprolol was up to 200 mg/day.

Contraindications include

- Bronchospasm, asthma
- Symptomatic bradycardia with heart rate below 60/minute.
- Higher grades of blocks in patients who have no implanted pacemakers.
- Patients on IV inotropic support
- Acutely ill patients

Benefits of Beta Blockers

1. Reduction in mortality, especially by retarding progression of CHF and abolition of fatal arrhythmias.
 2. Reduces symptoms
 3. Retards progression of CHF
 4. Improves NYHA class
 5. Reduces the risks of hospitalization
 6. Improves ejection fraction.
- Beta blockers produce additive effects with ACEI.

Risks of treatment with beta blockers include

- Hypotension
- Fluid retention and worsening of CHF
- Bradycardia and heart blocks

5. DIGOXIN

This is the most commonly used digitalis glycoside and the most time-honoured drug used in treatment of CHF. William Withering (British) published his treatise on the use of foxglove (*digitalis purpurea*) in 1785.

Indications

It is indicated in patients with congestive heart failure and atrial fibrillation with fast ventricular rate. It is also indicated in patients who continue to be symptomatic despite treatment with ACEI or beta blockers.

Mechanism of Action

It inhibits Na^+ , K^+ -ATPase enzyme in the myocytes and increases the contractility. Digoxin also decreases the sympathetic outflow from CNS. Thus, it acts both as a positive inotropic agent and neurohumoral attenuator.

Clinical Effects

It reduces the heart rate, relieves symptoms, enhances diuresis and brings about overall symptom benefit even though it does not affect the ultimate fatal outcome.

Adverse Effects

Digoxin is a double – edged weapon since the difference between the therapeutic and toxic levels is narrow.

- i. Arrhythmias—ventricular ectopics and bigeminy, paroxysmal atrial tachycardia with block;

ventricular tachycardia (VT) especially bidirectional VT and ventricular fibrillation. These arrhythmias may be fatal unless proper care is taken. The therapeutic margin of digoxin is narrow and therefore in selected cases estimation of serum digoxin levels should be done to guide therapy.

ii. Different grades of AV blocks

- b. GIT symptoms—anorexia, nausea, vomiting
- c. CNS symptoms—disorientation, visual disturbances

Optimal therapeutic level of digoxin in serum is 1-1.5 ng/mL especially women. Serum levels of > 2.0 ng/mL are toxic. Those at particular risk include elderly patients, with renal failure, hypokalemia, hypothyroidism and on concurrent medication with quinidine, verapamil, amiodarone, spironolactone and flecainide. Estimation of serum digoxin levels are helpful for optimal therapeutic benefit, without the risk of toxicity.

Dosage

Tablets are available in strengths of 0.0625 mg; 0.125 mg and 0.25 mg. Parenteral preparation containing 0.25 mg/mL is available for IV injection. Effect of oral dose of digoxin manifests in 30-45 minutes. **The drug is cumulative on repeated administration. The digitalising dose is the total dose of digoxin required to produce optimum therapeutic effect.** Following the full digitalising dose, maximal action is seen in 3-5 hours and some activity persists for 2-6 days. Rapid digitalisation is done by giving 0.5-0.75 mg initially followed by 0.25-0.5 mg at 48 hrs intervals. In the majority of patients the digitalising dose is 2-2.5 mg. In slow digitalisation 0.25 mg is given once or twice a day and the serum level reaches the desired maximum in 5-7 days. After initial digitalisation, the serum level is kept up by maintenance therapy given in a dose of 0.125-0.25 mg daily for 5-6 days a week.

Intravenous digoxin is only rarely used. Dose is 0.5-1 mg slowly over 3-5 minutes. After a loading dose the clinical effect starts within minutes, and the full effect occurs in 2-3 hours. A lower maintenance dose of digoxin is advised in patients above 70 years and those with impaired renal function. In appropriate situations it is life saving.

Contraindications to Digoxin

1. AV blocks—second degree, complete heart block and unstable AV blocks
2. Pure diastolic dysfunction
3. Wolff-Parkinson-White syndrome
4. Suspected digitoxicity
5. Hypertrophic obstructive cardiomyopathy

Treatment of digitoxicity: The remedial measures depend on the serum levels of the drug. Depending the severity

of toxicity and serum levels, the therapy has to be modified.

Principles of therapy include the following:

1. Withdrawal of digoxin
2. Potassium supplementation—2-4 g orally once or twice a day
3. Phenytoin, beta blockers or lignocaine for ventricular arrhythmias
4. Temporary pacing for AV blocks or symptomatic sinus bradycardia
5. Digoxin antibodies in severe grades of toxicity. These are available for use in critical situations.

Benefits of Digoxin

1. Improves symptoms, quality of life, functional capacity and effort tolerance
2. Improves ejection fraction
3. Withdrawal results in hemodynamic and clinical deterioration
4. No significant reduction in mortality

6. ANTICOAGULANTS

CHF patients are at increased risk for thromboembolic complications. Incidence is 1-3% annually. Current recommendation is that warfarin is justified in patients with heart failure who have experienced a previous embolic episode or who are in atrial fibrillation (see also Section 15).

7. HYDRALAZINE AND ISOSORBIDE DINITRATE

The combination acts as venodilator and arterial dilator agents. They reduce the preload and afterload and improve ejection fraction. This combination is recommended in patients who are intolerant to ACEI, or having renal insufficiency. There is no evidence to support the use of nitrates alone or hydralazine alone.

8. ALDOSTERONE ANTAGONISTS

Aldosterone antagonists exert favourable effects on the neurohumoral system and decrease the risk of progression of CHF. Spironolactone has been shown to reduce mortality, improve symptoms and decrease hospitalization in CHF patients. Use of spironolactone is recommended in patients with recent or current class IV symptoms. Dose recommended is 25 mg/day.

9. ANTIARRHYTHMICS

Patients with CHF have frequent complex arrhythmias and are at high risk for sudden death. Hence there has been considerable interest in the use of antiarrhythmic

intervention. Three groups of antiarrhythmics have been evaluated in patients with heart failure.

Class I agents (quinidine, procainamide, flecainide and encainide)—These drugs have shown increased mortality in clinical trials.

Class II agents—Beta blockers have shown definite benefit.

Class III agents (amiodarone, d-sotalol and dofetilide)—Amiodarone may have benefit in nonischemic CHF patients and in those with supraventricular and ventricular arrhythmias.

10. POSITIVE INOTROPES

Though theoretically these drugs may be expected to produce benefit, in clinical trials their effects are disappointing and hence drugs such as dobutamine, milrinone and vesnarinone are not routinely used in CHF.

Mechanical Devices

I. Ventricular Assist Devices (VADs)

Both left ventricular and dual chamber assist devices are available. These include

- i. Hemopumps—indicated only for a short-term use
- ii. Centrifugal devices (Biomedicus Biopump)
- iii. Pulsatile devices (Abiomed BVS—5000)
- iv. Implantable devices, e.g. Heart mate

These are used in many cases to tide over the waiting period before cardiac transplantation. Newer assist devices are being introduced.

II. Extracorporeal Membrane Oxygenator (ECMO)

This device has a centrifugal pump to drive blood from patient to a membrane for CO₂ and O₂ exchange.

III. Implantable Cardioverter Defibrillator (ICD)

This is a multifunctional multiprogrammable electronic device designed to abort life-threatening arrhythmias. Patients with CHF who had episodes of definite VT/VF are likely to benefit from ICD. These are capable of producing regular impulses for contraction and also defibrillate the heart in case of emergencies.

IV. Pacemakers in CHF

There is growing evidence in support of hemodynamic benefits and long-term improvement in clinical status of patients with CHF after biventricular dual chamber (DDD) pacing. The main mechanism is by resynchronization of LV activity. Clinical trials have established the beneficial role of single chamber and dual chamber pacing.

Surgical Options

1. Dynamic Cardiomyoplasty

In this procedure the latissimus dorsi muscle with its pedicle is wrapped around the cardiac apex and a myostimulator is implanted. Though there is improvement in the cardiac indices, long-term outcome is disappointing.

2. Mitral Annuloplasty and Mitral Valve Repair

Where there is associated secondary MR, these procedures are indicated.

3. Partial Left Ventriculectomy (Batista procedure)

This procedure was introduced in 1994 by the Brazilian surgeon Batista. The principle is that return of the dilated ventricle to a more normal volume/mass/diameter relation reduces the wall stress and improves the function. Basic procedure involves resection of the lateral wall from apex to the atrioventricular groove. The results are good in experienced hands.

4. Aneurysmectomy

LV aneurysm causes paradoxical expansion and loss of effective contraction and it contributes to CHF. Aneurysmectomy improves the cardiac function.

Cardiac Transplantation

When the myocardium is damaged beyond repair life cannot be sustained by the failing heart. Cardiac transplantation is indicated under such circumstances if a donor heart and technical expertise are available.

Indications

1. Persistent cardiogenic shock requiring mechanical assistance
2. Refractory CHF with continuous inotropic infusion
3. NYHA class 3-4 with a poor 12 months prognosis
4. Progressive symptoms despite maximal therapy
5. Severe symptomatic hypertrophic cardiomyopathy (HCM) or restrictive cardiomyopathy
6. Refractory angina with unsuitable anatomy for revascularization
7. Life-threatening ventricular arrhythmias despite aggressive medical and device interventions
8. Cardiac tumours with only low tendency for metastasis
9. Hypoplastic left heart syndrome and complex congenital heart disease.

Pre-requisites for surgery

1. Received maximal medical therapy
2. Been considered for alternative surgical options

3. Been addressed for all reversible causes
4. Peak oxygen consumption ($\text{VO}_2 \text{ max}$) falls below 14 mL/kg/mt or it shows a marked and steady decline.

Gene Therapy

This is an evolving treatment strategy where attempt is made to increase the myocardial contractility at molecular level. This is accomplished by using nanoparticles as potential gene therapy carriers or vectors.

In this method, over expression of β_2 receptors in the myocardium is accomplished using adenovirus vector. Genes expressing SERCA2a are increased by using adenovirus transfection of myocytes. Preliminary studies have shown that this improves contraction and relaxation, but there was increased incidence of arrhythmias.

Refractory Cardiac Failure

Definition: Refractory CHF is defined as NYHA class III or IV CHF, in whom symptoms have not improved or have actually worsened following recent attempts to escalate therapy. Triple therapy with digoxin, diuretics and vasodilators should have been attempted prior to labelling the heart failure as refractory.

Management

- I. Take a fresh look to find out conditions causing recent deterioration in CHF like
 1. Excessive diuretics
 2. Digitoxicity
 3. Electrolyte abnormalities
 4. Renal failure
 5. Untreated medical problems such as infections.
- II. Search for factors causing refractory CHF
 1. Myocardial problems like ongoing or recurrent ischemia, mitral regurgitation, arrhythmia, hypertension
 2. Compounding illnesses like renal failure, infections, pulmonary embolism, uncontrolled diabetes, hypothyroidism.
 3. Patient factors—Dietary indiscretion, non-compliance, alcohol abuse
 4. Iatrogenic problems—NSAIDs, steroids, antiarrhythmics
- III. Optimize the medical therapy
- IV. Consider positive inotropic agents
- V. Consider devices
- VI. Consider surgical options

Intractable Cardiac Failure

If patient fails to respond to the above measures and needs a mechanical assist device, heart failure is considered intractable and they are candidates for transplantation.

Emergency Treatment of Acute Pulmonary Edema

1. *Patient is hospitalized* and put to rest with a back rest or cardiac table, in the position of maximum comfort.
2. *The patient is given oxygen immediately at a flow rate of 7-10L/minute.*
3. *Morphine sulfate* 3-5 mg is given intravenously over three minutes and repeated to a total dose of 15-20 mg, at 15 min. intervals. In less acute cases the drug can be given intramuscularly in doses of 15-20 mg. Morphine abolishes anxiety, depresses the respiratory center, allays dyspnea, and reduces the adrenergic vasoconstrictor stimuli.
4. *Diuretic:* Frusemide 40 mg should be given intravenously. If the effect is not evident in 30 min the dose may be repeated.
5. *Aminophylline* in a dose of 5 mg/kg given intravenously slowly is very effective in increasing the cardiac output and relieving bronchospasm. Aminophylline has different actions such as improvement of cardiac output, stimulation of the respiratory center, bronchodilation and diuresis. Hypotension and anaphylaxis are potential complications. In many cases the effect of aminophylline is dramatic.
6. *Reduction of preload:* Tourniquets are applied to the extremities proximally to reduce venous return and thus reduce preload. The venous return from three limbs is obstructed at a time and the tourniquets are rotated at 15 min. intervals. This method of physiological venesection is very effective. Rarely open venesection to remove 300-500 mL blood rapidly may be required. Venesection should not be done on hypotensive patients.
7. *Digitalisation:* Rapid digitalisation is done by intravenous injection of 0.5-1 mg digoxin when there is clear indication.
8. *Vasodilators* such as nitroprusside given intravenously may be required in intractable cases. Once the emergency is managed successfully, further elective management depends upon the underlying condition.

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Shock

C.G. Bahuleyan

13

Chapter Summary

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3. Cardiogenic
Intrinsic
Compressive
4. Septic
Hyperdynamic
Hypodynamic
5. Neurogenic
6. Hypoadrenal

General Considerations

Definition: Shock is a clinical syndrome resulting from gross impairment of tissue perfusion and widespread cellular dysfunction caused by diminution in oxygen delivery.

Classification of Shock

1. Hypovolemic
2. Traumatic

Pathophysiology

In shock there is a disparity between the blood volume and the circulatory bed. This may be due to loss of blood volume, diminished cardiac output or loss of vascular tone affecting the circulatory bed. Shock is reversible in the early stages. Compensatory phenomena such as sympathetic overactivity leading to vasoconstriction and reflex tachycardia serve to maintain the blood pressure and systemic perfusion. These vascular responses are maximal

in the vessels of the skin, kidneys, splanchnic areas, and skeletal muscles. These vasomotor phenomena serve to redirect the available blood to the vital organs like brain and heart. If shock persists or becomes severe, the compensatory mechanisms fail and progressive tissue damage occurs. Blood supply to the vital organs also suffers.

When the perfusion of tissues and delivery of oxygen are decreased, anaerobic metabolism supervenes. Hypoxia, hypercapnia, and acidosis (both metabolic and lactic) ensue. Cellular injury created by the inadequate delivery of oxygen and substrates also induces the production and release of inflammatory mediators that further compromise perfusion through functional and structural changes within the microvasculature. Integrity of the capillary wall is lost leading to extravasation of protein-rich fluid into the extravascular space. This leads to a vicious cycle in which impaired perfusion is responsible for cellular injury which causes maldistribution of blood flow, further compromising cellular perfusion leading to multiorgan dysfunction. Intense ischemia damages the intestinal mucosa resulting in the entry of bacteria and toxins into the circulation. This leads to further aggravation of hypotension and shock. Release of histamine and histamine like substances enhances vasodilation and capillary permeability. Disseminated intravascular coagulation results from the release of thromboplastic substances and this further damages the microcirculation of vital organs. This worsens the shock. Irrespective of the primary cause, persistence of shock leads to myocardial dysfunction and further reduction in cardiac output.

CLINICAL FEATURES

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Clinically shock is usually accompanied by hypotension i.e, a mean arterial pressure < 60 mmHg in a previously normotensive person. The shock syndrome is characterized by rapid thready pulse and cold clammy skin. Alteration in the consciousness such as agitation, somnolence, confusion or coma is a common feature. The urinary output falls below 20 mL/h with the urinary sodium falling below 30 mmol/liter. Metabolic acidosis manifests with tachypnea and Kussmaul's respiration. Several complications develop if shock continues. The majority of cases end up fatally, if left untreated.

Complications

Pulmonary	Adult respiratory distress syndrome (ARDS), characterized by tachypnea, diffuse bilateral rales, and respiratory failure.
Cardiac	Myocardial dysfunction and arrhythmias.

Renal	Acute tubular necrosis and obstruction of tubules by casts
Gastrointestinal	Hepatocellular failure, mesenteric vasoconstriction, hemorrhagic necrosis of bowels.
Hematological	Disseminated intravascular coagulation (DIC).

Cardiogenic Shock

Intrinsic Cardiogenic Shock

This form of shock is caused by failure of the heart to act as an effective pump. The onset is usually sudden. It occurs most commonly as a complication of acute myocardial infarction. It can also occur due to severe brady or tachyarrhythmias, valvular heart disease, or in the terminal stage of chronic heart failure of any cause, including ischemic heart disease and dilated cardiomyopathy. Cardiogenic shock is characterized by a low cardiac output, diminished peripheral perfusion, pulmonary congestion, and elevation of systemic vascular resistance and pulmonary vascular pressures. Acute right heart failure can arise as a result of right ventricular myocardial infarction or may complicate the acute respiratory distress syndrome and severe pulmonary hypertension of any etiology. As a consequence of right ventricular failure, left ventricular preload falls, and this, in turn, reduces systemic perfusion. In contrast to other forms of shock, absolute or relative hypovolemia is usually not present in cardiogenic shock.

Compressive Cardiogenic Shock

This is caused by extrinsic compression of the heart. The heart becomes less compliant and, therefore normal filling pressures are inadequate to achieve proper diastolic filling. Blood or fluid collecting in the pericardial sac may cause tamponade since the pericardium is not distensible. Any cause of increased intrathoracic pressure such as tension pneumothorax, herniation of abdominal viscera through a diaphragmatic hernia, or use of excessive positive pressure ventilation produces compressive cardiogenic shock. Acute right heart failure with sudden decline in cardiac output can be caused by pulmonary embolism obstructing right ventricular outflow tract and this impairs ventricular filling. Although initially this condition responds to increased filling pressures produced therapeutically by volume expansion, as the compression increases, cardiogenic shock ensues.

Treatment

General measures: Shock should be diagnosed early. Survival is inversely related to the duration of the shock

before starting treatment. Prompt institution of specific treatment reduces mortality. The patient is put to bed with foot-end of the bed elevated to increase the venous return to the heart. Patency of the airway is established by removing foreign bodies from the mouth and throat and by keeping the neck extended backwards to prevent the tongue from falling back. If there is pain, morphine 5 mg is given intravenously and repeated, if needed, every 10-15 minutes to reach a total dose of 15-20 mg. Vital signs like pulse, respiration, blood pressure and urine flow are monitored. A venous cannula introduced into the jugular vein helps in monitoring the central venous pressure and also in administering fluids, if prolonged treatment becomes necessary. It is ideal to keep the central venous pressure at 10-14 cm of water. Metabolic acidosis is corrected by administration of 50-100 mmols of sodium bicarbonate given as a 7.5% solution.

Vasopressor drugs: Sympathomimetic drugs are used to improve vascular tone. **Dopamine** is given intravenously at a rate of 3-15 µg/kg/min, depending upon the response of blood pressure and urine output. Other drugs in this group are **isoprenaline** (4-8 µg/min.) and **dobutamine** (3-15 µg/kg/min). These drugs cause improvement in cardiac output and blood pressure, but cardiac arrhythmias may be precipitated.

Vasodilator drugs: Commonly used vasodilator drugs include:

1. **Sodium nitroprusside** given IV at a dose of 10-20 µg/min,
2. **Nitroglycerine** given IV at a dose of 10-20 µg/min, or
3. **Phentolamine** given IV at a dose of 0.5 µg/min.

Vasodilators have the following effects.

1. Reduction of ventricular afterload due to dilation of systemic arterial bed.
2. Decrease in ventricular preload by dilating venous capacitance vessels and reducing pulmonary capillary, arterial and right ventricular pressures.
3. Decrease in myocardial oxygen demand and increase in the subendocardial flow of blood.

Vasodilators should be started in small dosage and the dose should be worked up, depending on the response. Combination of vasodilators with inotropic agents gives better results.

Apart from these general measures each type of shock demands appropriate specific management. For example, thrombolytic therapy and surgical revascularisation for acute myocardial infarction, antibiotics for septic shock and dialysis procedures for poisoning.

Hypovolemic shock: Rapid replacement of the blood volume by administration of the appropriate fluid (depending on the fluid lost) is life-saving and this should be undertaken without delay. Blood, isotonic saline or plasma volume expanders such as 6% w/v dextran or other colloidal solutions should be used. The rate of infusion should match the rate of fluid loss. In severe cases of gastroenteritis up to 3-4 litres of fluid may have to be infused in the first 1-2 hours. Fluid infusion is continued until the systolic blood pressure comes up to 100 mm Hg. Further maintenance depends on rate of fluid loss. If the shock is unresponsive to replacement of conventional fluids, infusion of 7.5% saline (100-400 mL) may help to restore the blood pressure.

Cardiogenic Shock

Inotropic agents to improve cardiac contractility, vasodilators to reduce the afterload on the heart and correction of the cardiac abnormality are the main principles of treatment. If the cardiac output is persistently low, the circulation can be assisted by means of balloon counterpulsation in the aorta if facilities permit. The balloon is positioned in the upper part of descending aorta. It is inflated during diastole and deflated during systole. This helps to reduce afterload in systole and to increase the filling pressure of the ventricles and coronary arteries during diastole. By these mechanisms, balloon counterpulsation improves the cardiac output and coronary circulation. In conditions such as rupture of inter-ventricular septum or acute damage to a valve, emergency surgery may have to be undertaken if the shock remains unresponsive to medical treatment. In shock due to acute myocardial infarction thrombolytic therapy is beneficial, but results are less rewarding than in those without shock. Early revascularization procedures such as percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass surgery (CABG) bring about dramatic benefit and improve survival and in many centres early revascularization is the method of choice.

Anaphylactic Shock

It is treated by intramuscular injection of 1 mL of 1/1000 adrenaline, repeated if needed every 5-10 min. Adrenaline corrects the hypotension and bronchospasm. If the bronchospasm is severe, 250 mg of aminophylline is given intravenously slowly. In severe cases hydrocortisone in doses of 100 mg or its analogues (betamethasone or dexamethasone 8 mg) are given intravenously either by repeated injections or through an intravenous drip, until the condition improves. If laryngeal edema obstructs the airways, emergency tracheostomy has to be done to save life.

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accompany at least 25% of significant cardiac defects and they may aggravate morbidity and mortality. They are often multiple and about a third of them are classified into distinct syndromes.

Congenital heart disease results from abnormal development of particular portions of the heart during embryonic development, e.g. defective development of the interventricular septum results in various types of ventricular septal defects (VSDs). Abnormal development of a single structure can also lead to multiple abnormalities, e.g. abnormal development of the spiral septum results in ventricular septal defect, right ventricular outflow tract obstruction, overriding of aorta, and right ventricular hypertrophy which are all seen in tetralogy of Fallot.

Etiology

The exact etiology of the disease is unknown. It is generally believed that congenital heart disease is multifactorial in origin, mainly an interplay between genetic as well as environmental factors. Some of the congenital heart diseases are found to be familial, e.g. mitral valve prolapse, atrial septal defect, patent ductus arteriosus and pulmonic stenosis. The incidence of congenital heart disease in the offspring or siblings of an index patient is 2-5%.

The genetic mechanisms tend to be different. Atrio-ventricular septal defects seem to be single gene disorders. Tetralogy of Fallot is polygenic in origin. Isolated transposition of great vessels arise from sporadic defects. Identification of 22q11 deletion by fluorescent *in situ* hybridization (FISH) is correlated with a variety of conotruncal abnormalities in relation with Di George's syndrome. Recognition of thymic hypoplasia is important in that they should avoid live vaccinations and may need irradiated blood for transfusion when indicated. Similarly these children should be evaluated for hypocalcemia and neonatal convulsions can be avoided with adequate supplementation.

The environmental factors include maternal age above 35 years, maternal infections like rubella and cytomegalo-

Congenital heart disease (CHD) can be defined as abnormalities in the cardiovascular system occurring at birth. A primary abnormality occurring in one part of the cardiovascular system *in utero* can lead on to functional abnormalities resulting in further anatomical defects. This process gives rise to various complex types of cardiac defects at birth. The frequency of major congenital heart disease has been estimated to be approximately 0.8% of all live births. This does not take into account the common congenital abnormalities like mitral valve prolapse and bicuspid aortic valve. Though the different types of congenital heart disease show no predilection for either sex, in general males are affected more than females. However Atrial septal defects (ASD), persistent ductus arteriosus (PDA) and Ebstein's anomaly of tricuspid valve are more common in females. Extracardiac abnormalities

Extracardiac anomalies in association with congenital heart disease		
Syndrome	Cardiovascular anomaly	Clinical features
1. Holt-Oram syndrome	Secundum ASD	Hypoplastic thumb with three phalanges, absent thumb, hypoplasia of metacarpals extending onto radius
2. Chance association (not a specific syndrome)	Conotruncal anomalies (TOF, truncus arteriosus) aortic arch anomalies (interrupted aortic arch)	Coloboma, heart defect Choanal atresia, growth/mental retardation Genitourinary anomalies, ear anomalies, genital hypoplasia
3. Vater association (vateral syndrome)	VSD	Vertebral defects, anal atresia, cong. heart disease, tracheo-esophageal fistula, renal dysplasia
4. Pierre-Robin syndrome	VSD/PDA	limb anomalies (radial dysplasia) Deafness, cataract, CHD mental deficiency, hepatosplenomegaly, jaundice, thrombocytopenia anemia
5. Cornelia de Lange syndrome	VSD	Prenatal growth retardation, microcephaly, hirsutism, anteverted nares, downturned mouth mental retardation,
6. Fetal alcohol syndrome	VSD, PDA, ASD	Microcephaly, mental deficiency
7. Noonan's syndrome	Pulmonary valve dysplastic	Webbed neck, mental deficiency
8. Ellis-van Creveld syndrome	Common atrium	Malignant hyperthermia
9. Rubinstein-Taybi syndrome	PDA	Multiple frenulae post axial Polydactyly Chondroectodermal dysplasia. Broad thumb and toes mental retardation

CHD in selected chromosomal aberrations	
Condition	Common defects
1. Trisomy 21 (Down's syndrome)	Endocardial cushion defects
2. Turner's syndrome	Coarctation of aorta, AS, ASD
3. Klinefelter's syndrome	PDA
4. Cri Du Chat syndrome	VSD, PDA, ASD
5. Trisomy 13 (Patau's syndrome)	VSD, PDA
6. Trisomy 18 (Edward's syndrome)	VSD, PDA, PS

virus, drugs consumed by the mother during the first trimester of pregnancy, nutritional status of the mother and alcoholism. Maternal rubella results in congenital rubella syndrome (cataract, deafness, microcephaly, patent ductus arteriosus with pulmonary valve stenosis or pulmonary arterial stenosis). Chronic maternal alcohol abuse results in birth of babies with *fetal alcohol syndrome* (microcephaly, micrognathia, microphthalmia, and ventricular septal defect).

Prenatal teratogens	
Agent	Cardiac defect
Ethanol	VSD
Phenytoin	VSD
Lithium	Ebstein's anomaly
Retinoic acid	TGA
Rubella	PDA, PS
Valproic acid	Coarctation of aorta
Vitamin D	Supravalvular PS
Warfarin	PDA, PS

Insulin dependant diabetes mellitus at conception in the mother predisposes to cardiac diseases like TGA, VSD, coarctation of aorta and cardiomyopathy in the offsprings. Macrosomia and benign cardiac hypertrophy mimicking hypertrophic cardiomyopathy is more common with gestational diabetes. SLE is associated with congenital complete AV block in the offspring due to transfer of maternal autoantibodies across the placenta, which produce inflammatory damage to the conduction system of the fetus. Carrier state for phenylketonuria in the mother is associated with a variety of congenital cardiac malformations.

Congenital heart disease can be broadly classified into cyanotic and acyanotic varieties. Cyanotic lesions may be accompanied by reduced as well as increased pulmonary blood flow, the former being the more common.

Classification

Acyanotic

Left to right shunt

1. Atrial septal defect (ASD)
2. Ventricular septal defect (VSD)
3. Patent ductus arteriosus (PDA)

Obstructive lesions

1. Aortic stenosis (AS)
2. Pulmonary stenosis (PS)
3. Coarctation of aorta (CoA)

Cyanotic

Reduced pulmonary blood flow

1. Tetralogy of Fallot (TOF)
2. Transposition of great arteries (TGA), VSD, PS
3. Corrected TGA (c-TGA)-VSD—PS
4. Tricuspid atresia-VSD—PS

- 5. Single ventricle—PS
 - 6. Endocardial cushion defect (ECD)—PS
- Increased pulmonary blood flow
- 1. TGA
 - 2. Truncus arteriosus
 - 3. Tricuspid atresia—VSD with no PS
 - 4. Total anomalous pulmonary venous connection (TAPVC)
 - 5. Endocardial cushion defect
 - 6. Single ventricle—no PS

Malpositions of the Heart

The position of the heart and major blood vessels may be abnormal due to aberrations during embryonic development. Cardiac malpositions can be associated with or without visceral heterotaxy. The term heterotaxy refers to anomalous placement or location of viscera and vascular structures. In patients with visceral heterotaxy the organ and vascular arrangements are not in an orderly concordant manner.

There are three basic cardiac malpositions in patients without visceral heterotaxy—situs inversus with dextrocardia, situs solitus with dextrocardia and situs inversus with levocardia.

Dextrocardia

One of the common anomalies is dextrocardia. This term refers to the condition in which the heart is in the right hemithorax and the left sided chambers are on the right, the left ventricular apex being palpable on the right side. Dextrocardia may be associated with situs inversus in which the other organs such as liver and stomach are also

reversed, i.e. liver is on the left and stomach is on the right. Such dextrocardias are termed mirror-image dextrocardias. This condition is generally asymptomatic and not associated with other serious congenital anomalies.

In dextrocardia with situs solitus the abdominal organs are not reversed. Such dextrocardias are usually associated with several other congenital defects.

Dextroversion is the condition in which the viscera, atria and aortic arch are in the normal position, but the cardiac apex is on the right.

Dextrocardia gives rise to diagnostic findings in the skiagram and ECG (Fig. 118.3). Dextrocardia has to be differentiated from dextroposition of the heart in which the heart is shifted to the right hemithorax due to lesions such as pulmonary fibrosis, pleural effusion or thoracic skeletal abnormalities.

Visceral heterotaxy can occur with right or left isomerism. The term isomerism refers to bilateral similarity, if not equivalence of structures (Figs 118.1 and 118.2).

Right Isomerism—Features

- 1. Right Isomerism
 - a. Bilateral morphologic right bronchi
 - b. Bilateral morphologic right atrial appendages
- 2. Visceral heterotaxy
 - a. Liver: transverse
 - b. Stomach: left sided, right sided or rarely midline
 - c. Lungs: trilobed
- 3. Heart: Dextrocardia (common)
- 4. Asplenia common but not invariable

Left Isomerism—Features

- 1. Left isomerism
 - a. Bilateral morphologic left bronchi
 - b. Bilateral morphologic left atrial appendages

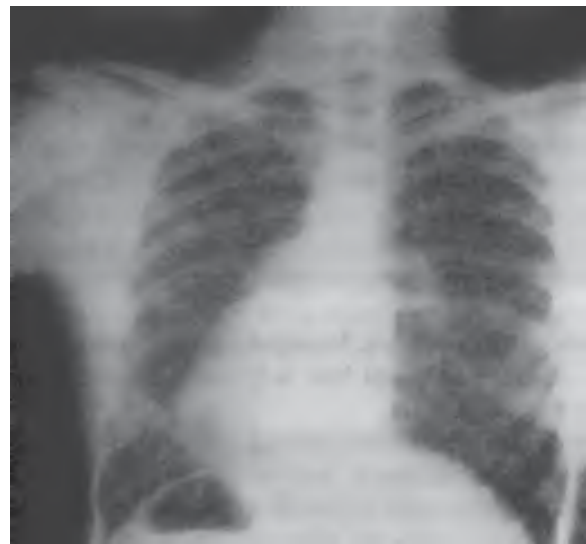


Fig. 118.1: Dextrocardia with situs inversus

Note: The heart is in the right hemithorax with apex to the right. The stomach (G) is under the right hemi-diaphragm which is at the lower level than the left. The liver is on the left side (situs inversus). Associated anomalies are rare



Fig. 118.2: Dextrocardia with situs solitus

Heart is on the right with apex pointing to the right, stomach (G) is on the left, and liver is on the right. This anomaly is associated with complex malformations

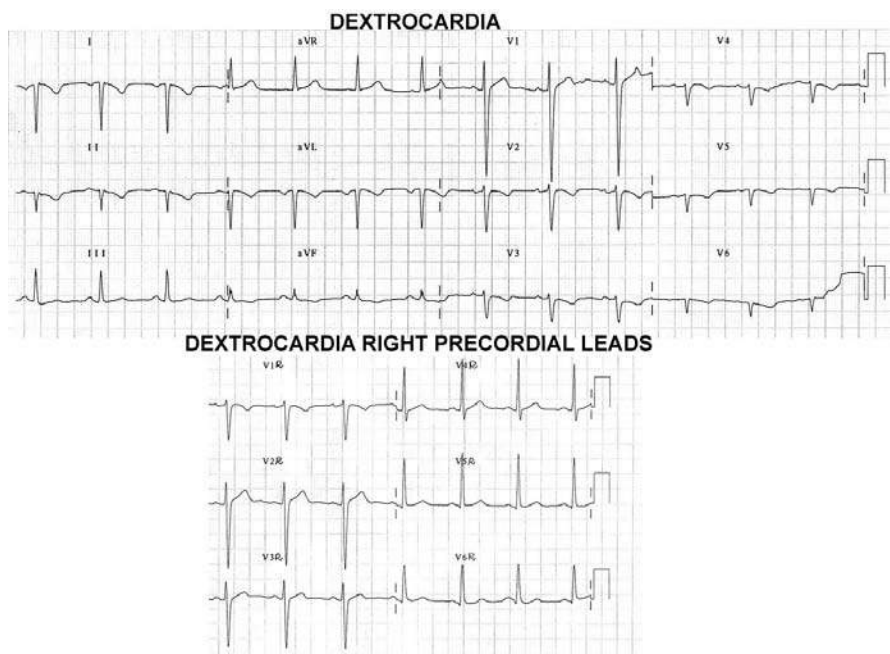


Fig. 118.3: ECG — Dextrocardia (1) Standard leads (2) Right precordial leads
Note: (1) Inverted ‘P’ waves in lead I and aVL and upright ‘P’ in the other leads. (2) The pattern of lead I is a mirror image of the normal. The pattern in aVL resembles the normal pattern observed in lead aVR. (3) The precordial leads V₁ to V₆ show only S waves of decreasing amplitude without R waves. The normal transition from right ventricular to left ventricular pattern can be recorded from leads placed further on the right side V₃R to V₆R.

- 2. Visceral heterotaxy
 - a. Liver-transverse
 - b. Stomach right sided, occasionally left sided but not midline
 - c. Lungs bilobed
- 3. Heart
 - a. Levocardia (common)
- 4. Polysplenia

Congenital Aortic Stenosis

Obstruction to the left ventricular outflow tract may be valvular, subvalvular, or supravalvular, the valvular form being the commonest. The stenotic aortic valve is most often bicuspid, although tricuspid aortic valve may also become stenotic in the younger age group.

Morphology of congenital valvular aortic stenosis	
Bicuspid valve	44%
Bicuspid valve with rudimentary commissure on one cusp	23%
Tricuspid valve	30%
Unicuspid valve	3%

Mild cases are asymptomatic and are picked up during routine examination or when complications occur. Moderately severe and severe cases present with exertional syncope, effort angina or cardiac failure. Aortic stenosis predisposes to infective endocarditis. Unicuspid valve is

inherently stenotic even at birth and this is the one presenting with aortic stenosis in the newborn. Bicuspid valves develop degenerative changes early and lead to stenosis on an average by 20-30 years of life.

Critical aortic stenosis produces congestive heart failure in infancy. In moderate and severe cases the pulse is characteristically small in volume with slow-rising ascending limb of the pulse wave and pulse pressure less than 20 mm Hg. The heart may not be enlarged, but the apex beat is heaving in nature. In most of the cases there is a systolic thrill, best felt in the right upper sternal border as well as over the carotids. Auscultation reveals ejection systolic murmur preceded by a constant ejection click, best audible over the right upper sternal border, and conducted to the carotids. In many cases the murmur and click are very well audible over the cardiac apex also. An early diastolic murmur of associated mild aortic regurgitation may also be heard in some cases. In mild cases of aortic stenosis the murmur may be present without any abnormality in the pulse or apex beat.

The presence of a constant ejection click suggests that the stenosis is at valvular level. This is associated with poststenotic dilatation of the ascending aorta. Both these features are absent in subvalvular stenosis.

Congenital subvalvular aortic stenosis may take the form of a discrete membrane or a tunnel type of obstruction.

Supravalvular aortic stenosis may be familial, associated with a characteristic facies, hypercalcemia, and mental retardation (**Williams' syndrome**). In supravalvular aortic stenosis, the jet of blood flow may be directed towards the innominate artery resulting in a higher pulse volume and higher blood pressure in the right arm than on the left.

Treatment: Mild cases have been treated with balloon valvotomy, though the results are less satisfactory when compared to balloon dilation of the pulmonary valve. In more severe cases open valvotomy or valve replacement may be required. Substituting the pulmonary valve for the aortic valve is done in the innovative Ross procedure. Low pressure pulmonary circulation can be supported by either autologous pericardial valve or rarely a homograft valve.

Coarctation of Aorta

This condition is characterized by obstruction of the aorta in the region of the ductus arteriosus or ligamentum arteriosum just distal to the left subclavian artery. Very rarely it may occur at a more proximal site in the arch or in abdominal aorta. In the majority of cases coarctation occurs as a discrete infolding of the dorsal aortic wall. In about 20% of cases coarctation exists as the only abnormality, whereas the rest have associated abnormalities like bicuspid aortic valve, patent ductus arteriosus, ventricular septal defect, atrial septal defect, mitral stenosis, mitral regurgitation, and transposition of great vessels. Bicuspid aortic valve is the commonest associated anomaly, majority of them being hemodynamically insignificant. When coarctation is severe, arterial blood from the proximal part is taken to the distal part through collateral circulation which develops from the intercostal arteries and the subclavian system. **Taussig-Bing anomaly** refers to double outlet right ventricle with sub pulmonic VSD and has a good association with coarctation. **Shone's complex** consist of coarctation with supramitral membrane and subaortic or aortic valve obstruction. In Turner's syndrome, coarctation is a typical manifestation. Coarctation is uncommon with cyanotic congenital heart diseases with large VSD like tetralogy of Fallot and pulmonary atresia since these conditions lead to dilatation of the aortic root and good growth of the isthmus.

Classification

1. Simple — without PDA
— with PDA
2. Complex—associated with
VSD
Valvular aortic stenosis
Combination (VSD + AS)

Clinical features: Approximately 50% of coarctation present in the neonatal period, many of them with varying

degrees of heart failure. Those who present during adolescence and adulthood give history of intermittent claudication of legs, mild fatigue, and dyspnea. In older individuals it may present as congestive heart failure. Disproportionate development of the arms, chest, and shoulder girdle compared to the legs may be noted in some patients. The upper limb pulses, suprasternal pulse, and carotid pulse are prominent and the blood pressure is high in the arms. The femoral pulse is felt feebly and is delayed. The apex beat may be heaving in nature. Usually there is an ejection systolic murmur with a constant ejection click, best heard over the right sternal border. This is caused by the associated bicuspid aortic valve. Sometimes, there may be an early diastolic murmur of aortic incompetence. The collaterals may be visible and palpable over the back of the chest, around the scapula, and sometimes in front of the chest. Continuous murmur may be produced from the site of coarctation or from the collaterals.

Diagnosis: The diagnosis should be suspected by the finding of absence or delay of the femoral pulses, presence of high blood pressure in the upper limbs, low blood pressure in the lower limbs, and the cardiac abnormalities.

Investigations

ECG shows left ventricular hypertrophy.

X-ray shows localized indentation of aorta at coarctation site with dilatation above and below (3 sign). X-ray also shows rib notching (Fig. 118.4). On barium swallow, esophageal indentation due to aortic dilatation occurs (E sign, reverse 3 sign).

Echocardiogram: Suprasternal view shows narrowing of aorta just beyond left subclavian artery. Colour flow localizes the site of narrowing. Continuous wave Doppler can assess gradient across coarctation.

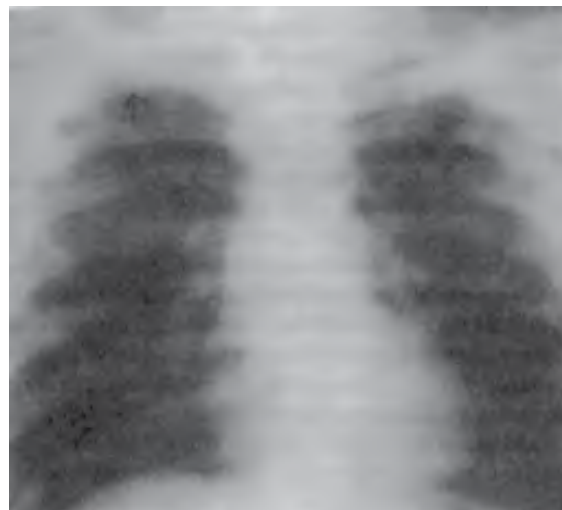


Fig. 118.4: Coarctation of the aorta. Note 3 sign on the aorta—'x', and rib notching (arrows)

Catheterization can be avoided with a good echo study. However, it is indicated for precise definition of anatomy of coarctation site, assessment of ductus and collaterals and for assessment of other intracardiac lesions (Fig. 118.5).

Management

1. Medical management: This includes stabilization of infants with cardiac failure and infective endocarditis prophylaxis. Neonatal coarctation is a surgical emergency. It manifests as a ductus dependent systemic circulation keeping the patent ductus arteriosus open. Prostaglandin infusion helps to stabilize the child for transport to a neonatal cardiac surgical unit.
2. Surgery is the preferred treatment in native coarctation. Surgical methods include resection and end-to-end anastomosis, prosthetic patch aortoplasty and subclavian flap aortoplasty. Ideal time for surgery is between 3 and 5 years. Surgery done less than 3 years of age results in restenosis and beyond 5 years of age chances of residual hypertension are more.
3. Catheter based techniques: Balloon angioplasty is the first choice in postsurgical restenosis. In native coarctation, angioplasty carries a high risk of aneurysm development and rupture. In postsurgical cases due to surrounding fibrosis chances of rupture are less. The balloon size is chosen to equal the diameter of aortic isthmus just distal to left subclavian artery and inflation time is limited to 10 seconds.
4. Stenting of the coarctation is at present the procedure of choice in adolescence and adults. Palmaz-Schatz stents, Jo-Med stents and CP stents are the favourite stents. Presently all these stents are compatible with MRI examination. Postsurgical aneurysm rupture of the aorta during dilatation and simultaneous closure

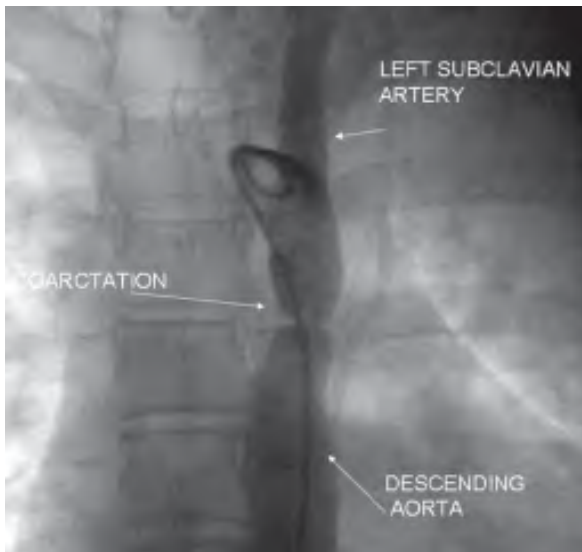


Fig. 118.5: Descending aortogram showing coarctation

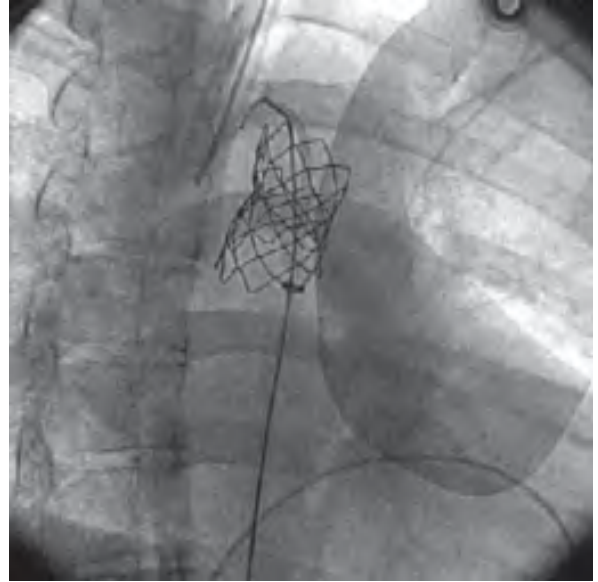


Fig. 118.6: Metallic stent after its deployment at the coarctation using a balloon

of ductus can all be undertaken with the covered CP stents. These stents are usually deployed under fluoroscopic guidance under anesthesia after crossing the coarctation segment using suitable guide catheters. Intermediate term follow-up results are favourable. Rarely self expanding nitinol stents are also used (Fig. 118.6).

Pulmonary Stenosis

Right ventricular outflow obstruction may be valvar, supra-ventricular or sub-ventricular. As an isolated anomaly pulmonary valve stenosis is the commonest type of right ventricular outflow obstruction. This is characterized by a thick valve with fused commissures and central or eccentric opening. The valve demonstrates characteristic doming with varying degrees of restriction of opening during systole. The main pulmonary artery shows post-stenotic dilatation with prominence of the left pulmonary artery. Mild cases may show only an ejection systolic murmur, best audible in the left upper sternal border. This is preceded by phasic (inconstant) ejection click which is more prominent during expiration and less prominent during inspiration. In moderate and severe cases the murmur is harsh and may be associated with thrill. The ejection click becomes closer to the first heart sound and the pulmonary second sound becomes feeble and delayed. There is right ventricular hypertrophy as evidenced by left parasternal heave. The jugular venous pulse shows prominent 'a' wave due to rise of right atrial pressure. In severe cases the right ventricular and right atrial pressures become elevated and a right to left shunt may develop through a stretched patent foramen ovale. In this stage right ventricular failure may develop.

Mild cases usually do not progress further. Moderate and severe cases require valvotomy. Critical pulmonary stenosis is associated with the risk of sudden death in the pediatric age group and, therefore, surgery should not be delayed if the diagnosis is confirmed. Balloon valvuloplasty has replaced surgical therapy as the first approach. Via the femoral vein a balloon catheter is advanced into the right side of heart and then across the pulmonary valve. Two types of balloons are available, Mannsfield and Tyshak. Balloon is inflated to about 20-40% greater size than the measured pulmonary annulus thus ripping the valve. If measured pulmonary annulus is more than 20 mm double balloon technique is used. Inflation time is restricted to 10 seconds. A dysplastic valve as in the case of Noonan's syndrome is not suitable for balloon valvuloplasty. Presence of other cardiac lesions which cannot be tackled by catheter technique, puts the patient into surgical group. Significant reduction of gradient across pulmonary valve is seen immediately and is maintained long term. Major complications reported are less than 0.6%. Predictors of suboptimal results include dysplastic valve, complex valve morphology, age of child at dilatation less than 2 years and use of balloon:annulus ratio less than one.

Left to Right Shunt Lesions

ATRIAL SEPTAL DEFECT (ASD)

This is the most common congenital heart disease found in the adults. This is characterized by the presence of one or more defects in the interatrial septum. Based on the developmental defect there are mainly three types.

1. Ostium secundum
2. Ostium primum
3. Sinus venosus

Ostium secundum defect occurs in the region of the fossa ovalis and this is the most common. This results from the maldevelopment of the septum secundum. The only abnormality is the presence of the atrial septal defect.

Ostium primum defect is the result of abnormal development of the endocardial cushion. The defect is in the lower portion of the interatrial septum. This may be associated with cleft mitral or tricuspid valve resulting in their incompetence.

Sinus venosus type of defect occurs in the upper portion of the interatrial septum. It is due to the abnormality of development of the upper part of the interatrial septum and it is associated with anomalous connection of one or more pulmonary veins to the superior vena cava or right atrium.

Hemodynamics

In ASD the blood is shunted from left atrium to right atrium and then to the right ventricle. The right ventricular

output and the pulmonary blood flow are considerably increased. This leads to progressive enlargement of the right atrium, right ventricle, and pulmonary arteries. Even though pressures are equal, shunt occurs from left atrium to right atrium as right ventricle is more compliant than left ventricle. As there is no pressure difference shunt *per se* does not produce a murmur.

Atrial septal defect is found more in females. This may occur as an isolated anomaly or in association with other intracardiac anomalies like pulmonic stenosis or ventricular septal defect. Rheumatic mitral stenosis may coexist with ASD (Lutembacher's syndrome).

CLINICAL FEATURES

Palpitation and recurrent respiratory infection are the usual symptoms. Effort intolerance usually develops in the third and fourth decades and thereafter features of congestive heart failure develop. Clinically there is cardiac enlargement with hyperactive precordium as a result of right ventricular enlargement. Pulmonary artery pulsation is felt in the left second intercostal space. In some cases a systolic thrill may be felt over the upper part of the sternum on the left. A pulmonic systolic murmur may be heard. The murmur and the thrill are produced by increased blood flow through the pulmonary valve. The second sound in the pulmonary area is widely split since the pulmonic valve closure is delayed by the larger volume of blood to be ejected by the right ventricle. During inspiration more venacaval blood flows into the right side of the heart and during expiration more of left atrial blood flows through the shunt. These phenomena account for the ejection of the same quantity of blood across the pulmonary valve during inspiration and expiration. Therefore, the split of the pulmonary second sound remains fixed. The **auscultatory hallmark is wide fixed split of second heart sound**.

Increased flow across the tricuspid valve during diastole may produce a tricuspid mid-diastolic murmur, best heard along the left lower sternal border. This is usually preceded by a right ventricular third heart sound.

Severity of shunt is assessed by cardiomegaly, presence of RVS₃, and tricuspid mid-diastolic murmur. A thrill palpable in pulmonary area can occur in large shunt or with associated mitral stenosis or associated pulmonary stenosis.

Course and prognosis: Small atrial septal defect may remain asymptomatic. Small atrial septal defects below 2 mms are common in infants upto one year. They are known to close spontaneously or remain as persistent foramen ovale. Persistent foramen ovale, can be identified in about 25% of normal hearts in various autopsy studies. Recently they have been implicated in variety of problems like migraine, paradoxical embolism causing **stroke, decompression sickness** and **orthodeoxia** (development of desaturation on lying down). Attempts

to close these defects with **amplatzer PFO devices** to prevent stroke and TIAs are under trial.

Defects more than 4 mm in infancy have been noted to become larger in natural history studies. When the shunt is large, the right-sided chambers progressively enlarge. Pulmonary hypertension develops in course of time. The pulmonary pressure may be elevated to high levels and the same is reflected in the right ventricle and right atrium. When right atrial pressure exceeds that of the left atrium, the blood flow is reversed and this leads to the development of central cyanosis. This phenomenon is called **Eisenmenger's syndrome**. Pulmonary hypertension and reversal of shunt occurs in less than 10% patients. Primum type of ASD carries a poorer prognosis than the secundum type.

Other complications include paradoxical embolism, arrhythmias like atrial fibrillation and very rarely infective endocarditis.

Investigations

ECG: Shows rsR' pattern in lead V1, right ventricular hypertrophy and right axis deviation. Left axis deviation is seen in Ostium Primum ASD. PR interval prolongation is seen in familial types of ASD and in ostium primum defects.

Chest X-ray: Shows cardiomegaly, enlargement of right atrium without the engorgement of the superior vena cava, increased pulmonary vascularity as evidenced by multiple end on vessels and enlargement of main pulmonary artery, right pulmonary artery and left pulmonary artery if the shunt is large (Fig. 118.7).

Echo with colour Doppler: Can diagnose the type of ASD, measure the size of ASD, note the direction of shunt and quantify the shunt. The suitability for device closure can also be assessed by echo. Pulmonary venous drainage

can also be visualised and anomalous pulmonary venous drainage can be made out. Doppler with colour mapping is comparable with angiographic visualization of intracardiac shunting.

Cardiac catheterization: Generally this is not required for preoperative diagnosis. It is indicated for the following reasons (i) in adults, to assess pulmonary vascular resistance and hence to decide on surgery, (ii) to assess coronary arteries above the age of 40, when corrective surgery is contemplated, (iii) if any disparity between clinical and echo quantification of shunt exists. Catheterization will show increase in oxygen saturation from superior vena cava to right atrium. Left atrium can be entered from right atrium through the ASD and the pressures in the two chambers are equal can be measured.

Management

Medical: ASD by itself has very low risk for infective endocarditis. If associated mitral regurgitation is present, infective endocarditis prophylaxis is advised. In late stages as the patient goes in for cardiac failure, digoxin and diuretics are to be used.

Surgical: Any shunt more than 1.5:1 should be closed. In adults surgery is advised only if pulmonary vascular resistance is low. Median sternotomy, right thoracotomy or atrial wall approach can be used. ASD closure is done by suturing the edges of ASD directly or by using pericardial patch or prosthetic material.

Catheter based techniques: Various devices have been used. Previously used devices include double umbrella device by King and Mills, Rashkind single umbrella device (first generation); Lock clamshell device, ASDOS, Das Angel Wings (second generation).

Presently used devices are of the third generation and include Amplatzer device and Cardioseal. Advantages of new devices are smaller size of the delivery system. Amplatzer device is made of Nitinol which after extrusion from its sheath, forms into a double button with a connecting waist, the left atrial button being larger than the right. Careful sizing of the defect using a balloon catheter by pulling it from left atrium to right atrium is to be done before the procedure. Prerequisites for device closure include (i) ostium secundum location, (ii) small and moderate sized defects (iii) margins of at least 5 mm all around the defect, and (iv) distinctly away from A-V valves. Success of Amplatzer device is more than 90% and residual shunt is reported only in 1.2-6% cases. Presence of atrial septal aneurysm, if it can not be contained inside the device is a contraindication to its use.

The approximate cost of Amplatzer device will come to Rs. 1,200,00 in India. More than 25,000 devices have been successfully deployed all over the world since 1995. In the Amplatzer registry about 50 life-threatening complications have been documented including complete



Fig. 118.7: Atrial septal defects

Note: Cardiac enlargements, prominent main pulmonary artery and plethoric lung fields



Fig. 118.8: Amplatzer ASD occluder deployed to close an ASD

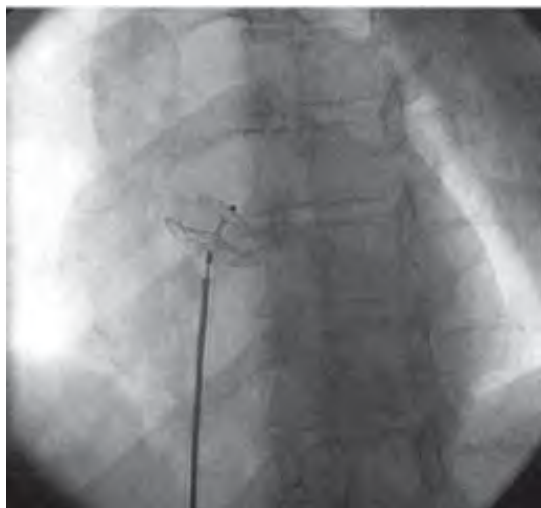


Fig. 118.9: Amplatzer PFO occluder being deployed: Note the smaller disc on the left atrial side

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heartblock, device thrombus, air embolisation, erosion of device to adjacent structures, and infective endocarditis (Figs 118.8 and 118.9).

Ventricular Septal Defect (VSD)

This is the most common congenital heart disease in the pediatric age group. This is characterized by one or more defects in the ventricular septum.

Types

1. 80% perimembranous with variable extension into the inlet, trabecular or outlet sections of muscular septum.
2. 5-7% subarterial defects.
3. 5-8% inlet defects.
4. Muscular septum defects.

Crista is considered to be a part of the right ventricle, which demarcates the outflow tract from the body.

Infracristal type of defects is the commonest. Ventricular septal defect may occur as an isolated anomaly in the majority, or in association with other cardiac anomalies such as ASD, right ventricular outflow obstruction, coarctation of aorta and transposition of great vessels. The blood flows from left ventricle to the right and then to the pulmonary circulation. This leads on to enlargement of left and right ventricles, pulmonary artery, and the left atrium.

Large VSDs can lead to congestive cardiac failure in infancy. Recurrent respiratory infection and failure to thrive may also be noticed. Those who survive develop varying degrees of pulmonary hypertension. Small VSDs are asymptomatic and they are detected on routine examination. Moderate VSDs present with palpitation and recurrent respiratory infections.

CLINICAL FEATURES

Small VSDs are characterized by a harsh pansystolic murmur associated with thrill, best heard in the left third and fourth intercostal spaces. Moderate and large VSDs produce pansystolic murmur and cardiac enlargement. The apex beat is forcible with hyperactive precordium. Pulmonary artery pulsation may be felt. There may be left ventricular third heart sound and mid-diastolic murmur heard over the cardiac apex suggestive of increased blood flow across the mitral valve.

Severity: Left ventricular third heart sound, mid-diastolic murmur over mitral area and cardiomegaly indicate a large shunt.

Complications may occur. These include congestive cardiac failure, Eisenmenger's syndrome, infective endocarditis and aortic incompetence due to prolapse of the aortic valve cusp through the defect.

Investigations

ECG: Can be normal with small defects or show biventricular involvement with large defects.

X-ray: With small defects, heart size and pulmonary blood flow are normal. With large defects, moderate to marked enlargement of heart, prominent main pulmonary artery and pulmonary plethora are seen. There is no right atrial enlargement unlike ASD and unlike PDA, the aorta is not prominent.

Echocardiogram: Visualization of the site of VSD and size measurement are possible with 2D-Echo. Colour flow mapping can identify small muscular defects. Continuous wave Doppler can detect the pressure gradient between the two ventricles and from this RV systolic pressure can be derived.

Catheterisation: Shows increase in oxygen saturation at the right ventricular level. With large defects right ventricular and pulmonary artery pressures are elevated.

Left ventricular angiogram delineates the number of defects and the exact site and size of the defect.

MANAGEMENT

Medical: This includes infective endocarditis (IE) prophylaxis and treatment of cardiac failure.

Surgical: Surgery is to be done between 2-5 years of age if shunt is more than 1.5:1. Earlier surgery in infancy is indicated if the child remains symptomatic despite medications or the pulmonary artery pressure shows elevation on follow up. Transatrial and transventricular approaches are utilized for VSD closure.

Catheter based techniques: VSD closure has been attempted with double umbrella device. The catheter has to be passed across interatrial septum and mitral valve into left ventricle and from there across the ventricular septal defect into right ventricle. This procedure is yet to achieve wide popularity. The more popular method at present is to access the VSD by an arterio venous loop. This loop is created by passing a balloon catheter through the aorta into left ventricle. This balloon floats along with the flow through the VSD into the pulmonary artery. Then a guide wire is passed through the balloon and is snared from the venous side. This continuous guide wire from the venous to the arterial end allows smooth passage of variety of large sheaths across the VSD from the venous end through which the VSD closure devices can be positioned. The difficulty in positioning a device in the subaortic position without touching the aortic valve is being overcome by eccentric VSD devices. Larger VSDs in children pose a challenge to both the surgeon as well as the interventional cardiologist. Hence hybrid procedures are adopted where, in the surgical theatre, the surgeon exposes the heart and under transesophageal echo guidance large devices can be positioned to achieve good closure. The surgeon helps the interventionist in putting an appropriate large sheath into the heart in between purse string sutures, which is otherwise impossible in small children either by venous or arterial access. The procedure time is shortened and cardiopulmonary bypass is avoided for the surgeon.

Patent Ductus Arteriosus (PDA)

Embryologically the ductus arteriosus is the posterior part of the persistent left sixth aortic arch. In the fetus it allows the egress of blood pumped from the right ventricle into the pulmonary trunk to the descending aorta bypassing the lungs which are non-functional. Normally, as the lungs get aerated after birth, functional closure of the ductus occurs in 24 h and anatomical closure within 1-2 weeks after delivery. Patency of the ductus after birth results in the flow of blood from the aorta to the pulmonary artery since the pulmonary artery pressure is lower. The aortic end of the ductus lies beyond the origin of the left

subclavian artery and the pulmonary end is located immediately to the left of the bifurcation of the pulmonary trunk. In the early stages of the disease blood from the aorta flows to the pulmonary artery throughout systole and diastole. When pulmonary hypertension develops this blood flow diminishes, initially the diastolic flow. The blood flow may be reversed when **Eisenmenger's syndrome** develops. Patent ductus arteriosus is more common in females and in premature infants. It may occur as an isolated lesion or as part of a complex anomaly with other congenital heart diseases. Maternal rubella is associated with increased incidence of PDA in the child. Clinical features depend upon the amount of left to right shunt through the ductus.

CLINICAL FEATURES

Many cases remain asymptomatic, even though the mother would have detected the murmur and thrill in the child. Palpitation and exertional dyspnea set in if the ductus is large and pulmonary hypertension develops. Later, congestive heart failure supervenes. The pulse may be collapsing in character. There is left ventricular type of cardiac enlargement. Cases with pulmonary hypertension may reveal left parasternal heave. In the vast majority of cases a continuous thrill may be felt over the left second intercostal space outside the sternal border. The most characteristic auscultatory finding is the presence of a continuous machinery type of murmur, audible most loudly over the left upper sternal border. The murmur is louder during systole and less so during diastole. The systolic phase is interrupted by multiple systolic clicks. Less commonly, large shunts may be accompanied by left ventricular third heart sound followed by a decrescendo mid-diastolic murmur best heard over the apex beat. This indicates large blood flow across the mitral valve. The second heart sound is usually immersed in the murmur. In cases with pulmonary hypertension the pulmonic component becomes louder and well-heard.

Course and prognosis: Mild cases do not impair cardiac function and they may remain asymptomatic. Large ductus may present with congestive heart failure in infancy. Those cases which recover from heart failure may develop pulmonary hypertension later in life. Large left to right shunt leads to enlargement of left atrium, left ventricle, aorta and pulmonary artery.

Complications: Cardiac failure, infective endocarditis, paradoxical embolism and Eisenmenger's syndrome may complicate PDA.

Investigations

ECG: Left ventricular hypertrophy is noted with large shunts.

X-ray chest: It shows cardiomegaly, pulmonary plethora, prominent aortic arch and sometimes ductal calcification.

Echocardiogram: Colour flow mapping shows shunt flow into left pulmonary artery. Using Doppler the gradients in systole and diastole between aorta and pulmonary artery can be calculated and this gives an idea regarding pulmonary artery pressures.

Catheterization: This is mostly done as a pre-device-closure procedure. Catheterization shows oxygen step up in pulmonary artery and sometimes catheter passes from pulmonary artery, through ductus to the aorta. Aortic angiograms demonstrate the length, diameter and any tortuosity of the ductus and help to plan device closure (Fig. 118.10).

MANAGEMENT

Closure of PDA is advised in all cases due to high risk of infective endocarditis.

Medical: Indomethacin 0.1 mg/kg body weight, can be given in the neonatal period for ductus closure. It acts by inhibiting prostaglandin. Other medical measures include correction of cardiac failure and infective endocarditis prophylaxis.

Surgical closure: Is resorted to if the type of PDA precludes device closure.

Catheter based techniques: A ductus, which is less than 10 mm wide and, has a roomy ampulla and is not very tortuous can be occluded by *Gianturco coil*. Ductus is crossed from aortic to pulmonary artery side or vice versa and the spring coil is deployed with the intent to leave at least one loop on pulmonary artery side and at least three loops on aortic side. Complete closure is reported in 93% cases. Amplatzer ductal occluder is a conical device, that is self-expanding at aortic end and useful for large ductus.

Eisenmenger's Syndrome

Pulmonary hypertension may develop at variable periods of time in congenital heart disease with initial left to right shunt. When severe pulmonary hypertension develops the volume of left to right shunt diminishes. As the pulmonary artery pressure increases, the shunt becomes bidirectional and finally the flow is only from right to left. When the right to left shunt produces cyanosis, the condition is designated as Eisenmenger's syndrome. The common congenital anomalies which cause Eisenmenger's syndrome are ventricular septal defect, patent ductus arteriosus, and atrial septal defect. The VSD and PDA give rise to Eisenmenger's syndrome in childhood itself whereas ASD gives rise to this picture usually after the third decade of life.

Clinical features: The clinical hallmark of Eisenmenger's syndrome is the combination of central cyanosis, digital clubbing, and pulmonary hypertension. In some cases the central cyanosis may be mild and not obvious at rest. Exercise unmasks the cyanosis in such cases. In PDA with Eisenmenger's syndrome, the cyanosis and clubbing are present only in the lower limbs (*called differential cyanosis and clubbing*) because the patent ductus joins the aorta after the origin of the left subclavian artery so that the desaturated blood goes only to the lower limbs.

The second heart sound is the key to diagnosis of the underlying shunt lesion in Eisenmenger's syndrome. ASD-Eisenmenger is characterized by persistence of wide and fixed splitting. PDA is characterized by normally split S2 and VSD by single S2 when they develop Eisenmenger's syndrome.

Course and prognosis: Once Eisenmenger's syndrome develops, the symptoms related to left to right shunt

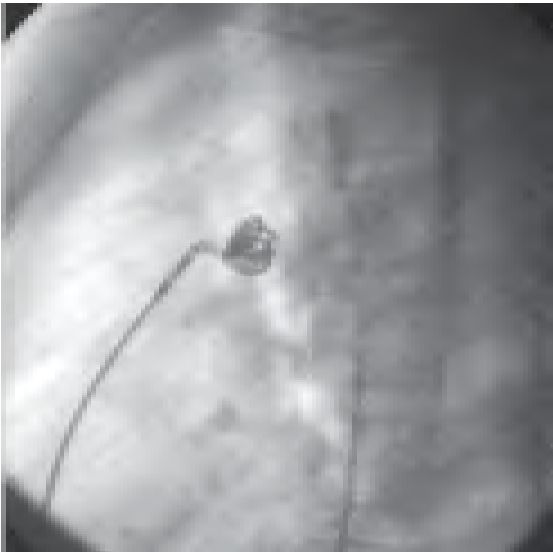
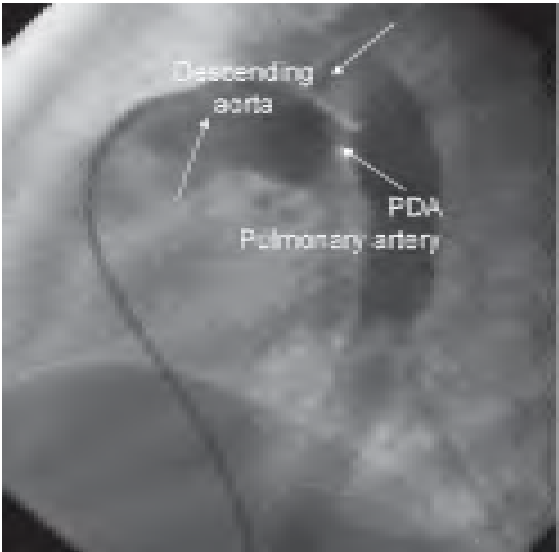


Fig. 118.10: Aortogram showing the ductus and the positioning of coils using a bioprobe inserted via the femoral vein right ventricle and pulmonary artery to occlude the ductus

disappear. At this stage easy fatigability and tiredness dominate the clinical picture. Once congestive heart failure sets in, steady deterioration occurs culminating in death within 3-5 years. Heart lung transplantation or single lung transplant with appropriate surgical correction of the cardiac lesion are the treatment options available at advanced centres.

Congenital Cyanotic Heart Disease

These are all characterized by cyanosis from birth. The common congenital cyanotic heart diseases are associated with reduced pulmonary flow, the commonest being tetralogy of Fallot (TOF).

Tetralogy of Fallot (TOF)

In this condition there is pulmonary stenosis, ventricular septal defect, overriding of the aorta, and right ventricular hypertrophy. The essential abnormality in TOF is obstruction to the right ventricular outflow associated with ventricular septal defect (VSD). The perimembranous VSD is responsible for the aortic override. Right ventricular outflow obstruction leads to right ventricular hypertrophy. In two-thirds of the cases the right ventricular obstruction is caused by infundibular stenosis and in one-third it is caused by pulmonary valvar stenosis. Annular or supra-valvular stenosis may coexist in some.

The right ventricular outflow tract (RVOT) obstruction causes reduction in pulmonary blood flow. Arterial desaturation occurs because of right to left shunt across the VSD. Both right and left ventricular blood enter the aorta.

CLINICAL FEATURES

The main symptoms are cyanotic spells, squatting, and exertional dyspnea. The age at which the symptoms appear depends upon the severity of right ventricular outflow obstruction. However, tetralogy of Fallot seldom presents with cyanosis at birth. Cyanotic spells usually occur after the age of three to six months when the child becomes increasingly active. It is characterized by sudden onset of dyspnea, restlessness and increasing cyanosis. Irritability, incessant crying and hyperventilation are common in younger infants. Sometimes, such attacks may be fatal. Grown up children adopt the squatting position when they become breathless since they obtain relief in this posture.

Varying grades of central cyanosis and clubbing are detectable early. Palpation reveals normal-sized heart without left parasternal heave or pulmonary artery pulsation. This is often referred to as the “*silent precordium*”. In some cases a systolic thrill may be felt in the left upper sternal border. Auscultatory findings are the presence of an ejection systolic murmur over the pulmonary area and left sternal border. The second sound is mostly single and is loud. This is the aortic component. In milder cases the pulmonic component may also be

heard as a feeble sound. The murmur is caused by the right ventricular outflow tract obstruction. The length of the murmur bears an inverse relationship with the degree of RVOT obstruction. In some cases an aortic ejection click may be audible. In cases with severe RVOT obstruction, bronchopulmonary collaterals may develop in an attempt to increase the pulmonary blood flow. These give rise to the presence of continuous murmurs over the chest as well as along the paraspinal region.

Assessment of severity

1. Early onset of symptoms
2. Severe cyanosis
3. Squatting
4. Growth retardation
5. Short murmur
6. Soft murmur

Course and prognosis: This is the commonest cyanotic congenital heart disease which often survives into adolescence and adulthood. In severe cases frequent cyanotic spells occur in infancy and these may be fatal in some cases. TOF predisposes to infective endocarditis. Some cases may develop aortic regurgitation due to prolapse of the aortic cusp into the VSD. In adults with TOF, congestive heart failure may occur. Anemia, infective endocarditis, severe aortic regurgitation and hypertension are the associated conditions which tip these patients into heart failure.

Investigations

ECG: It shows right atrial overload, right ventricular hypertrophy (RVH), right axis deviation and early transition of R waves from lead V₁ to V₂.

X-ray: In classic cases the cardiac size is normal, pulmonary artery is not prominent, there is reduced pulmonary vascularity and the heart is boot shaped (Figs 118.11A and B).

Echocardiogram shows ventricular septal defect with aortic override, right ventricular outflow tract narrowing, pulmonary valve stenosis and also the size of the pulmonary arteries. Doppler evaluation can assess the gradient across right ventricular outflow tract.

Cardiac catheterization: It is useful to rule out coronary artery anomalies, assess the pulmonary artery size and presence of additional VSD if any.

MANAGEMENT

Medical: It includes prophylactic beta-blockers such as atenolol to prevent cyanotic spells and infective endocarditis prophylaxis. The dose of atenolol is 12.5 mg bd or tid.

Surgical: It includes palliative surgeries like **Blalock-Taussig (B-T) shunt** wherein subclavian artery is



Fig. 118.11A: Tetralogy of Fallot

Note: Normal heart size with upturned apex. Concavity at the site of the pulmonary artery. Lung vascularity is reduced. Aorta is left sided in the majority



Fig. 118.11B: Tetralogy of Fallot with right sided aortic arch
Note: Concave pulmonary artery segment, decreased lung vascularity and right sided aortic arch. This occurs in 20% of subjects

anastomosed to pulmonary artery. Modified B-T shunt using Goretex tube to connect subclavian artery to pulmonary artery and corrective surgery, i.e. intracardiac repair during which the RVOT obstruction is corrected by resection, VSD is closed and a trans-annular patch is placed across the pulmonary valve in selected cases.

If there are repeated cyanotic spells or failure to thrive, surgery may have to be undertaken in severely affected children even within the first six months of birth. The procedure of choice is total correction.

Catheter based techniques: Dilatation of pulmonary valve, and dilatation of pulmonary artery stenosis are tried using catheters. Closure of aortopulmonary collaterals using coils is also tried following intracardiac repair.

Pulmonary Atresia

This is characterized by total discontinuity between the right ventricle and the pulmonary artery. The obstruction may take different anatomical forms. These childrens present with cyanosis and reduced pulmonary flow early in infancy. Two types are recognized depending upon the presence or absence of VSD. Pulmonary atresia with VSD is essentially like the tetralogy of Fallot, but the RVOT obstruction is complete. Pulmonary atresia with intact ventricular septum has been divided into two types on the basis of right ventricular (RV) size. In the majority of cases the RV is of diminutive size and in a small percentage RV is of normal size. Blood flows into the pulmonary artery from the aorta though the ductus if it is patent, otherwise, through the bronchopulmonary collaterals. They usually present with progressive neonatal cyanosis, respiratory distress, and early death.

Untreated cases of pulmonary atresia die before the first year of life due to congestive heart failure. In severely cyanotic children, pulmonary blood flow can be increased by doing a *Blalock-Taussig shunt*, which is a palliative procedure. Definitive surgery is undertaken in those with good right ventricular function. The principle of surgical correction is to perform pulmonary valvotomy with a systemic-pulmonary shunt procedure. Trans-catheter perforation of the atretic pulmonary valve using laser and radiofrequency wires, followed by graded dilatation using balloons have achieved impressive results. Till good antegrade flow is achieved the ductus can be kept patent using either prostaglandin E₂ infusion or ductal stenting.

Tricuspid Atresia

Tricuspid atresia is a complex of several separate anatomic abnormalities. These are: (1) Atresia of the tricuspid valve; (2) defect in the inter-atrial septum; (3) hypoplasia of the sinus portion of right ventricle, and (4) usually a ventricular septal defect. The great vessels may be normally connected or transposed. The tricuspid valve is atretic and its location is marked by a dimple. The major clinical finding is moderate generalized cyanosis, often present from the first day of life. In cases with large pulmonary blood flow the left atrium and left ventricle will be dilated and infants present with congestive heart failure.

Severe cases of tricuspid atresia die in infancy due to congestive heart failure. In cyanotic children with small inter-atrial communication a balloon septostomy (creating a large orifice in the septum by using a suitable balloon catheter introduced percutaneously) can be done to allow more free mixing of blood in the atria and this improves the cyanosis. Definitive surgery is **Fontan's procedure** in which the right atrium is connected to the pulmonary artery by a conduit which increases pulmonary blood flow.

Another procedure introduced recently is total cavopulmonary connection in which the superior and inferior vena cavae are anastomosed to the pulmonary artery. The results are better than that of atriopulmonary anastomosis.

Complete Transposition of Great Vessels

Complete transposition of great vessels is the most common cardiac anomaly producing cyanosis in the newborn. The venous connections of the heart are normal, the ventricles occupy normal position, but the right ventricle is connected to aorta which is anterior and the left ventricle is connected to pulmonary artery which is posterior. The two circulations are parallel, and independent of each other. Right ventricle pumps blood into the aorta and this blood is returned by the systemic veins and the vena cavae into the right atrium. Left ventricle pumps blood into the pulmonary artery, which is returned by the pulmonary veins into the left atrium. Life is sustained by the mixing of blood returning from the pulmonary and the systemic veins through VSD, ASD, or PDA.

Clinical features: The condition presents with cyanosis and increased pulmonary blood flow and such cases lead on to congestive heart failure in infancy. Those who survive may develop pulmonary vascular disease. Unless emergency surgery is done, infants presenting with congestive cardiac failure invariably die. Patients with reduced pulmonary blood flow have better prognosis than those with increased blood flow (Fig. 118.12).

Surgical procedures commonly employed to save life	
Corrective surgery	Time
Anatomic repair (arterial switch) (Jatene)	Less than 2 weeks of age
Physiologic repair (atrial switch) (Mustard or Senning)	Neonatal period to 1 year of age
Palliative	
Balloon atrial septostomy	Less than 2 months of age
Blade atrial septostomy	More than 2 months of age
Palliative atrial switch	Other children

Treatment: As soon as the diagnosis is established, an emergency balloon septostomy is made in the inter-atrial septum. This permits flow of at least some oxygenated blood from the left atrium to the right sided chambers and aorta, thereby improving the oxygen saturation in systemic circulation. Keeping the ductus open using prostaglandins can stabilize the baby till it can be transported to a tertiary centre where septostomy is possible.

Later, depending upon the child's condition and availability of surgical expertise more radical procedures can be attempted.

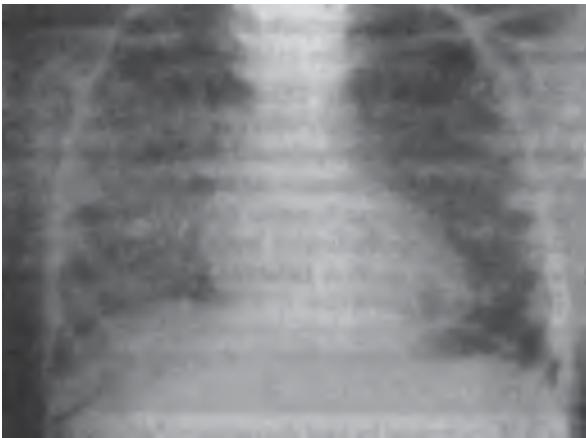


Fig. 118.12: Chest X-ray—Transposition of great arteries
Note: (1) 'Egg on side' appearance of the heart, (2) Relatively narrow vascular pedicle, and (3) Increased pulmonary vascularity

- 1. An arterial switch operation is done in which the aorta is connected to the left ventricle and the pulmonary artery is connected to the right ventricle.
- 2. An alternate procedure which can be undertaken at the age of 6-12 months is to re-route the venous return intra-atrially so that blood from the pulmonary veins is redirected to reach the right ventricle and aorta, and the venacaval blood is redirected to reach the left ventricle and pulmonary artery.

Anomalous Pulmonary Venous Connection

This is also known as total anomalous pulmonary venous drainage. It is the condition in which all the four pulmonary veins enter the right atrium, or vena cava or other systemic veins. In the partial variety, one or more of these veins enter the right atrium (Fig. 118.13).



Fig. 118.13: Chest X-ray—Total anomalous pulmonary venous drainage (supra cardiac type)
Note: Figure of '8' configuration. Right border formed by SVC and left by the vertical vein — slight cardiomegaly and pulmonary plethora.

Often there is associated atrial septal defect. In total anomalous pulmonary venous drainage the site of entry of the pulmonary veins may be supradiaphragmatic (left superior vena cava, vertical vein, coronary sinus, right superior vena cava or right atrium) or infradiaphragmatic (portal vein, hepatic veins or inferior vena

cava). Varying degrees of pulmonary venous obstruction may exist.

The clinical picture is variable. Some may be cyanotic, others present with congestive heart failure from early life, yet others present a picture similar to atrial septal defect. Correction of the defects is by surgery.

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Chronic Valvular Heart Disease

C.G. Bahuleyan

Chapter Summary

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over four months or longer lead to cardiac valvular insufficiency, especially mild AR and MR.

Chronic valvular heart disease—etiology

- Rheumatic fever
- Congenital
- Ischemic heart disease
- Degenerative changes
- Infiltrative and storage diseases
- Heritable disorders of connective tissue, e.g.: Marfan's syndrome
- Collagen vascular diseases
- Rheumatoid disease
- Tumours of heart
- Infective causes
 - Infective endocarditis
 - Syphilis
 - Coxsackie B virus
- Miscellaneous causes
 - Trauma
 - Anticardiolipin antibody
 - Hypereosinophilic syndrome

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GENERAL CONSIDERATIONS

At present in India rheumatic fever is the most common cause for chronic valvular heart disease. In several other countries the incidence is falling. The heart valves are inflamed in the rheumatic process. Approximately 40% of patients with acute rheumatic carditis develop chronic valvular lesions as sequelae. The incidence of rheumatic heart disease varies from 1.8-11.0/1000 school children in the school surveys conducted by Indian Council of Medical Research in different parts of India. Currently there is a decrease in the incidence of rheumatic fever in India. The mitral, aortic, tricuspid and pulmonary valves are affected in the order of frequency. In many cases valvular lesions are multiple. Very rarely all the four valves may be involved.

It has been recognized that appetite suppressant drugs such as fenfluramine, phenteramine and dexfenfluramine when taken alone or in combination for weight reduction

Recent evidence suggests that Coxsackie group B virus which causes carditis may also be involved in the genesis of chronic valvular heart disease. Other causes are syphilis, myxomatous degeneration occurring in Marfan's syndrome, congenital abnormalities of valves, direct infection by bacteria or other pathogens in infective endocarditis, sclerosis affecting the valves, and connective tissue disorders. All valvular heart diseases lead to hemodynamic disturbances in one or both the ventricles and often the atria as well. This is initially overcome by compensatory mechanism but ultimately they lead to

muscle dysfunction, congestive heart failure and sometimes, sudden death.

Mitral Stenosis (MS)

Rheumatic Fever

About 50% of patients with mitral stenosis give history suggestive of antecedent rheumatic fever or other rheumatic manifestations. Others may have subclinical episodes. In the developed countries MS was found to develop 7-10 years after the episode of rheumatic fever. In India, this interval is shorter (2-3 years). This may be a manifestation of the severe nature of the disease in Indian subjects. It is not uncommon to find fullfledged mitral stenosis in children (juvenile MS) (Refer also Section: 6 Chapter 37).

Pathology and pathophysiology: Stenosis results from the involvement of the cusps, commissures and the chordae of the mitral valve apparatus. The cusps become thickened and fibrosed, the commissures fuse and the chordae are thickened, shortened and fused. Anterior leaflet is deformed and there occurs restricted mobility of leaflets. These pathological processes cause distortion and narrowing of the mitral valve orifice. In long-standing cases calcification develops. Normal mitral valve orifice is 4-6 cm² in area. When it is reduced to 2.5 cm² auscultatory findings suggestive of mitral stenosis develop. Aperture size of 2.5-1.6 cm² is mild mitral stenosis and further reduction to 1.5-1.1 cm² leads to moderate stenosis. Valve area below 1 cm² is called severe mitral stenosis. A valve area of < 0.6 cm² is called pinhole MS.

In MS obstruction to left atrial blood entering the left ventricle leads to elevation of intra-atrial pressure. In severe cases, left atrial pressure is often 25-30 mm Hg. The left atrial pressure is reflected back in the pulmonary veins leading to pulmonary venous hypertension. Subsequently pulmonary arterial hypertension sets in. The symptoms and signs of pulmonary venous hypertension decreases when pulmonary arterial hypertension supervenes. Pulmonary arterial hypertension is the result of the following factors:

1. *Passive transmission of pulmonary venous pressure to the arteries (passive pulmonary hypertension);*
2. *Reflex spasm of the arterioles in response to the rise in left atrial and pulmonary venous pressure (reactive pulmonary hypertension);*
3. *Structural changes in the pulmonary vascular bed (obliterative pulmonary hypertension).*

Generally pulmonary artery hypertension correlates with severity of MS. But disproportionate elevation of PA pressure reaching up to systemic or suprasystemic pulmonary pressures may be seen, especially in Indian population.

Chronic pulmonary hypertension leads to right ventricular hypertrophy and eventually right ventricular failure and tricuspid regurgitation.

Clinical Features

Symptoms: Mild to moderate MS may remain asymptomatic and be picked up on routine examination. Severe MS is mostly symptomatic. However, patients may reduce their activities and remain asymptomatic. Commonest symptom is exertional dyspnea and its severity depends upon the degree of stenosis. Exertion leads to tachycardia and increased venous return. These may cause sudden rise in left atrial pressure on account of the narrowed mitral orifice. This in turn causes pulmonary venous engorgement and reduced compliance of the lung which manifests as *dyspnea*, *paroxysmal nocturnal dyspnea* and *orthopnea*. Occasionally this may lead on to *acute pulmonary edema*. Patients with severe pulmonary arterial hypertension and congestive heart failure may experience fatigue, loss of appetite, and occasionally chest pain.

Other common symptoms are *palpitations*, *cough*, and *hemoptysis*. **Hemoptysis is an early symptom** in significant MS. This may result from the following causes:

1. Rupture of dilated intrapulmonary bronchial veins due to rise in pulmonary venous pressure;
2. Recurrent bronchitis;
3. Acute pulmonary edema; and
4. Pulmonary infarction.

Hemoptysis tends to subside as pulmonary arterial hypertension develops.

In long-standing cases of mitral stenosis with gross enlargement of the left atrium, *atrial fibrillation* (AF) develops as a frequent complication. AF occurs in 40% of patients with MS. Incidence is related to duration as well as severity of MS. As age increases, incidence increases. In patients more than 50 years age, 80% are in AF. Atrial fibrillation predisposes to the formation of thrombi in the atria and further embolization. In the younger age groups MS is the commonest cause of atrial fibrillation. The symptoms are aggravated during pregnancy.

Physical signs: In tight MS the pulse is of low volume. Totally irregular pulse should suggest the presence of atrial fibrillation. Jugular venous pulse shows prominent 'a' wave in cases with pulmonary arterial hypertension and prominent 'v' wave in cases with tricuspid regurgitation. In patients with congestive heart failure the mean jugular venous pressure (JVP) is elevated. Signs of right ventricular hypertrophy may be evident. Pulmonic component of S2 may be palpable. The apex beat is characteristically tapping and it is usually felt in the normal position. A diastolic thrill may be palpable over the apex beat. This can be made more prominent by

palpating in the left lateral position with the breath held in expiration. Exercise accentuates the thrill and murmur. The *characteristic auscultatory features of MS are*: (1) Loud first heart sound; (2) mid-diastolic murmur with presystolic accentuation; and (3) the opening snap. The murmur is low-pitched, rough and rumbling in character, and it is preceded by the opening snap. The opening snap is a sharp sound (high-pitched) which is best heard over the apex beat, but conducted widely over the precordium, especially towards the sternum. The duration of the murmur and the interval between the second heart sound and opening snap (A2-OS) correlate with the severity of MS. A short A2-OS interval of < 0.08 sec. indicates severe MS, but converse need not be true. A loud and sharp S1 and OS indicate a pliable valve and hence suitability for balloon mitral valvotomy (BMV). When atrial fibrillation sets in, the presystolic accentuation of the murmur is generally lost in most cases. The pulmonary second sound is accentuated due to pulmonary arterial hypertension. Tricuspid regurgitation gives rise to systolic murmur best audible in left lower sternal border. Its hallmark is the accentuation with inspiration.

Radiology: Plain X-ray film shows features, generally referred to as “mitralization”. These include

- Straightening of the left border of the heart, which is often due to left atrial enlargement
- Prominent main pulmonary artery segment
- Enlargement of the left atrium, may be seen as elevation of left bronchus with widened carinal angle; enlarged left atrial appendages; a shadow with increased density having a convex border medial to right atrial border (shadow through shadow); or as a shadow extending outside the right atrial border (Figs 119.1 and 119.2).

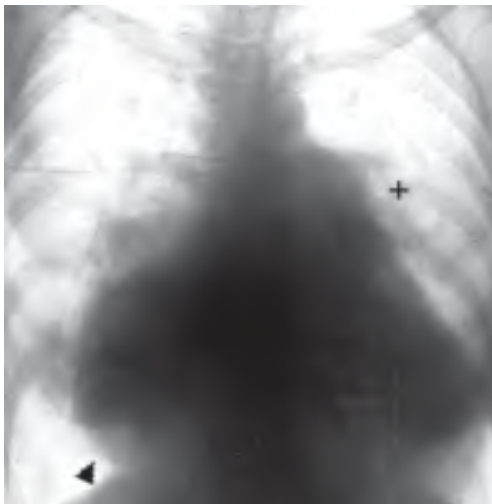


Fig. 119.1: X-ray chest advanced mitral stenosis. Note: 1. Prominence of pulmonary artery segment (+) (previously referred to as pulmonary conus) 2. left atrial shadow within the right atrial border—arrowhead 3. cardiomegaly

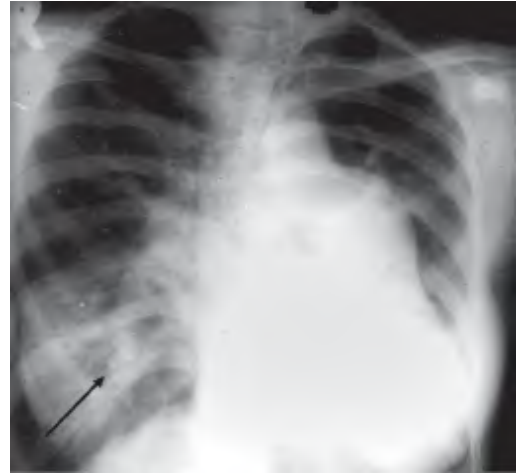


Fig. 119.2: X-ray chest gross pulmonary hypertension etc. Note: (1) right ventricular pattern of cardiac enlargement (2) prominent pulmonary artery segment (3) moderate cardiomegaly

When the left atrium enlarges it bulges posteriorly leading to pressure on the esophagus. The indentation caused by the enlarged left atrium can be demonstrated by a barium swallow picture taken in the right anterior oblique (RAO) view (Fig. 119.3).

Calcification of the mitral valve, may be seen on X-ray by careful examination. Fluoroscopy using image intensifiers brings out calcification better. In a small number of cases the chest X-ray may even appear normal. Acute or chronic pulmonary edema can be seen in the

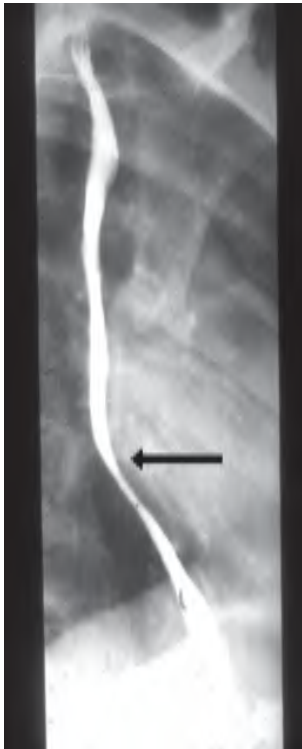


Fig. 119.3: X-ray chest with barium swallow – mitral stenosis. Note: The indentation caused by the left atrium on the barium filled esophagus—arrow

skigram as fluffy shadows radiating laterally from the hilum.

One of the early features of pulmonary venous hypertension is redistribution of blood flow. Blood vessels of the upper lobes dilate, the lower lobe vessel calibre remaining normal. Later all veins are affected.

Chronic venous congestion leads to collection of fluid in interlobar fissures and interlobar septa. The latter appears as **Kerley-B lines** which are dense, short straight, horizontal lines in the costophrenic angles (Fig. 119.4).

Since echocardiography is a much more reliable method to visualize the abnormal anatomy and the presence of atrial thrombi, the importance of radiological methods has come down.



Fig. 119.4: X-ray chest mitral stenosis: Kerley's B lines indicating chronic pulmonary venous hypertension (arrow)

Electrocardiogram (ECG): The ECG reveals left atrial enlargement in patient with sinus rhythm.

Features of left atrial enlargement includes.

- Longer duration of P wave (> 0.10 sec) with notching, the summit of the notches separated by > 0.03 sec.
- Biphasic P in V1 with P terminal force ≥ 0.04 mm sec.
- Leftward shift of P wave axis.
- Duration of P wave (Macruz index) > 1.6 of the PR segment

Right axis deviation and right ventricular hypertrophy are demonstrable in cases with pulmonary arterial hypertension. QRS axis correlates with severity of MS. When QRS axis is $0 \pm 60^\circ$ the mitral valve area (MVA) is $> 1.3 \text{ cm}^2$ and if $> +60^\circ$, MVA is $< 1.3 \text{ cm}^2$. Axis $> +150^\circ$ indicates PA pressures at systemic levels. Atrial fibrillation is a common complication in long-standing mitral stenosis (Fig. 119.5A).

Echocardiography: This is the most useful and reliable non-invasive method for evaluation of MS. Echocardiography can detect the structural details. Hemodynamic abnormality can be assessed by Doppler's echocardiography. Structural details of the mitral valve including calcification, thickening, mobility and subvalvular pathology can be assessed and presence of clot can be found. Mitral valve area can be measured and severity can be graded. Information on LA, RV and LV size and function can be obtained. A scoring system by Abascal *et al* has been found useful in assessing the suitability of mitral valve for balloon mitral valvotomy (BMV). This score evaluates 4 factors—leaflet mobility; leaflet thickening; calcification and degree of subvalvular fusion. A score of 8 or less indicates excellent results with BMV and score more than 10 indicates suboptimal results.

Transesophageal echocardiography provides better images of the left atrium and mitral valve and this is more sensitive in detecting LA thrombi (Figs 119.6 and 119.7).

Cardiac Catheterization

This is done only in the following indications:

- To assess coronary artery disease when mitral valve replacement is planned in persons > 40 years of age.
- To assess the hemodynamic changes due to associated mitral or aortic regurgitation (Fig. 119.8).
- To assess the extent of pulmonary vascular abnormality in cases where the clinical and echocardiographic findings are contradictory.

Course and prognosis: This depends on the severity of the stenosis. Though mild cases are generally asymptomatic, heavy exertion may lead to acute pulmonary edema. In moderate and severe cases the disability progressively increases. Pulmonary hypertension becomes established and progresses over many years leading to right ventricular hypertrophy and subsequently failure.

ATRIAL FIBRILLATION

Atrial fibrillation is a very frequent complication. AF is seen in 40% of patients. AF increases risk for embolism and incidence of embolism may be as high as 20%. It also increases mortality and morbidity.

The frequency of atrial fibrillation increases with the duration of the disease and with the enlargement of the left atrium. Onset of atrial fibrillation marks a downhill course in mitral stenosis. Clots form in the atria and, therefore, the risk of systemic and pulmonary embolism is high. **Systemic embolism** manifests as hemiplegia, other neurological deficits, embolism in the arteries of the limbs, mesenteric embolism, renal infarcts and embolism in other parts of the circulation. Clots arising from the right atrium give rise to multiple pulmonary emboli (see also Section 14 chapter 140).

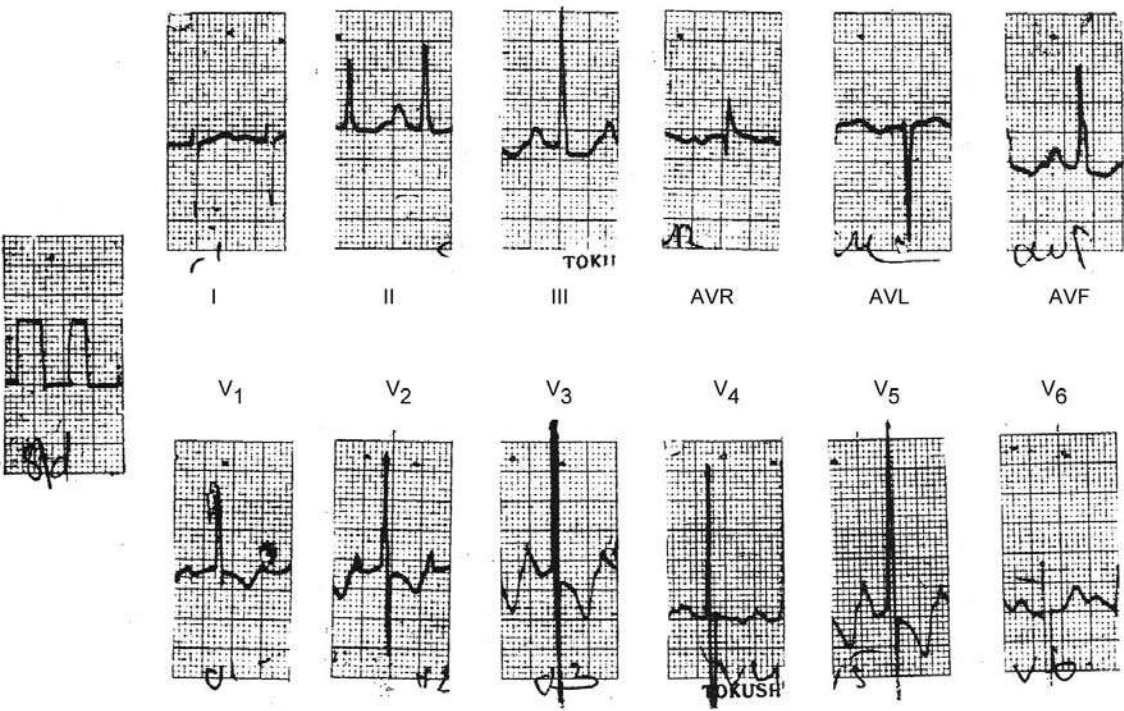


Fig. 119.5A: Right ventricular hypertrophy. Note: prominent R waves in lead V₁

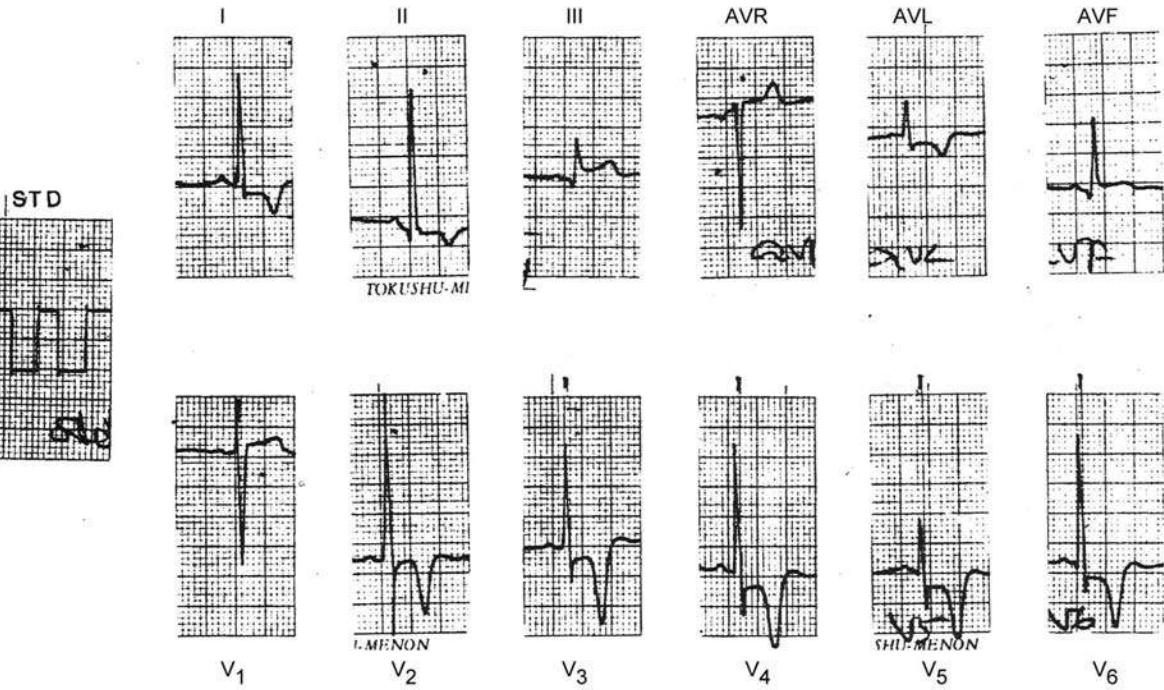


Fig. 119.5B: Left ventricular hypertrophy
Note: S in V₁ + R in V₆ exceeds 35 mm

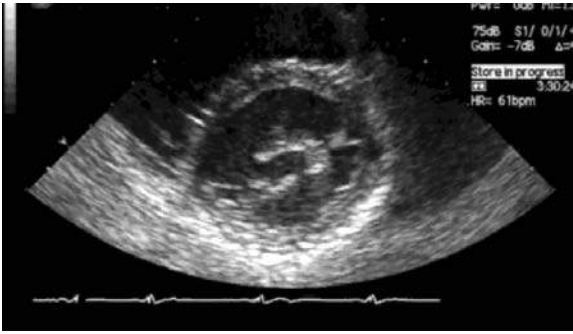


Fig. 119.6: Echocardiogram in mitral stenosis: Short axis view
Note: The stenotic mitral valve orifice. Valve aperture below 1cm^2 indicates severe stenosis

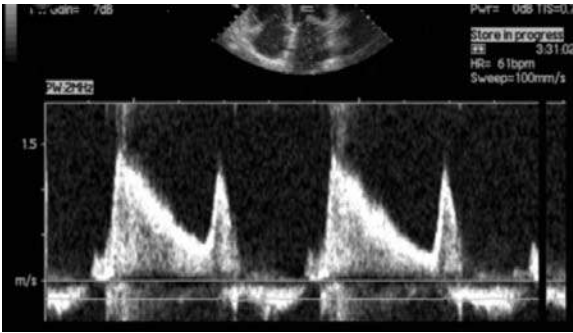


Fig. 119.7: Continuous wave Doppler tracing used to assess blood flow across the valve. This tracing is from a normal person

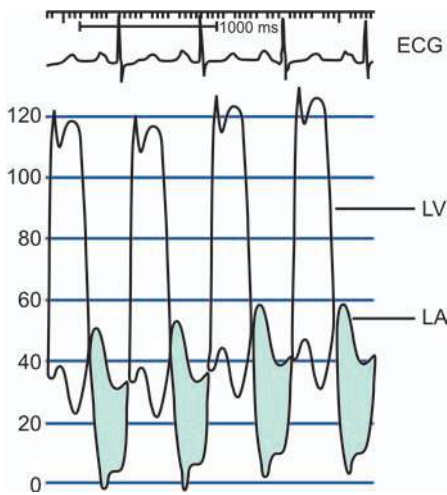


Fig. 119.8: Mitral stenosis: cardiac catheterization; LV and LA pressures are superimposed, showing the gradient in diastole between LA and LV indicating high pressure in the atrium in mitral stenosis

Onset of atrial fibrillation further reduces cardiac output in cases of critical mitral stenosis and, therefore, precipitates cardiac failure. In mitral stenosis all forms of cardiac failure may develop. These include acute pulmonary edema, congestive heart failure and right sided heart failure.

Acute pulmonary edema may occur in unexpected circumstances and this may prove fatal, if emergency treatment is not given. The most common type of cardiac failure is **congestive heart failure** involving both sides of the circulation. Events such as pregnancy, parturition, systemic infection or unaccustomed exercise precipitate cardiac failure and this may be the mode of presentation in at least a few cases.

Infective endocarditis may complicate pure mitral stenosis, but the incidence is low. Combined lesions such as mitral stenosis and regurgitation are more prone to develop secondary infection. Ten years mortality in class III patients is 85% while none of class IV patients survive beyond 10 years. Majority of deaths are due to CHF (around 60%) and systemic embolism (around 20%).

TREATMENT

General measures: As such, mitral stenosis does not resolve through medical treatment. In a considerable proportion of cases, however, several coexistent remediable factors aggravate the disability. These include anemia, pulmonary eosinophilia, systemic and respiratory infections, obesity, thyrotoxicosis, and pregnancy. Proper management of these conditions may give considerable symptomatic relief.

Medical therapy includes:

1. Long-term anticoagulation in patients with AF with previous history of embolism and/or in those > 35 years with AF
2. Infective endocarditis prophylaxis
3. Rheumatic fever prophylaxis
4. To reduce heart rate using negative chronotropic drugs. In patients with AF, A-V blocking drugs like beta blockers, diltiazem, and verapamil or digoxin can reduce ventricular rate and reduce symptoms. Even in patients with sinus tachycardia, reducing the heart rate with beta blockers can reduce the pulmonary venous pressure and reduce the symptoms.
5. Diuretics are used if symptoms of pulmonary or systemic venous congestion develop.

Dose of drugs

Diltiazem—30-90 mg oral b.d or t.i.d

Verapamil—40-80 mg oral b.d or t.i.d

Digoxin—0.125-0.25 mg daily oral for 5 days a week continuously

Diuretics-frusemide—40 mg oral o.d in the morning

Ethacrynic acid—50-100 mg oral o.d

Triamterene—150-250 mg oral o.d

Catheter Interventions

Balloon Mitral Valvotomy (BMV): Inflatable balloon (Inoue, Accura) are introduced through the femoral vein and manipulated to enter LA by puncturing interatrial septum and positioned across the mitral valve and dilated.

This has now become the treatment of choice in patients with pliable valve. BMV should be considered in patients with $MVA \leq 1.5 \text{ cm}^2$ who are symptomatic class II and above or in asymptomatic patients if pulmonary artery systolic pressure is $> 50 \text{ mm Hg}$. BMV is now done in many centers in India, the approximate cost of which is Rs. 25,000. 5-7 year survival without mortality, repeat valvotomy or MVR is 80-90%. Most frequent complication is development of mitral regurgitation (MR).

Though initially only ideal pliable valves were taken-up for BMV, with technical improvements and expertise, especially with newer devices like **Cribier Commissurotome**, patients with calcification and mild to moderate MR are also being taken for BMV with good results.

Randomised clinical trials comparing BMV and surgical techniques like open mitral valvotomy and closed mitral valvotomy have shown no significant differences in terms of acute results, complication rates, clinical improvement and exercise time at 1 year and 3 years.

Surgical Treatment

1. **Closed mitral valvotomy (CMV):** In this technique, closed surgical commissurotomy is performed without cardiopulmonary bypass, using either transatrial or transventricular approach. Pliable noncalcified valves without subvalvular fusion achieve best results. CMV remains the surgical treatment of choice in many centers in India. In expert hands the mortality is less than 2% and the immediate results are excellent. Success of the procedure depends on the degree and quality of split of the valve achieved. Complications include improper split, tear of the valve with production of significant MR, and dislodgement of atrial clots with thromboembolism. Reported 5 years reoperation rate is 5-7%.
2. **Open mitral valvotomy (OMV):** In developed countries OMV is the surgical procedure of choice. OMV allows direct inspection of the valve under cardiopulmonary bypass so that commissures can be split under direct vision and other repair procedures can be undertaken. Mortality in different centers varies from 1-3%.
3. **Mitral valve replacement (MVR):** MVR is an accepted procedure for patients who are not candidates for surgical commissurotomy or BMV. Mortality is less than 5%. However postoperative complications of prosthetic valve like risk of anticoagulation, infective endocarditis, valve malfunction and embolic events may occur. The cost of open heart surgery varies from Rs 60,000 to 100,000.

Actuarial analysis done on Indian series has shown that 94%, 89.4%, 85% and 78.3% survived without need for second procedure after mitral valvotomy at 6, 12, 18 and 24 years follow-up. The restenosis rate ranged from

4.2-11.2 per 1000 patient years annually, on 5 and 15 years follow-up.

Pregnancy and Mitral Stenosis

MS is the most common rheumatic valvular lesion complicating pregnancy. Previously asymptomatic patients may present with symptoms. Pregnancy has to be avoided in patients with tight mitral stenosis, till the latter is corrected. If MS is diagnosed during middle or late pregnancy, and if symptoms persist despite medical management, surgical intervention may be necessary. If patient develops acute pulmonary edema refractory to medical therapy, emergency intervention is indicated. Risk to mother and fetus is quite acceptable, and hence intervention should not be delayed. BMV is very safe, the fetal and maternal mortality has been virtually nil.

MITRAL REGURGITATION (MR)

Syn: Mitral incompetence

The mitral valve apparatus consists of six components:

1. Valve cusps,
2. Mitral annulus,
3. Chordae tendinae,
4. Papillary muscles,
5. Portion of the left ventricle where the papillary muscles are implanted, and
6. Portion of the left atrium adjacent to the mitral annulus.

Defective function of one or more of these components may lead to inadequate coaptation of the mitral leaflets in systole giving rise to various degrees of mitral regurgitation. The common *etiological factors* of isolated mitral regurgitation are:

Mitral Regurgitation—Etiology
• Rheumatic • Congenital • Myxomatous degeneration • Ischemic heart disease • Cardiomyopathies • Infective endocarditis • Mitral annulus calcification • Trauma • Post-surgical/intervention • Collagen vascular disease • Abnormalities of collagen, e.g. Marfan's syndrome

At present, in many countries severe grades of mitral valve prolapse syndrome (MVP) is the commonest cause for mitral incompetence. In India also this is probably so, though rheumatic mitral incompetence is also quite common. On account of the wide prevalence of MVP among Indian subjects, it is described separately.

In rheumatic mitral regurgitation the valve leaflets are thickened, fibrosed and contracted. The chordae are also

shortened and fused. This process causes inadequate closure of the mitral leaflets in systole and hence MR results.

Ischemic heart disease leading to MR is commonly seen in males after the age of 40 years. Transient or permanent dysfunction of the papillary muscles leads to MR. Posterior papillary muscle is more commonly involved. Occasionally rupture of the papillary muscles may complicate myocardial infarction and this results in severe acute mitral regurgitation. Ischemia of the myocardium can result in transient dyskinesia of the portion of left ventricle where the papillary muscles are implanted and this may result in MR. Chronic ischemic heart disease with ventricular aneurysm may also be associated with MR.

Cardiomyopathy involving the left ventricle results in MR. It may be seen in all the three main types of cardiomyopathy (endomyocardial fibrosis, dilated cardiomyopathy and hypertrophic cardiomyopathy). Severity of mitral regurgitation varies widely in these cases. In infective endocarditis, rupture of chordae may occur and this gives rise to acute mitral regurgitation.

Hemodynamic changes: Left ventricular blood regurgitates into the left atrium during systole. The blood returning from the left atrium is larger in volume, leading to diastolic overfilling of the left ventricle. Since part of the blood flowing into the left ventricle shuttles between the left atrium and ventricle without participating in cardiac output the left ventricular work load is increased. The output into the aorta is maintained normal or near normal for considerable periods, but the systolic ejection time is shortened and this gives the characteristic rapid upstroke for the pulse. In mild cases the cardiac function is well compensated, but in severe cases gross left ventricular dilatation and hypertrophy develop. Ultimately left ventricular failure supervenes resulting in pulmonary hypertension and right ventricular failure as well. Fall in the ejection fraction below 60% and rise in the end systolic volume of left ventricle worsen the prognosis.

CLINICAL FEATURES

This depends on the severity of MR. Symptoms include palpitation, exertional dyspnea, weakness, and fatigue. The only abnormality in mild cases is the presence of a pansystolic murmur over the cardiac apex. In moderate and severe cases other features develop. The pulse of severe MR is described as pseudocollapsing with the pulse pressure above 40 mm Hg, it is normal in volume, but short in duration. Left ventricular enlargement is evidenced by the forcible apex beat which is shifted down and out. The characteristic murmur of MR is medium to high-pitched pansystolic murmur heard best over the apex beat. In cases where the anterior mitral leaflet is damaged,

the murmur is conducted to the axilla because the direction of the regurgitant stream from the left ventricle is towards the body of the left atrium. In cases with posterior leaflet involvement the murmur is conducted to the anterior chest and to the right upper sternal border because the regurgitant stream is directed towards the interatrial septum. In moderate and severe cases the murmur occupies the whole of systole and is moderately loud in intensity. Such cases show evidence of left ventricular enlargement. A left ventricular third heart sound is common. A mid-diastolic murmur which is decrescendo in character may be heard over the apex beat following the third heart sound. The third heart sound and the diastolic murmur indicate increased flow across the mitral valve. In severe cases evidence of pulmonary arterial hypertension may be evident.

Electrocardiogram is normal in mild cases. In moderate and severe cases left ventricular hypertrophy and left atrial enlargement are seen. The ECG may also help in determining the etiology of MR as in the case of ischemic heart disease, or cardiomyopathy (Fig. 119.5B).

Chest X-ray: Moderate and severe cases show left ventricular type of cardiac enlargement. The left atrium is also enlarged. Very large left atrium (giant left atrium) occurs in some of the severe cases. Evidence of pulmonary venous and arterial hypertension may be seen (Fig. 119.9).

Echocardiography—is useful in the assessment of etiology and severity of MR. It is also useful to decide the timing of surgery and suitability for surgical repair. With widespread use of Doppler and colour Doppler echocardiography, severity of MR can be assessed accurately, even though the quantitation remains only approximate. Information on ventricular function and

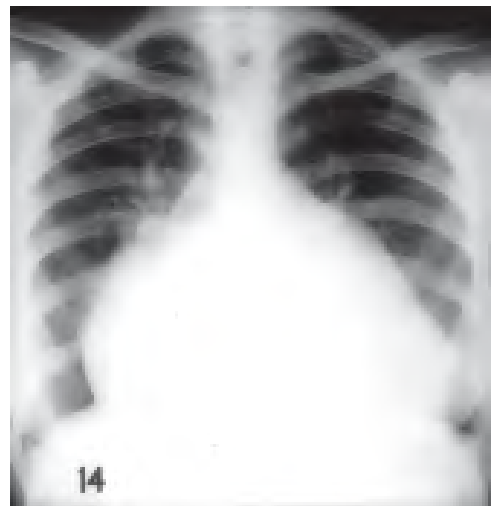


Fig. 119.9: X-ray chest showing cardiac enlargement of left ventricular type. Note: The convex left border with the apex reaching down. Note also left atrial enlargement

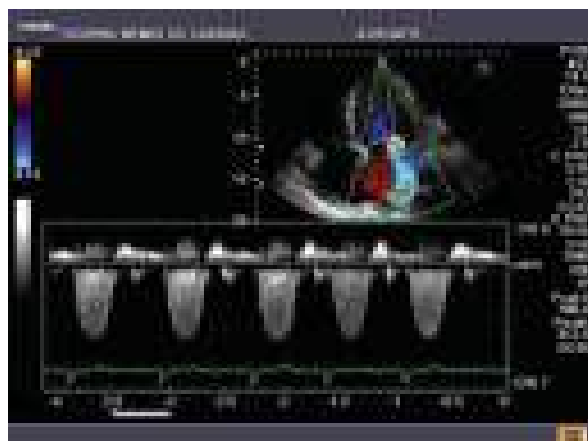


Fig. 119.10: 1. Upper panel showing colour Doppler echo with mitral regurgitation 2. lower panel showing continuous wave Doppler of mitral incompetence

pulmonary hemodynamics are obtainable from echo studies obviating the need for invasive investigations (Fig. 119.10).

Cardiac catheterization may be indicated in situations where associated coronary artery disease is to be assessed or coexisting valvular lesions are to be quantified.

Complications: These include congestive heart failure, atrial fibrillation and infective endocarditis. It should be remembered that MR is one of the best tolerated lesions and, therefore, may remain asymptomatic for several years.

Course and prognosis: Mild MR may remain asymptomatic. Unless complicated by infective endocarditis, it may not progress further. Moderate and severe cases become symptomatic. Development of pulmonary hypertension is relatively slow in MR and the pulmonary pressure tends to be lower than that seen in mitral stenosis. In India where rheumatic heart disease is still rampant, severe grades of pulmonary arterial hypertension are seen in MR. Severe MR usually progresses and results in congestive heart failure. Atrial fibrillation may develop as a complication, but embolic episodes are less frequent compared to mitral stenosis.

Acute severe MR is almost always a medical emergency and even with emergency treatment, the mortality is high. Common causes of acute severe MR are acute myocardial infarction with papillary muscle rupture, infective endocarditis, trauma and acute rheumatic fever.

TREATMENT

Medical: Treatment includes:

- Infective endocarditis prophylaxis
- Rheumatic fever prophylaxis
- Diuretics if pulmonary or systemic venous congestion occurs
- Treatment of congestive heart failure if present

e. Afterload reduction—In acute MR, IV nitroprusside to reduce afterload may be life-saving. In chronic MR, ACE inhibitors or oral hydralazine may be used which can reduce the severity of symptoms.

Surgical management: Mitral valve repair and valve replacement are the available options. Valve repair is indicated for less damaged valves. Valve replacement is needed for more grossly damaged and calcified valves. Both are open heart surgical procedures with surgical mortality of 1-2%. Valve replacement also necessitates long-term anticoagulation.

Optimal timing of surgery is important. Patients with asymptomatic MR should be followed up periodically to decide the progression of MR as well as detect onset of LV dysfunction. Aim is to give the corrective treatment before onset of LV dysfunction. Recently the mortality of MVR has declined in good centers to 1-2% so that surgical corrective treatment can be advised more liberally.

Indications for surgery in chronic MR

- Symptomatic severe MR
- Moderate MR with class III/IV symptoms
- Asymptomatic severe MR if
 - LVEF < 60%
 - LV end systolic diameter ≥ 4.5 cm
 - LV dp/dt ≤ 90 mmHg/s

COMBINATION OF MITRAL STENOSIS AND INCOMPETENCE

In a large number of cases of rheumatic affection of the mitral valve there is a combination of mitral stenosis and incompetence. Either may predominate. The clinical findings are modified depending upon the severity of each lesion. In such cases mitral valve replacement is the treatment of choice.

Mitral Valve Prolapse (MVP)

Syn: Midsystolic click syndrome, floppy valve syndrome, Barlow's syndrome

Prolapse of the mitral valve into the left atrial cavity during systole may develop in 5-10% of apparently healthy young adults. MVPS is a heterogenous condition. Strict echocardiographic criteria have been formulated for diagnosis. When these are applied, the frequency of this disorder is 3% in the general population. Most of the cases are sporadic, but autosomal dominant familial incidence is noted in a few. In most of them the abnormality remains asymptomatic till detected by routine medical examination or investigative procedures. In some the valve cusps show myxomatous degeneration which makes them redundant. Prolapse resulting from myxomatous degeneration of the valves and unaccompanied by other defects is called *primary mitral valve prolapse*. In classic MVP, the valves

are more thickened and the prolapse is more. In non-classic prolapse, thickening and the extent of prolapse are less. MVP may also be associated with other defects like atrial septal defect, tetralogy of Fallot, Marfan's syndrome, straight back syndrome, acute rheumatic fever, ischemic heart disease, pectus excavatum, Ebstein's anomaly, and hyperthyroidism. This type is called *secondary mitral valve prolapse*. MVP may exist with or without mitral regurgitation. The mechanism of myxomatous degeneration of the valve leaflets is not clear. The middle spongiosa layer of the valve cusps is thickened due to accumulation of proteoglycans. The leaflets and chordae become abnormal. There are abnormalities in the distribution and architecture of fibrillin, elastin and collagen I and II. Chordal rupture may develop which can result in severe mitral regurgitation.

CLINICAL FEATURES

Symptoms occur only in a small proportion of patients with MVP. These include palpitation, vague chest pain, dyspnea, and non-cardiac symptoms such as vascular headache and anxiety state. In most cases chest pain is non-cardiac. In a few there may be associated spasm of the coronary artery. Undue stretch on the papillary muscles may also impair the blood flow in the branches of the coronary artery adjacent to them. These factors may lead to anginal pain. Palpitation may result from anxiety or arrhythmias such as ectopic beats and paroxysmal tachycardias (both supraventricular and ventricular). Diagnosis is made on the presence of a non-ejection systolic click with or without late systolic murmur, best made out over the apex on auscultation. The click moves towards the first sound and the murmur becomes louder and prolonged when the patient stands. These changes are reversed when the patient squats. The degree of MVP correlates inversely with the size of left ventricular cavity, and this accounts for the change in auscultatory phenomena with the position of the patient. ECG may show non-specific ST-T changes in II, III, aVF and sometimes in anterior chest leads and this can mimic ischemic heart disease especially if patients present with atypical chest pain. Diagnosis can be confirmed by echocardiography which is the investigation of choice. *Often there is an overdiagnosis of MVP with echocardiography and this may lead to anxiety neurosis. More than 2 mm displacement of one or both leaflets in parasternal long axis view as well as apical 4 chamber view is diagnostic.* In the vast majority of patients the prognosis is excellent for life and health.

Complications: All cases of MVP have increased risk of developing infective endocarditis. 90% are hemodynamically normal. Ten percent develop significant mitral regurgitation, in whom some may progress and become severe. Acute mitral regurgitation may result from chordal rupture. Sudden cardiac death due to ventricular arrhythmias and thromboembolism are rare complications.

Treatment: Those presenting with symptoms of anxiety and chest pain may be benefited by the use of tranquilizers like chlordiazepoxide 10 mg. Propranolol 20-40 mg/day may alleviate chest pain and palpitation. Cardiac arrhythmias should be treated with antiarrhythmic drugs. Cases developing severe mitral incompetence may require valve repair or replacement. All subjects with mitral valve prolapse should be informed about the condition so as to avoid undue anxiety, and invasive investigations. All of them should have prophylaxis against infective endocarditis, when indicated. MVP patients with thromboembolic phenomenon in whom no other cause is found may be started on aspirin. Operative risk of mitral valve repair in MVP is <1%.

Further reading: EMIL HAYEK, et al. Mitral valve prolapse syndrome. The Lancet 2005;365:500-18.

Acquired Aortic Stenosis (AS)

Etiology: Current evidence is that stenosis developing in congenital bicuspid aortic valve is the most common cause below the age of 30 years. Between 30-70 years bicuspid aortic valves, rheumatic valvulitis and calcification account for the majority of cases. Above the age of 70 years degenerative calcification, bicuspid valves, and rheumatic valvulitis are the frequent causes.

Rheumatic aortic stenosis: Active rheumatic endocarditis of the aortic valve leads on to thickening of the valve cusps with fusion of all commissures or fusion of a single commissure. This results in varying degrees of narrowing of the aortic valve orifice. Subsequently, hemodynamic stress on this abnormal valve produces further degenerative changes and consequent calcification. However, calcification occurs much later than in the case of congenital bicuspid aortic valve. Pure aortic stenosis is rare to develop in rheumatic heart disease. In most cases it is associated with aortic incompetence and mitral valve disease. In the series reported from CMC Vellore mitral stenosis was present in 11.8% of cases with aortic valve disease. 91.7% has a combination of aortic regurgitation and stenosis.

Degenerative calcification of aortic valve: This results from the degeneration and calcification of the tricuspid aortic valve. The calcification is more towards the base of the aortic leaflets and the commissures are free. Hypertension and hypercholesterolemia accentuate the process.

Hemodynamic changes: The aperture of the normal valve is 2.5 cm². Narrowing of the aperture to 0.75 cm² or less produces severe obstruction to left ventricular ejection and a pressure gradient across the aortic valve develops which may reach 50 mm to even 200 mm Hg. In critical AS the valve area is < 0.5 cm². The left ventricle undergoes

concentric hypertrophy which clinically manifests as heaving apex beat. The hypertrophy is both adaptive – to increase the force of contraction and maladaptive in that the hypertrophied myocardium is less perfused even in the presence of normal coronary arteries. Finally, the left ventricle dilates and fails. Heart failure may be the result of diastolic dysfunction, systolic dysfunction or both. The former is due to increased thickness of the left ventricle. Systolic dysfunction results from excessive afterload, decreased ventricular contractility or both. When the force of contraction of the ventricle reduces, the intensity of the murmur diminishes. Due to the fixed cardiac output, syncope results when the subject exerts. Angina is caused by increased oxygen demand resulting from left ventricular hypertrophy and reduction of coronary blood flow due to increased intraventricular pressure.

CLINICAL FEATURES

The symptoms are not very reliable in assessing the severity of aortic stenosis, since even significant aortic stenosis may remain asymptomatic for long periods. Sudden death may occur as a result of fatal arrhythmias even in asymptomatic subjects. **The three most important presentations of significant aortic stenosis are angina pectoris, syncope, and left ventricular failure.** Fifty percent of patients with angina are found to have associated significant coronary artery disease on coronary angiogram. Other symptoms include palpitation, exertional fatigue and visual field defects probably secondary to minute calcific emboli from the aortic valves.

The characteristic physical findings develop in significant aortic stenosis. The pulse is described as *anacrotic*. This is a small volume and slow rising pulse. The decrease in amplitude and delay in time is referred to as *pulsus parvus et tardus*. The pulse pressure is usually less than 30 mm of mercury because of depression of the systolic pressure. In the elderly subjects even with significant aortic stenosis the systolic pressure may occasionally reach 160 mm Hg more due to inelasticity of the aorta. Consequently, in such patients the severity of aortic stenosis cannot be predicted from the amplitude of pulse pressure. Apex beat is characteristically forcible and sustained (*heaving*). There may be a systolic thrill, best felt in the second right intercostal space, or along the left sternal border and very rarely over the apical impulse also. Auscultation reveals a harsh grunting ejection systolic murmur which is conducted to the carotids and well heard over the apical impulse as well. The ejection systolic murmur corresponds to the period of ejection, i.e. it starts with the opening of the aortic valves and is over before the second sound is heard. The murmur becomes louder with the phase of maximal

ejection and towards the latter part of systole the murmur comes down. In severe stenosis the murmur is longer, louder, and its peak is reached later in systole. The aortic component of the second heart sound is delayed and soft. The second heart sound may be split paradoxically. P2 is accentuated when PAH develops and S4 may be audible. If valve cusps are mobile ejection click may be present and this disappears when the valve gets calcified or infective endocarditis occurs. In patients with calcified valves, high frequency components of the murmur may be selectively radiated to the apex, a phenomenon called **Gallavardin phenomenon**. When LV fails, cardiac output falls and the murmur becomes soft and may disappear.

Electrocardiogram is normal in mild cases. In significant aortic stenosis, ECG shows left ventricular hypertrophy as well as left atrial overload pattern. The ECG pattern of left ventricular hypertrophy generally correlates with the severity and prognosis of aortic stenosis (Fig. 119.11).

Radiological findings: In aortic stenosis the heart is not usually enlarged. The ascending aorta is dilated. Post-stenotic dilation of the aorta may be seen. This post-stenotic dilation does not have any relation with the severity of aortic stenosis. Calcification of the valve may be seen (Fig. 119.12).

Echocardiography: It is helpful in visualizing the nature of the aortic valve and the severity of the stenosis. Doppler studies can estimate the gradient across the valve, and the valve area, and assess the severity.

Cardiac catheterization and angiography help in the accurate determination of the severity of aortic stenosis. Intracardiac pressure studies reveal the gradient between left ventricular pressure and aortic pressure. Coronary angiography should be performed to exclude coronary artery disease (Fig. 119.13).

Course and prognosis: Mild cases do not progress and may remain asymptomatic. However, the course of aortic stenosis cannot be predicted with confidence because of the variability in its progression due to the deposition of calcium. Rapid progression may be seen in elderly.

Grave symptoms may develop abruptly in an asymptomatic patient. In patients with significant AS, 5-year survival is 64%. Once they become symptomatic with angina, syncope or LVF, the average survival is only 5, 3 and 2 years respectively. Sudden cardiac death usually occurs in symptomatic patients. In asymptomatic patients it is rare (2%).

Aortic stenosis due to any cause detected clinically or echocardiographically is associated with increased mortality as an independent factor even in the absence of hemodynamic abnormalities.

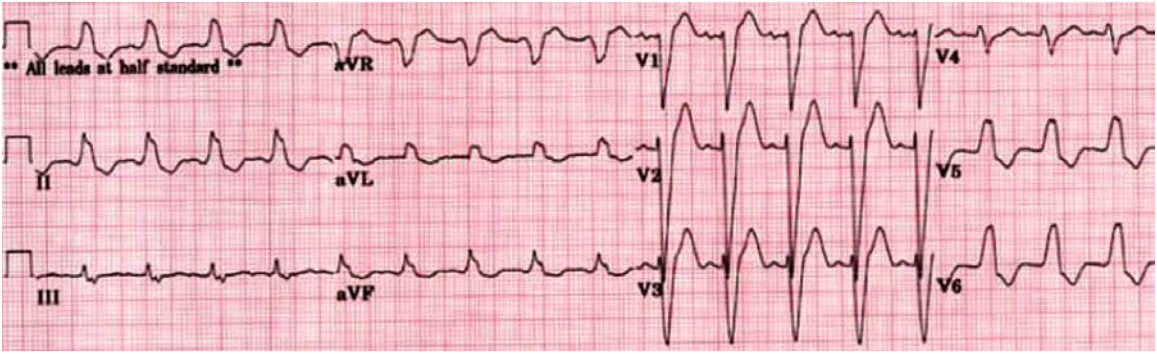


Fig. 119.11: ECG showing left ventricular hypertrophy in aortic stenosis. Note: 1. Deep S waves in V1 and V2 and tall broad R waves in V5, V6. ST depression in leads V5, V6. The amplitude of SV2 + RV5 or V6 is above 35 mm

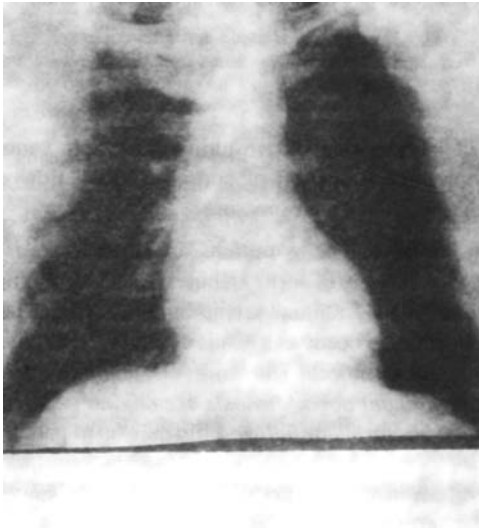


Fig. 119.12: X-ray chest – Aortic stenosis
Note: Left ventricular type cardiac contour. Muscle hypertrophy is more prominent than dilatation

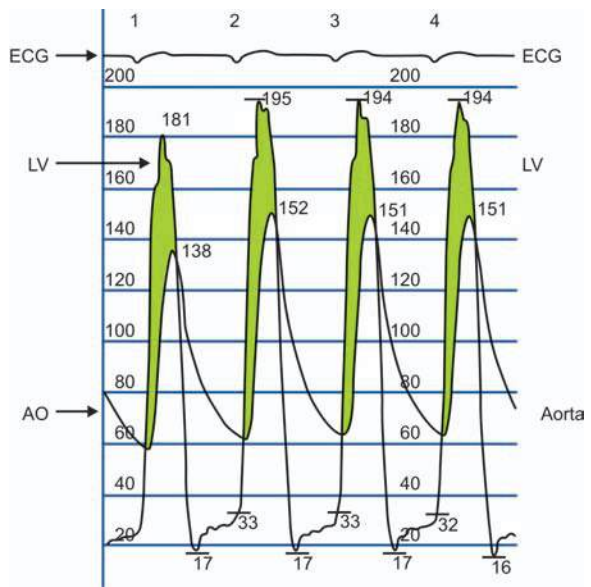


Fig. 119.13: Cardiac catheterization in aortic stenosis (AS): LV and aortic pressures are superimposed. This shows gradient in systole between LV and aorta indicating aortic stenosis. In severe AS the peak systolic pressure gradient exceeds 75 mm Hg and the mean gradient is more than 50 mm Hg

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Management

Medical: Management includes

- Infective endocarditis prophylaxis
- Rheumatic fever prophylaxis
- Evaluation and treatment of coronary risk factors
- Treatment of congestive heart failure

Surgical interventions include

- AVR (aortic valve replacement)
- Aortic valvotomy—surgical or balloon
- AVR along with CABG if associated coronary artery disease is present.

Indications for surgery

- Symptomatic patients
- Asymptomatic severe AS

Aortic valve replacement (AVR) is the surgical intervention of choice. Balloon or surgical valvotomy is

effective in children with congenital AS, but is much less successful in adults.

Aortic Regurgitation (AR)

Syn: Aortic Incompetence

Aortic regurgitation results when the aortic valve cusps are not able to close the aortic orifice completely during diastole. This may be caused by abnormalities of the valve or dilation of the aortic root. Aortic valve cusps are inflamed in acute rheumatic carditis giving rise to mild aortic regurgitation. Moderate to severe aortic regurgi-

tation may *develop* later. Generally, aortic valve and the mitral valve are affected simultaneously in rheumatic fever.

Causes of aortic regurgitation

- Congenital—bicuspid, tricuspid, quadricuspid valves
- Rheumatic valvulitis
- VSD—Ventricular septal defect
- Infective endocarditis
- Syphilis
- Ankylosing spondylitis
- Marfan's syndrome
- Aortoarteritis
- Rheumatoid arthritis
- Aortic aneurysm
- Aortic dissection
- Annulo-aortic ectasia
- SLE—Systemic lupus erythematosus
- Hypertension—severe and acute
- Myxomatous degeneration
- Ehlers-Danlos syndrome
- Trauma
- Reiter's syndrome
- Behcet's syndrome
- Osteogenesis imperfecta
- Mucopolysaccharidoses

The most common cause of isolated aortic regurgitation is congenital bicuspid aortic valve. Such valves may be primarily incompetent or further damage by infective endocarditis may make them so. In subaortic stenosis also varying degree of AR may be present. Ventricular septal defect may be associated with AR. Diseases such as syphilis, ankylosing spondylitis, Reiter's disease, rheumatoid arthritis, annuloaortic ectasia, aneurysm of the aorta and aortic dissection which affect the root of the aorta can all produce abnormality in valve closure resulting in varying degrees of aortic regurgitation.

Infective endocarditis produces and worsens aortic regurgitation. Acute rupture of the valve cusps in infective endocarditis leads to acute AR. Blunt trauma to chest and acute elevation of systemic blood pressure also account for a few of the cases. In Marfan's syndrome aortic regurgitation is not uncommon.

Hemodynamic disturbances: In AR part of the blood pumped out into the aorta leaks back into the left ventricle during diastole. The proportion of the cardiac output regurgitating may vary widely. The left ventricle receives blood from the left atrium and the aorta during diastole and this leads to diastolic overfilling. The ventricle undergoes dilatation and hypertrophy. Stroke volume is increased. The systolic blood pressure may go up. Peripheral vasodilatation develops in moderate to severe cases and the peripheral resistance falls. Regurgitation of aortic blood and fall in peripheral resistance result in considerable lowering of the diastolic pressure. The pulse

pressure is markedly increased. The heart compensates and maintains the cardiac output for considerable periods by dilatation and hypertrophy, but ultimately left ventricular failure develops. **AR is an example of combined volume overload (distended ventricle) and pressure overload (increased systolic BP of left ventricle).**

CLINICAL FEATURES

Mild and moderate cases may remain asymptomatic. Chronic severe AR is associated with symptoms like palpitation, exertional dyspnea, and chest pain. The symptoms are gradually progressive and when the compensatory mechanisms become inadequate, congestive heart failure ensues. Angina especially at night also may occur in chronic severe AR. Acute severe AR presents as a medical emergency because it results in congestive heart failure.

Mild cases may have only an early diastolic murmur as evidence of AR. This murmur is high-pitched and is best heard along the left sternal border. The murmur is best appreciated when the patient leans forward and holds the breath in expiration. The murmur of AR resulting from aortic root dilatation may be best heard along the right sternal border (Fig. 119.14).

In moderate and severe cases the peripheral signs are present. These are high volume collapsing pulse (**Corrigan's pulse**), wide pulse pressure (high systolic and low diastolic), prominent carotid pulsation and prominent capillary pulsation demonstrable in the nail bed as well as in the retina. Pistol shot sounds can be heard over the femoral arteries. While auscultating over the femoral artery proximal compression gives rise to systolic murmur and distal compression gives rise to diastolic murmur (**Duroziez Murmur**). The systolic blood pressure recorded in the lower limb is 60 mm above that recorded in the upper limb (**Hill's sign**).

Peripheral signs of AR are shown below. They are of value in diagnosis only in the absence of conditions like fever, anemia, thyrotoxicosis, beriberi and other high output states.

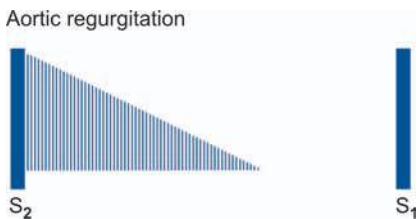


Fig. 119.14: The timing of murmur of AR: The diastolic murmur starts with the aortic component of the second sound and extends for variable duration in to diastole

Peripheral signs of AR

Alfred de Musset's sign	Head nodding with heart beat
Landolfi's sign	Change in pupil size with heart beat
Muller's sign	Uvula pulsation
Rosenbach's sign	Liver pulsations
Gerhardt's sign	Spleen pulsations
Quincke's sign	Digital capillary pulsations
Pistol shot sound	Systolic booming sound over femoral artery
Traube's sign	Systolic and diastolic booming sound over femoral artery
Duroziez's sign	Systolic sounds on proximal compression and diastolic sounds on distal compression over femoral arteries
Hill's sign	Lower limb systolic BP exceeding Upper limb systolic BP by ≥ 60 mmHg
Corrigan's pulse	High volume collapsing pulse
Becker's sign	Retinal artery pulsations
Corrigan's sign	Prominent carotid pulsation

Precordium is hyperactive. Apex beat is characteristically shifted down and out and it is forcible. A mid-diastolic, or presystolic murmur or a combination of both may be heard well over the apex beat (Austin-Flint murmur). This is produced because of the premature closure of the mitral valve caused by the regurgitant stream of blood. There may be an ejection systolic murmur heard along the left sternal border as well as over the aortic area, and this murmur is conducted to the carotids. This is caused by the increased flow across the aortic valve in systole. The aortic component of the second sound is usually soft in severe AR. In cases with pulmonary arterial hypertension, the pulmonary second sound is loud. Acute severe AR is conspicuous by the absence of peripheral signs and left ventricular enlargement. LV gallop may be present if patient develops LV dysfunction.

Electrocardiogram shows left ventricular hypertrophy.

Chest radiograph shows left ventricular enlargement. The aorta in most of the cases appears dilated and on fluoroscopy it is hyperdynamic (Fig. 119.15).

Echocardiography: 2D echo along with Doppler and colour flow can provide anatomical information on the aortic valve, aortic root, etiology of AR, measurements of ventricular function, and estimates of severity of AR. Echo also helps in assessing the pulmonary artery pressures and deciding the timing and type of surgery (Fig. 119.16).

Cardiac catheterization and angiography can provide accurate assessment of the hemodynamic abnormality.



Fig. 119.15: X-ray chest AR showing cardiac dilatation (LV type) and dilated aorta

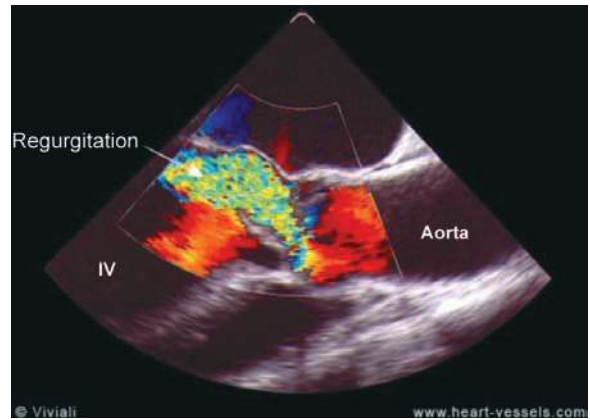


Fig. 119.16: Colour Doppler echocardiograph showing aortic regurgitation

Course and prognosis: Mild cases usually do not progress. However, infective endocarditis may complicate even mild cases. Moderate and severe cases progress with time at varying rates leading to progressive left ventricular enlargement and left ventricular failure. Once cardiac failure occurs, the course is rapidly downhill and majority of patients die within 2 years. Patients with CHF, angina and those in NYHA class III and IV are at high risk of mortality of 25% per year, if untreated. Marked ventricular enlargement is associated with increased risk of sudden death. Risk of aortic dissection is increased in those with annuloaortic ectasia and those with wider aorta. Doppler echography is the mainstay of conservative assessment of severity of AR. *If the regurgitant valve orifice is $>0.3\text{cm}^2$ and the regurgitant volume is $> 60\text{ mL/beat}$ it is severe AR.*

TREATMENT

Medical

- Infective endocarditis prophylaxis
- Rheumatic fever prophylaxis

- c. Treatment of CHF
- d. Afterload reducing agents: These are beneficial in asymptomatic patients with severe AR and normal LV function. Nifedipine and ACE inhibitors have been tried with benefit. Sustained release nifedipine has been shown to postpone the need for aortic valve replacement (AVR)
- Dose: Nifedipine 5-10 mg b.d or t.i.d oral
- Enalapril 5 mg b.i.d or t.i.d oral.

Surgical techniques include aortic valve and root repair, aortic homograft and pulmonary autograft. Associated coronary artery disease may need CABG if indicated.

Indications for surgery

Symptomatic patients with severe AR
Asymptomatic patients with severe AR and depressed LV function
LV EF $\leq$ 50%
End diastolic dimension > 75 mm
End systolic dimension > 55 mm
AR due to aortic root dilatation > 50 mm
Acute AR

Early surgery is less risky and more effective. Asymptomatic patients with ejection fraction between 50-53% should also be considered for surgery. The surgical mortality ranges from 4-6.8%.

Tricuspid Valve Lesions

TRICUSPID STENOSIS (TS)

Normal tricuspid orifice is larger than the mitral orifice (7cm²). The tricuspid leaflets differ from the mitral leaflets in being thinner, more translucent and less clearly separated into well defined leaflets. The three major leaflets are anterior, septal, and posterior. The tricuspid valve may be stenotic, regurgitant or both. Tricuspid stenosis is clinically detectable in 3-5% of cases with multivalvular involvement, but tricuspid lesion can be demonstrated in a much higher proportion (up to 30%) during autopsy. Rheumatic TS is almost always associated with MS.

Etiology

1. Rheumatic valvulitis,
2. Congenital tricuspid stenosis,
3. Carcinoid syndrome,
4. Endocardial fibroelastosis,
5. Endomyocardial fibrosis,
6. Systemic lupus erythematosus.

Rheumatic valvulitis causes fusion of the adjacent free edges of the leaflets. The valve cusps are also moderately

thickened. The involvement of the subvalvular apparatus is less marked compared to the distortion in mitral stenosis. When the valve area falls below 1 cm² it leads to severe tricuspid stenosis. If the valve area is between 1 and 1.5 cm², it is designated as moderate stenosis. In tricuspid stenosis the flow of blood from the right atrium to the right ventricle is hampered. This results in reduction in cardiac output and elevation of the right atrial pressure. Ultimately this leads to systemic venous hypertension.

CLINICAL FEATURES

Rheumatic tricuspid stenosis is almost always associated with mitral stenosis. Presence of tricuspid stenosis leads to reduction in pulmonary venous congestion and, therefore, the symptoms of mitral stenosis such as paroxysmal nocturnal dyspnea, pulmonary edema and hemoptysis are considerably less. The most common symptoms attributable to tricuspid stenosis are effort intolerance and easy fatigability produced as a result of the low cardiac output. Physical examination reveals small volume pulse. The jugular venous pulse shows elevation of mean pressure, prominent 'a' waves with slow 'y' descent. In the presence of atrial fibrillation the characteristic 'a'-wave is lost, but the slow 'y' descent persists. The left parasternal heave seen in mitral stenosis is usually absent. The characteristic auscultatory feature is the presence of a mid-diastolic or pre-systolic murmur which is best heard at the lower left sternal border. Though the murmur is also rumbling in character, its pitch is higher than the murmur of mitral stenosis. It increases in intensity with inspiration (*Carvallo's sign*). The first sound is often split as a result of delay in tricuspid valve closure.

The ECG shows evidence of right atrial enlargement. Chest X-ray shows right atrial dilatation without significant enlargement of the pulmonary arteries. Echocardiography clearly demonstrates the lesion in the valve. Cardiac catheterization is seldom required for tricuspid valve disease.

Course and prognosis: Though the symptoms of pulmonary venous hypertension in patients with mitral stenosis are ameliorated by the coexistence of tricuspid stenosis, the cardiac output is considerably reduced and systemic venous hypertension develops. In such cases, failure to identify tricuspid stenosis preoperatively, and correct it during surgery of the mitral and aortic valves, leads to poor postoperative results.

Treatment: Moderate or severe tricuspid stenosis should be corrected by commissurotomy at the time of surgery for the mitral lesion. Balloon valvotomy has also been found feasible in TS.

TRICUSPID REGURGITATION (TR)

Tricuspid regurgitation (TR) results from inadequate closure of the tricuspid orifice by the valve leaflets. Right ventricular blood regurgitates into the right atrium during systole. The most frequent cause of TR is functional incompetence secondary to pulmonary hypertension which may be primary or secondary. As the right ventricle dilates secondary to the effect of pulmonary hypertension, the valve becomes incompetent. Secondary tricuspid incompetence may be seen in cases of severe mitral stenosis.

In primary tricuspid regurgitation, which is relatively rare, the valve is abnormal.

Causes of primary TR

1. Rheumatic valvulitis,
2. Congenital anomalies (Ebstein's malformation, atrioventricular cushion defects),
3. Carcinoid syndrome,
4. Infective endocarditis, and
5. Trauma.

With the onset of TR, the pressure in the right atrium increases during systole. The elevated mean right atrial pressure is reflected back as elevation of the systemic venous pressure. Ultimately the right atrium and right ventricle dilate with clinical features of systemic venous hypertension.

CLINICAL FEATURES

The usual symptoms are easy fatigability and effort intolerance resulting from reduction of cardiac output. In severe cases there is usually peripheral edema and in some cases there may be ascites. The liver is enlarged and tender and shows systolic pulsation. The most conspicuous finding is elevation of jugular venous pressure with prominent 'v' wave and exaggerated 'y' collapse. When the jugular veins are overdistended, pulsations may not be prominent. In such cases the ear lobes may reveal pulsations. Atrial fibrillation is present in 80-96% of patients with TR. When atrial fibrillation is present, the pulsation in the jugular vein is monophasic with only prominent 'v'-wave. *The characteristic murmur of TR is a high pitched pansystolic murmur best heard in the lower left sternal border. This murmur increases in intensity with inspiration. Inspiratory augmentation of the murmur may not be very conspicuous in cases with severe congestive cardiac failure.* In primary TR, the murmur is medium-pitched and short. The inspiratory augmentation is less conspicuous. When TR is severe, there is usually a third heart sound as well as a mid-diastolic flow murmur heard along the lower left sternal border. The ECG and X-ray chest may show evidence of right atrial enlargement.

Echocardiogram delineates the lesion well. Using Doppler echocardiogram, pulmonary pressures can be assessed and this may help in differentiating primary and secondary TR. Cardiac catheterization and angiography may be required in selected cases.

Course and prognosis: With treatment of congestive heart failure the features of secondary TR come down, and the duration of the murmur comes down. If the damage to the right ventricle is irreversible such cases follow a downhill course.

Treatment: Medical treatment is given for those cases with functional tricuspid regurgitation. Valvuloplasty or valve replacement may be necessary in cases with primary TR. Even in functional TR surgical correction may have to be done if the lesion is severe.

Acquired Lesions of the Pulmonary Valve

Etiology: The pulmonary valve is only rarely involved by acquired heart disease. In carcinoid syndrome, the pulmonary valve shows fibrous scarring with retraction leading to pulmonary stenosis and regurgitation. In severe forms of rheumatic heart disease the pulmonary valve also may be involved as part of the quadrivalvular affection. Bacterial endocarditis may affect congenitally abnormal or even normal pulmonary valve. The pulmonary valve may be the seat of tumours such as myxoma or fibroma in rare cases. In Marfan's syndrome the valve shows myxomatous degeneration. The valve may be damaged during surgery for tetralogy of Fallot or pulmonary stenosis. Severe pulmonary hypertension resulting from any cause may produce functional pulmonary regurgitation with pulmonary diastolic murmurs (*Graham-Steell murmur*). Very rarely pulmonary valve may be involved by tuberculosis and syphilis.

CLINICAL FEATURES

Clinical manifestations depend upon the severity of valve involvement and its cause. In quadrivalvular involvement identification of the pulmonary lesion is difficult because the clinical features are influenced by the lesion of the more proximal valve. In isolated involvement the murmur of *pulmonary stenosis* is easily recognized as an ejection systolic murmur often associated with a thrill, most prominent over the left upper sternal border.

Pulmonary regurgitation (PR) produces an early diastolic murmur along the left sternal border, and this murmur may closely resemble that of aortic regurgitation (AR) in timing and quality. Careful examination can distinguish them in most cases.

Differentiation of AR and PR diastolic murmurs		
Features	AR	PR
Inspiratory increase	–	+
Murmur begins with A2	+	–
Murmur begins with P2	–	+
Murmur increases with phenylephrine and hand grip	+	–
Murmur decreases with amyl nitrate	+	–

Course and prognosis: In quadrivalvular disease, the hemodynamic abnormalities are largely determined by the lesions of the proximal valves. Pulmonary valve disease may not alter the natural history significantly. However, recognition of pulmonary valve disease is important to

decide the line of management. When pulmonary regurgitation is mild or moderate, right ventricle accommodates the increased diastolic blood volume without considerable hemodynamic disturbance, but severe pulmonary regurgitation may lead on to progressive right ventricular failure.

Treatment: Management largely depends on the severity and etiology of pulmonary valve disease. Pulmonary valve replacement may have to be considered under the following indications.

1. Severe and progressive pulmonary regurgitation following surgical correction of tetralogy of Fallot or pulmonary stenosis;
2. Tumours involving the pulmonary valve; and
3. Infective endocarditis, when medical treatment fails.

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Syphilitic Affection of Cardiovascular System

C.G. Bahuleyan

Chapter Summary

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Introduction

Cardiovascular involvement is one of the important manifestation of syphilis in its tertiary stage. About 10% of patients with syphilis develop clinical evidence of cardiovascular disease. These include aortitis, aortic insufficiency, aneurysm of aorta, coronary ostial stenosis, gumma of the myocardium, and syphilitic endarteritis. Cardiovascular syphilis occurs more common and earlier in men than in women.

AORTITIS

This may occur in 70-80% of the untreated cases, if allowed to progress. The causative organism, *Treponema*

pallidum, invades the adventitial layer of the aorta soon after the primary infection, spreading later to the media through the lymphatics surrounding the vasa vasorum after several years. Endarteritis of vasa vasorum results in necrosis of the elastic and connective tissues of the media. At first the intima overlying the areas of medial necrosis becomes thickened. Later it becomes pitted and scarred to resemble the bark of a tree. *Treponema pallidum* may survive in the aortic wall for 20 to 30 years (Fig. 120.1).

Inflammatory changes are most frequent and severe in the ascending aorta and arch and they are least in the distal parts. Damage to the media causes ectasia of proximal part of the aorta, which increases to as much as twice its normal diameter. If left untreated, 10% of subjects with syphilis may develop aortic regurgitation or coronary ostial narrowing due to involvement of the proximal aorta. Longer the delay in treatment, greater is the likelihood of lethal complications. Damage to the media increases the severity of atherosclerosis in the proximal aorta.



Fig. 120.1: Rough pitted intimal surface (tree bark appearance) characteristic of syphilitic aortitis



Fig. 120.2: Dilated ascending aorta with calcification in a patient with syphilitic aortic aneurysm

Clinical features: The patient may complain of a burning type of retrosternal pain or true anginal pain felt over the retrosternal region.

Diagnosis

1. Prominent parasternal heave suggestive of dilatation of the ascending aorta,
2. A ringing loud aortic component of second heart sound (tambour like second heart sound) in a normotensive subject without evidence of atherosclerosis, and
3. A systolic murmur in the aortic area.

Calcification of the anterolateral wall of aorta may be seen on fluoroscopy (calcification due to atherosclerosis is more frequently along the medial border of the ascending aorta and arch). Dilatation of aorta is detectable by echocardiography and angiography (Fig. 120.2).

AORTIC INSUFFICIENCY

Aortic valvular regurgitation, the most frequent complication of syphilitic aortitis, results from dilatation of aortic valve ring and improper apposition of the leaflets due to mesoaortitis of proximal aorta. The aortic valve cusps may be thickened and rolled up at the edges without calcification or stenosis. Left ventricular dilatation and hypertrophy may occur. In addition, coronary ostial narrowing and aneurysm of aorta may coexist.

CLINICAL FEATURES

Males are affected four times more frequently than females. Around 10-25 years may elapse between the primary lesion and the onset of AR. When the AR is significant, cardiac signs and all the peripheral signs of free aortic regurgitation may be detectable. The high-pitched decrescendo early diastolic murmur of aortic

regurgitation is best appreciated with the diaphragm of the stethoscope firmly applied in the second right intercostal space with the patient leaning forward and holding his breath in expiration. As the AR is the result of dilatation of the aortic root the murmur is often better heard in the right sternal border than the left. A hyperdynamic apical impulse, soft first heart sound, a ventricular diastolic gallop and mid-diastolic rumble at the apex (**Austin Flint murmur**) constitute the other physical signs. *Austin Flint murmur* can be distinguished from the mid-diastolic murmur of mitral stenosis by the absence of loud first heart sound.

Echocardiography demonstrates the lesions in the valve, aorta and the cardiac chambers. Doppler studies help to quantify the hemodynamic abnormality. Angiography and cardiac catheterisation are required only in a few cases.

History of syphilitic infection, evidence of syphilis elsewhere in the body, positive serological tests for syphilis and the presence of murmur of AR are pointers to the diagnosis. Since syphilis may coexist with other conditions such as bicuspid aortic valve or degenerative disease which can lead on to aortic regurgitation, the etiological diagnosis during life is mostly presumptive.

Prognosis: Syphilitic lesion of the valve tends to progress with time if it is not treated. Some cases develop **Jarisch-Herxheimer reaction** and edema of the coronary ostial lesion leading to acute myocardial ischemia when instituting penicillin therapy. This should be borne in mind when giving antisyphilitic therapy.

Once syphilitic damage has happened the valvular lesion does not recover even with full antisyphilitic therapy. Presence of heart failure and angina worsen the prognosis, and if left untreated, end up fatally within three years.

Treatment: If the lesion is detected before the valve is grossly damaged, antisyphilitic treatment arrests the progress of the disease and may prevent deterioration.

In such cases moderate restriction of heavy physical exertion and prophylaxis for infective endocarditis may be the only treatment needed. If the valve lesion has progressed so as to produce major hemodynamic disturbance, surgery has to be done after clearing syphilitic activity. Surgical treatment consists of replacement of aortic valve to correct AR and coronary artery bypass grafting when there is coronary ostial stenosis.

ANEURYSM OF AORTA

This is a late complication of syphilis which occurs from 15-30 years after primary infection. Aortitis may lead to a generalized dilatation and fusiform aneurysm or a localized dilatation to form saccular aneurysm. As aortitis most frequently involves the ascending aorta, more than 50% of aneurysms also occur in this location (see pp 690).

Clinical features: Symptoms and signs of aneurysm arise from compression of adjacent structures. Ascending aortic aneurysms compress the pulmonary artery, superior vena cava or right main bronchus. Aneurysms of the arch compress the oesophagus, trachea, bronchus, recurrent laryngeal nerve, sympathetic nerves, and vertebrae. These lead to dysphagia, dyspnea, stridor, cough, hoarseness of

voice, Horner's syndrome and pain over the vertebra. An interesting physical sign in aneurysm of the arch is the **tracheal tug**, which is a tugging sensation felt when the neck is extended and larynx is held up. Aneurysms of the descending aorta compress the lungs, erode vertebrae or ribs, and impinge on nerve roots. Descending thoracic or abdominal aortic aneurysms may present as pulsatile or non-pulsatile masses. Aneurysms may rupture into bronchus, pulmonary artery, pleura, pericardium or esophagus leading to fatal hemorrhage. Once symptomatic, the life expectancy for a patient with syphilitic aneurysm is only a few months. Antisyphilitic therapy should be followed up by surgery to resect the aneurysms without delay.

Coronary ostial stenosis: In syphilitic aortitis occlusion of the coronary opening is a slow process and, therefore, acute myocardial infarction is rare. Ostial stenosis is often associated with AR. Diagnosis is made by aortic root angiography and coronary arteriography. Angina and sudden death due to arrhythmia may occur. Coronary artery bypass graft may be required after antisyphilitic therapy.

Myocardial gummata: They may produce bundle branch block or A-V block or electrocardiographic pattern of myocardial infarct. Antemortem diagnosis is extremely difficult.

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- Diagnosis 802
- Treatment 803

Definition: Infective endocarditis is defined as microbial infection of the endothelial surfaces of heart and great

vessels (Infective endarteritis). Endocarditis may be acute or subacute.

Acute infective endocarditis: The heart valves and endocardium may be the seat of direct invasion by microbes. Virulent organisms such as *Staphylococcus aureus*, *Streptococcus hemolyticus*, and pneumococci produce acute ulcerative endocarditis during the course of a septicemia and these affect normal valves. Fortunately, this complication is rare.

TABLE 121.1

Showing the primary cardiac lesion and the most common precipitating event

Pre-existing heart disease	Precipitating factors
Congenital heart disease	Dental procedures, abortion, procedures on lower urinary tract, intravenous drug use
Rheumatic valvular disease	Dental procedures, minor surgery, systemic infections.
Atherosclerotic valve lesions and degenerative lesions	Urinary endoscopy and other manipulations
Prosthetic heart valves	Bacteremias
Cardiac surgery	Intravenous cannulae and shunts, foreign materials
Normal valves in immuno-compromised individuals	Emergency room procedures including IV catheter and injections
Drug addicts: Normal valves	Intravenous drug injection, needle-sharing

Acute infective endocarditis and subacute bacterial endocarditis differ in their etiology, microbial flora, pathology, clinical features and management. Whereas acute endocarditis presents as part of a more fulminant generalized infection, the subacute form often takes the picture of a stealthy superinfection on an already existing cardiovascular lesion by organisms which are of low virulence in normal individuals (Table 121.1).

Etiology—Subacute Bacterial Endocarditis (SBE)

Predisposing causes: Infection is predisposed to by congenital heart disease or rheumatic heart disease. Organisms may colonize on the endocardium, valves or arteries that are already damaged or subjected to hemodynamic abnormalities. Combined valvular lesions are more often the seat of vegetations than pure stenosis or incompetence. Among the congenital lesions, ventricular septal defect, patent ductus arteriosus, pulmonary stenosis, Fallot’s tetralogy and coarctation of the aorta may be complicated by infective endocarditis. This risk is less in the case of secundum type of atrial septal defect. Open heart surgery and surgical introduction of prosthetic heart valves, grafts and pacemakers are associated with increased risk of bacterial colonisation. Atherosclerotic lesions may form nidus for infective endocarditis.

In immunodeficient individuals and intravenous drug users, even normal valves may become colonized by pathogens.

Microbial flora: Common organisms are *Streptococcus viridans*, *Streptococcus fecalis* and other streptococci. Less common organisms include *staphylococci*, *pneumococci*, *H. influenzae*, *gonococci*, *meningococci*, *salmonellae*, *E. coli*. *Bacterium anitratum*, *Candida* sp.,

aspergillus sp., *anaerobes* and *Coxiella burneti*. Most of these organisms are commensals in the human body, particularly abundant in sites such as the mouth, upper respiratory tract, genitalia, and urinary tract. Any infective illness or minor surgical procedures such as dental surgery, tonsillectomy, urinary instrumentation, parturition, abortion or medical termination of pregnancy causes transient bacteremia which conveys the organisms to the abnormal cardiac tissues, where they settle and multiply.

PATHOLOGY

On the endocardial surface the organisms multiply and proliferate. Fibrin is deposited over the organisms and this gives a protective coat against the defences of the host. Further growth of the organisms and fibrin deposition result in the formation of friable vegetations which show three layers—the inner layer made up of erythrocytes, leukocytes and platelets; the middle layer containing a heavy growth of the organisms; and an outer layer made up of fibrin. As fibrin gets deposited further, the vegetations grow and they get embolized from time to time. Organisms which reach the cardiac tissues adhere to the damaged valves and other parts within minutes. After adhesion to tissues they multiply and envelope themselves in fibrin and lead to the development of vegetations. Monocytes which adhere to these sites do not engulf the organisms. On the other hand they produce procoagulant factors which favour the development of further fibrin and vegetations. Normally adhesion of platelets tends to inhibit organisms, but in infective endocarditis, this does not happen; but further growth of vegetations occur. Tissue invasion and abscess formation follow (Fig. 121.3B).

The vegetations are located differently on the different valves. Generally vegetations are located at the downstream portions of a communication between high and low pressure areas.

- Mitral valve — Atrial surface and line of apposition
- Aortic valve — Ventricular surface
- Ventricular septal defect — On the right ventricular endocardium where the abnormal jet impinges, and around the defect.
- Patent ductus arteriosus — Pulmonary artery and the ductus

The chordae tendineae and papillary muscles may be affected. These may rupture leading to acute valvular incompetence or they undergo fibrosis when they heal.

Embotic episodes form an integral clinical feature of infective endocarditis. The emboli may be septic or sterile. Embolism leads to infarction of organs. Septic emboli reaching the vasa vasorum lead to weakness of the arterial wall and the formation of mycotic aneurysms especially in the intracranial vessels.

Repeated release of organisms into the circulation starts off immunological processes. Large amounts of

antibodies are formed which give rise to the formation of immune complexes. Complement activation occurs. As a result, immunological lesions like glomerulonephritis, perisplenitis and vasculitis develop. Septic emboli also lead to focal glomerulonephritis. Spleen enlarges due to reticuloendothelial hyperplasia and formation of microabscesses.

Untreated cases end fatally. Death is caused by massive embolism to vital organs (brain or heart), cardiac failure or renal failure.

CLINICAL FEATURES

Symptomatology can be described under four groups:

1. **Features of subacute infection:** This manifests as low-grade or high-grade intermittent or continuous fever, often associated with chills and rigor. Digital clubbing may develop within weeks and this may be painful. In some cases the symptoms may be non-specific. Even unexplained fatigue, anemia or resistant cardiac failure should draw attention to endocarditis. Splenomegaly develops and the organ is well palpable by the second week. A brownish pigmentation develops over the face and limbs—*cafe-au-lait pigmentation* (meaning, coffee with milk) (Fig. 121.1).

2. **Hemodynamic changes:** Destruction of a valve may result in valve rupture leading to the development of fresh murmurs, aggravation of existing murmurs and sudden cardiac failure. In some cases the vegetations obstruct the valves. The papillary muscles and the chordae tendineae may rupture giving rise to incompetence of the atrioventricular valves.

3. **Embolic phenomena:** The emboli are generally small though large fatal emboli may develop at times. Emboli produce several manifestations.

Cutaneous embolism: This leads to painless, erythematous or hemorrhagic lesions on palms and soles called *Janeway lesions*.

Nails: *Splinter hemorrhages* occur as longitudinal streaks under the nails.

Spleen: Painful splenomegaly and splenic infarcts may develop.

Peripheral arteries: Occlusion of the arteries to the extremities gives rise to absence of peripheral pulses, claudication and distal gangrene.

Central nervous system: The carotid or vertebral system may be involved giving rise to paralysis, convulsions, visual loss, aphasia, and cerebellar disturbances.

Renal infarction: This condition causes hematuria and renal failure.

Pulmonary embolism gives rise to pulmonary infarction, pleurisy, and pleural effusion.



Fig. 121.1: Male 25 mitral valve disease with infective endocarditis. Note: Pallor, splenomegaly, cardiomegaly

4. **Immunological disturbances:** These lead to vasculitis which manifests as **Osler's nodes** (raised tender nodules on the pulps of the fingers), **Roth's spots** (circular hemorrhages with central white spots) seen on the retina, and **glomerulonephritis**.

Diagnosis

A high index of clinical suspicion is very essential for early diagnosis. In persons with congenital or acquired heart disease, fever, anemia, clubbing, refractory cardiac failure, changing murmurs, development of emboli or even vague ill health should suggest the possibility of infective endocarditis. Infective endocarditis should be differentiated from activation of rheumatic fever, disseminated lupus erythematosus, drug toxicity, and other prolonged fevers. Development of normocytic normochromic anemia, mild leukocytosis, elevation of ESR, proteinuria, and microscopic or frank hematuria should strengthen the clinical diagnosis.

Criteria for diagnosis evolved from Duke university (Duke criteria) in 1994. These criteria offer improved sensitivity and specificity for diagnosis of endocarditis.

Duke's Criteria for Diagnosis of Infective Endocarditis

Definite Infective Endocarditis

Pathologic criteria: Pathologic lesions: vegetation or intracardiac abscess present, confirmed by histology showing active endocarditis.

Microorganisms: demonstrated by culture or histology in a vegetation, or in a vegetation that has embolised, or in an intracardiac abscess or

Clinical criteria, using specific definitions listed below:

Two major criteria or

One major and three minor criteria, or five minor criteria

Possible Infective Endocarditis

Findings consistent with infective endocarditis that fall short of “definite” but not “rejected”.

Rejected Firm alternate diagnosis for manifestations of endocarditis.

Or

Resolution of manifestations of endocarditis, with antibiotic therapy for 4 days or less or

No pathologic evidence of infective endocarditis at surgery or autopsy after antibiotic therapy for 4 days or less.

Definitions of Clinical Criteria

Major Criteria

Positive blood culture for infective endocarditis

Typical microorganism for infective endocarditis from two separate blood cultures, or persistently positive blood culture, defined as recovery of a microorganism consistent with infective endocarditis from:

1. Blood cultures drawn more than 12 hours apart or
2. All of three or a majority of four or more separate blood cultures, with first and last drawn at least 1 hour apart

Evidence of Endocardial Involvement

Positive echocardiogram for infective endocarditis

1. Oscillating intracardiac mass on valve or supporting structure, or in the path of regurgitant jet or on implanted material in the absence of an alternative anatomic explanation, or
2. Abscess, or
3. New partial dehiscence of prosthetic valve, or New valvular regurgitation (increase or change in pre-existing murmur not sufficient).

Minor Criteria

- **Predisposition:** Predisposing heart condition or intravenous drug use
- **Fever** $\geq 38.0^{\circ}\text{C}$ (100.4°F)
- **Vascular phenomena:** Major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhage, Janeway lesions.
- **Immunologic phenomena:** Glomerulonephritis, Osler’s nodes, Roth’s spots, rheumatoid factor.

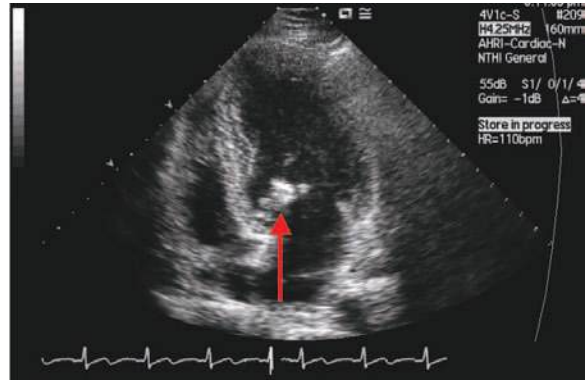


Fig. 121.2: Transthoracic echocardiogram shows vegetation attached to anterior mitral leaflet—arrow

- **Microbiologic evidence:** Positive blood culture but not meeting major criterion as previously defined or serologic evidence of active infection with organism consistent with infective endocarditis.
- **Echocardiogram:** Consistent with infective endocarditis but not meeting major criteria as previously defined.

Echocardiogram: Vegetations above 0.5 cm can be detected easily. Smaller vegetations may escape detection and, therefore, a negative result should not be a reason for ruling out the diagnosis. In practice demonstration of vegetations by echocardiogram is the most rapid and definite method to establish the diagnosis. Since demonstrable vegetations take days to weeks to develop, repetition of echocardiography is indicated if clinical suspicion is strong. Echocardiogram also helps to assess progress with treatment (Figs 121.2 and 121.3).

Organisms can be cultured from blood and this should be attempted in all cases. Blood is collected before starting antimicrobial drugs. Three separate sets of blood culture; each from separate venupuncture, obtained over 24 hours are recommended to evaluate patients with suspected endocarditis. Each sample should be inoculated in aerobic medium and anaerobic medium. The organisms are slow growers and, therefore, the cultures should be continued for 2-3 weeks. In doubtful cases they should be subcultured. In many cases mixed flora may be seen, or with treatment, the microbial flora may change. Hence repeat cultures should be done when treatment is prolonged or the progress is not fully satisfactory. Drug sensitivity of the organisms should be determined to assess the choice of antibiotics. The organisms vary considerably in their drug sensitivity and, therefore, prior assessment of the antibiotic sensitivity is of great value in ensuring successful therapy.

TREATMENT

Treatment use of bactericidal antibiotics is the corner stone of successful therapy.

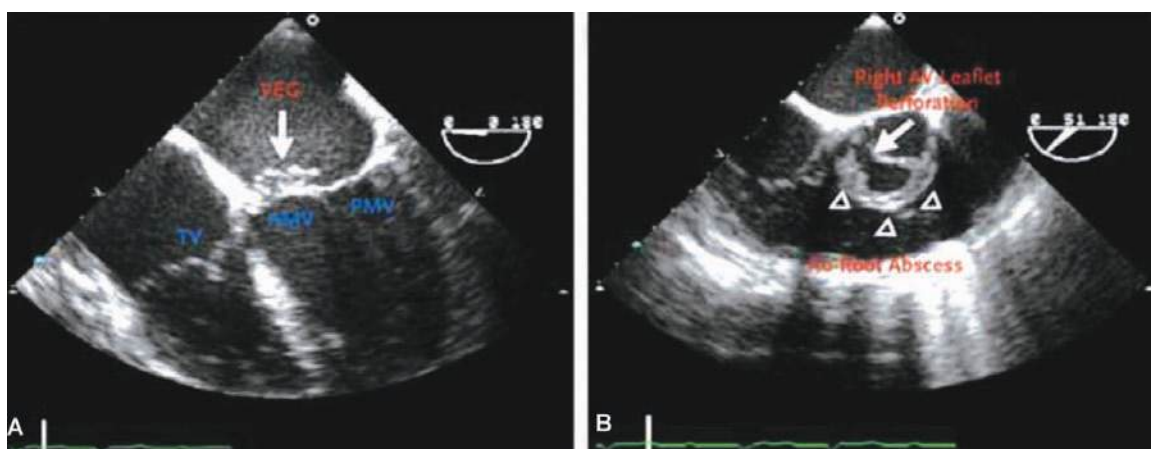


Fig. 121.3: Transesophageal echocardiogram picture of a (A). Vegetation attached to mitral valve (B) Aortic root abscess on right side - arrow

Empirical Therapy

When the causative organism is not known, the choice of empirical therapy should depend on whether the patient has acute or subacute disease. Acute bacterial endocarditis (ABE) requires broad-spectrum therapy that covers *Staph. aureus* as well as many species of streptococci and gram-negative bacilli. Subacute bacterial endocarditis (SBE) requires a regimen that eradicates most streptococci, including *E. fecalis*.

- For acute bacterial endocarditis (ABE): Nafcillin 2.0 g IV q 4 h + ampicillin 2.0 g IV q 4 h + gentamicin 1.5 mg/kg IV q 8 h. If methicillin-resistant *Staph. aureus* is a possibility, for example, in a hospital-acquired case, vancomycin, 1.0 g IV q 12 h should be substituted for nafcillin
- For SBE: Ampicillin 2.0 g IV q 4 h + gentamicin 1.5 mg/kg IV q 8 h.

Treatment should be appropriately modified when the etiologic organism is identified and antibiotic sensitivity established.

The standard treatment for endocarditis due to penicillin susceptible viridans streptococci is aqueous penicillin G 12-18 million unit/24 hours either continuous or every 4 hours in six equally divided doses for 4 weeks and gentamicin 1 mg/kg IM/IV 8 hourly for first 2 weeks. Vancomycin is recommended for patients allergic to penicillin.

Surgery: When medical treatment fails to clear the infection, the underlying abnormality may have to be corrected surgically and this has to be done as a life-saving procedure. Other indications for surgery include acute valvular incompetence leading to cardiac failure, large friable vegetations which are likely to embolize, unstable prosthesis, and perivalvular extension of infection.

Prognosis: With the help of echocardiography and microbiological studies the diagnosis can be confirmed in most cases if clinical suspicion is high. Prognosis depends on

the timely institution and prolonged administration of appropriate antibiotic combination. *Prognosis is best when the specific organism and its antibiotic sensitivity are known. Therefore, it is of utmost importance, that blood should be taken for microbiological studies before starting antibiotics empirically, even if treatment may be delayed slightly.*

It is important to prevent the onset of infective endocarditis in all patients with anatomical lesions in the cardiovascular system.

Recommendation for Endocarditis Prophylaxis

Indication

High risk category

- Prosthetic heart valves, including bioprosthetic homograft and allograft valves
- Previous bacterial endocarditis
- Complex cyanotic congenital heart disease (e.g. single ventricle states, transposition of the great arteries, tetralogy of Fallot)
- Surgically constructed systemic pulmonary shunts or conduits

Moderate risk category

- Most other congenital cardiac malformations (other than that listed above or below)
- Acquired valvular dysfunction (e.g. rheumatic heart disease)
- Hypertrophic cardiomyopathy
- MVP with auscultatory evidence of valvular regurgitation
- MVP with auscultatory evidence of valvular regurgitation and or thickened leaflets

Low or negligible risk category

- Isolated secundum atrial septal defect

TABLE 121.2		
Endocarditis prophylaxis regimens for dental, oral, respiratory tract or esophageal procedures		
Situation	Agent	Regimen*
Standard general prophylaxis	Amoxycillin	Adults: 2.0 g; children 50 mg/kg PO 1 h before procedure
Unable to take oral medication	Amoxycillin	Adults: 2.0 g IM or IV; children: 50 mg/kg im or IV within 30 min before procedure
Penicillin-allergic	Clindamycin or	Adults: 600 mg; children: 20 mg/kg PO 1 h before procedure
	Cephalexin† or cephadroxi† or	Adults: 2.0 g; children 50 mg/kg PO 1 h before procedure
	Azithromycin or clarithromycin	Adults: 500 mg; children 15 mg/kg PO 1 h before procedure
Penicillin-allergic and unable to take oral medications	Clindamycin or Cefazolin†	Adults: 600 mg; children 20 mg/kg IV within 30 min before procedure
		Adults: 1.0 g; children 25 mg/kg IM or IV within 30 min before procedure
* Total children's dose should not exceed adult dose		
† Cephalosporins should not be used in individuals with immediate type hypersensitivity reaction (urticaria, angioedema, or anaphylaxis) to penicillin. From Dajani <i>et al</i> (with permission)		

TABLE 121.3 Endocarditis prophylaxis regimens for genitourinary/gastrointestinal (excluding esophageal) procedures		
Situation	Agent(s)*	Regimen†
High-risk patients	Ampicillin plus gentamicin	Adults: ampicillin 2.0 g I.M/IV plus gentamicin 1.5 mg/kg (not to exceed 120 mg) within 30 min of starting the procedure. Six hours later, ampicillin 1 g IM/IV or amoxcillin 1 g PO Children: ampicillin 50 mg/kg IM or IV (not to exceed 2.0 g) plus gentamicin 1.5 mg/kg within 30 min of starting the procedure. Six hours later, ampicillin 25 mg/kg IM/IV or amoxicillin 25 mg/kg PO
High-risk patients allergic to	Vancomycin plus gentamicin	Adults: vancomycin 1.0 g IV over 1-2 h plus gentamicin 1.5 mg/kg IV/IM (not ampicillin/amoxicillin to exceed 120 mg). Complete injection/infusion within 30 min of starting the procedure Children:vancomycin 20 mg/kg IV over 1-2 h plus gentamicin 1.5 mg/kg IV/IM. Complete injection/infusion within 30 min of starting the procedure
*A second dose of vancomycin or gentamicin is not recommended.		
† Total children's dose should not exceed adult dose. From Dajani <i>et al</i> (with permission)		

- Surgical repair of atrial septal defect, ventricular septal defect or patent ductus arteriosus (without residual lesion > 6 mo)
 - Previous coronary artery bypass graft surgery
 - MVP without valvular regurgitation
 - Physiological functional or innocent heart murmurs
 - Previous Kawasaki disease without valvular dysfunction
- Cardiac pacemakers and implanted defibrillators.

Infective endocarditis prophylaxis is indicated in all high risk and and moderate risk categories (Tables 121.2 and 121.3).

Since oral sepsis is a very common cause for transient and recurrent bacteremia proper dental hygiene is the most effective and definite prophylactic measure.

122

Cardiac Arrhythmias

K. Suresh

Chapter Summary

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General Considerations

13

The myocardial cells have the property of spontaneous excitability (automaticity). This is responsible for the pacemaking function of the heart. The sino-atrial (SA) node which has the fastest rate of excitability controls the heart rate. The SA node contains specialized electrically active cells known as P cells which are most excitable. The rate of impulse production and conduction are controlled by various physiological, pharmacological and pathological processes. In normal adults the heart rate varies between 60 and 100/min.

The action potential: The cardiac action potential is generated by movement of charged ions across the cell membrane through various channels. The action potential has five phases [phase 0,1,2,3 and 4]. However the two major phases involved in depolarization are - the spike [phase 0] and the plateau [phase 2]. A large fast inward movement of Na^+ through the fast sodium channel is responsible for the early spike. A slower steady influx of Ca^{++} through a separate set of slow channels accounts for

the plateau phase. The SA node and the atrio-ventricular node [AV node] contain cells whose action potential is dominantly mediated by the slow calcium channels. In contrast, the Purkinje cells and the working myocardial cells have both fast and slow channels.

The calcium channel: The exact structural details of the calcium channels in the sarcolemmal membrane are not known. It is believed that each ionic channel is a specific protein that floats in a lipid bilayer matrix with a water filled central pore for ion movement. These channels have a selective filter which determines the nature of ions passing through them. In addition, the channels are also influenced by intracellular voltage variations, and hence they are also called “voltage-dependent channels.”

The slow response type of action potential seen mainly in the SA node and AV node, is mediated by the slow channels. Although there are various types of slow channels, the calcium-mediated slow channel is most widely recognized. Compared to the fast channels, these channels are not only kinetically slower, but they also operate at a less negative to a more depolarized voltage range. A variety of agents block the slow channels. Local anesthetics, volatile general anesthetics and others produce a non-specific blockade of both fast and slow channels. In contrast, drugs like verapamil, nifedipine and diltiazem produce a selective direct blocking action on the slow channels. The result is blockade of calcium entry into the cell. Calcium channel blockers are extensively used in the treatment of arrhythmias and hypertension.

The conduction system: From the SA node, the impulse travels through the atria to the A-V node. There are three functionally specialized pathways in the atria which conduct impulses from the sinus node to the A-V node. These are the anterior, middle and posterior internodal tracts. A branch of the anterior tract – the Bachmann’s bundle connects the two atria also. From the A-V node the impulse travels through the bundle of His, bundle branches and the Purkinje system to reach the ventricular musculature.

In general, arrhythmias may be of two types- disorders of impulse production or disorders of impulse conduction

and may be caused by abnormalities of automaticity, and/or abnormalities of conduction. When the main pacemaker is suppressed, the lower centres become active and take up the pacemaking function. This gives rise to escape rhythms such as junctional escape or ventricular escape. Enhanced automaticity of ectopic foci may occur and this leads to the development of ectopic rhythms and ectopic tachycardias (junctional ectopics and junctional tachycardia).

Abnormality in the conduction of impulses may give rise to “re-entry phenomenon” which is considered as one of the common mechanisms of tachyarrhythmias. When the normal conducting pathway becomes refractory, an incoming impulse may take a different course and pass down. By the time it reaches lower down, the refractoriness of the distal end of the normal pathway, would have passed off and it may become capable of conduction. Hence, the abnormal impulse gets into it and it is conducted in a retrograde direction. This is designated as re-entry phenomenon and is responsible for genesis and perpetuation of ectopic tachycardias. In order for re-entry to occur three conditions must be met (1) two functionally distinct conducting pathways (2) Unidirectional conduction block in one of the pathways (3) A differential in the conduction rates in the pathways, with slow conduction via one pathway and return of conduction via the second.

In some individuals, accessory pathways for conduction exist. These accessory pathways are anomalous extranodal connections which connect the epicardial surfaces of the atrium and ventricles along the A-V groove. Accessory pathways may conduct impulses in both antegrade and retrograde directions – the former mostly silent. The accessory and normal pathways conduct impulses from the atria to the ventricles in various combinations resulting in the production of re-entrant tachyarrhythmias, e.g. WPW syndrome.

Sinus Arrhythmia

Even in normal subjects with sinus rhythm, slight beat to beat variation in time-interval occurs. When the difference between the longest and the shortest cycles exceeds 0.12 sec., it is termed sinus arrhythmia. This is seen more often in children and young adults. In the vast majority of cases, this is a benign condition with no detectable underlying disorder of the heart.

Sinus arrhythmia may occur in 2 forms (1) phasic and (2) nonphasic. In the phasic form, which is more common, there is characteristic acceleration of the heart rate with inspiration and slowing with expiration. This is caused by the respiratory fluctuations in the vagal tone mediated through the ‘Bainbridge’s reflex’. The nonphasic form does not show any relation to the phases of respiration.

The electrocardiogram shows a difference of at least 0.12 sec between the longest and the shortest P-P intervals. The configuration of the P-wave and the P-Q intervals remain constant (Figs 122.1A and B).

Sinus Bradycardia

Sinus bradycardia implies a sinus rate below 60/min. Often this is seen normally in athletes and heavy manual labourers. Disease states such as hypothyroidism, obstructive jaundice, raised intracranial tension and acute inferior wall myocardial infarction may be associated with bradycardia. Drugs like digoxin, verapamil and propranolol may produce sinus bradycardia. Pathological processes affecting the S-A node give rise to sick sinus syndrome in which the patients may present with extreme sinus bradycardia, sinus arrest, sinus blocks and escape rhythms.

Sinus Tachycardia

Sinus tachycardia implies a sinus rate of more than 100/min. It is seen normally during exercise and anxiety. Fever, thyrotoxicosis, infections, hypoxia, anemia, hemorrhage, hypotension, heart failure and shock are the common pathological causes. Drugs like atropine, adrenaline and ephedrine cause sinus tachycardia. Usually the heart rate does not exceed 150/min (Fig. 122.2).

Ectopic Beats

Heart beat produced prematurely as a result of impulse originating in areas other than the sinus node is designated as ectopic beat. It may be early or late in diastole. Following a premature beat the normal impulse reaching the A-V node finds the ventricle refractory and so the subsequent normal beat is missed. This is the “compensatory pause”. If the R-R interval in the ECG encompassing the ectopic is twice the normal it is called fully compensated, otherwise it is partial. Premature beat may be atrial, junctional or ventricular.

Atrial premature beats (APB): These are premature beats arising from ectopic foci in the atria. Ectopic foci may be single or multiple. All age groups may be affected and in many cases, there is no detectable organic disease of the heart. Common causes include anxiety, excessive intake of coffee or tea and heavy tobacco smoking. However, in the presence of organic heart disease it can predispose to atrial tachyarrhythmias such as atrial tachycardia, flutter and fibrillation. Clinically, premature beats are appreciated as dropped beat. The compensatory pause is not full in atrial premature beat. The normal beat coming after the compensatory pause is more forceful on account of the longer diastolic filling and this may be felt as a thud by

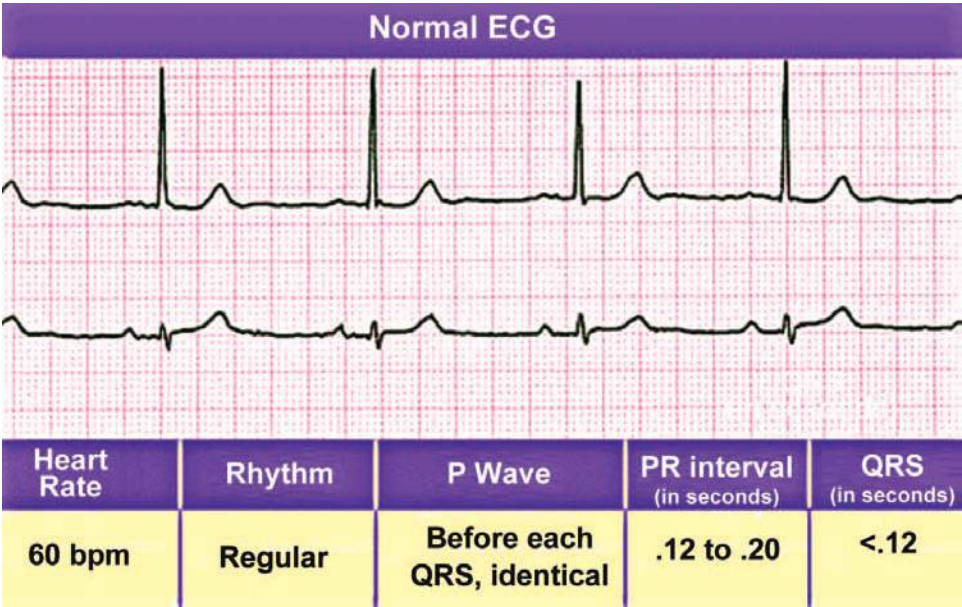


Fig. 122.1A: Normal ECG with sinus bradycardia. Note: The QRS rate is around 60/minute. The rhythm is regular with normal P and other complexes. QRS duration is less than 0.12 seconds



Fig. 122.1B: Sinus arrhythmia: Note the change in heart rate with inspiration and expiration – increase during inspiration with shorter R-R intervals and decrease during expiration. This is a normal phenomenon

13



Fig. 122.2: ECG sinus tachycardia: Note: 1. Rate 150/minute 2. P waves precede all QRS complexes



Fig. 122.3: Atrial premature beats: Note: 1. The 3rd and 7th beat of the rhythm are premature beats. 2. The QRS morphology of premature beat is same as the normal beat 3. The premature beat is preceded by abnormal P wave (arrow)

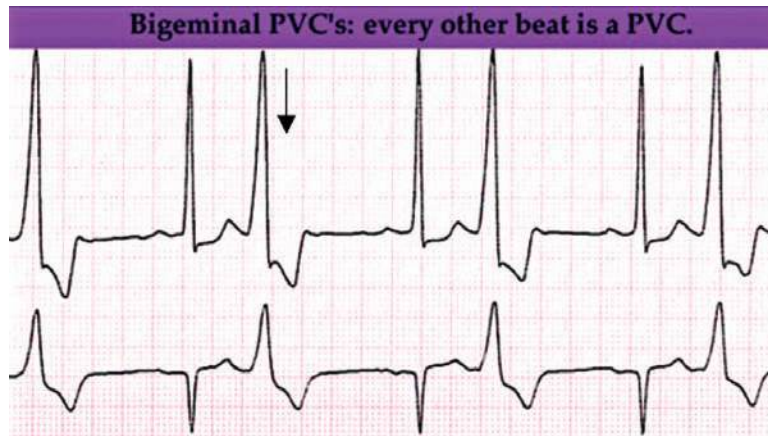


Fig. 122.4: Premature ventricular beat (PVC) Note the bizarre ventricular ectopic beat. Note the compensatory pause—arrow



Fig. 122.5: Paroxysmal atrial tachycardia (PAT): Note: The first half of the rhythm strip shows rate of nearly 190/minute. The run of tachycardia terminates and is replaced by sinus rhythm in the latter part (arrow)

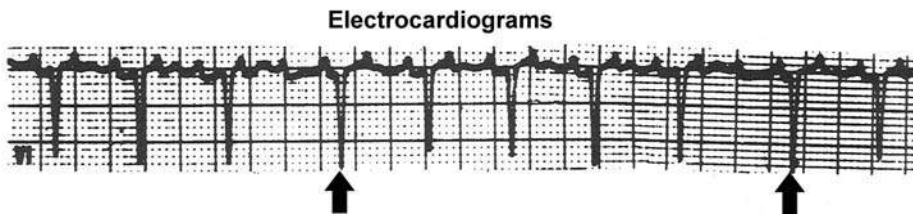


Fig. 122.6: Paroxysmal atrial tachycardia with block



Fig. 122.7: Multifocal atrial tachycardia (MAT) Note: 1. The varying morphology of the P waves indicated by arrows 2. Tachycardia with a rate of nearly 150/min

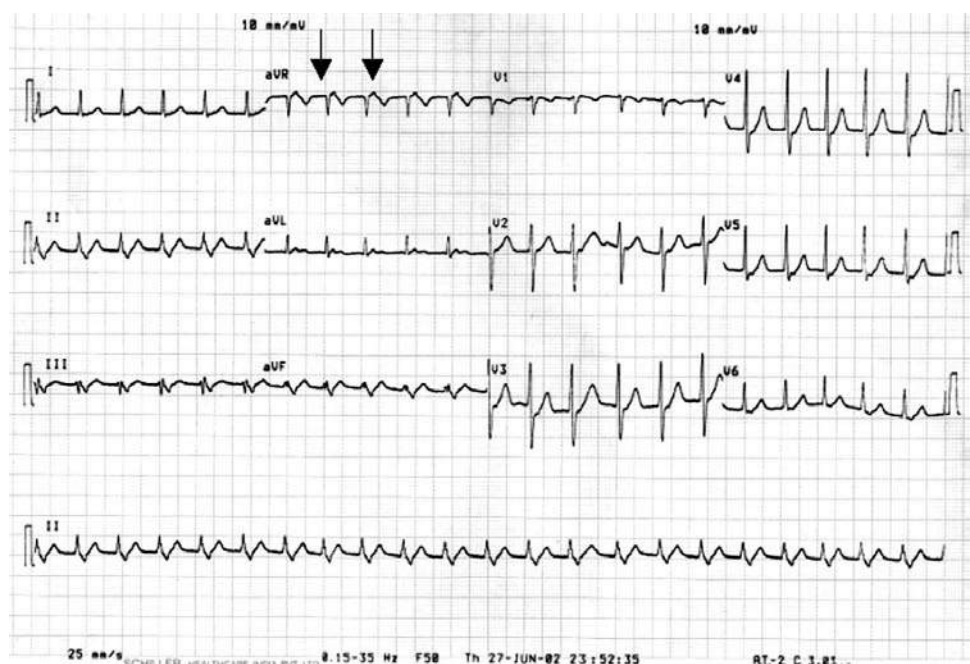


Fig. 122.8: AVNRT (A V nodal re-entrant tachycardia): Note: 1. AVNRT is a re-entrant tachycardia which utilizes the fast and slow pathways in the AV node for its circuit. The uniform and narrow QRS complexes at a rate of nearly 180/min 2. Short RP intervals and long PR intervals (marked by arrows in aVR) is a hall mark of AVNRT

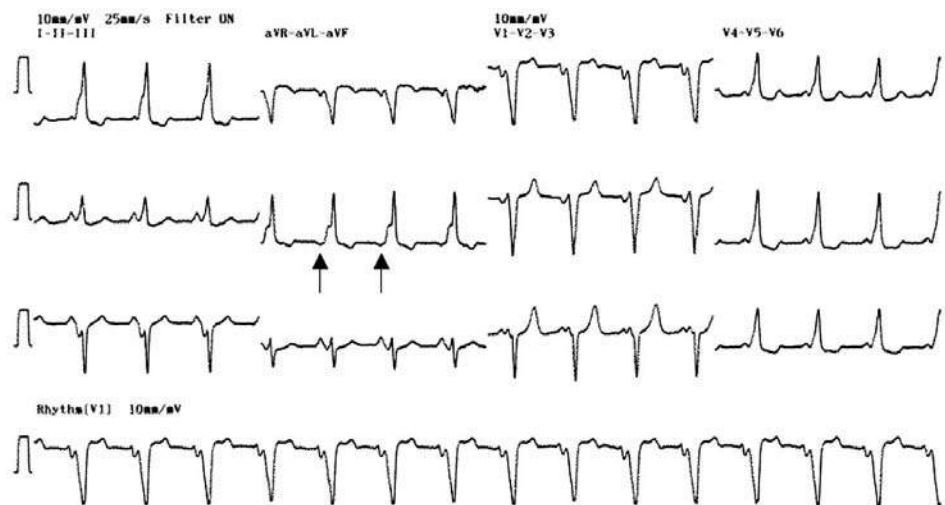


Fig. 122.9: Wolff-Parkinson-White (WPW) syndrome: Note: The classic triad of WPW syndrome include: 1. short PR interval 2. delta wave (arrows) and 3. QRS widening. The delta wave represents the conduction through the aberrant bypass tract

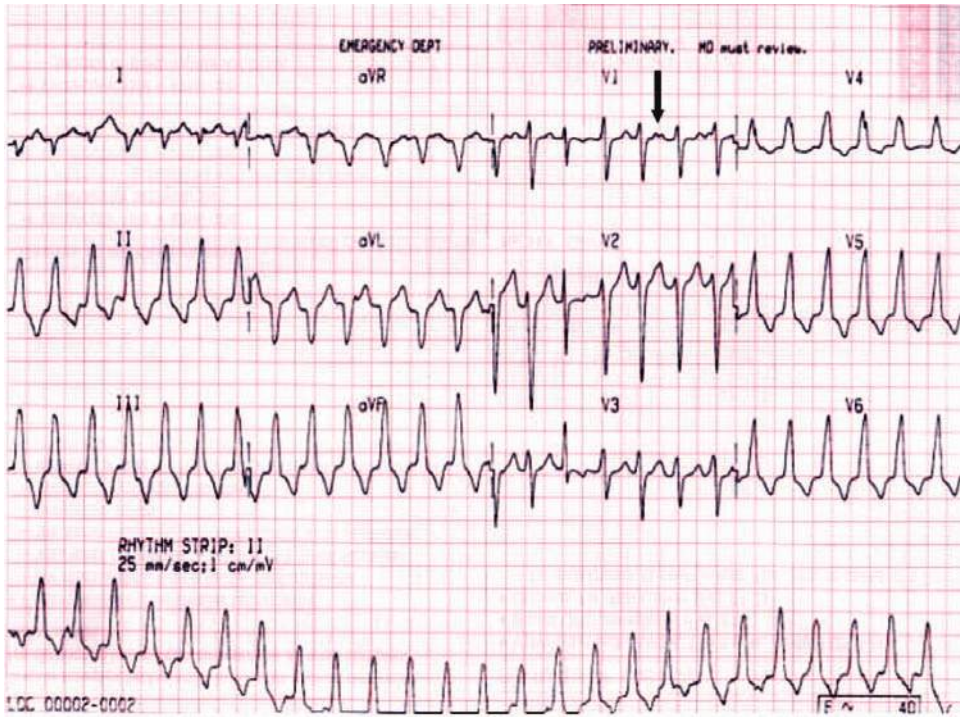


Fig. 122.10: Ventricular tachycardia (VT). Note: The non-uniform QRS complexes 1. Broad QRS complexes at rate of 150 per minute. 2. Mild irregularity in RR intervals. 3. Mild variation in morphology of QRS complexes. 4. Evidence of AV dissociation. Marked by arrow in V1

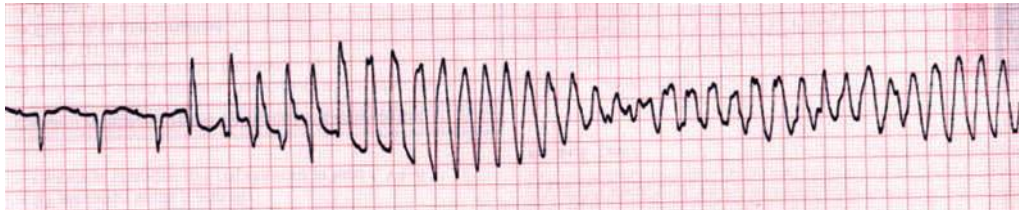


Fig. 122.11: Torsade de pointes: Note: 1. Torsade is a form of malignant ventricular tachycardia 2. The QRS is polymorphic 3. The axis of the QRS shifts across the baseline around a point 4. Often this occurs in the setting of prolonged QT interval

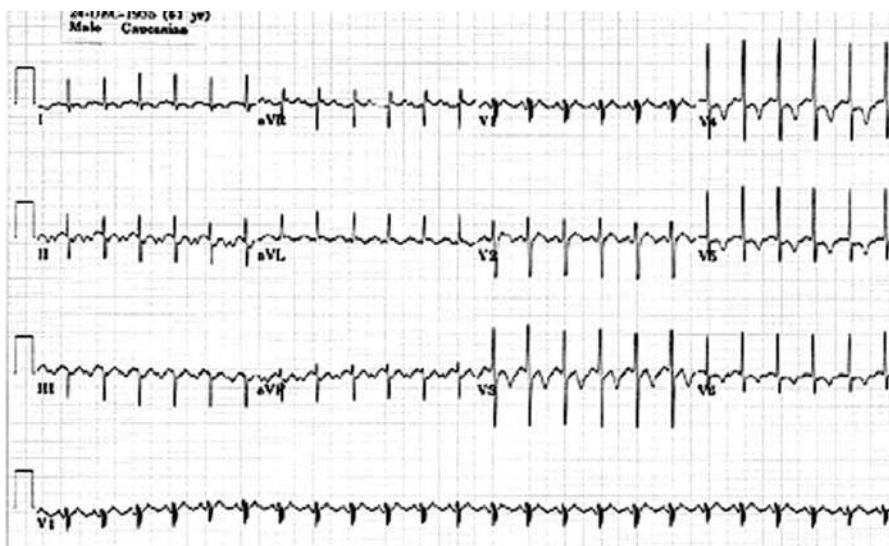


Fig. 122.12: Atrial flutter without A-V block: Note 1. Ventricular rate above 180/minutes 2. Large and negative P waves in leads II, III and aVF. Comment: Generally when the atrial rate increases functional A-V block develops



Fig. 122.13: Atrial flutter: Lead V_1 to show the flutter waves 1. The rapid flutter waves (marked by arrow) which are usually inverted in leads II, III and avF 2. The QRS rate is much slower due to associated AV block (arrow head)

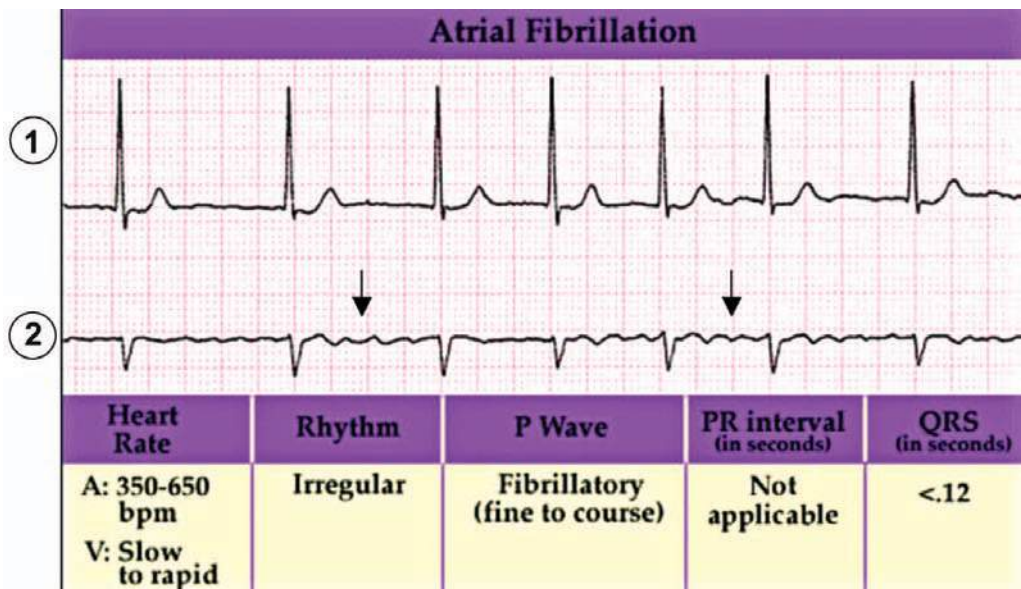


Fig. 122.14: Atrial fibrillation: Note: 1. Totally irregular RR intervals 2. Absence of $-P$ waves 3. Fibrillatory waves marked by arrows. Usually the QRS rate is fast in untreated atrial fibrillation. This record is made after starting treatment and showing of the heart rate
(1) Upper tracing lead 2
(2) Lower tracing shows the fibrillatory waves best brought out in lead V_1

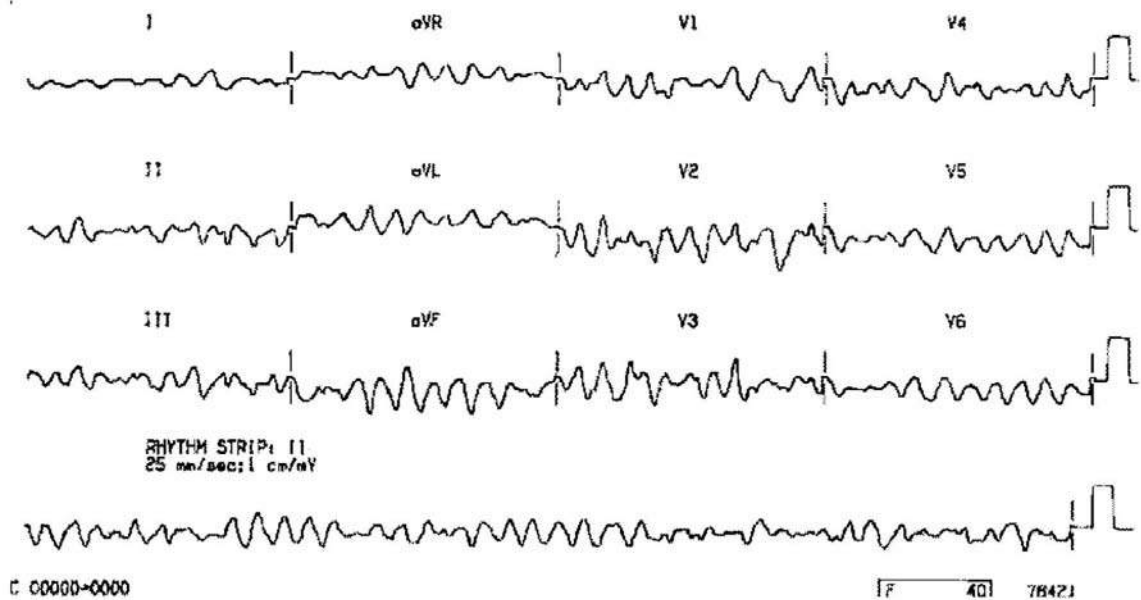


Fig. 122.15: Ventricular fibrillation: Note: 1. Totally irregular QRS activity with undulating base line.
2. Absence of normal QRS and T waves

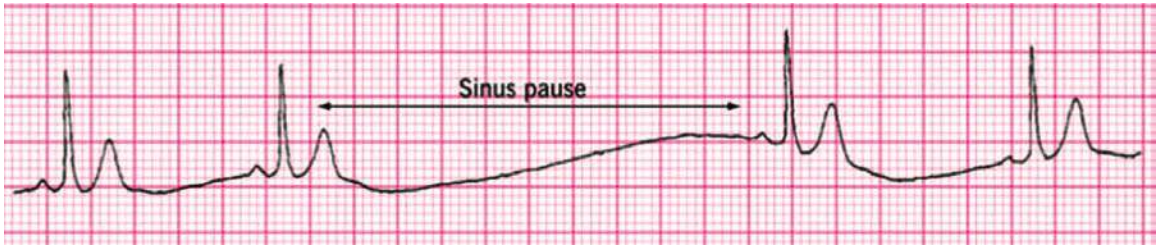


Fig. 122.17: Sinus arrest: Note the absence of all complexes with long pause



Fig. 122.18: SA block: The PR interval is normal. The sinus fails to produce impulse as is seen by the absence of P wave and the QRS (arrow)



Fig. 122.19: First degree A-V block: Note the prolonged PR interval beyond 0.2 second (i.e.) > 5 small divisions



Fig. 122.20: Second degree heart block Mobitz type 1: Note: 1. progressive prolongation of PR interval 2. The fourth P wave is blocked and is not followed by a QRS (arrow) Wenckebach's phenomenon

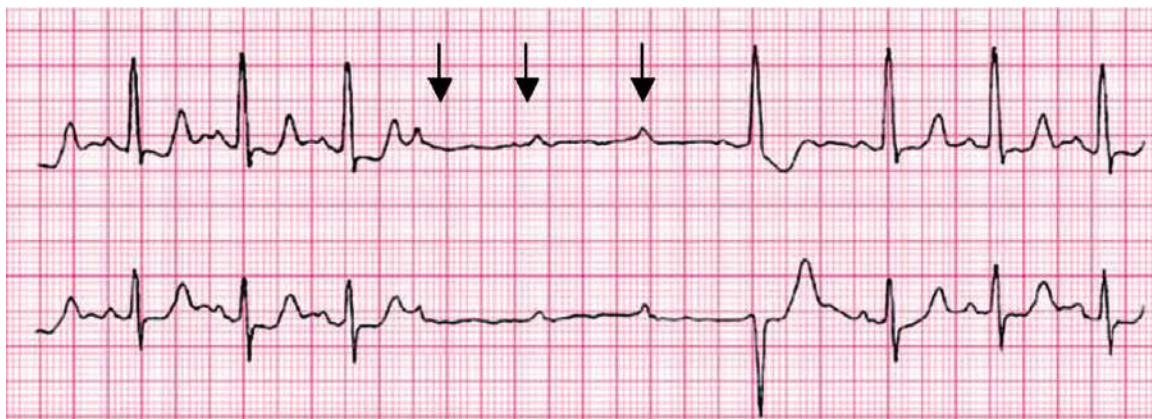


Fig. 122.21: Second degree heart block Mobitz type 2: High grade AV block: Note: the 4th, 5th and 6th P waves (marked by arrows) are not conducted to the ventricles indicating high grade A-V block 2. All the conducted beats show PR interval which remain constant



Fig. 122.22: Third degree A-V block. 1. P waves are regular and normal in rate 2. QRS are also regular but much slower in rate and wider 3. No relation between P and QRS

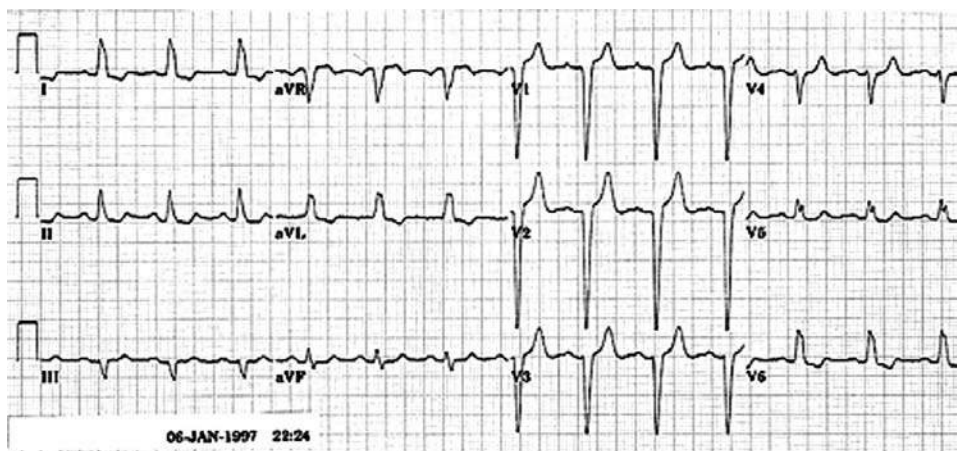


Fig. 122.23: ECG left bundle branch block (LBBB Note 1). duration of QRS exceeds 0.12 seconds 2) widened, slurred and bizarre R waves in lead 1 aVL, V5 and V6 slurred S waves in V1 and V2

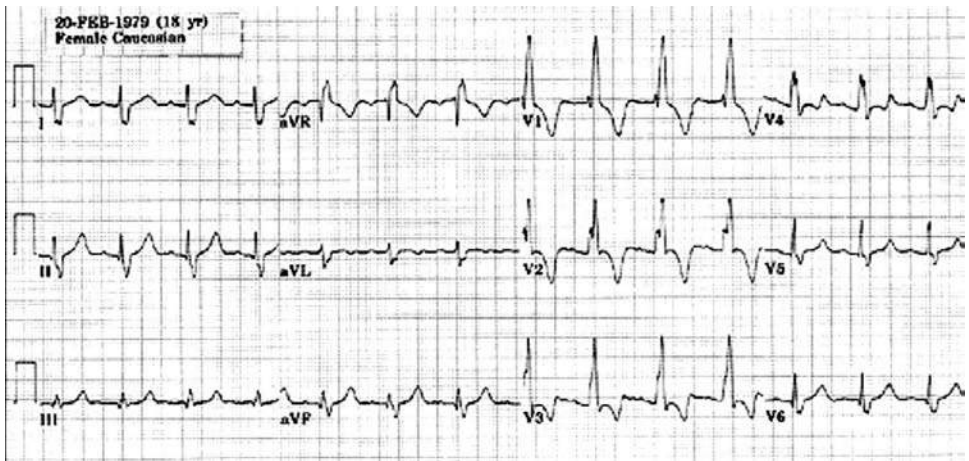


Fig. 122.24A: RBBB: complete right bundle branch block Note: 1. Prolongation of QRS duration above 0.12 seconds 2. Slurred R’waves in V1 and V2 3. Wide S waves in L1, aVL and V5 and V6

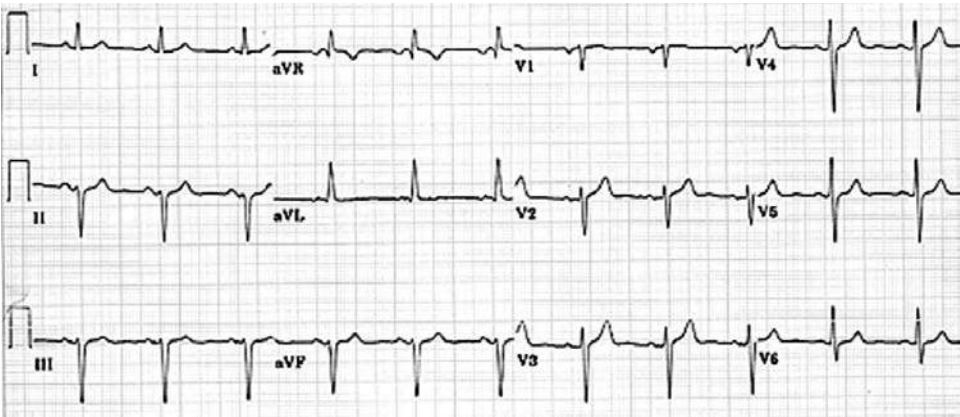


Fig. 122.24B: LAHB Note: 1. QRS axis is abnormally shifted to the left (left axis deviation) 2. Small Q, tall R morphology in aVL 3. Persistent S waves in V5 and V6



Fig. 122.25: Asystole: Note complete electrical silence (ventricular standstill)



Fig. 122.26: Sick sinus syndrome: note the tachy and bradyarrhythmias. 1. The first half shows atrial fibrillation with fast heart rate 2. The latter half shows a long pause

the patient. Electrocardiogram shows the abnormally shaped ectopic P-wave preceding the normal QRS complex. The compensatory pause is not full. The PQ interval is usually short though sometimes it may be prolonged (Fig. 122.3).

Junctional premature beats: These beats arise from the A-V junction. These are less common than atrial and ventricular premature beats. The physical findings resemble those of atrial premature beats. Sometimes cannon waves may be observed in the neck veins, if the atria contract while the A.V valves remain closed. The conduction of impulse in the atrium is retrograde and so the P-wave appears inverted in L_{II}, L_{III} and aVF, but it is upright in lead aVR. They may precede the QRS with a shortened P-Q interval, be immersed in the QRS, or follow the QRS. The QRS of the junctional premature beat is usually normal. The compensatory pause is not full.

Ventricular premature beats (VPB): An ectopic focus in any part of the ventricle can give rise to ventricular premature beats (VPBs). This is the commonest arrhythmia seen both in health and in disease. Continuous monitoring has shown that even apparently healthy individuals may show this arrhythmia. Ventricular premature beats occurring in a healthy heart usually disappear on exercise. The ventricular premature beats are seen pathologically in ischemic heart disease, acute myocardial infarction, cardiomyopathy, myocarditis, hypertension and digitalis toxicity. VPB occurring after every normal beat leads to pulsus bigeminus in which after two beats a pause occurs regularly. This is the characteristic arrhythmia seen in digitalis toxicity.

Clinically, VPB manifests as irregularity in the pulse. The premature beat may be felt as an early feeble pulse or the strong post ectopic beat may give rise to a pounding sensation in the chest. Jugular venous pulse may show irregular cannon waves. In the electrocardiogram the ventricular premature beat appears as a widened QRS which is often bizarre in shape. The ST segment and T wave is in a direction opposite to the direction of the QRS. The QRS is not preceded by the P-wave. The compensatory pause is often complete. Sometimes a ventricular premature beat may be seen sandwiched in between two sinus beats. They are known as *interpolated ventricular premature beats*. The R-R interval encompassing the VPB is equal to one cardiac cycle. The interval between the sinus beat and the VPB is known as coupling interval. Coupling interval is constant in case of unifocal VPB, but it is variable in multifocal VPBs (Fig. 122.4).

Paroxysmal Tachycardias

These are tachycardias produced as a result of enhanced impulse production from ectopic foci (in contrast to sinus tachycardia in which the normal pacemaker produces

impulses) or as a result of re-entry phenomenon. All the paroxysmal tachycardias are characterized by abrupt onset. Paroxysmal tachycardias depending on the focus of impulse production may be divided into:

1. **Supraventricular** – Atrial or A-V junctional
2. **Ventricular** – Right or left ventricular

Irrespective of the type of tachycardia, symptoms tend to be similar. Paroxysmal tachycardias usher in abruptly with a feeling of rapid thumping cardiac contractions in the chest. This may make the patient extremely uneasy and anxious. Autonomic phenomena such as sweating, syncopal feeling and tachypnea may develop. In patients with coronary artery disease, angina may be precipitated. If the arrhythmia tends to be prolonged beyond a few hours, signs of cardiac failure may develop especially if there are underlying abnormalities. Termination of the attack is also felt as an abrupt cessation of the tachycardia. This may be accompanied by diuresis, usually in supraventricular tachyarrhythmias.

In predisposed individuals, tachyarrhythmias are triggering factors to induce cardiac failure. In all forms of these arrhythmias, ECG is absolutely essential to arrive at the diagnosis.

Paroxysmal atrial tachycardia (PAT): Impulses arise in the atrium and the arrhythmia is usually produced as result of reentry phenomenon. The heart rate varies from 140-230/min and the rhythm is regular. The ECG shows normal QRS with a rate of 140-230/min. In some cases the P-waves may be identifiable preceding the QRS. Vagal stimulation (carotid pressure, dipping the face in or swallowing ice-cold water or pressure over eyeball) generally slows the rate and abolishes an attack. In the majority there is no underlying cardiac disease. Common causes are excess of caffeine or tobacco, alcohol, anxiety or thyrotoxicosis (Fig. 122.5).

Paroxysmal atrial tachycardia with block (PATB): This is a special form of PAT in which some of the atrial impulses are not conducted down to the ventricles. This gives rise to varying grades of atrioventricular block. Electrocardiographically P waves occur at a rate of 140-230/min, with an isoelectric shelf separating the P waves, and a slower QRS rate. This abnormality is characteristically seen in digitalis toxicity. It is an indication for withdrawing digitalis (Fig. 122.6).

Multifocal atrial tachycardia: This is characterized by an irregular rhythm and P waves with different morphology. It is seen in conditions such as bronchitis emphysema syndrome, cor pulmonale, hypoxia from any cause, ischemic heart disease, diabetes mellitus and after cardiac surgery. It indicates a poor prognosis. Diagnosis of multifocal atrial tachycardia can be made only with ECG. The ECG criteria include (Fig. 122.7):

1. Rate above 100/min.

2. At least three different forms of P waves in the same lead and
3. Variability of P-P, P-R and R-R intervals.

Management

1. Carotid sinus massage in the recumbent posture may serve to abolish PAT. Only one side should be massaged at a time;
2. Intravenous administration of verapamil or propranolol in small doses of 5 -10 mg at a time may terminate the episode;
3. Other antiarrhythmics that may be tried include amiodarone, or the Class I antiarrhythmics.

In resistant cases DC shock may be required. Investigation for the underlying condition and specific measures should be instituted to prevent recurrence.

A-V junctional tachycardia: Both paroxysmal (ventricular rate 130-240/min) and non-paroxysmal (ventricular rate 70-140 min) forms exist. The ECG shows normal QRS complexes, but the P-wave usually follows the QRS.

AV Nodal Re-entrant Tachycardia (AVNRT)

AVNRT is a tachycardia with a narrow QRS complex and a ventricular rate typically in the range of 150-250 beats/min. The mechanism in AVNRT appears to be a re-entrant circuit composed of separate slow and fast pathways involving the AV node. It is generally seen in subjects without underlying heart disease. Palpitations and dyspnea are common presenting complaints. Angina, CHF and rarely shock may be seen in those with a history of underlying heart disease. Syncope occurs rarely. ECG shows narrow QRS regular tachycardia with a rate of 150-250/min. P waves are generally not seen as they are hidden within the QRS complex (Fig. 122.8).

AV Re-entrant Tachycardia (AVRT)

AVRT is another narrow QRS tachycardia with ventricular rates often greater than 200/min.

The clinical features are very similar to those of AVNRT but are distinct on an electrophysiological basis. The mechanism in AVRT relies on the presence of re-entrant circuit comprising of an accessory pathway as one portion of the circuit and the AV node as the other portion. Accessory pathways may be “concealed” (inapparent by ECG) due to having only retrograde conduction properties (V to A) or “manifest” (apparent on ECG as delta waves) due to variable degrees of antegrade conduction [e.g. Wolff-Parkinson-White pattern as described below].

AVRT may be orthodromic or antidromic. Orthodromic AVRT is a narrow-complex tachycardia that uses the AV node as the antegrade limb and the accessory pathway as the retrograde limb of the circuit. Antidromic

AVRT is a wide QRS complex tachycardia that is the opposite such that the accessory pathway serves as the antegrade limb and the AV node as the retrograde limb of the circuit.

Orthodromic AVRT is the most common re-entrant AVRT accounting for 95% of cases. It is a narrow QRS complex regular tachycardia and the P wave will be seen just after the QRS complex inscribed on the ST segment (unlike AVNRT where the P waves are hidden in the QRS).

Wolff-Parkinson-White Syndrome (WPW syndrome) (Pre-excitation Syndrome)

WPW syndrome is not an uncommon cause of tachyarrhythmia seen in both sexes. In this condition an abnormal band of atrial tissue connects the atria and ventricles. In sinus rhythm this tissue conducts impulses faster bypassing the AV node. Conduction of impulse from atrium to ventricle occurs partly through the AV node and partly through the faster bypass tract. The ECG shows shortening of the PR interval and slurring of the ascending limb of the QRS complex, termed the delta wave, in addition to widening of the QRS complex (Fig. 122.9).

Since the AV node and the abnormal conducting tract have different conduction velocities, re-entrant tachycardias occur frequently resulting in paroxysmal tachycardias. Depending upon the direction of passage of the impulse through the AV node and the abnormal conducting tissue, the re-entry mechanisms vary giving rise to ECG patterns either resembling supraventricular tachycardia or with broader QRS complexes resembling ventricular tachycardias. Atrial fibrillation and ventricular fibrillation may occur at times. The condition is disabling since it affects the quality of life of the patient.

Management of SVT

This includes pharmacological therapy, radio-frequency ablation of the abnormal conduction pathway or surgical treatment. At present, catheter ablation is done for life-threatening arrhythmias [e.g. WPW syndrome, VT, incessant SVT, AF, atrial flutter etc] where accessory pathways are demonstrable and medical treatment fails.

i. Pharmacological therapy

Mainly 3 types of drugs are employed.

Those that prolong the conduction time or refractoriness in the AV node, e.g. Adenosine, propranolol and digoxin.

ii. Those that prolong the conduction or refractoriness of the accessory pathway, e.g. Class 1A and Class 1C drugs.

iii. Prolongation of conduction time and refractoriness of both pathways. Class III drugs, e.g. Amiodarone, sotalol.

Digoxin, IV verapamil and lignocaine can be used, but with caution, and not if the patient presents with atrial fibrillation. In patients with anterograde conduction through the accessory pathway, use of digoxin, adenosine, Calcium blockers, beta blockers etc may be contraindicated since these drugs increase accessory pathway conduction and predispose to fast ventricular rates.

Amiodarone: This is a potent antiarrhythmic drug which is effective both in supraventricular and ventricular arrhythmias. It may be given both parenterally as well as orally. Peak levels occur within 4-5 hours after an oral loading dose. It has a long half-life in the body (more than eight days). It is concentrated in the myocardium. Initial dose is 100-200 mg, 6- 8 hourly orally for 5-7 days and then the dose is reduced gradually to reach a maintenance dose of 100-200 mg/day. Adverse side effects include antagonism to vitamin K dependent coagulation factors and photosensitivity. This drug is useful in the treatment of resistant supraventricular and ventricular arrhythmias and WPW syndrome. This drug can also be given IV as a bolus injection in a dose of 150 mg, followed by a continuous infusion of 1.0 -1.2 gm over 18 to 24 hrs.

Calcium channel blockers: Verapamil and diltiazem have pronounced antiarrhythmic properties. They reduce the SA node activity and AV nodal conduction. Verapamil is very effective in the treatment of supraventricular tachycardias when given intravenously in a dose of 5 mg to be repeated ten minutes later, if necessary. Diltiazem is also effective particularly when given parenterally and also in the more conventional mode orally. Both these drugs are contraindicated in the presence of left ventricular failure, shock and conduction defects. They are not effective in the treatment of ventricular tachycardias.

When drug therapy fails and the condition of the patient demands rapid termination of the arrhythmia, more aggressive methods have to be used. These include DC shock and catheter ablation of the abnormal conduction pathways. In the latter, radio-frequency energy is used to ablate the abnormal pathways.

Termination of an Acute Episode

If there is no hemodynamic compromise, vagal pressure can be applied initially to reduce the rate. This is followed up with IV adenosine (6-12 mg IV rapid bolus) and later intravenous verapamil or diltiazem. Atrial fibrillation with fast heart rate may occur after drug administration, particularly adenosine. This should be treated with electrical cardioversion.

In those with very rapid ventricular rates or signs of hemodynamic impairment, electrical cardioversion is the treatment of choice.

For atrial flutter or fibrillation, drugs that prolong refractoriness in the accessory pathway often coupled with

drugs prolonging AV nodal refractoriness such as procainamide and propranolol are used (Fig. 122.16).

Prevention of Tachycardia

Drug combinations are usually employed

- Quinidine and propranolol or procainamide and verapamil
- Amiodarone or sotalol can be used singly. Dose of sotalol 80-320 mg/day in divided doses

Radio-frequency catheter ablation of the accessory pathway is advisable for the following groups:

- Symptomatic arrhythmia not fully controlled by drugs.
- Drug intolerance.
- Reluctance to take medication.

In experienced hands for electrical ablation the success rate varies from 95-98%.

Surgical ablation: Rarely surgical interruption of accessory pathway may be necessary.

Ventricular Tachycardia (VT)

When three or more ventricular ectopic beats occur in succession, it is called ventricular tachycardia. The common causes are ischemic heart disease, myocarditis, digitalis toxicity, electrolyte disturbances and cardiomyopathies. Rarely this may occur in an otherwise normal heart. The ventricles beat regularly at the rate of 150-210/min, slight irregularity may occur. VT can be monomorphic or polymorphic. The blood pressure is low and the patient may go into shock. Carotid massage does not bring down the rate as in the case of supraventricular tachycardia.

Ventricular tachycardia may be preceded by the occurrence of ventricular ectopics. Frequency of more than 6 ectopics/min, multifocal ectopics, ectopics occurring in succession and ectopics falling on the T-wave of the preceding beat (R on T phenomenon) are features which are associated with a higher risk of developing VT.

Diagnosis: VT is confirmed by the ECG which shows wide, regular, QRS complexes with evidence of dissociation between P-waves and QRS. Occasional sinus capture beats and fusion beats due to the inherent AV dissociation may be seen. VT needs to be distinguished from other wide QRS complex tachycardias like SVT with aberrant intraventricular conduction, pre-existing bundle branch block, antegrade conduction over an accessory pathway. Presence of AV dissociation (more QRS complexes than P waves) is diagnostic of VT (Fig. 12.10).

Prognosis: Ventricular tachycardia is a grave arrhythmia associated with high mortality, since it usually indicates serious underlying heart disease. Death is due to shock or transition to ventricular fibrillation.

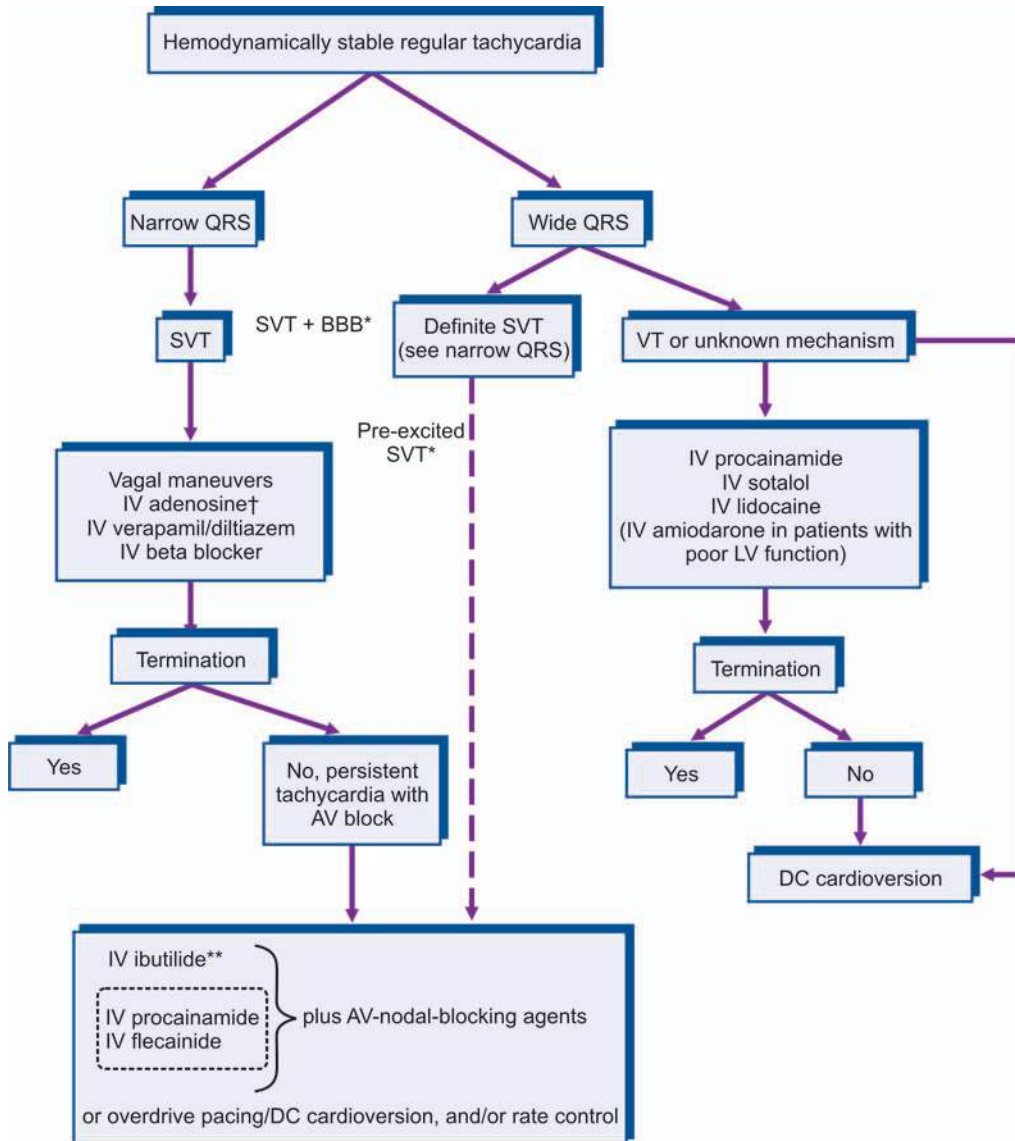


Fig. 122.16: Guidelines for the management of tachyarrhythmias. Acute management of patients with hemodynamically stable and regular tachycardia. *A 12-lead ECG during sinus rhythm must be available for diagnosis. Adenosine should be used with caution in patients with severe coronary artery disease and may produce AF, which may result in rapid ventricular rates for patients with pre-excitation. **Ibutilide is especially effective for patients with atrial flutter but should not be used in patients with EF less than 30% due to increased risk of polymorphic VT. AF indicates atrial fibrillation; AV, atrioventricular; BBB, bundle-branch block; DC, direct current; IV, intravenous; LV, left ventricular; QRS, ventricular activation on ECG; SVT, supraventricular tachycardia; VT, ventricular tachycardia.

Modified from ACC/AHA/ESC guidelines for the management of tachyarrhythmias. Ref: Circulation 2003;108:1871-1909.

Management: Patient presenting with shock and ventricular tachycardia should be given synchronized DC shock of 100-150 joules to convert the rhythm to normal without delay. Antiarrhythmic drugs tend to take time for action and aggravate hypotension. Pressor agents such as dopamine may be required if the blood pressure does not come up.

In uncomplicated cases the drug of choice is lidocaine (lignocaine). It is given as a 2% solution intravenously. Bolus doses of 50-100 mg are repeated (up to a total dose

of 250 mg) till the tachycardia is arrested. Then a maintenance dose of 2-4 mg/min is given continuously as an intravenous drip, 1g added to 500 mL 5% glucose and 1-2 mL given every minute. The drip is tapered off within 48-72 hours. If the VT recurs despite lignocaine, other antiarrhythmic drugs should be tried to control the arrhythmia. Drugs like procainamide, disopyramide, mexilitine, propranolol or amiodarone are given intravenously for immediate control of VT. The dose of amiodarone is 150 mg IV bolus in 15 mts followed by a

infusion of 900 mg in 24 hrs (1 mg/kg for 6 hrs and then 0.5 mg/kg for 18 hrs). Once the VT is controlled oral maintenance therapy can be continued preferably with the same drugs. The following drugs are for oral use.

1. Procainamide 1-3 g daily in divided doses.
2. Quinidine sulphate 0.8-2 g daily in divided doses.
3. Disopyramide 400-600 mg daily in divided doses.
4. Dilantin sodium 100 mg thrice daily.
5. Amiodarone: 100-300 mg/day.
6. Mexiletine 200 mg three times daily to start with and then continued at 100 mg thrice daily.
7. Sotalol dose 80-320 mg/day in divided doses.

In acute myocardial infarction with a slow ventricular rate, transvenous pacing to increase the heart rate prevents the development of ventricular tachycardia. The development of curative catheter based therapies especially in patients with normal heart and implantation of ICD (implantable cardioverter defibrillator) especially in post ischemic VT have reduced the role of antiarrhythmic drugs in the prevention of recurrence.

Torsade-De-pointes

This is an acquired or congenital polymorphic ventricular tachycardia in the range of 180-250/min characterised by QRS complexes of progressively changing amplitude and contour, that seem to revolve around the isoelectric line. Successive bursts of unsustained ventricular tachycardia occur. Sometimes these attacks may be prolonged and lead to syncope. The ECG shows prolonged Q-T interval (Fig. 12.11).

Arrhythmogenic Right Ventricular Dysplasia (ARVD)

ARVD is a cardiomyopathy in which the right ventricular muscle becomes increasingly replaced by adipose and fibrous tissue as the disease progresses. VT arising in the right ventricle is often an early manifestation of this disorder. VT has an LBBB morphology, although in sinus rhythm there is often inversion of T waves in the anterior leads and a slurring of the terminal portion of the QRS complex known as an "epsilon wave".

General points in the management of acute tachycardias: Paroxysmal tachycardias present as medical emergencies demanding acute care management. The ECG gives the clue to the nature of the tachycardia – whether VT or SVT. Wide QRS complex with a duration of > 140 msec is suggestive of VT unless proved otherwise. Based on the ECG, the tachycardias may be classified as regular or irregular and narrow or wide QRS complex. Regular narrow complex tachycardia can be treated with adenosine or drugs that slow the AV conduction. Irregular narrow complex tachycardia is due to AF and warrants treatment with drugs to achieve rate control by AV nodal blocking

action. Monomorphic wide QRS tachycardia should be presumed to be VT unless otherwise proved, and procainamide, amiodarone, or electrical cardioversion should be tried. Polymorphic wide complex irregular tachycardia should be classified into those with wide QT, those with normal QT and those with AF with WPW. Treatment of choice in these situations is magnesium, beta blockers and procainamide or amiodarone respectively.

Atrial Flutter

This is an uncommon arrhythmia in which the atria contract at the rate of 300/min. The mechanism is one of re-entrant tachycardia affecting the atria. Since the A-V node cannot conduct impulses at this rate, a physiological block develops and only half, a third, or a fourth of the atrial impulses are transmitted to the ventricles. The ventricles contract at a lower rate, but regularly. Flutter waves are seen in the jugular vein. Carotid pressure increases the block and reduces the ventricular rate further (Figs 12.12 and 12.13).

Treatment: Generally atrial flutter is resistant to drug treatment, but it responds to DC shock readily, 50 joules may be sufficient. Digoxin either abolishes the arrhythmia or converts it into atrial fibrillation and reduces the ventricular rate. On withdrawing digoxin normal rhythm may be restored. Quinidine is also effective in the treatment of atrial flutter.

Atrial Fibrillation

This is the condition in which the coordinated contraction of the atrium is abolished and the atrial muscle fibrillates. Abnormality of atrial activation is caused by impulses arising from different foci at the rate of 400-600/min. Since coordinated contraction at this rate is not possible, fibrillation sets in. This is the most common sustained arrhythmia in clinical practice. Prevalence increases with age. Above the age of 65 years, AF occurs in 5% of persons and above 75 years it affects 10% or more. 5% of persons with paroxysmal AF and 20% of those with persistent or permanent AF have no other demonstrable pathology.

Etiology: Atrial fibrillation (AF) may be due to different causes. In the order of frequency these are:

1. Rheumatic mitral valvular disease, mixed mitral lesions, mitral stenosis and mitral regurgitation.
2. Ischemic heart disease
3. Hypertensive heart disease
4. Thyrotoxicosis
5. Myocarditis
6. Cardiomyopathies
7. Digoxin toxicity

8. Chronic pericardial disease
9. Pneumonia
10. Congenital heart disease esp atrial septal defect
11. Sick sinus syndrome
12. Lone atrial fibrillation [AF without any predisposing diseases]
13. Familial AF [An abnormality of chromosome 16 occurring as an autosomal dominant disorder]
14. Infections and alcoholic bouts (Holiday heart syndrome).

Classification

- a. *Paroxysmal AF*: transient, reverting to normal sinus rhythm spontaneously.
- b. *Persistent AF*: does not revert spontaneously, but does so with electrical or pharmacological intervention.
- c. *Permanent AF*: cannot be reverted to sinus rhythm by electrical or pharmacological intervention.

Pathophysiology: Ectopic impulses arise in the atria, or pulmonary veins and their ostia at the rate of 400-600/min. They reach the A-V node at irregular intervals. Many of them find the A-V node totally or partially refractory and therefore, conduction to the ventricle is totally irregular. In AF the electrical activity produces multiple wavelets which circle round the atria. Some of these circle back themselves forming re-entry loops. The conduction velocity and refractory periods of portions of the atrial wall vary so that wavelets follow altering courses. A few complete classic re-entrant loops. Atrial enlargement predisposes to AF by accommodating more wavelets.

Rheumatic valvular disease predisposes to AF since it leads to deranged hemodynamics, atrial inflammation, fibrosis and impaired propagation of the impulse.

Ventricular contraction occurs irregularly – both in rhythm as well as in force. The ‘a’-wave in the jugular vein disappears since the atrium fails to contract as a whole. Loss of atrial contraction abolishes the augmented transit of atrial blood into the ventricle during end diastole, thereby abolishing the stretch to the ventricular muscle preceding systole (atrial booster effect). In normal hearts this may not be clinically significant, but in a diseased heart, atrial fibrillation precipitates cardiac failure because of the loss of atrial booster effect. Thrombi form in the atria as a result of stagnation. These embolize periodically resulting in systemic or pulmonary embolism.

Clinical features: The onset of atrial fibrillation may be felt as palpitation, especially so if the heart rate is high. Atrial fibrillation may be acute with duration less than a few days, paroxysmal or chronic and insidious in onset and course.

The pulse is totally irregular in rhythm and volume (irregularly irregular). The irregularity is best felt when the heart rate is rapid. In slow heart rates with ventricular

contraction around 70/min, the arrhythmia may be more difficult to detect clinically at rest. Pulse deficit can be made out by simultaneous palpation of the pulse and auscultation of the heart rate (by two different observers). A difference of more than 10 beats per min is highly suggestive of atrial fibrillation. The irregularity increases with exertion. Auscultation reveals total irregularity and varying intensity of the first heart sound. The ‘a’ wave of the jugular venous pulse is abolished. The presystolic accentuation of the mid-diastolic murmur of mitral stenosis disappears in most cases. If the fourth heart sound was audible prior to the onset of AF, it disappears. Confirmation of the diagnosis is made by ECG which shows absence of P-waves and the presence of fibrillary waves instead. The QRS complexes are irregular in rhythm but may be normal in pattern (Fig. 122.14).

Differential diagnosis: Frequently occurring irregular extra systoles may be mistaken for AF, especially if the heart rate is slow. Exercise abolishes the extrasystoles whereas it aggravates atrial fibrillation. In a few cases where clinical distinction is difficult electrocardiogram is needed for final diagnosis.

Course and prognosis: When the underlying condition is reversible such as myocarditis, pneumonia or thyrotoxicosis, treatment of the primary cause corrects the AF also. In chronic conditions such as valvular or congenital heart disease, cardiomyopathy and ischemic heart disease, the arrhythmia tends to persist even after treatment of the primary disease.

Atrial fibrillation gives rise to thromboembolic episodes, especially so when there is obstruction to atrioventricular flow as in mitral stenosis. Risk of thromboembolism is increased considerably in all cases of atrial fibrillation, compared to sinus rhythm. The risk of thromboembolism occurs in all types of atrial fibrillation. In paroxysmal AF usually embolization occurs on restoring sinus rhythm. Other abnormalities such as LV function impairment, disturbances of hemostatic mechanism and hypercoagulability accentuate the risk. In general 65% of emboli arise from the atrial appendage. Presence of mitral stenosis increases this risk several fold further.

Occurrence of atrial fibrillation leads to deterioration in the cardiac status and a progressive downhill course in chronic rheumatic heart disease, cardiomyopathies and systemic hypertension. Total mortality is doubled by the presence of AF in all forms of serious underlying heart disease.

Management : The aims of treatment are:

To restore sinus rhythm if possible [rhythm control]

1. If not, reduce the ventricular rate so as to improve the cardiac output [rate control]
2. Prevent recurrences and maintain sinus rhythm
3. Prevention of thromboembolism

Direct current (DC) shock helps to convert AF to sinus rhythm in 70-80% of cases. If the AF is less than 2 days duration electrical conversion can be attempted without anticoagulation. Flecainide is given to maintain sinus rhythm if the left ventricular function is good. If it is compromised amiodarone is the drug of choice.

If the AF is more than 2 days duration cardioversion should be attempted only after instituting anticoagulation with warfarin for 3 weeks. Warfarin has to be continued for 4 weeks after the procedure. The INR has to be kept between 2-3.

Ventricular rate control in atrial fibrillation can be done with digoxin, beta-blockers, amiodarone and calcium channel blockers (verapamil or diltiazem). In acute cases these drugs can be given IV, but for long-term use oral route is preferred.

Conversion to sinus rhythm can be achieved with drugs such as flecainide [90% success], propafenone [72%], and amiodarone [64%] also. AF < 48 hours duration responds well. In AF >48 hrs duration, drugs are less effective – dofetilide or amiodarone maybe tried [success rate 25-40%].

Atrial pacing is effective on long-term to prevent recurrences of AF, by preventing bradycardia and suppressing ectopic beats. Ablation of the ectopic foci in the atria or pulmonary vein ostia or isolation of these foci from conducting to the rest of the heart can be done by either catheter based radio-frequency techniques or surgically. The Maze procedure and the corridor procedure are such methods. The re-entrant circuits perpetuating AF are disrupted.

The risk factors for stroke in AF include mitral valve disease, age > 65 yrs, hypertension, LV dysfunction and previous h/o TIA or stroke. In patients less than 65 yrs of age with no risk factors for stroke only aspirin (150 mg/day) is required to prevent thromboembolic episodes, in all other patients with AF anticoagulation with warfarin is required, titrated to maintain INR (2-3) to prevent thromboembolic episodes.

Ventricular Fibrillation (VF)

This is the commonest fatal arrhythmia in ischemic heart disease. The myocardium of the ventricles contract asynchronously and fractionally to produce a fibrillary movement without any sustained synchronous beat. Pumping action of the heart is abolished, circulation comes to a standstill and death ensues if resuscitatory measures are not instituted immediately. The physical signs are exactly those of cardiac asystole. The ECG distinguishes ventricular fibrillation from asystole.

Management: Electrocardiogram is mandatory for diagnosis. Ventricular fibrillation is recognised on the ECG by the absence of QRS complexes and T-waves and

the presence of low amplitude baseline undulations which are quite variable both in amplitude and rhythm. The heart is defibrillated by direct current (DC) shock of 300-400 joules. Management of VF is the same as that of sudden cardiac arrest (Fig. 122.15).

Bretylium tosylate given intravenously in a dose of 5-10 mg/kg body weight is very effective in preventing the recurrence of ventricular fibrillation. Implantable cardioverter defibrillators (ICD) have become available in recent years. These compact devices detect ventricular tachycardia and fibrillation and automatically deliver shocks on to the myocardium, to terminate the arrhythmias.

Shock resistant VF is defined as VF persisting even after 3 attempts of electrical defibrillation.

Life Support Measures

In many developed countries the public has been trained to give emergency cardiac support by external cardiac massage, mouth-to-mouth respiration and external cardiac defibrillation. In many of the public places emergency defibrillators are also provided. If cardiac rhythm is restored within three minutes of onset of ventricular fibrillation or asystole the chance for recovery and brain function are good. Standardized practice guidelines have been laid down to assist physicians in clinical decision making in such emergencies.

Heart Blocks

Delay or interruption of the conduction of impulses from the SA node along the normal pathway to the ventricular myocardium results in heart block. The SA node produces impulses at the rate of 70-80/min. Velocity of conduction in the atria is 1m/Sec. It is 0.2 milliseconds in the A-V nodal tissues and 4 milliseconds in the Purkinje system. The A-V node being less conductive, there is a delay of 80-120 milliseconds, at this level. Heart block can be caused by abnormalities of impulse conduction at the SA node as in sinus blocks or conduction at the A-V node, the bundle of His and its branches.

Sinus arrest: In this condition the sinus node ceases to produce impulses (Fig. 122.17).

Sinoatrial block: impulses arising from the SA node are blocked at the junction of the SA node with the atrial musculature and hence the beat is missed. The ECG shows a pause with total absence of the PQRST complexes, corresponding to the missed impulses. Sometimes escape beats or escape rhythms may occur (Fig. 122.18).

Atrioventricular block (A-V block): This is caused by abnormalities at the A-V junction or along His Purkinje system. Three forms may occur.

1. **First degree A-V block:** Clinical detection of this form may be difficult. The ECG shows prolongation of P-R interval exceeding 0.20 sec (Fig. 122.19).
2. **Second degree A-V block:** This block is of two types. In both the types some of the impulses from the S-A node fail to reach the ventricles resulting in dropped beats.
 - a. **Mobitz type I block (Wenckebach's phenomenon):** The P-R interval increases progressively till a QRS is totally missed. This is clinically evident as a regular irregularity. Almost always this is caused by a block in the A-V node (Fig. 122.20).
 - b. **Mobitz type II block:** This is a more serious arrhythmia than type I block. The P-R interval of the conducted beats is fixed, but some of the P-waves are not conducted to the ventricles and are not followed by QRS. The P-waves outnumber the QRS complexes. Mostly this is due to a block in the His-Purkinje system and often the QRS may show some widening (Fig. 122.21).
3. **Third degree heart block (complete heart block):** In this condition impulses from the SA node are totally interrupted from reaching the ventricular muscle. The ventricles respond to impulses produced by the A-V junction or areas distal to that. When the impulses arise from the ventricles (idioventricular rhythm) the rate is usually less than 40/min. The ECG shows regular P-waves occurring at 70-80/min, and QRS complexes are usually bizarre occurring at a rate of about 30-40 /min. There is total dissociation between the P-waves and QRS complexes. The pulse is regular in established complete heart block because the QRS complexes are produced regularly (Fig. 122.22).

Clinical features: First degree heart block is an abnormality usually detected by ECG. Second degree heart block causes regular missing of heart beats and the pulse. Unlike benign extrasystoles in which the irregularity disappears with exertion, the irregularity in heart block tends to persist. Mobitz type II is associated with more serious disorders such as acute myocardial infarction or degenerative disorders of the conduction system. It may also be seen in digitalis toxicity, rheumatic carditis or cor pulmonale. It is considered a more serious block because often it progresses to complete A-V block.

Etiology of Heart Block

1. Primary degeneration of the conducting tissues. (Lev's disease, Lenegre's disease)
2. Diseases affecting the myocardium: myocardial infarction, chronic coronary artery disease and myocarditis.
3. Drugs and toxins: digoxin, quinidine, procainamide, beta adrenergic blocking drugs, cerbera thevetia and cerbera odollam.
4. Trauma to the conducting tissue during surgery.

5. Congenital abnormality of the conducting tissue (congenital heart block).
6. Infections: Tertiary syphilis, South American trypanosomiasis (Chagas' disease) and cysticercosis.
7. Sick-sinus syndrome.

Complete heart block should be suspected when the heart rate is 30-40/min or less, not increasing with exercise. The patients may complain of palpitation or syncopal attacks on exertion or even at rest. Syncope is transient loss of consciousness as a result of diminution of arterial blood supply to the brain. The patient complains of dimness of vision, a sinking feeling and may become unconscious. In the majority of cases consciousness is regained on falling down due to resumption of cerebral circulation.

If the heart beats are not resumed, the patient develops convulsions – *Stokes Adams- attacks*. These attacks are seen when periods of asystole or transient ventricular tachycardia or ventricular fibrillation occur in complete heart block. This may also be seen when one idioventricular focus changes over to another. If the heart beat is not resumed within minutes, the condition ends fatally. When the lesion is fully established and the rhythm is regular even at a slow rate, compensatory mechanisms develop and the frequency of syncopal attacks diminish.

Physical examination reveals slow, high volume pulse, forceful apex beat (due to diastolic overdilatation), presence of irregular cannon waves in the jugular veins, widened pulse pressure (high systolic and normal or low diastolic), and varying intensity of the first heart sound. Independent atrial sounds may be heard.

The ECG shows the slow ventricular rate and complete dissociation of the P and QRS complexes.

Diagnosis: Complete heart block should be suspected when the heart rate is slow and regular. His-bundle electrography gives further information about the site of lesion (infra-Hisian or supra-Hisian).

Prognosis: First and second degree heart blocks may resolve completely with treatment or proceed to complete heart block when the lesion is progressive. During the stage of evolution the prognosis should be guarded. In the stage of evolution and when the lesion is unstable complete heart block can progress to cardiac arrest or ventricular fibrillation.

Management

First and second degree heart blocks: Apart from close ECG monitoring and observation of the clinical state, no specific treatment may be indicated. Treatment of the primary condition clears the conduction defect as well. Atropine 0.5 mg given intravenously abolishes vagal tone and improves the heart rate in A-V blocks. Isoprenaline

or adrenaline given intravenously increases the heart rate and this is life-saving in an emergency. The heart rate can be maintained at a high level by giving ephedrine 30 mg orally thrice daily. These sympathomimetic drugs have the risk of triggering off serious tachyarrhythmias and hence in acute myocardial infarction these are not recommended.

When a patient with myocardial infarction develops progressive heart block leading to complete heart block, it is an indication for **transvenous pacing** using an external pacemaker and electrode catheter introduced into the right ventricle.

In established complete heart block, long-term prognosis is poor and therefore, **permanent pacemakers** are implanted. Pacemaker consists of two components.

(1) Pulse generator which is made of various type of batteries and (2) The lead which can be connected to the heart. The pulse generator is implanted into the body by making a pocket in the subcutaneous tissue in the infraclavicular area or on the abdominal wall. The generator is connected to one end of the lead and the other end of the lead may be placed in the right ventricle transvenously (endocardial pacemaker) or over the left ventricular apex (epicardial pacemaker). Dual chamber pacemakers are available in which stimulation of the atrium is followed by stimulation of the ventricle so that the normal sequence of contraction is reproduced. These are also known as physiological pacemakers. Modern pacemakers are programmable regarding the rate, voltage output and refractory period by telemetry from outside. Sensors which recognize the level of activity of the patients are incorporated in the pacemakers so that the rate of pacing is automatically adjusted to the requirement.

Since the advantage of pacemakers in giving symptomatic relief and prolonging life has been established it should be the aim to provide pacemakers wherever indicated. The cost ranges from Rs. 40000 to 60000 for the basic models to higher prices for more advanced options. Majority of them have a trouble free life exceeding 15 years. Dual chamber pacemakers probably are more effective with less of complication rate.

It is important that patients with implanted pacemaker should avoid strong magnetic fields such as MRI installations and metal detecting equipments. It is ideal to implant pacemakers early to avoid the development of Stokes- Adams attacks or sudden cardiac death. Once implanted, they require regular follow-up care.

BUNDLE BRANCH BLOCK (BBB)

His bundle divides into right and left branches, the left further divides into the anterosuperior and posteroinferior fascicles. Conduction of impulse below His bundle occurs thorough these three fascicles (trifascicular conduction). Conduction disturbance occurring in the right bundle branch (RBB) is known as right bundle branch block

(RBBB) and left main bundle as left bundle branch block (LBBB). Blocks at the fascicles of the bundle are called fascicular blocks. These may be involving two or three fascicles (bifascicular or trifascicular blocks). *Bundle branch blocks do not produce any arrhythmia by themselves.*

Complete left bundle branch block (LBBB): This involves the main stem of the left bundle. The anterosuperior or posteroinferior fascicle may be selectively affected at times. These are called left anterior hemiblock (LAHB) and left posterior hemiblock (LPHB) respectively. Sometimes the main left bundle may be affected, along with one or both of its branches (Fig. 122.23).

Complete right bundle branch block (RBBB): Interruption of the right bundle may occur as the lone abnormality or along with block of one or both of the branches of the left bundle. The combination of RBBB with LAHB or LPHB is called bifascicular block. In trifascicular block, RBBB exists with alternating LAHB and LPHB. RBBB plus LAHB /LPHB with prolonged PR interval is also a form of trifascicular block .

PARTIAL BUNDLE BRANCH BLOCKS

Left Anterior Hemi Block (LAHB) (Fig. 122.24)

Complete interruption of conduction of impulses in the bundle branch causes the QRS complex to prolong beyond 0.12 sec. When there is only delay without complete block of the impulse (partial bundle branch block) the duration of the QRS is between 0.10 and 0.12 sec. (normal 0.08 sec).

Bifascicular and trifascicular blocks give rise to characteristic ECG patterns. When the bundle branches are blocked, ventricular activation takes place through the remaining bundle or its fascicles.

Bundle branch block may result from ischemic heart disease, sclerodegenerative disorder of the conduction system of the heart, myocarditis, cardiomyopathy, drugs like quinidine and surgical trauma. In addition, RBBB may be seen in atrial septal defect, acute pulmonary embolism, right ventricular dilation and right ventricular failure. Congenital RBBB may occur rarely.

In myocardial infarction, presence of bifascicular or trifascicular block is considered an indication for temporary transvenous pacing of the heart, since complete heart block or the fatal arrhythmias are likely to develop in such patients.

VENTRICULAR STANDSTILL (VENTRICULAR ASYSTOLE) (FIG. 122.25)

When there is total cessation of stimuli reaching the ventricles, ventricular standstill develops. The ECG shows

absence of QRS (Fig. 122.26). Often the P-wave may also be absent. Cardiac asystole may occur in myocardial infarction and other forms of ischemic heart disease or in complete heart block. Treatment involves external cardiac massage and instituting the procedure for cardiac resuscitation.

Cardiac arrest and its management: Cardiac arrest is a most dramatic medical emergency which may happen in all unexpected situations from time-to-time. The picture is one of an apparently healthy or ailing person falling unconscious, with total loss of consciousness and cessation of heart beat and pulse. The most common causes are ventricular fibrillation and ventricular asystole. If cardiac standstill is not corrected within 3-4 minutes, irreversible damage occurs to the brain and vital centers. Resuscitation becomes futile thereafter or even if the cardiac rhythm is restored, full consciousness is not regained. Such a patient may continue to live a vegetative existence without regaining consciousness and other cerebral functions.

Other supportive evidences are:

1. Dilation of the pupils.
2. Cessation of breathing or gasping respiration.
3. Cyanosis or pallor.
4. Loss of consciousness.

The ECG will confirm whether the heart is in asystole or ventricular fibrillation.

A planned line of management is absolutely essential to avoid these catastrophies.

Resuscitative measures should be instituted if the main pulses are not palpable and heart sounds are not heard. Management of cardiac arrest is a team work. One person starts the procedure, the others soon join him for assistance. It is mandatory to distinguish between the ventricular asystole and the ventricular fibrillation for specific management.

Steps to be followed:

1. Put the patient on a firm non-resilient surface and clear the airway. Remove dentures and foreign bodies from the mouth and throat, loosen clothing, pull the chin up so that the tongue does not fall back to obstruct the throat, and remove secretions from the air passages by proper positioning and suction. Introduce an airway, if available.
2. Start external cardiac massage by pressing firmly over the sternum (so as to compress the precordium) and releasing it, at the rate of 50-60/min. If the maneuver is properly done, the carotid pulse will be felt.
3. Start artificial ventilation simultaneously by mouth-to-mouth respiration, or using an Ambu bag. If facilities are available, the trachea is intubated with a cuffed endotracheal tube and positive pressure

respiration given with oxygen-enriched air at the rate of 10-12 L/min, without interference to the external cardiac massage.

4. Start an intravenous line with 5% glucose, to act as a route of medication.
5. If ECG shows ventricular fibrillation, apply the electrodes and give a DC shock of 200 joules (100-400 joules). Often the fibrillation disappears and heart resumes normal beat. The DC shock can be repeated if conversion is not achieved with single shock. If ventricular asystole is detected, adrenaline 0.5 mg is given intravenously or intracardiac (0.5 mL of 1/1000 solution) into the cavity of the right ventricle using a lumbar puncture needle inserted through the third or fourth left intercostal space. Often this converts asystole into ventricular fibrillation and this can be converted by DC shock. In many centres adrenaline is given by the intravenous route. This is adequate if external cardiac massage is performed effectively.
6. Other drugs: Sodium bicarbonate is given I V in a dose of 100 mmol (100 mL of 7.4% solution) for an adult, rapidly to counteract metabolic acidosis.
7. If the heart returns to activity, continue massage till the systolic blood pressure is maintained at 70-80 mm Hg.
8. If the heart is beating, but BP is low, dopamine may be started as an intravenous drip at the rate of 2-3 µg/kg/min.
9. If the heart continues in asystole after adrenaline, and massage, 20 mL of 5% solution of calcium chloride can be given IV, after repeating sodium bicarbonate and adrenaline.

External cardiac massage and resuscitatory measures are stopped if the heart fails to recover within one hour, or the pupils remain dilated and fixed despite adequate massage.

As soon as the emergency team starts to give first aid, steps are taken to transport the patient to the hospital in a suitably equipped ambulance. Emergency first aid management of cardiac arrest is taught to several groups such as ambulance personnel, paramedical staff, porters, scouts and so on. Periodically, guidelines are published to simplify the procedure so that more persons can practice emergency resuscitation. Life saving equipment such as defibrillators, ventilators and oxygen delivery systems are available in public places and in several aircraft. Emergency resuscitation helps to prevent death and permanent morbidity.

Sick Sinus Syndrome (SSS)

Normal sinus node produces impulses at the rate of 60-70 per minute under basal conditions. Depending on physiological demands it may increase the rate upto

180 per/min (exceptionally 200 per min.). During sleep, heart rate may go down to 50-60 per minute (exceptionally as low as 40 per min). Persons with increased vagal tone achieved by physical training or otherwise have lower resting heart rates. In them the rate of rise of heart rate with exercise is also lower. When the sinus node is diseased and consequently the impulse production becomes defective it may give rise to various electrophysiological abnormalities of the heart. The clinical spectrum resulting from these is termed sick sinus syndrome (SSS). In about 30% of cases A-V node (A-V Junction) may also show abnormality.

SSS is relatively common in clinical practice, particularly among the elderly. Although various drugs such as digitalis, propranolol, and quinidine produce dysfunction of the sinus node, these functionally reversible situations are not considered as part of SSS. Ischemic heart disease, idiopathic sclerodegenerative processes, toxic myocarditis, various types of cardiomyopathies, Friedreich's ataxia, infiltrative disorders like amyloidosis, hemochromatosis and metastatic deposits account for the vast majority. In many cases, the etiological factor may not be apparent. The clinical picture may be dominated by bradyarrhythmias such as severe sinus bradycardia, sino-atrial block, intermittent sinus arrest or sinus pause singly or in combination. Because of this, patient may develop dizziness, mental confusion, syncope or near syncope. In patients with underlying heart disease progressive congestive heart failure may result.

The other group of manifestations results from atrial tachyarrhythmias, such as recurrent atrial fibrillation, flutter, or re-entrant tachycardia. Sudden onset atrial fibrillation with relatively slow ventricular response, especially in elderly subjects, should alert the possibility of SSS. Palpitation, confusion, syncope, near-syncope, angina pectoris and congestive heart failure may result from the tachyarrhythmia. SSS may produce extreme bradyarrhythmia associated with sudden change into

tachyarrhythmia in the same patient. This is termed as bradytachyarrhythmia syndrome (BTS).

Diagnosis can be suspected from the clinical manifestations. Routine 12 lead ECG is very useful in the diagnosis. ECG manifestations may include:

1. Persistent, inappropriate and marked sinus bradycardia
2. S-A block
3. Sinus arrest
4. Long pause following an atrial premature contraction
5. Chronic atrial fibrillation or flutter with slow ventricular rate
6. Carotid sinus hypersensitivity
7. Unstable sinus rhythm after cardioversion
8. A-V junctional escape rhythm with or without slow and unstable sinus activity and (Fig. 122.26)
9. Bradytachyarrhythmia syndrome.

Ambulatory electrocardiogram (Holter's monitoring) is particularly useful for diagnosis and prognosis. Those with equivocal findings can be studied by treadmill exercise test, or response to drugs like atropine or isoproterenol. Electrophysiological studies for determining the sinus node recovery time or sino-atrial conduction time and His bundle electrocardiography may be required in selected cases for diagnosis and management.

Prognosis: The abnormality of the sinus node tends to be chronic, progressive and permanent. In those who present with symptoms of recurrent syncope or near syncope, progressive angina and congestive heart failure especially with underlying heart disease, the prognosis is bad. Sudden death may occur in untreated cases.

Management: Once the diagnosis is established, in symptomatic patients, implantation of suitable permanent pacemaker is the treatment of choice, particularly in those with symptomatic bradycardias. It helps to relieve the symptoms and improve the quality of life. Tachyarrhythmias due to SSS may be safely managed with antiarrhythmic drugs, provided a pacemaker is also implanted.

Appendix

Anti Arrhythmic Drugs – Dosage and Indications				
Sl.No.	Anti arrhythmic drugs	Dosage		Indications
		Oral	Parenteral	
1.	Quinidine	200-400 mg 3-4 times a day (up to 600 mg Q 6 H)	IM-600 mg followed by 400 mg every 2 hours or IV-800 mg in 50 mL 5% Dextrose @ 1mL/mt infusion	Atrial flutter, atrial fibrillation AVNRT
2.	Procainamide	2-4 g/day in 3-4 divided doses (max daily dose 6 gm)	IM or IV 25-50 mg over 1 mt to rpt at 5 mts interval till arrhythmia is controlled. Or IV infusion 2-6 mg/mt	Atrial fibrillation SVT (AVNRT, AVRT)
3.	Disopyramide	100-200 mg Q 6H Max 1200 mg/day	IV – 1 -2 mg/kg bolus followed by 1 mg/kg/hr	SVT (AVNRT, AVRT), atrial flutter, atrial fibrillation, VT
4.	Lignocaine	N A	IV 1-2 mg/kg bolus max 5 mg/kg then infusion at 1-4 mg/mt	Rapid termination of VT refractory VT/VF
5.	Mexiletine	200 mg tid	100-250 mg I V bolus followed by 250 mg infusion over 1-2 hrs	Ventricular tachycardia
6.	Phenytoin	1 g loading dose day 1 followed by 500 mg on D2 and D3 and 300-400 mg daily thereafter	IV 100 mg, repeated, up to max 1 g	Digoxin related atrial and ventricular arrhythmias
7.	Flecainide	100 mg every 12 H max 400 mg/day	I V – 2 mg/kg then 100-200 mg Q 12 H	Paroxysmal AF, SVT, VT
8.	Esmolol	N A	I V 500 mcg/kg loading followed by 50-200 mcg/kg/mt	Rapid rate control in SVT
9.	Amiodarone	200 mg tid × 1 week then 200 mg bd for a week, maintenance 100-200 mg/d	150-300 mg I V bolus then 1 mg/kg/mt for 6 hrs and 0.5 mg/kg/mt for 18 hrs	Atrial flutter fibrillation AVNRT refractory VT/VF and VF
10.	Sotalol	80 mg/d in 1-2 divided doses, max of 640 mg/d	I V 100 mg over 1-2 mt	Atrial flutter atrial fibrillation, VT
11.	Bretylum	4 mg/kg/daily	I V 5-10 mg/kg bolus followed by 0.5-2 mg/mt infusion	Refractory VT and VF
12.	Ibutilide	N A	I V 1 mg over 10 mts to repeat if needed	Termination of a/c episode of atrial flutter/ atrial fibrillation
13.	Dofetilide	0.1-0.5 mg BD	IV 2.5 mcg/kg, to repeat if needed	Acute and chronic AF
14.	Verapamil	120-480 mg/day in 3-4 divided doses	I V 5-10 mg over 2-3 mts	SVT
15.	Adenosine	N A	6-12 mg I V as rapid bolus	Termination of PSVT
16.	Digoxin	0.5-1 mg loading followed by 0.125 mg 0.25 mg daily	I V 0.5-1 mg	Atrial flutter fibrillation control of heart rate

Key: SVT – Supraventricular tachycardia
 VT – Ventricular – do –
 AVNRT – AV nodal re-entrant – do –
 VF – Ventricular fibrillation
 AF –Atrial fibrillation
 PSVT – Paroxysmal SVT

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Systemic Hypertension

K. Suresh

Chapter Summary

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GENERAL CONSIDERATIONS

Systemic arterial hypertension is one of the most common maladies of mankind, affecting about 20% of the population globally. Though it was considered to be a disease related to affluence, it is no longer so. All sections of the population in India suffer from the disease, the prevalence in urban population is higher compared to that of the rural population. This is a major public health problem for India along with diabetes, ischemic heart disease and strokes. Diabetes and hypertension coexist in about 30-40% of cases and the combination adversely affects the long-term prognosis mutually. Hypertension leads to damage of the target organs – heart, brain, optic fundi, kidneys and blood vessels both acutely and on a long-term basis.

The damage to the target organs correlates generally with the values of elevated blood pressure (both systolic and diastolic). This is not always so since other factors such as hyperlipidemias and tobacco smoking may also influence the final outcome.

Measurement of Blood Pressure

This is ideally done using a mercury sphygmomanometer. The patient should be seated in a quiet room for 15 minutes before recording BP. BP may also be recorded in

the supine and standing position. At all postures, the arm should be supported at heart level. The BP cuff for adults should have a bladder 13-15 cm wide and 30-35 cm long, which is adequate for most of the average sized persons.

Larger cuffs are required for stout arms and vice versa. Using a cuff of smaller size gives erroneously higher values. The cuff is rapidly inflated to 30-40 mm Hg above the level at which the pulse becomes palpable and then deflated at the rate of 2 mm/sec. Auscultating over the cubital fossa, the onset of Korotkoff's sounds (phase I) and their disappearance (phase V) are recorded. The former denotes the systolic and the latter, the diastolic blood pressure. At least two measurements made three minutes apart are taken and the average values taken as the blood pressure. The unit of BP is expressed as mm Hg or as kilo Pascals (KPa = 7.5 mm Hg). All other instruments used to record blood pressure such as aneroid manometers, electronic devices and others should be periodically calibrated with the mercury instrument. Other modalities of measuring BP are automatic instruments preset to record at regular intervals, direct intra-arterial measurement, instruments that can be fitted to a finger with the patient lying supine and ambulatory recording.

The blood pressure values in a community follow a bimodal pattern lying within a broad range of normalcy. The cut off points separating normal and abnormal BP tend to be arbitrarily based on statistical evidence of adverse consequences of raised pressure – both systolic and diastolic.

The blood pressure recorded in the doctor's clinic or office, are quite reliable for purpose of diagnosis and management. The presence of physician or nurse while measuring blood pressure may cause elevation of BP due to emotional causes. This is known as the "white coat effect". This should not be set aside as non-pathological. On follow-up many white coat hypertensives may show sustained elevation of BP levels. Ambulatory BP recording is a more reliable predictor of cardiovascular risk than a routinely determined BP measured by sphygmomanometer. This can be undertaken in special cases. The test is expensive.

In more than 2/3rd of cases of hypertension both the systolic and diastolic blood pressure levels (SBP and DBP) are elevated. In about a third the SBP is greater than 140 mm Hg while the DBP is 90 mm Hg or less (Isolated systolic hypertension). SBP is also associated with higher risk of vascular occlusions in the coronary and cerebral vasculature. SBP and DBP together and also individually are associated with increased risk of complications. Systolic BP increases with age upto the 8th decade, whereas DBP increases only upto the age of 50 yrs. In the elderly the DBP may actually fall and pulse pressure widens. In the Framingham study, SBP and widening of pulse pressure were found to be important predictors of risk in the elderly.

Factors which Influence Blood Pressure

Age: There is a positive relation between age and BP in most of the population groups.

Sex: Males have slightly higher values than females of the same age.

Ethnic groups: Some communities show higher prevalence of hypertension. In USA the BP in the black races is higher than that in the whites.

Risk factors

Hereditary factors: Family history of hypertension is the strongest predictor for the development of hypertension.

Genetic factors: Several factors and genes have been studied. The inheritance seems to be polygenic.

Birth weight: Low birth weights and adverse environment in early life are associated with higher prevalence of hypertension and diabetes.

Obesity: In adults obesity may confer a two-fold risk to develop hypertension. Central obesity is the stronger predictor of risk.

Dietary sodium and potassium intake: The SBP and DBP are related directly with sodium intake and urinary sodium loss. Reduction of dietary sodium by 100 mmol/day definitely leads to lowering of SBP on long-term follow up. Potassium intake bears an inverse relation to blood pressure. Higher potassium intake lowers blood pressure.

Other factors: Alcohol intake, tobacco smoking, sedentary life style and noise pollution markedly elevate the BP level. Modification of life style helps to lower the BP considerably.

In clinical practice over 97% of hypertension belong to idiopathic or primary variety. 3% may be secondary. Clinical features which should suggest the possibility of secondary hypertension include a positive history of hypertension and renal diseases in the family, history of

TABLE 123.1		
Showing SBP and DBP in different age groups		
Age	Normal	Significant hypertension
< 2 years	104-111 70-73	112-117 74-81
10-12 years	122-125 78-81	126-133 82-89
Note: BP in a one day old infant is ± 70 mm Hg. It rises to ± 85 mm Hg at 1 year. Boys have a slightly higher BP than girls.		

intake of drugs, endocrinological disorders and resistance to the action of common anti-hypertensive drugs.

Systemic Hypertension Systemic hypertension is a major risk factor for coronary artery disease, heart failure, stroke and renal disease. So early detection and effective management of hypertension is important in reducing the morbidity and mortality attributed to it. The risk of cardiovascular diseases in a hypertensive patient is determined also by the other coexisting cardiovascular risk factors in addition to the level of blood pressure.

Definition: Hypertension is defined as systolic blood pressure of 140 mm Hg or greater, and diastolic BP of 90 mm Hg or greater. Isolated systolic hypertension is defined as systolic BP of 140 mm Hg or greater and diastolic BP below 90 mm Hg (Tables 123.1 and 123.2).

When the blood pressure is elevated without an evident organic cause, it is called **essential hypertension**. Hypertension produced by an identifiable cause is called **secondary hypertension**.

Essential hypertension far outnumbers secondary hypertension. It is necessary to detect the primary cause for secondary hypertension since correction of the cause leads to regression of the hypertension. In essential hypertension since no underlying removable cause is detectable, treatment has to be, at best, palliative.

TABLE 123.2			
JNC VII classification of blood pressure for adults (≥18 years) (Joint national committee on prevention, detection, evaluation and treatment of high blood pressure)			
BP classification	SBP (mmHg)		DBP (mmHg)
Normal	< 120	and	< 80
Prehypertension	120-139	or	80-89
Stage 1 Hypertension	140-159	or	90-99
Stage 2 Hypertension	≥ 160	or	≥ 100
When SBP and DBP fall in different categories, higher category should be selected to classify the individual's BP status.			

Causes of Secondary Hypertension

I. Renal

A. Renal parenchymal disease

1. Acute glomerulonephritis
2. Chronic nephritis
3. Polycystic disease of kidney
4. Diabetic nephropathy
5. Hydronephrosis
6. Post-traumatic renal damage

B. Renovascular

1. Renal artery stenosis
2. Intrarenal vasculitis

C. Renin producing tumours

D. Primary sodium retention

II. Endocrine

A. Acromegaly

B. Hypothyroidism and hyperthyroidism

C. Hyperparathyroidism

D. Adrenal

1. Cortical
 - Cushing's syndrome
 - Primary hyperaldosteronism (Conn's syndrome)
 - Congenital adrenal hyperplasia
2. Medullary – pheochromocytoma

E. Exogenous hormones

- Estrogen
- Glucocorticoids
- Mineralocorticoids
- Sympathomimetic drugs
- Tyramine containing foods and mono-amine oxidase inhibitors

III. Vascular causes: Coarctation of aorta

IV. Pregnancy induced hypertension

V. Neurological disorders

- a. Increased intracranial pressure
 - Brain tumours
 - Encephalitis
- b. Guillain-Barré syndrome
- c. Familial dysautonomia

VI. Miscellaneous causes: Sleep apnea, acute stress, postoperative, hypoglycemia, burns, post-resuscitation, alcohol withdrawal, etc.

standardized prevalence was 17%. The body mass index and waist-hip ratio were significantly higher in the hypertensive group. The prevalence of diabetes mellitus, obesity and coronary artery disease were significantly higher in those with hypertension.

Ref: Shanterani, et al. JAPI 2003;51:20-7.

Longitudinal study of the population at Framingham (USA) has revealed that the prevalence of hypertension was 29.7%. The blood pressure showed a rise of 20 mm in SBP and 10 mm DBP when persons were followed up from 30-65 years. Systolic blood pressure continued to rise in women up to 80 years and in men up to 70 years. There was strong genetic and familial predisposition to hypertension. Persons with diabetes mellitus and impaired glucose tolerance have a high prevalence of hypertension (even up to 50%), whereas hypertensives have a 15-18% chance of having associated abnormalities of glucose metabolism.

Contributory factors: Following factors contribute to the occurrence of this condition.

- a. *Genetic factors:* Essential hypertension shows a polygenic pattern of inheritance.
- b. *Psychological stress:* Persons who have to undergo mental stress during the course of their duties and those with tense personality are affected more.
- c. *Salt and water intake:* Communities with high salt intake have a higher prevalence of essential hypertension.
- d. *The renal hormones:* The role of renin- angiotensin aldosterone system has been extensively studied. Renin is produced by the juxtaglomerular apparatus in response to various stimuli. The control of renin release is complex. Several stimuli lead to renin release. These are:
 1. the impulses from pressor receptors in the afferent arterioles of the glomeruli;
 2. chemoreceptors of the macula densa which are stimulated by hyponatremia;
 3. the sympathetic stimuli which lead to renin release on assuming the upright posture;
 4. chemical stimuli such as hypokalemia, etc.

Renin converts angiotensinogen to angiotensin I, which is further converted to angiotensin II, by the converting enzyme. Angiotensin II stimulates the production of aldosterone. Angiotensin II causes vasoconstriction and aldosterone leads to retention of salt and water. Among the hypertensives, 60% have normal, 30% have low, and 10% have high values of plasma renin activity.

- e. *Other factors* such as deficiency of prostaglandins and kinins which normally help in lowering the vascular tone have also been incriminated in the production of essential hypertension.

EPIDEMIOLOGY

Overall prevalence of hypertension in India is about 26.2% in men and 23.6% in women. The prevalence is significantly more in urban subjects (30.9%) than in rural population (21.2%). A prospective study conducted at Chandigarh showed that the prevalence of hypertension rose from 26.9% in 1968 to 44.9 in 1996-97.

Ref: Akhlawat SK, et al. J Ind Med Asso 2002;100-92:547-55.

A report from Chennai showed the crude prevalence rate of hypertension was 21.1% whereas the age

- f. **Atrial natriuretic hormone:** Atrial tissue secretes a group of peptides, at least one of which is secreted as a regulatory hormone. *In vivo* experimental studies show that this peptide produces immediate marked increase in sodium loss, increase in glomerular filtration rate (without altering the total renal blood flow) and fall in arterial blood pressure. The other effects include inhibition of renin secretion, aldosterone secretion and opposing the vasoconstrictor effect of angiotensin II.

PATHOLOGY

Main pathological process occurs in the heart and several parts of the arterial tree.

Cardiac changes: The left ventricle hypertrophies in 20-50% of mild to moderate hypertensives. The muscle fibres hypertrophy and this process is reversible with anti-hypertensive therapy. At autopsy, left ventricular hypertrophy is diagnosed if it weighs above 131 g/m² body surface in men and 100 g/m² body surface in women. Unlike physiological hypertrophy occurring as a result of exercise, in hypertension left ventricular hypertrophy leads to diastolic dysfunction, arrhythmias, acceleration of coronary atherosclerosis and left ventricular failure. Cardiac failure is caused by degeneration and lysis of myofibrils. The extent of hypertrophy and levels of blood pressure do not correlate in all cases but hypertrophy is more pronounced in those with early onset hypertension.

Arterial changes: Arteries and arterioles show thickening (arteriosclerosis). Arteriolar changes are well seen in the kidneys. Renal vessels show medial hypertrophy and intimal fibrosis. Progressive occlusion of arterial lumen leads to scarring of glomeruli and tubular atrophy.

In the coronary arteries there is accelerated progression of atherosclerosis. Cerebral arteries, renal arteries, aorta and its major branches show progressive atheromatous change. Small arteries of the brain show microaneurysms, known as Charcot-Bouchard aneurysms, which may rupture resulting in cerebral hemorrhage. Thrombotic and embolic occlusion of atheromatous arteries gives rise to infarction in the heart, brain and kidneys.

CLINICAL FEATURES

Essential hypertension: The condition is asymptomatic and over 50% of the patients are unaware of the condition. Elevated blood pressure is detected during a routine medical examination in such subjects. A few of them present for the first time with one of the major complications. Many develop symptoms after knowing that they are hypertensives. The symptoms are vague and non-specific in such patients. These symptoms include fatigue, dizziness, palpitation, headache and anxiety.

Though many types of headache have been described, throbbing headache, felt in suboccipital region on waking up after sleep is suggestive of hypertension.

Physical examination may reveal a heaving apex beat and loud aortic second sound in many cases. The pulse may show rise in tension (requiring more pressure to obliterate) in some. Further physical signs develop as the target organs (heart, brain, kidneys and retinae) are involved.

In **secondary hypertension** evidence of the primary disorder may be detectable in many cases. In the others, hypertension may be the only evident abnormality and the diagnosis has to be established by investigation.

Coarctation of the aorta has to be diagnosed by the detection of weak or delayed femoral pulse and the presence of hypertension in the upper limbs with lower pressure in the lower limbs. Renal artery bruit may be auscultated over the abdomen lateral to the umbilicus or over the renal angles and this finding is a clue to renovascular cause for hypertension. Palpability of the kidneys suggests polycystic disease, hydronephrosis or tumour.

COMPLICATIONS OF HYPERTENSION

Hypertensive

- Accelerated – malignant hypertension (grade III and IV retinopathy)
- Encephalopathy
- Cerebral hemorrhage
- Left ventricular hypertrophy
- Congestive heart failure
- Renal insufficiency
- Aortic dissection

Atherosclerotic

- Cerebral thrombosis
- Coronary artery disease
- Peripheral occlusive vascular disease

1. Cardiovascular system:

1. Left ventricular hypertrophy [LVH]: This is the most common cardiac abnormality in hypertension. LVH is a powerful predictor of serious cardiovascular sequelae. Echocardiography is more sensitive and specific than ECG for detection of LVH.
2. Congestive heart failure [CHF]: The various alterations of LV systolic and diastolic function seen with LVH ultimately leads to the development of CHF. Hypertension remains as an important and major preventable factor leading to the development of CHF.
3. Ischemic heart disease is more common in them. This may present as angina pectoris, myocardial infarction or sudden death. Acute myocardial infarction may be unrecognized in 30-32%.

4. Atherosclerosis is accelerated. Atherosclerosis of the coronary, cerebral, renal and peripheral arteries lead to their progressive occlusion.
5. Arrhythmias – both supraventricular and ventricular are more common in hypertensives. Tobacco smoking worsens the cardiovascular complications.

2. Central nervous system: Strokes are among the most common complications in hypertension. The lesion may be an ischemic infarct resulting from thrombosis or a hemorrhage resulting from rupture of an artery. Hypertension is the most important single factor leading to all forms of strokes in the general population.

Hypertensive encephalopathy: It is a specific complication seen in hypertensives when there is a rapid rise of blood pressure. The incidence is higher in acute glomerulonephritis, pheochromocytoma and malignant hypertension. The cerebral arteries go into spasm in response to a rapid rise in blood pressure. Edema and ischemia of the brain develop.

Clinically it is characterized by intense headache, visual disturbances, convulsions, loss of consciousness and varying degrees of focal neurological deficits. Prompt reduction of blood pressure completely reverts the attacks and restores the normal state. This feature distinguishes hypertensive encephalopathy from cerebral infarction or hemorrhage in which the neurological deficit persists.

3. Kidneys: Atheroma of the renal arteries results in reduction of blood supply to the kidney and progressive loss of renal function. In malignant hypertension renal function deteriorates rapidly, ending in renal failure.

4. Retina: The retinal arterioles undergo changes. These have been graded. The retinal changes give an indication of the progress of hypertension and help to determine the prognosis. Grades I and II are seen in the early phases of hypertension. Grade III is suggestive of the accelerated phase and grade IV indicates transition to the malignant phase.

Grade I : Arteriolar narrowing and increase in light reflex over the arterioles.

Grade II : Marked arteriolar narrowing and arterio-venous nicking.

Grade III: Grade II + flame-shaped hemorrhages and fluffy (soft) exudates.

Grade IV: Grade III + papilledema.

5. Malignant hypertension and accelerated hypertension: If hypertension is allowed to progress unchecked, many cases may go into the malignant phase. Its exact mechanism is not still clear. Secondary hypertension occurring in renal disease and pheochromocytoma shows a greater tendency to progress to the malignant phase. It is characterized by further elevation of blood pressure and grade IV retinal changes. At this stage, there is widespread fibrinoid necrosis of arterioles. Retinopathy may lead to visual impairment. The diagnosis of the malignant phase

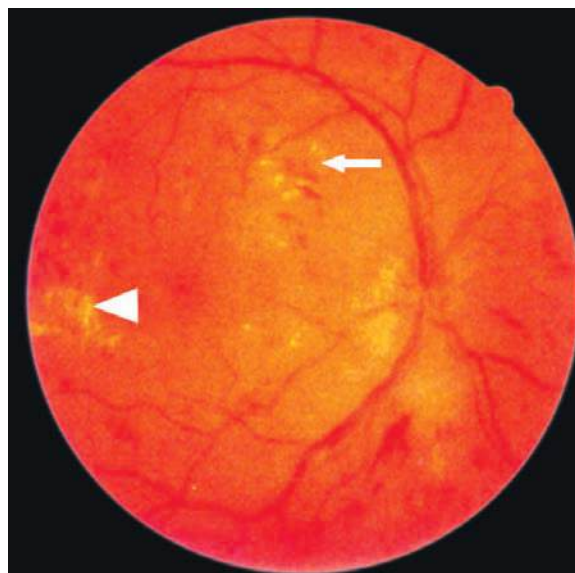


Fig. 123.1: Hypertensive retinopathy in malignant hypertension. Note: Papilledema, hemorrhages (arrow and soft exudates—arrowhead)

and the accelerated phase depends on the evidence of vascular damage in a patient with severe hypertension. Malignant hypertension is characterized by papilledema whereas accelerated hypertension shows only grade III retinopathy. Once the malignant phase sets in, death occurs within two years as a result of cardiac failure, renal failure, or cerebral hemorrhage. Prompt treatment arrests the malignant phase and its complications. The retinal changes also regress and revert to Grade II (Fig. 123.1).

Prognosis: Hypertension leads to reduction of lifespan, and also considerable morbidity. Death is caused by cardiac failure, cerebrovascular diseases or renal failure. Damage to the target organs worsens the prognosis considerably. Target organ damage should be diagnosed if any one or more of the following abnormalities are detectable. Hypertension is associated with higher incidence of retinal venous and retinal arterial occlusions and visual loss.

1. Cardiac failure,
2. Signs and symptoms of atherosclerotic vascular disease,
3. ECG evidence of myocardial infarction, ischemia or left ventricular hypertrophy,
4. Evidence of previous stroke,
5. Renal insufficiency or proteinuria, and Hypertensive changes on funduscopy.

ECG evidence of left atrial enlargement and presence of late diastolic gallop (S_4 gallop) indicate the presence of diastolic dysfunction. Proper control of blood pressure leads to reduction of the complications.

Reduction of strokes	– 35-40%
Coronary artery events	– 20-30%
Congestive heart failure	– 50-60%
Cardiovascular mortality	– 20%

MANAGEMENT

The goal of management of hypertension is to reduce morbidity and mortality by the least invasive means as possible. This may be accomplished by achieving and maintaining systolic blood pressure below 140 mm Hg and diastolic blood pressure below 90 mm Hg and lower, if tolerated, while controlling other modifiable risk factors for cardiovascular disease. Blood pressure reduction therapy is required particularly to prevent stroke, to preserve renal function and prevent or slow heart failure progression. This goal may be achieved by lifestyle modification alone or with pharmacologic treatment.

Risk stratification: Risk of cardiovascular disease in patients with hypertension is determined not only by the levels of blood pressure but also by the presence or absence of target organ damage or other risk factors. Hypertensive patients can be classified into risk group A, B and C based on the presence or absence of major risk factors, target organ damage and clinical cardiovascular disease.

Major Risk Factors

- Smoking
- Dyslipidemia
- Diabetes mellitus
- Age older than 60 years
- Sex (men and postmenopausal women)
- Family history of cardiovascular disease.

Target Organ Damage (TOD) / Clinical Cardiovascular Disease (CCD)

Heart disease

- Left ventricular hypertrophy
- Angina/prior myocardial infarction
- Prior coronary revascularization
- Heart failure

Stroke or transient ischemic attack

Nephropathy

Peripheral arterial disease

Retinopathy

Risk group A – No risk factors, no TOD/no CCD

Risk group B – At least one risk factor excluding diabetes mellitus, no TOD/CCD

Risk group C – TOD/CCD and/or diabetes mellitus, with or without other risk factors.

This empiric classification stratifies patients with hypertension into risk groups for making therapeutic decisions.

Life Style Modifications

- Lose weight, if overweight

- Moderation of alcohol intake to less than 30 ml spirits per day
- Increase aerobic physical activity (30–45 minutes on most days of the week, at least five sessions)
- Reduce sodium intake to less than 100 mmol per day.
- Maintain adequate intake of dietary potassium (90 mmol/day)
- Maintain adequate intake of dietary calcium and magnesium for general health.
- Stop smoking and reduce intake of dietary saturated fat to below 7% of total calorie intake for overall cardiovascular health.
- Relaxation and biofeedback technique– transcendental medication, yoga exercise such as Savasana.

Lifestyle modification brings down blood pressure and also helps to reduce the dosage of drugs needed (Table 123.3).

Pharmacological Treatment

Reduction of blood pressure with drugs clearly decreases cardiovascular morbidity and mortality. Objective reduction of stroke, coronary events, heart failure, progression of renal disease, progression to more severe hypertension and all cause mortality has been demonstrated in several trials.

GENERAL GUIDELINES

Dosage and Follow-up

Therapy for most patients with uncomplicated hypertension, (stages 1 and 2) should begin with the lowest dosage in order to avoid the adverse effects of abrupt reduction in blood pressure. In hypertensive patients, abrupt lowering of blood pressure produces signs of cerebral hypoperfusion. If blood pressure remains uncontrolled after 1 or 2 weeks of drug therapy the next dosage levels should be tried.

- Optimal formulation should provide 24 hour efficacy with once daily dosage with at least 50% of peak effect remaining at the end of 24 hour.
- For most patients the initial choice of therapy is a diuretic or a beta blocker unless there is a compelling indication for another type of drug. There are numerous randomized controlled trials which have shown a reduction in mortality and morbidity with these agents.

Drug Combinations

Combinations of low doses of two agents from different classes have been shown to provide additional antihypertensive efficacy, thereby minimizing the likelihood of dose dependent adverse effects. Very low dose of diuretics can potentiate the effects of other agents without producing adverse metabolic effects. Low dose combinations with

TABLE 123.3

Lifestyle modifications to manage hypertension (JNC VII)

Modification	Recommendation	Approximate systolic BP reduction, range
Weight reduction	Maintain normal body weight (BMI, 18.5-24.9)	5-20 mmHg/10 Kg weight loss
Adopt DASH eating plan	Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat	8-14 mm Hg
Dietary sodium reduction	Reduce dietary sodium intake to no more than 100 mEq/L (2.4 g sodium or 6 g sodium chloride)	2-8 mm Hg
Physical activity	Engage in regular aerobic physical activity such as brisk walking (at least 30 minutes per day, most day of the week)	4-9 mm Hg
Moderation of alcohol consumption	Limit consumption to no more than 2 drinks per day (1 oz or 30 mL ethanol [e.g. 24 oz beer, 10 oz wine, or 3 oz 80-proof whisky]) in most men and no more than 1 drink per day in women and lighter-weight persons	2-4 mm Hg

Abbreviation: BMI, body mass index calculated as weight in kilogram divided by the square of height in meters; BP, blood pressure; DASH, Dietary Approaches to Stop Hypertension

*For overall cardiovascular risk reduction, stop smoking. The effects of implementing these modifications are dose and time dependent and could be higher for some individuals.

ACE inhibitor and a non-dihydropyridine calcium antagonist may reduce proteinuria more than either drug given singly. Combination of dihydropyridine calcium antagonist and ACE inhibitor reduces the incidence of pedal edema compared to calcium antagonist given alone.

Management of Blood Pressure in Persons Aged 18 yrs or Older (JNC VII guidelines)

The most crucial factor in the selection of drugs is the presence of concomitant conditions like cardiac failure, renal insufficiency, ischemic heart disease and diabetes mellitus (Table 123.4).

Renal insufficiency

ACE inhibitor (caution in renovascular HTN and creatinine > 3 mg/dL)
Alpha blockers

Dyslipidemia

The following drugs may have unfavourable effects on comorbid conditions.

Asthma

Beta blocker

Depression

Beta blocker, reserpine

Diabetes mellitus

Beta blockers, high dose diuretic

Peripheral vascular disease

Beta blocker

Renal insufficiency

Potassium sparing agents

Pregnancy

ACE inhibitors,
Angiotensin II receptor blockers.

Step-down Therapy

An effort to decrease the dosage and number of antihypertensive drugs should be considered after hypertension has been controlled effectively for at least 1 year. Step-down therapy is often successful in patients who are also making lifestyle modifications. This may be possible in approximately 10% of patients.

DRUGS USED IN HYPERTENSION AND THEIR DOSAGES

Diuretics: Diuretics initially lower blood pressure by increasing urinary sodium excretion and by reducing plasma volume, ECF volume and cardiac output. Within 6-8 weeks the lowered plasma volume, ECF volume and cardiac output returns towards normal. On long-term

Compelling indications, unless contraindicated

Diabetes mellitus with proteinuria	ACE inhibitor
Heart failure	ACE inhibitor, diuretics
Isolated systolic hypertension (older patients)	Diuretics preferred Calcium antagonists
Myocardial infarction	Beta blocker (non ISA*), ACE inhibitor (in those with systolic dysfunction)

*Note: ISA: intrinsic sympathomimetic activity.

The following drugs may have favourable effect on comorbid conditions.

Angina	Beta blocker, calcium antagonist
Prostatism	Alpha blocker

Individual Choices of Drug Therapy – JNC VII Guidelines

TABLE 123.4

Scheme of treatment of hypertension						
BP classification	Management					
	Systolic BP, mm Hg*		Diastolic BP, mm Hg*	Lifestyle modification	Initial drug therapy	
					Without compelling indication	With compelling indications†
Normal	< 120	and	< 80	Encourage		
Prehypertension	120-139	or	80-89	Yes	No antihypertensive drug indicated	Drug(s) for the compelling indications‡
Stage 1 hypertension	140-159	or	90-99	Yes	Thiazide-type diuretics for most; may consider ACE inhibitor, ARB, β-blocker, CCB, or combination	Drug(s) for the compelling indications Other antihypertensive drugs (diuretics, ACE inhibitor, ARB, β-blocker, CCB) as needed
Stage 2 hypertension	≥ 160	or	≥ 100	Yes	2-Drug combination for most (usually thiazide-type diuretic and ACE inhibitor or ARB or β-blocker or CCB)§	Drug(s) for the compelling indications Other antihypertensive drugs (diuretics, ACE inhibitor, ARB, β-blocker, CCB) as needed
Abbreviations: ACE angiotension-converting enzyme; ARB, angiotension-receptor blocker; BP, blood pressure; CCB, calcium channel blocker						
Treatment determined by JNC VII guidelines						
‡Treat patients with chronic kidney disease or diabetes to BP goal of less than 130/80 mm Hg						
§Initial combined therapy should be used cautiously in those at risk of orthostatic hypotension						

basis, antihypertensive effect is due to a fall in peripheral vascular resistance – mechanism responsible for lowering peripheral vascular resistance is not clearly known.

Dosage and choice of agent: A thiazide diuretic is the usual initial choice often in combination with a potassium sparing agent. Loop diuretics should be reserved for those patients with renal insufficiency, resistant hypertension or hypertension associated with acute left ventricular failure or congestive cardiac failure.

Hydrochlorothiazide	: 6.25-50 mg/day (OD)
Chlorthalidone	: 12.5-50 mg/day(OD)
Indapamide	: 1.25-5 mg/day(OD)
Furosemide	: 40-240 mg/day (2-3 times)
Amiloride	: 5-10 mg/day (OD)
Spironolactone	: 25-100 mg/day (OD)
Triamterine	: 25-100 mg/day (OD)

Side effects: hypokalemia, hypomagnesemia, hyperuricemia, hyperlipidemia, hyperglycemia and insulin resistance, hypercalcemia, impotence.

Inhibitors of adrenergic system

- I. Peripheral neuronal inhibitors
 - a. Reserpine

- II. Central adrenergic inhibitors
 - a. Methyldopa
 - b. Clonidine
- III. Alpha-receptor blockers
 - a. Alpha 1 and alpha 2 receptors
 - 1. Phenoxybenzamine
 - 2. Phentolamine
 - b. Alpha 1 receptor
 - 1. Prazosin
 - 2. Doxazosin
 - 3. Terazosin
- IV. Beta receptor blockers
 - Nonselective
 - Propranolol
 - Nadolol
 - Timolol
 - Pindolol
 - Cardioselective
 - Atenolol
 - Acebutolol
 - Metoprolol
 - Bisoprolol
- V. Alpha and beta receptor blockers
 - Labetalol

Note: Pindolol, acebutolol and bisoprolol also have intrinsic, sympathomimetic activity (ISA). These do not lower the heart rate like the other beta blockers without ISA activity.

Reserpine: It acts by depleting the levels of norepinephrine in postganglionic adrenergic neurons by inhibiting the uptake of norepinephrine into storage vesicles. It depletes the central catecholamine levels. Daily dose is 0.1 to 5 mg. Adverse side effects include nasal congestion, mental depression and the development of parkinsonism. This drug is seldom used now. Initial studies on reserpine were conducted by Rustom Jal Vakil, the celebrated cardiologist from Bombay, in the 1950's.

Methyldopa: The primary site of action of methyldopa is central nervous system. It stimulates central alpha adrenergic receptors, thereby reducing the sympathetic outflow from the central nervous system. It is effective in a dose of 250 to 500 mg given orally 3-4 times a day. It does not reduce the renal blood flow and therefore can be given safely even in the presence of renal impairment. Adverse side effects include dryness of mouth, sedation, extrapyramidal features, fever, hepatitis and hemolytic anemia. Currently the role of methyl dopa is mainly in the management of resistant hypertension and also in pregnancy induced hypertension.

Clonidine: It acts centrally and is effective in an oral dose of 0.1 to 1 mg a day. Dryness of the mouth and drowsiness are the adverse side effects. Sudden withdrawal of the drug causes rebound hypertension.

Alpha Adrenergic Receptor Blocking Drugs

Nonselective [alpha1 and alpha 2 blockers]

Phenoxybenzamine and phentolamine belong to this class. Mainly they are used to control the excessive rise of blood pressure in pheochromocytomas. The former is slow in action and the effect is sustained. The latter is quicker in action, but the effect is short lived. The dose is 5-30 mg given intravenously in a drip, the rate of flow is adjusted depending upon the response. Phentolamine is used to control the hypertensive crisis occurring in pheochromocytomas. It is also used as a diagnostic test.

Selective Alpha 1 Blockers

Prazosin: Is a selective antagonist of postsynaptic alpha I receptors. It acts by blocking alpha mediated vasoconstriction, thereby reducing peripheral vascular resistance. Total daily dose is 2-30 mg given two or three times a day. It may cause first dose hypotension.

Terazosin and doxazosin: These are also alpha I receptor blockers. Beyond longer duration of action and less propensity for first dose hypotension, they differ little

from prazosin. They can be safely and effectively used in patients with renal failure. Lipid profile is not adversely altered by treatment. Alpha blockers are ideal for older men with benign prostatic hypertrophy. However in the elderly these drugs should be started cautiously to avoid hypotension. Tachyphylaxis on long-term use, and also less impressive reduction in adverse clinical outcomes as compared to the other major antihypertensive drug classes are the major limitations of most alpha blocking drugs.

Beta-adrenergic blocking drugs are the second most widely used antihypertensive drugs after diuretics. They reduce cardiac output, inhibit renin release and reduce sympathetic tone by central mechanisms. In cases with coexistent ischemic heart disease, beta blockers are found to be more useful. Long-term use of beta blockers has been shown to reduce mortality by preventing major cardiac events such as myocardial infarction and fatal arrhythmias.

Although beta blockers were formerly thought to be contraindicated in patients with heart failure, they have now been found to be useful, especially metoprolol, carvedilol and bisoprolol.

Side effects: The most common side effect is fatigue. It may cause worsening of other concomitant problems like bronchospasm and peripheral vascular disease. In diabetics, warning signs of hypoglycemia may be masked. Other problems are insomnia, nightmares, depression, impotence and alteration of lipid metabolism leading to hyperlipidemia.

Cardioselective beta blockers are available for use. These are acebutalol 100-200 mg/day, metoprolol 100-400 mg/day, atenolol 100 mg/day, and pindolol 10-40 mg/day. Of these atenolol and metoprolol have become the most popular drugs due to their effectiveness, ease of administration and freedom from major adverse effects.

Drug with both alpha and beta blocking action: e.g. Labetolol is given orally in doses of 100 mg twice daily orally.

Vasodilators: These drugs cause vasodilation in the various vascular compartments.

Hydralazine: This drug causes predominantly arteriolar dilation. It is effective in a dose of 20-50 mg thrice daily. This drug increases the renal, coronary and hepatic blood flow. Adverse side effects include angina induced by reflex tachycardia and lupus erythematosus, which regresses on withdrawing the drug. Though it is at present rare to start a patient on hydralazine as the first drug, many patients who are on this drug for a long-term, find it acceptable to continue with the same.

Sodium nitroprusside: This is an effective vasodilator which rapidly lowers blood pressure and, therefore, it is used in hypertensive emergencies. It is given only as an

intravenous drip, 50 mg being added to 500 mL 5% glucose and infused at the rate of 1-8 µg/kg/min, the response being monitored continuously. The drug is withdrawn when the emergency is controlled. Adverse side effects include severe hypotension, nausea, psychotic behaviour and muscle spasms.

Diazoxide: This is a potent vasodilator with short action and therefore, it is used in hypertensive emergencies. When given in a dose of 100-300 mg intravenously, it lowers the blood pressure rapidly.

Minoxidil: This is effective when given orally in doses up to 20-40 mg daily. It is effective in patients with severe hypertension associated with renal impairment. Side effects may be troublesome, but uncommon. These include hypertrichosis (increased hair growth), coarsening of facial appearance, salt and water retention, and tachycardia. Minoxidil should always be given along with diuretics.

Angiotensin Converting Enzyme Inhibitors (ACE inhibitors)

These drugs inhibit the enzyme [ACE] which converts angiotensin I to angiotensin II, thereby leading to the reduction in the production of angiotensin II and also aldosterone. In addition, this group of drugs has other beneficial effects in correcting impaired cellular metabolism and improving myocardial function. Drugs in this group are **captopril, enalapril, lisinopril, ramipril, perindopril** and others. The same enzyme, ACE is involved in the breakdown of bradykinin, and therefore ACEI also reduce the breakdown of bradykinin. Bradykinin is responsible for some of the adverse side effects such as cough, angioedema, renal dysfunction and hypotension. ACE inhibitors do not abolish the production of angiotensin II completely, since it may be formed by other pathways also.

Captopril is effective in oral doses of 150-400 mg daily. It is particularly effective in high renin hypertension. Captopril lowers peripheral resistance without altering the cardiac output and heart rate. It is effective in hypertension resistant to other drugs. It can be combined with other drugs. Side effects include fever, rashes, pruritus, distaste in the mouth, orthostatic hypotension, nephropathy, bronchospasm, hyperkalemia and leukopenia.

Enalapril is an analogue similar in action but with a longer half-life of 12-24 hrs. It is given in a total dose of 5-40 mg per day in divided doses. Lisinopril is a lysine derivative of enalapril. It is absorbed and is effective when given orally. The action is prolonged and therefore the whole dose may be given together once a day. The initiating dose is 2.5-5 mg once or twice a day. This may be increased up to 20 mg daily. In patients with renal

impairment the dose should be reduced. Ramipril is effective in a single oral dose of 1.25-10 mg daily. Perindopril is given in doses of 2 to 8 mg daily, starting at 2 mg and working up to 8 mg if needed.

Angiotensin II Receptor Blockers (ARBs)

Drugs in this class, act by displacing angiotensin II from its specific receptor. They are at least as effective as ACE inhibitors. However, since they do not cause accumulation of bradykinin, cough as a side-effect is infrequent. The major advantage is the minimal side effect profile for this class of antihypertensives. Moreover since they act on the final common pathway viz the receptor, alternate pathway production of angiotensin II does not blunt the effectiveness. There is total blockade of angiotensin II effects.

Currently available drugs in this class are **losartan, valsartan, telmisartan, candesartan and irbesartan**. Studies have found that they are at least as effective as ACEI in controlling BP. Dose: losartan –25-100 mg/day, valsartan – 80-320 mg/day, telmisartan –40-80 mg/day, candesartan – 8-16 mg/day and irbesartan –150-300 mg/day.

Calcium Channel Blocking Drugs

Calcium antagonists are commonly used in the treatment of hypertension. Dihydropyridine calcium antagonists (**nifedipine, amlodipine and felodipine**) have the greatest peripheral vasodilator action with little effect on cardiac automaticity, conduction or contractility. Vasodilation leads to dependent edema.

The nondihydropyridine calcium antagonists (diltiazem, verapamil) cause less peripheral vasodilatation compared to dihydropyridines, but they have profound effects on cardiac contractility, automaticity and conduction. So they cause fewer side effects related to vasodilatation. They may aggravate established cardiac failure.

Dosage: Amlodipine 2.5-10 mg/day once a day, felodipine 2.5-20 mg/day once a day, nifedipine extended release 30-120 mg once a day. These drugs may cause dependent edema in some patients due to peripheral vasodilatation. Withdrawal of the drug leads to prompt relief.

Dose of diltiazem is 30-90 mg and that of verapamil is 40-80 mg twice or thrice a day. Parenteral preparations are available for emergency. Verapamil 5-10 mg IV is given over 3 minutes.

GENERAL PRINCIPLES IN ANTIHYPERTENSIVE THERAPY

Optimum benefit is obtained only if the blood pressure is maintained at the desired levels throughout the day and night continuously. Proper adjustment of dosage, frequent consultation, and counselling to ensure drug compliance

Commonly used antihypertensive drugs		
Drugs	Oral.dose/day (frequency/day)	Parenteral dose
<i>Diuretics</i>		
Hydrochlorthiazide	12.5-50 mg (1)	
Amiloride	5-10 mg (1)	
Triamterine	25-100 mg (1)	
Furosemide	40-240 mg (2-3)	
Indapamide	1.25-5 mg (1)	
<i>Central alpha agonists</i>		
Clonidine	0.2-1.2 mg (2-3)	
Methyldopa	500-300 mg (2)	
<i>Alpha-adrenergic blockers</i>		
Doxazosin	1-16 mg (1)	
Prazosin	2-30 mg (2-3)	
Terazosin	1-20 mg (1)	
<i>Beta-adrenergic blockers</i>		
Atenolol	25-100 (1)	
Metoprolol	50-300 (2)	5 mg IV, repeated at 5-10 minutes to a maximum of 15 mg to be used in emergencies
Propranolol	40-480 (2)	
Carvedilol	12.5-50 (2)	
Labetolol	200-1200 (2)	
<i>Direct vasodilators</i>		
Hydralazine	50-300 mg (2)	
<i>Calcium channel blockers</i>		
Nifedipine (SR)	30-120 mg (1)	
Felodipine	2.5-20 mg (1)	
Amlodipine	2.5-10 mg (1)	
Diltiazem	180-240 mg (3)	
Verapamil	160-240 mg (3)	
<i>ACE inhibitors</i>		
Enalapril	5-40 mg (1-2)	
Captopril	25-150 (2-3)	
Lisinopril	5-40 (1)	
Ramipril	1.25-20 (1)	
<i>Angiotensin 2 receptor blockers</i>		
Losartan	25-100 (1-2)	
Valsartan	80-320 mg (1-2)	
Telmisartan	40-80 mg (1-2)	
Candesartan	8-16 mg (1-2)	
Irbesartan	150 mg (1)	
<i>Emergency drugs</i>		
Sodium nitroprusside		0.25-10 micro-gram/kg IV infusion
Nitroglycerine		50-100 micro-gram/mt IV infusion
Diazoxide		50-100 mg IV bolus repeated or 15-30 mg/mt infusion
Enalapril		

are all important to ensure success. Since adverse side effects may lead to loss of morale and discontinuation of therapy, all patients should be fully informed of the side effects.

ACE inhibitors are preferable when there is left ventricular dysfunction with ejection fraction below 40% and in those with diabetes mellitus. In both groups ACE inhibitors reduce mortality. In the latter it also delays the onset of renal failure.

In patients with signs of prostatism alpha-blockers are useful, since these reduce both hypertension and prostatic symptoms.

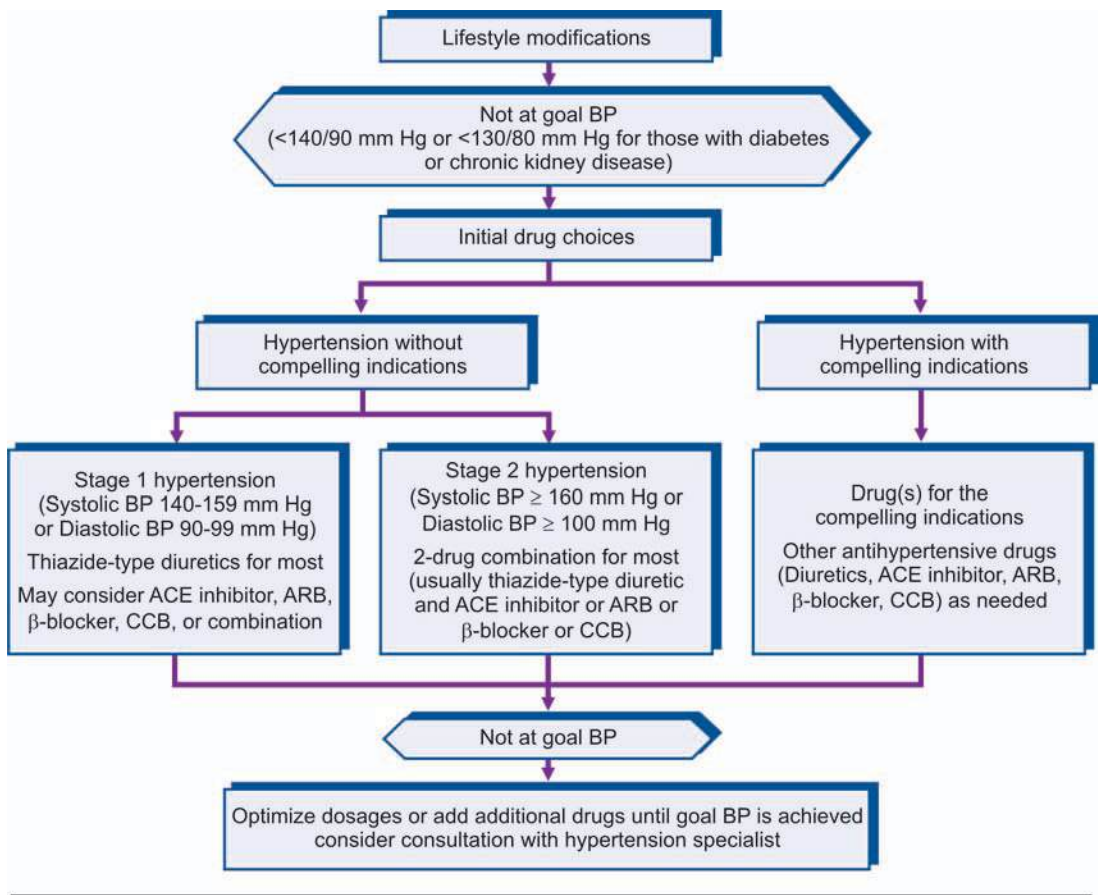
Failure to comply with therapy is the most frequent cause for failure of control of hypertension. Abrupt withdrawal of therapy may lead to rebound rise of blood pressure and hypertensive complications such as hypertensive encephalopathy or cerebrovascular accidents. Once established, essential hypertension tends to persist and, therefore, life-long therapy may be required in most cases but it may be possible to reduce the dose in many or even withdraw drugs in a few (see Fig. 123.2).

Resistant Hypertension

Resistant hypertension is the failure to reach the goal BP in patients who are adhering to full doses of an appropriate three-drug regimen that includes a diuretic. After excluding potential identifiable causes of hypertension, clinicians should carefully explore reasons why the patient is not at the goal BP. (See Table 123.4). Particular attention should be paid to the type of diuretic and its dose in relation to renal function. Consultation with a hypertension specialist should be considered if goal BP cannot be achieved.

Causes of Resistant Hypertension

1. Improper BP Measurement
2. Volume overload and pseudotolerance
 - Excess sodium intake
 - Volume retention from kidney disease
 - Inadequate diuretic therapy
3. Drug-Induced or other Causes
 - Nonadherence
 - Inadequate doses
 - Inappropriate combinations
 - Nonsteroidal anti-inflammatory drugs esp. cyclo-oxygenase 2 inhibitors
 - Cocaine, amphetamine, other illicit drugs
 - Sympathomimetics (decongestants, anorectics)
 - Oral contraceptives
 - Adrenal steroids
 - Cyclosporine and tacrolimus
 - Erythropoietin
 - Licorice (including some chewing tobacco)



BP indicates blood pressure; ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; and CCB, calcium channel blocker.

Fig. 123.2: Algorithm for treatment of hypertension (JNC VII)

- Selected over-the-counter dietary supplements and medicines (ephedrine)
- 4. Associated Conditions
 - Obesity
 - Excess alcohol intake, smoking tobacco
- 5. Identifiable Causes of Hypertension (sleep apnea, renal diseases, endocrine causes, etc.)

Hypertensive Urgencies and Emergencies

Patients with marked BP elevations and acute target-organ damage (emergency) (e.g., encephalopathy, myocardial infarction, unstable angina, pulmonary edema, eclampsia, stroke, head trauma, life-threatening arterial bleeding, or aortic dissection) require hospitalization and parenteral drug therapy. Patients with markedly elevated BP but without acute target organ damage (urgency) usually do not require hospitalization, but they should receive immediate combination oral antihypertensive therapy. They should be carefully evaluated and monitored for hypertension-induced heart and kidney damage and for identifiable causes.

Additional Considerations in Antihypertensive Drug Choices

Antihypertensive drugs can have favourable or unfavourable effects on other comorbidities.

Potential Favourable Effects

Thiazide-type diuretics are useful in slowing demineralization in osteoporosis. Beta-adrenergic blockers (BB) can be useful in the treatment of atrial tachyarrhythmias/fibrillation, migraine, thyrotoxicosis (short term), essential tremor, or perioperative hypertension. Calcium channel blockers (CCB) may be useful in Raynaud’s syndrome and certain arrhythmias, and alpha-blockers may be useful in prostatism.

Potential Unfavourable Effects

Thiazide diuretics should be used cautiously in patients who have gout or who have a history of significant hyponatremia. BBs should generally be avoided in individuals who have asthma, reactive airway disease, or

second or third degree heart block. ACEIs and ARBs should not be given to women likely to become pregnant and are contraindicated in those who are. ACEIs should not be used in individuals with a history of angioedema. Aldosterone antagonists and potassium-sparing diuretics can cause hyperkalemia and should generally be avoided in patients who have serum potassium values more than 5.0 mmol/L while not taking medications.

Renal Hypertension

See also chapter 175.

Renal parenchymal hypertension which results from primary glomerular and tubulointerstitial disease of the kidney is both volume dependent and renin-mediated. These account for about 70% of all cases of renal hypertension. In glomerular disease renal symptoms and hypertension set in almost simultaneously, whereas in tubulointerstitial diseases hypertension precedes the renal symptoms by several years. Renovascular hypertension (RVH) constitutes only around 1% of the total cases of hypertension but in children below 15 years without gross urinary abnormalities, RVH constitutes more than 60% of cases.

Hypertension in Children

Blood pressure (BP) in children correlates more with that of their mothers. Elevated BP in children may be a forerunner of essential hypertension in adults. The clinical features of elevated BP in neonates and young infants is failure to thrive, irritability, feeding problems including vomiting, cyanosis, respiratory distress, cardiac failure and seizures. Most common causes include renal artery thrombosis following umbilical artery catheterization, coarctation of the aorta, congenital renal diseases, renal artery stenosis, hypercalcemia, neurofibromatosis and endocrine disorders.

Hypertension in Pregnancy

See also chapter 176

This may fall into three groups:

1. Chronic hypertensive patient becoming pregnant
2. gestational hypertension occurring during pregnancy and remitting after delivery and
3. preeclampsia and eclampsia (hypertension with proteinuria).

Maternal complications include increased risk of preeclamptic toxemia, abruptio placentae.

Fetal complications include intrauterine death, increased perinatal mortality and morbidity.

In the management of hypertension in pregnancy, care should be taken to ensure that the antihypertensive drug does not cause fetal damage and affect materno-fetal

placental circulation. Methyldopa is the drug of choice. Hydralazine and calcium channel blockers can also be used. Atenolol and ACE inhibitors should be avoided.

Mineralocorticoid Hypertension

This is caused mostly by increase in aldosterone production by the adrenal cortex, rarely it may be any other mineralocorticoid such as 11-deoxycorticosterone. Mineralocorticoid induced hypertension is associated with hypokalemia.

Normally aldosterone production is regulated by angiotensin II levels, which in turn is controlled by renin levels. Increased aldosterone levels in turn suppress renin levels, and low renin levels are the hallmark of primary hyperaldosteronism.

Primary hyperaldosteronism may result from aldosterone producing adrenocortical adenoma, bilateral adrenocortical hyperplasia or rarely carcinoma. The first two conditions may form part of familial multiple endocrine neoplasia type I (MEN-1).

Clinical features: In the early stages it may resemble other forms of hypertension, but when hypokalemia and alkalosis develop, additional features such as muscle weakness, tetany and cardiac arrhythmias may develop. Classic diagnostic markers are hypertension resistant to drug therapy and hypokalemia. Diagnosis is established by simultaneously estimating plasma levels of renin, aldosterone and potassium, in a patient who is seated for 5 minutes. The ratio of aldosterone to renin is very high in such cases. Further confirmatory tests are available. The site of overproduction of the hormone can be identified by sampling the adrenal venous blood on either side. CT may reveal the tumour if it is of sufficient size.

Treatment: Dexamethasone given orally with a view to suppress corticotrophin also suppresses aldosterone levels in familial hyperaldosteronism type 1. Familial hyperaldosteronism type II is not suppressible by glucocorticoid.

Adenomas have to be removed surgically. In the case of bilateral adrenal hyperplasia, medical treatment with spironolactone or amiloride is beneficial. Spironolactone may be required in small doses of 12.5-25 mg twice daily given orally. Dose of amiloride is 2.5 mg daily.

Orthostatic Hypotension

See also Chapter 201

Sudden fall of blood pressure may occur on adopting the erect posture leading to symptoms such as giddiness and syncope. Generally this may result from several underlying diseases. The term postural hypotension is used when the systolic blood pressure falls by 20 mm Hg or to below 100 mm Hg on standing for five minutes.

When a person stands, there is a tendency for 10-15% of blood to get sequestered in the splanchnic circulation and the lower limbs. The consequent fall in blood pressure (BP) is counteracted by counter-regulatory mechanisms which include sympathetic activity and discharge of hormones like catecholamines, renin, angiotensin and vasopressin. Peripheral vasoconstriction, increase in heart rate and rise in plasma volume help to maintain the BP steady. When a normal person stands, it takes about a minute for circulatory adaptation. The heart rate and diastolic BP rise by 10%. The systolic BP is not affected. In postural syncope the BP falls immediately after standing. Fainting occurs due to fall in cerebral perfusion.

Orthostatic hypotension may result from two groups of lesions:

- 1. Lesions affecting the afferent pathways from the baro-receptors to the vasomotor center, and
- 2. Lesions affecting the efferent pathways from the vasomotor center to the arterioles.

Various neurological disorders that can lead to orthostatic hypotension	
1. Afferent lesions	Neuropathies
2. Central lesions	Multiple system atrophy, Parkinson's disease
3. Spinal lesions	Lesions of cervical and dorsal regions of the spinal cord
4. Ganglionic lesions	Progressive autonomic failure
5. Post-ganglionic lesions	Neuropathies

Common Causes of Orthostatic Hypotension

- 1. Polyneuropathy in diabetes, beriberi and amyloidosis
- 2. Autonomic neuropathy in syringomyelia, tabes dorsalis and subacute combined degeneration
- 3. Following surgical or medical sympathectomy
- 4. Adverse reaction to drugs, especially antihypertensive drugs
- 5. Idiopathic autonomic neuropathy (Shy-Drager Syndrome)
- 6. Dehydration, blood loss, fever, severe anemia, convalescence from debilitating illnesses, prolonged bed rest and starvation.

Clinical features: Dizziness or fainting on standing is the presenting symptom. Fainting from autonomic failure differs from other causes of fainting by the absence of sweating, pallor and cardiac slowing in the former.

Shy-Drager syndrome: is the condition where postural hypotension is associated with other autonomic phenomena such as sphincter disturbances, anhidrosis and impotency and other neurological disorders such as external ocular palsies, parkinsonism and cerebellar disturbances.

Diagnosis: It is important to diagnose the condition and establish the cause since the outlook varies in the different types. In normal subjects the BP falls during sleep and rises prior to waking up. This circadian rhythm of blood pressure is reversed in patients with autonomic failure.

Management: Immediate management is to put the patient supine and elevate the legs or press the thighs against the abdomen to improve venous return. In many cases the patient recovers. Stimulating drinks such as coffee or lime juice containing 20 g sugar and 6 g salt help to raise the blood pressure within a short time. In more severe cases with syncope or sustained hypertension an intravenous drip of 10% glucose saline should be started. Still, if the condition does not recover pressor agents such as ephedrine 30 mg oral or intravenous infusion of dopamine may be required. Fludrocortisone in doses of 0.01 to 0.02 mg/day is the best treatment on a long-term basis. The underlying causes should be detected and corrected.

Long term management consists of dietary advice to take more salt, avoid hypotensive drugs and exercise programmes to improve muscle tone, and treatment of the cause.

The term orthostatic intolerance is given to a syndrome characterized by adrenergic symptoms that occur when upright posture is assumed. The heart rate increases by at least 30 beats/minute without developing orthostatic hypotension. Most subjects are women between the ages 20-50. These symptoms overlap with the clinical presentation of other functional disorders such as DaCosta's syndrome, Soldier's heart, neurocirculatory asthenia and also mitral valve prolapse.

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blood from the heart is drained into the right atrium through the coronary sinus, thebesian veins and the anterior cardiac veins.

Around 4-6% of the cardiac output flows into the coronary arteries in health. The coronary arteries run on the epicardial surface and their branches penetrate to supply the myocardium. The outer two-third portion is supplied by the epicardial branches and the inner one-third is supplied by perforating branches which form subendocardial ramifications. The left ventricular myocardium receives blood almost exclusively during diastole whereas the normal right ventricular myocardium receives blood during both phases of the cardiac cycle. In normal persons myocardial blood flow is controlled by constriction and dilation of the microcirculation (vessels < 400 μ m). The large coronary arteries offer no resistance to blood flow. When stenosis occurs the arterial pressure drops distally. In health coronary blood flow can increase 3.5-8 times the resting blood flow. When coronary obstruction occurs the microcirculation dilates and compensates to maintain the blood flow. When arterial stenosis becomes severe, even this vasodilation will fail to maintain adequate blood flow. Such occlusions become functionally important.

Metabolism of cardiac muscle is aerobic. The myocardium extracts 70% of the oxygen supplied to it in arterial blood. If the oxygen supply is interrupted for over two minutes, the myocardium becomes ischemic and the mechanical activity ceases totally. Ischemia may result from organic narrowing of the coronary arteries or spasm or both. In normal subjects blood flow to the myocardium is maintained even when the coronary diameter is reduced to 50%, i.e. the cross-section is reduced by 75%. The resting blood flow is maintained till the arterial lumen is reduced by 90%. Factors which further reduce coronary blood flow are extreme tachycardias (due to reduction of diastolic interval), hypertension, elevation of intraventricular pressure as in aortic and pulmonary stenosis, and cardiomegaly. Ischemia to the myocardium causes the characteristic pain.

General Considerations

13

A wide spectrum of clinical disorders is included under this term. All of these are caused by reduction in arterial blood supply to the myocardium. The lumen of the coronary arteries is narrowed leading to impairment of blood supply and in the vast majority of cases the lesion is atherosclerosis.

The right and left coronary arteries arise from the root of the aorta as its first branches. The left coronary artery divides into two major branches, the left anterior descending and left circumflex. Branches of the left descending branch supply the free wall of the left ventricle and a major portion of the interventricular septum. The left circumflex artery supplies the left atrium and parts of the posterior and lateral walls of the left ventricle. In 45% of cases this artery supplies the S-A node as well. The right coronary artery supplies the right ventricle, a major portion of the diaphragmatic surface of the left ventricle, the A-V node (in 90%) and the S-A node (in 55%). Venous

Etiology of Ischemic Heart Disease

1. **Coronary atherosclerosis:** This is the most common cause for myocardial ischemia.
2. **Non-atheromatous coronary artery disease**
 - a. **Arteritis:** Polyarteritis nodosa, Takayasu's disease, Kawasaki's syndrome, non-specific arteritis, syphilitic aortitis, systemic lupus erythematosus, thromboangiitis obliterans and others.
 - b. **Thickening of coronary arteries:** Mucopolysaccharidoses, amyloidosis.
 - c. **Spasm of coronary arteries:** Generally, spasm supervenes on diseased arteries but sometimes no other pathological lesion may be detectable. Under extreme conditions of stress, even normal arteries may undergo spasm. This can lead to myocardial ischemia and fatal arrhythmias.
 - d. **Dissecting aneurysm of the aorta, dissection of the coronary arteries.**
 - e. **Embolism:** Infective endocarditis, emboli from the left atrium or left ventricle, left atrial myxoma or paradoxical embolism may affect the coronary arteries.
 - f. **Congenital anomalies:** Anomalous origin of the left coronary artery from the pulmonary artery, single coronary artery, coronary arteriovenous fistula, aneurysms of the coronary arteries, myocardial bridges.
 - g. **Trauma to the coronary arteries,** penetrating wounds, injury during pericardiocentesis.
 - h. **Thrombosis without underlying atherosclerotic plaque:** Polycythemia, Thrombocytosis, hypercoagulability states
 - i. **Substance abuse:** Cocaine, amphetamines
 - j. **Imbalance between oxygen demand and blood supply:** Severe aortic stenosis, aortic regurgitation, prolonged hypotension, severe anemia, thyrotoxicosis and other conditions of ventricular hypertrophy

Epidemiology: In all the developed countries where reliable statistics are available ischemic heart disease is one of the most common causes of death and cardiac morbidity in middle and elderly age groups. Till the early part of this decade the incidence was rising, but there is a slight drop recently. Though complete statistics are not available, in India Cardiovascular diseases account for 24% of total deaths of which coronary heart disease appears to be the dominant form. Ischemic heart disease death rates are three times higher than stroke rates. Men suffer 9 times more frequently than premenopausal women, but after menopause the risk of coronary atherosclerosis rapidly increases to catch up with that of men over a period of several years. The disease is more common in the affluent classes of society, but the poor

socioeconomic groups and manual labourers are not totally spared.

ETIOLOGY

Risk factors for atherosclerosis: Several risk factors have been identified as contributing to the development of coronary atherosclerosis. For purposes of management, they have been broadly divided into modifiable and non-modifiable risk factors.

1. Non-modifiable Risk Factors

- a. **Genetic predisposition** to atheroma is revealed by a positive family history of ischemic heart disease (sudden deaths, myocardial infarction, or angina) or cerebrovascular accidents occurring at relatively younger ages among close relatives. The higher prevalence of coronary artery disease in persons having diagonal crease in the ear lobe has been found in many population groups including that in Kerala.
- b. **Personality factors:** High strung aggressive and competitive individuals (type A) are more prone to develop myocardial infarction than the more relaxed type of personality (type B).
- c. **Sex:** The disease is considerably less prevalent in women during their reproductive periods of life. In the Framingham study the male: female ratio in the 35-44 years age group was 6.8:1 but in the age group 75-84, the prevalence equalled in both sexes. Despite the lower prevalence, once the disease manifests, it runs a more aggressive course in women.

2. Modifiable Risk Factors

- a. **Cigarette smoking:** Cigarette consumption is the single most important modifiable risk factor for coronary artery disease. Even among non smokers passive exposure to cigarette smoke increases coronary risk. The offending agents are nicotine and carbon monoxide present in cigarette smoke.
- b. **Hyperlipidemia:** The risk of coronary atherosclerosis is directly related to elevation of serum cholesterol. Increase in levels above 250 mg/dL is associated with increasing risk. Lipids circulate in blood in the form of lipoproteins. Based on electrophoretic pattern and density gradient they can be classified into alpha-lipoproteins (high density HDL), beta lipoproteins (low density LDL) and prebeta lipoproteins (very low density lipoproteins—VLDL). An elevated LDL-cholesterol level appears to be the primary CHD risk factor, and the higher the total and LDL cholesterol levels are, the greater is the risk of an atherosclerotic event. A low level of HDL cholesterol is also a potent individual predictor for IHD. Many types of hyperlipidemias are genetically determined, but by proper dietary modification, exercise, and drug therapy the serum levels can be lowered and this risk

can be brought down to some extent. See also section: 10 Chapter: 93

- c. **Hypertension:** Systemic arterial hypertension is a major independent risk factor for CHD, although it pathogenetically appears to be a cholesterol-dependent accelerator of atherosclerosis. Raised blood pressure increases the rate of progression of atheroma, especially when present along with hyperlipidemia. It has been suggested that associated hormonal changes, including generation of angiotensin II by systemic and/or local renin-angiotensin systems, could also play a pathogenetic role.
- d. **Diabetes mellitus:** Another pathogenetically cholesterol-dependent, but statistically independent, major cardiovascular risk factor is diabetes mellitus. Diabetes and hypercholesterolemia interact strongly in the genesis of IHD. The precursor to type 2 diabetes, insulin resistance with impaired glucose tolerance also carries a strongly increased risk for cardiovascular disease. The risk of developing coronary atherosclerosis is considerably increased.
- e. **Exercise:** Persons with sedentary jobs develop coronary artery disease more often than those having regular physical exercise.
- f. **Novel Risk Factors:** Increased levels of homocysteine, C – reactive protein, plasma fibrinogen and fibrin D - dimer, and lipoprotein (a) have been implicated as independent risk factors for atherosclerosis and IHD.

Work done at Bangalore has shown that in resident Indians of South India, tobacco smoking, hypertension, diabetic state and central obesity were the more important risk factors seen in patients with the first attack of acute myocardial infarction. In western countries the incidence of IHD is coming down in the richer groups due to modification of lifestyles whereas it is increasing in the poorer groups.

Pathology

Atheroma commonly affects the epicardial vessels. This may lead to single or multiple obstructions.

The location of infarct depends upon the vessel occluded

Left anterior descending branch: Anterior and apical portions of left ventricle.

Left circumflex branch: Lateral and inferoposterior walls of the left ventricle.

Right coronary artery: Inferoposterior wall and inferior portion of the interventricular septum.

In atherosclerosis, focal fibrofatty elevations (plaques) develop in the intimal and subintimal regions resulting in progressive narrowing of the lumen. Inflammation is an important component in the development of atheroma. It is associated with activation and proliferation of

macrophages, endothelial cells and smooth muscle cells and generation of cytokines and growth factors. The lipid rich atheromatous material itself is a potent inducer of inflammation. Oxidised LDL is taken up by macrophages to form subintimal foam cells. Oxidised LDL also acts as a chemotactic factor for macrophage accumulation.

The inflammatory changes have been the focus of intense research in recent years. Inflammation within the arterial wall starts with the entry of low density lipid (LDL) through the damaged intima. This attracts cellular components such as monocytes, macrophages which are transformed monocytes and T. lymphocytes. Several cytokines such as IFN γ , TNF, IL-1 and others have been detected and incriminated in the process. Several microbial antigens have been detected. These include *Chlamydia pneumoniae*, herpes viridae, CMV and others. Several markers of inflammation such as C-reactive protein, fibrinogen, IL-7, IL-8 and others have been detected. All these point to a strong possibility of inflammation playing a major role in atherothrombotic coronary artery disease.

Several complications may develop in the atheroma. These include hemorrhage into the atheroma, ulceration of the intimal surface with thrombosis over the atheroma, embolization of the atheromatous material, and calcification. Progressive occlusion of the lumen of the coronary arteries may remain totally asymptomatic till the circulation is considerably diminished. In general the development of complications gives rise to one of the clinically detectable syndromes.

Once a coronary artery is occluded and the myocardium is infarcted, gross changes are noticeable by six hours. The infarct appears pale, blue and edematous. Early histological features are interstitial edema, neutrophilic infiltration and clumping of muscle cells. Granulation tissue appears by the tenth day. The infarcted area is converted into a scar by the sixth week. An infarct may involve the total thickness of the ventricular myocardium (transmural infarcts) or may be confined to the subendocardial region.

Further changes may develop over the area of initial infarction. These are: (1) extension of the infarct leading to further loss of ventricular function; (2) involvement of conducting tissues leading to disruption of impulse conduction; (3) rupture of the infarct resulting in hemopericardium; (4) inflammation of the overlying pericardium giving rise to pericarditis; and (5) formation of ventricular aneurysm. The ischemic myocardium is electrically unstable and heterogenous and this acts as a focus for re-entry, which give rise to several arrhythmias in the immediate postinfarction period.

Clinical Presentations

The following distinct clinical syndromes have been recognised:

1. Acute myocardial infarction; with ST segment elevation (ST elevation myocardial infarction – STEMI) without ST segment elevation (non ST elevation myocardial infarction – NSTEMI)
2. Unstable angina pectoris
3. Stable angina pectoris
4. Sudden cardiac death;
5. Arrhythmias and conduction defects;
6. Ischemic cardiomyopathy, and
7. Asymptomatic coronary artery disease.

Acute Myocardial Infarction

Despite impressive strides in diagnosis and management over the past three decades, acute myocardial infarction (AMI) continues to be a major public health problem. Almost all MIs result from coronary atherosclerosis, generally with superimposed coronary thrombosis. Before the thrombolytic era, clinicians typically divided AMI patients into those suffering a Q-wave or non-Q-wave infarct, based on the evolution of the pattern on the electrocardiogram (ECG) over several days after AMI. In the thrombolytic era, AMI is classified based on the presence or absence of ST segment elevation in the 12-lead ECG – into ST elevation myocardial infarction (STEMI) or non-ST elevation myocardial infarction (NSTEMI) (Figs 124.1 to 124.4).

Pathogenesis: Slowly developing high-grade stenoses of epicardial coronary arteries may progress to complete occlusion, but do not usually precipitate AMI, probably because of the development of a rich collateral network. During the natural evolution of atherosclerotic plaques, especially those that are lipid laden, an abrupt and catastrophic transition may occur, characterized by plaque rupture. After plaque rupture there is exposure of substances that promote platelet activation and aggregation, thrombin generation, and, ultimately, thrombus formation. The resultant thrombus that is formed interrupts blood flow and leads to an imbalance between oxygen supply and demand and, if this imbalance is severe and persistent, to myocardial necrosis.

CLINICAL FEATURES

This is characterized by the occurrence of severe retrosternal pain with the characteristic radiation. The pain is usually severe and excruciating, but at times it may be mild and rarely pain may be absent. The pain is described as crushing, tearing, bursting, burning, lancinating or vague. The pain generally lasts for more than 30 minutes and the attack occurs during rest. Several phenomena are associated with this pain. These are severe anxiety and a feeling of impending death, profuse sweating, dyspnea, shock, cardiac arrhythmias, syncope, nausea, vomiting, and epigastric pain. The attack follows the circadian

rhythm in that a good number of cases occur in the early hours of the morning. In some patients, especially diabetics and elderly there may be no chest pain. They may be totally asymptomatic or present with symptoms like dyspnea, extreme fatigue, syncope, confusion, arrhythmia or peripheral embolism.

Signs: In 20% of cases the symptoms may be trivial and physical examination may be unrewarding. In the majority the findings are diagnostic. Coldness of limbs, sweating and sudden onset of pulmonary edema are suggestive of acute left ventricular failure. In cardiogenic shock the extremities are cold and cyanosed and the blood pressure is low and often unrecordable. Heart rate is variable. In the initial stages, severe bradycardia may occur in some cases as a result of increased vagal tone. Others show tachycardia and arrhythmias such as frequent ventricular ectopics, atrial fibrillation or ventricular fibrillation. The blood pressure drops in most cases, but sometimes it may remain normal or even be elevated as a result of intense vasoconstriction. The jugular venous pressure may be elevated, if there is congestive heart failure or right ventricular infarction. About 24-48 h after the infarct fever may occur as a response to tissue necrosis.

Physical examination of the heart reveals muffling of sounds, presence of gallop suggesting ventricular failure, arrhythmias, and accentuation of the pulmonary second sound (P2), as a result of rise of pulmonary artery pressure. On the second or third day pericardial friction rub may be heard. If complications develop these will be clinically evident.

Diagnosis: Strong clinical suspicion is needed for early diagnosis. It should be remembered that in the middle-aged and elderly, one of the common causes for chest pain is myocardial infarction. Clinical suspicion is strengthened by the presence of the characteristic radiation and the associated phenomena. Even in the absence of pain, myocardial infarction should be suspected if a middle-aged person develops any of the complications suddenly. WHO criteria for diagnosis of acute myocardial infarction requires at least two of the following three elements to be present; (1) a history of ischemic type chest discomfort, (2) evolutionary changes on serially obtained ECG tracings and (3) the typical rise and fall in serum cardiac markers.

Investigations: Electrocardiogram (ECG) taken within a few hours of symptoms show diagnostic changes in over 80% of cases. More than 95% show positive ECG findings if recorded 12-24 h after the onset of symptoms. The changes depend upon the type of infarction, site of infarct, presence of arrhythmias, and conduction defects. Non ST elevation infarction produces depression of the ST segment or T wave inversion in ECG. Presence of ST elevation infarction is recognized by the elevation of ST

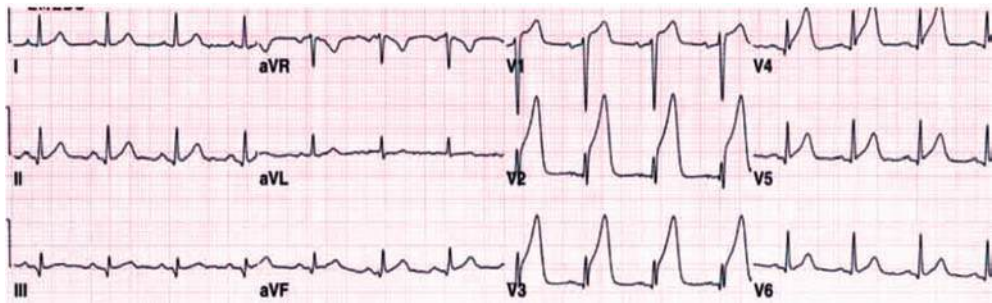


Fig. 124.1: ECG of anterior wall MI showing ST elevation in leads V1-V5

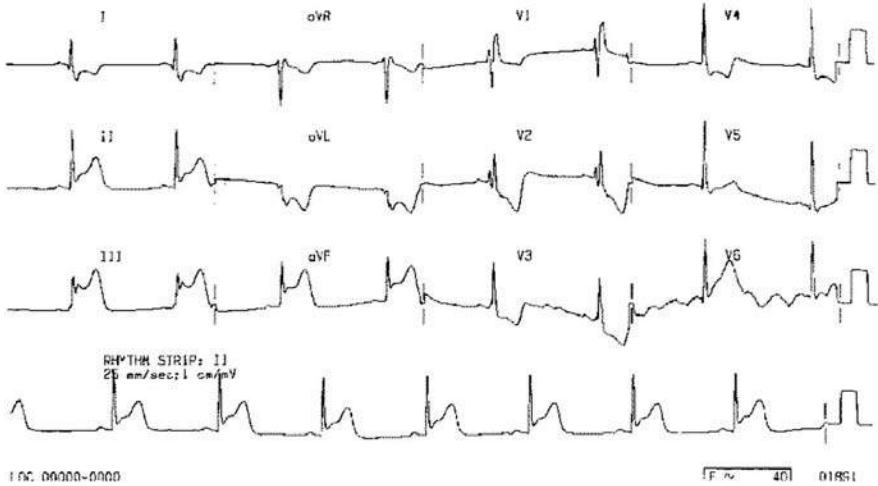


Fig. 124.2: ECG: Hyperacute inferior wall myocardial infarction. Note: (1) ST elevation in inferior leads– viz lead II, III, and aVF (2) Reciprocal ST segment depression in V2-V4

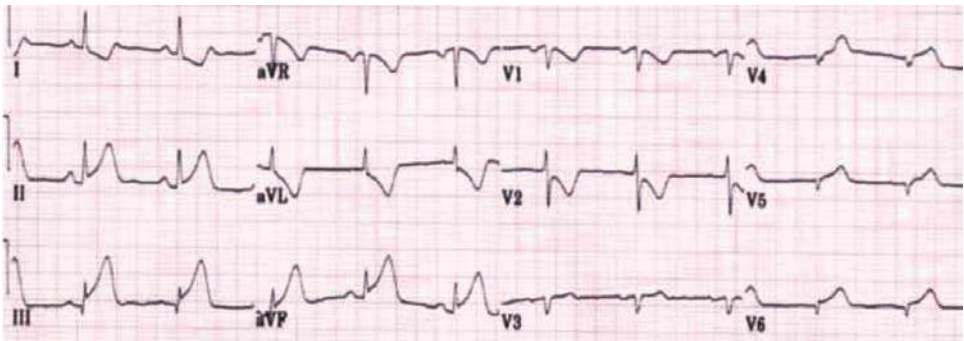


Fig. 124.3: ECG showing inferior and lateral MI. Note ST elevation in leads 2, 3, aVF, V5,V6 and ST depression in leads I, aVL, V1,V2

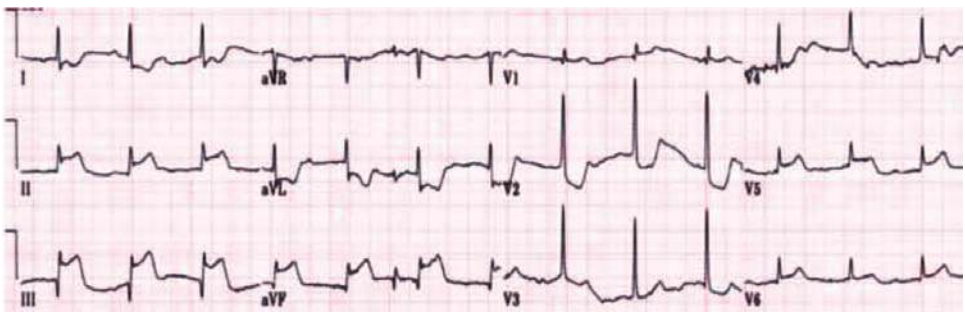


Fig. 124.4: ECG showing inferior and posterior wall MI. Note ST elevation in 2, 3, aVF and ST depression in I, aVL. Also tall R waves with upright T waves in V1 and V2

segment in ECG. Later majority of them will develop Q-waves and inversion of the T-waves. The site of infarct can be determined depending on the leads which show abnormalities.

<i>ECG leads showing changes</i>	<i>Location of infarct</i>
V1 to V3	anteroseptal
V4 to V6, L1 and aVL	anterolateral
aVF, L2 and L3	inferior wall
ST depression in V1 and V2	
Presence of tall R-waves and upright T-waves in lead V1 and V2	True posterior infarct
ST elevation in Rt sided chest leads and Q waves (V3R, V4R)	Right ventricular infarct
Note:	
1. In true posterior infarct. V1 will show upright R and T waves, unlike as in right ventricular hypertrophy in which T is inverted.	
2. Right ventricular infarction has to be suspected when there is jugular venous changes resembling constrictive pericarditis and shock without hypovolemia. In such circumstances right sided leads should be taken to demonstrate RV infarction. Presence of right ventricular infarction calls for special management.	

It should be remembered that in a small proportion of cases ECG may not show any diagnostic change even in the presence of the typical pain and enzyme changes.

Biochemical Markers of Myocardial Infarction

Several enzymes and other components of cardiac muscle are liberated into circulation from injured and necrotic myocardium. Their presence above diagnostic levels, their peak levels in the plasma and the pattern of their rise and fall, have all been studied in detail and their reliability in the diagnosis of myocardial infarction has been established. It is routine practice to estimate these components to establish or exclude the diagnosis of myocardial infarction (Table 124.1).

The transaminases: Serum glutamic oxaloacetic transaminase (SGOT) also known as aspartate transaminase is liberated from the myocardium when it undergoes infarction. The levels start rising in 8-12 hours, peak at 18-36 hours and come down in 3-4 days. Their estimation is cheap and freely available in several laboratories.

Creatine Kinase (CK)

The level rises within 4-8 hours of infarction, reaches its peak in 24 hours and falls to normal levels within 2-3 days. CK shows three isoenzymes—MM, BB and MB which can be identified electrophoretically. MM is more specific to skeletal muscle, BB to brain and kidney, and MB to the heart, though there is some degree of overlap. Thrombolytic therapy, percutaneous revascularization or spontaneous thrombolysis leads to early rise in the enzyme levels. CK is present in several other tissues and therefore non-MI conditions also cause increase in CK levels, e.g. muscle diseases, alcoholic bouts, diabetes mellitus, muscle injury, vigorous exercise, convulsion, intramuscular injections, thoracic outlet syndrome and pulmonary embolism. Estimation of the cardiac specific isoenzyme CKMB is more specific for MI.

CKMB shows two isoforms CKMB1 and CKMB2. Elevation of CK (MB2) is more suggestive of cardiac infarction in the absence of other obvious reasons. Levels of CKMB isoform >1.0 U/L or a ratio of CKMB2/CKMB1 >1.5 is diagnostic of acute MI.

Cardiac Specific Troponins

The troponin complex usually consists of three subunits that regulate the calcium mediated contractile process.

- Troponin C—binds to calcium
- Troponin I—binds to actin and inhibits actin-myosin interactions
- Troponin T (Tn-T)—binds to tropomyosin

TABLE 124.1
Showing the details of common biochemical markers diagnostic of myocardial infarction

Marker and normal level	Time to show rise in serum levels hours after onset	Peak level	Time to return to normal	Time for collection of blood
SGOT 5-40 IU/L	8-12	18-36 hours	3-4 days	Once in 12 hours
LDH 20-220 IU/L	10	24-48 hours	10-14 day	24 hours
CK MB	3-12	24 hours	48-72 hours	Every 12 hours for 3 days
C TnT	3-12	12 hours to 2 days	5-14 days	Once at least every 12 hours
C TnI	3-12	24 hours	5-10 days	Once at least every 12 hours

Myocardial injury leads to a rapid rise in cardiac troponin in plasma. Troponin I and troponin T are released into the plasma so that reliable diagnostic sensitivity is reached by 12 to 16 h and maximal activity is reached by 24 to 36 h. The levels return to normal within 10 to 12 days. Quantitative bedside assay tests for cardiac Tn-I and Tn-T are available for diagnosing acute MI.

In some patients with chest pain C Tn-T may be raised but CKMB is in the normal range. The term 'minor myocardial damage' has been used to denote this condition. Such patients have adverse outcome on follow-up including fatal and nonfatal MI.

Lactate Dehydrogenase (LDH)

This used to be done frequently before the availability of specific markers such as cardiac troponins. LDH is an enzyme found in the heart muscle, along with several other tissues in the body. It consists of five isoenzymes, among which LDH1 is principally seen in the heart. Levels of LDH1 increase following myocardial necrosis. Several other disorders also lead to rise in LDH, e.g. hemolysis, megaloblastic anemia, leukemia, hepatic disorders, renal disease, muscle disorders, pulmonary embolism, shock and others. Estimation of the ratio of LDH1 to LDH2 has been accepted as a more reliable test for diagnosing AMI. Ratios of LDH1/LDH2 >1 are diagnostic. However routine LDH isoenzyme analysis for the diagnosis of AMI is no longer recommended.

Conclusion

At present the diagnosis of AMI can be established within 12 hours of onset by estimation CKMB, C Tn-T or C Tn-I at intervals of 8-12 hours. Several other biochemical markers such as heart fatty acid binding proteins (hFABP), myosin light chains (MLC), myosin heavy chains (MHC) and glycogen phosphorylase isoenzymes are being studied for their promptness and reliability in diagnosis.

Levels of serum lipids such as cholesterol and HDL fall within 24-48 hours after MI and therefore the ideal time to determine the lipoprotein profiles of such patients is 8 weeks after the event.

Imaging Procedures

Chest X-ray film: Since the patient should not be moved, portable X-ray machine may be required. When present, prominent pulmonary vascular markings on the X-ray reflects elevation of pulmonary venous pressure indicating left ventricular failure. The chest film may also assist in excluding other causes of chest pain such as pneumothorax, pulmonary infarction with effusion, aortic dissection and skeletal fractures.

Echocardiography: Echocardiography is particularly valuable in assessing the patient with an equivocal ECG. The presence of a regional wall motion abnormality provides strong supportive evidence of acute coronary ischemia. Echocardiography also provides an assessment of ventricular function. It can provide information on complications like ruptured chordae tendineae with mitral regurgitation and ventricular septal defect. It can help to estimate cardiac hemodynamics by using colour Doppler studies.

Nuclear imaging: Radionuclide imaging, angiography, perfusion imaging, infarct avid scintigraphy and positron emission tomography are all in use to study the nature of the myocardial lesion, its viability and prognosis.

CT scan: It can be used to reveal cavity dimensions, wall thickness, aneurysms, and intracardiac thrombi.

MRI scan: It can be made use of to assess the perfusion of infarcted and non-infarcted tissue as well as the state of reperfused myocardium. It can also identify areas of jeopardised but not infarcted, myocardium.

Both CT scan and MRI are generally reserved for subsequent evaluation after the acute condition is managed.

Differential diagnosis: Acute chest pain may occur in pleurisy, pneumonia, pericarditis, pneumothorax, pre-herpetic neuralgia, dissecting aneurysm of the aorta or lesions on the chest wall. Pericarditis may closely resemble acute myocardial infarction in respect of the pain and its radiation. Fever, leukocytosis, and pericardial rub occur early in pericarditis, whereas these develop only 24 hours after the onset of myocardial infarction. Dissecting aneurysm of the aorta is uncommon. It causes tearing pain, which is abrupt in onset and severe from the beginning. Pain may radiate to the back, epigastrium, flank, and lower extremities. Ventricular dysfunction is less common to develop.

Sometimes the pain of myocardial infarction may be felt mainly under the jaws, shoulder, or epigastrium, and these may be mistaken for primary disease at these sites.

COMPLICATIONS

Several complications can occur following acute myocardial infarction and can lead to morbidity and mortality.

1. **Arrhythmias:** Several arrhythmias develop. These include frequent ventricular ectopics, ventricular tachycardia, ventricular fibrillation, sudden cardiac arrest, atrial fibrillation, and varying grades of heart block. The incidence of arrhythmias is higher in those patients seen earlier after the onset of symptoms. The treatment of tachyarrhythmias

involves not only the use of antiarrhythmic drugs but also correction of abnormalities of plasma electrolyte concentrations, acid-base balance disturbances, hypoxemia, anemia, and digitalis intoxication.

2. **Left ventricular failure:** Left ventricular dysfunction remains the single most important predictor of mortality after acute myocardial infarction. Clinical manifestations of left ventricular failure become more common as the extent of the injury to the left ventricle increases. In addition to infarct size, other important predictors of the development of symptomatic left ventricular dysfunction include advanced age and diabetes. Apart from myocardial necrosis, another condition which can lead to left ventricular failure is myocardial stunning

Myocardial stunning: The term myocardial stunning defines a prolonged but reversible contractile dysfunction observed after transient myocardial ischemia, i.e. even after blood supply to the myocardium is restored. The recovery of contractile function may take hours or days.

The term '**hibernating myocardium**' is used to denote the condition in which cardiac function is depressed due to persisting ischemia and which recovers fully on restoration of blood supply.

3. **Cardiogenic shock:** Cardiogenic shock is a severe form of left ventricular failure. Infarction of 40% or more of the ventricular myocardium leads to cardiogenic shock. Features of cardiogenic shock include systolic blood pressure <80 mm Hg, markedly reduced cardiac index (<1.8 L/min/m²) and an elevated pulmonary capillary wedge pressure. Mortality in cardiogenic shock is >70%.
4. **Pericarditis:** Pericarditis may occur as early as the first day and as late as 6 weeks after MI. This develops in 15-20% of patients. It is seen in full thickness infarcts. The development of pericarditis appears to be correlated with a larger infarct and greater hemodynamic compromise. Treatment of pericarditis pain consists of aspirin. Doses of 650 mg orally every 4 to 6 hours may be needed.
5. **Phlebothrombosis and pulmonary embolism:** These develop as a result of prolonged recumbency, venous stasis, and tendency for venous thrombosis.
6. **Arterial embolism:** Mural thrombi develop on the infarcted endocardium and these may embolize into several arterial trunks. This risk starts a day or two after the infarction and persists for a few weeks.
7. **Papillary muscle dysfunction and rupture:** Ischemia and infarction of the papillary muscles leads to mitral regurgitation. Rupture of the papillary muscles results in the development of

acute mitral incompetence which tips the patient into acute pulmonary edema.

8. **Rupture of the interventricular septum:** This condition leads to acquired ventricular septal defect. A ruptured interventricular septum is characterized by the appearance of a new harsh, loud holosystolic murmur that is heard best at the lower left sternal border and that is usually accompanied by a thrill. Biventricular failure generally ensues within hours to days.
9. **Cardiac rupture:** This may develop by the third to the fifth day. The infarcted area gives way giving rise to hemopericardium, cardiac tamponade, and death in the majority of cases. Rupture of interventricular septum carries a mortality of 24% in the first 24 hours, 46% at 1 week and 67-82% at 2 months. Surgical closure improves the prognosis.
10. **Delayed complications:**
 - a. **Cardiac aneurysm:** Weakening of the scar leads to bulging out of the ventricle and the development of ventricular aneurysm. The common sites are the anterior and apical regions. This leads to persistent congestive failure, recurrent embolism, and ventricular tachycardia. On palpation of the precordium the aneurysm can be felt as a see-saw pulsation in relation to the apex beat. The condition can be confirmed by X-ray examination, echocardiography, and angiocardiology.
 - b. **Dressler's syndrome:** This is probably an immune-mediated reaction in which pericarditis, pleurisy, fever, arthritis, and elevation of ESR develop 1-6 weeks after the infarction.
 - c. **Shoulder hand syndrome** may develop in a few cases weeks to months after the acute event.

PROGNOSIS

Myocardial infarction is a serious disease, with an overall immediate mortality ranging up to 25% if proper management is not instituted. About 50 percent of the deaths associated with AMI occur within 1 hour of the event and are attributable to arrhythmias, most often ventricular fibrillation. For the first six months after infarction, the risk of developing sudden death is still high, but this risk falls after this period. Anterior infarction carries a grave prognosis if accompanied by conduction disturbances. All the major complications worsen the prognosis. Age above 70 years, hypertension, diabetes mellitus, and heavy cigarette smoking worsen the outlook further. Women below the age of 75 years have higher mortality rates after AMI compared to men of similar age.

Several ECG criteria have been employed to predict increased risk of fatal arrhythmias and death in the post-infarct period.

These include:

- Signal averaged late potentials
- Heart rate variability and
- Q-T dispersion

Patients who had sudden cardiac death and required cardiopulmonary resuscitation during the course of the illness run a higher risk of fatal arrhythmias in the first few years after discharge from hospital.

Management

Prehospital care is an important factor in preventing sudden death and immediate complications and also improving long-term outcome. No time should be lost in seeking hospital admission after the initial symptoms manifest. The time elapsed between the onset of chest pain and reaching the appropriate hospital (pain to hospital time) and the time elapsed between the arrival at hospital and receiving the first dose of medication (door to needle time) are the most important factors which reduce immediate and in-hospital mortality and complications. Several attempts have been made from time-to-time to educate the public on the need to get immediate hospitalization. Provision of special trained teams with coronary care ambulances which can reach the patient's home within minutes and administration of thrombolytics in the ambulance with minimum delay have reduced early mortality in many countries.

EMERGENCY ROOM MANAGEMENT

Aspirin is given straight away in a dose of 325 mg to be chewed. A rapid decision as to the need for thrombolysis should be taken depending on the indication.

A 12 lead ECG forms the cornerstone in decision making regarding thrombolysis in acute myocardial infarction. Presence of ST segment elevation of 1mm or more in two or more contiguous leads with a history compatible with AMI are the indications for starting thrombolytic therapy if there are no absolute contraindications. There is no benefit in giving thrombolysis in the absence of ECG showing ST segment elevation. Before giving thrombolytic agents blood is collected for the biochemical parameters.

If the ECG is suggestive of ischemia without infarction (i.e.) S-T depression or T-wave inversion, start on anti-ischemic therapy.

If the ECG is not diagnostic, observe the patient repeating the ECG at 2 hour intervals, estimate the serum markers and if necessary, echocardiography. If there is no evidence of infarction on observation for 24-48 hours, the patient should be subjected to a stress test to provoke ischemia.

DRUG THERAPY

Aspirin

It is the first line drug in the initial management of AMI and all other forms of ischemic heart disease. Initial dose of aspirin should be 162 to 325 mg to be chewed to ensure rapid buccal absorption. Subsequent dose of aspirin is 75 to 162 mg.

Recent studies have shown that addition of clopidogrel to aspirin in AMI is beneficial.

Control of Cardiac Pain

Pain relief has to be achieved as early as possible. Persistent pain perpetuates sympathetic overactivity, especially so in the early phases of AMI. Control of pain is achieved by a combination of narcotic analgesics, nitrates and beta blockers.

Morphine is the analgesic of choice.

Morphine: Its mode of action includes central narcotic action, depression of vasomotor and respiratory centers, reduction of sympathetic tone, and reduction of histamine release from the periphery.

Administration of morphine leads to reduction of pain, anxiety, vasodilation, reduction of the heart rate and effort for breathing, all helping to reduce oxygen demand.

In the ICCU morphine should be given intravenously, initial dose of 4 to 8 mg and subsequently in doses of 2-8 mg repeated at intervals of 5-15 minutes until the pain is relieved or adverse effects appear. The adverse effects include hypotension, respiratory depression, vomiting, urinary retention and constipation. Maximum dose should not exceed 2-3 mg/kg in 24 hours.

Adverse effects of morphine are managed as follows:

Hypotension is counteracted by maintaining the supine position and elevating lower extremities if the systolic blood pressure is less than 100 mm Hg. Administration of atropine 0.5 to 1.5 mg helps to reduce the vagomimetic effects of morphine.

Respiratory depression is treated with naloxone in dose of 0.1-0.2 mg IV, repeated after 15 min if needed.

Nausea and vomiting can be treated with a phenothiazine.

OXYGEN

It was a routine practice to give oxygen to all patients with anginal pain for 24-48 hours based on the empirical assumption of hypoxia. But, augmentation of the fraction of oxygen in the inspired air does not elevate oxygen delivery significantly in patients who are not hypoxemic. Furthermore, it may increase systemic vascular resistance and arterial pressure and thereby lower cardiac output slightly. In view of these considerations, arterial oxygen

saturation may be estimated by pulse oximetry, and oxygen therapy may be given if oxygen saturation is less than 90%.

NITRATES

These are used for immediate relief of anginal pain, as well as prevention of its recurrence. For immediate action nitroglycerine (glyceryl trinitrate) is used IV or sublingually. The vasodilatory effect is immediate and the action is of short duration. For maintenance therapy other preparations are used. Their action is more prolonged.

Actions

Nitrates dilate the epicardial coronary arteries and collaterals, and improve the blood supply. It reduces the preload and also the myocardial oxygen demand. Blood flow of normally perfused areas is redistributed to ischemic areas of the myocardium. Other actions include inhibition of platelet aggregation, limitation of infarct size and improvement in exercise capacity.

Indications

In acute MI with angina, congestive heart failure, persistent angina or hypertension, nitrates are given for the first 24-48 hours. Maintenance dose is continued in patients with recurrence of angina and persistent pulmonary venous congestion.

Glyceryl trinitrate is available in vials of 5 and 25 mg at concentrations of 1 or 5 mg/mL. One vial is diluted in 500 mL normal saline prior to infusion and run at a rate of 5-10 mcg/minute to start with. It is increased by 5-10 mcg/minute until clinical effect is manifest. This includes relief of angina, fall of blood pressure by 10% in normotensive, and up to 30% in hypertensive patients.

Sublingual Dose

Glyceryl trinitrate is available as tablets containing 0.5, 2.6 and 6.4 mg. It is given initially at doses of 0.3-0.6 mg. Additional doses of 0.3 mg may be repeated every 5 minutes to a maximum of 1.2 mg in 15 minutes.

Other preparations are buccal spray containing 400 mcg metered doses, 2% skin ointment and transdermal patches containing 2.5, 5.0 and 15 mg, released over 24 hours.

Side Effects of Glyceryl Trinitrate

These include headache and flushing, hypotension, hypovolemia and ventilation-perfusion imbalance in the lungs. Methemoglobinemia may develop after large doses.

In general, reduction or withdrawal of the dose helps to relieve the side effects. Hypotension and hypovolemia

are managed by elevation of the foot end of the bed and intravenous fluids.

Tolerance to nitrates develops after all forms of nitrate administration if given continuously even within 12-24 hours, but generally it is delayed. The loss of effect is limited to the capacitance and resistance vessels. Large conductance vessels including epicardial coronary arteries and radial arteries are not affected.

Tolerance to nitrates is prevented by giving the drug at eccentric intervals allowing 10-12 hours of nitrate free intervals in between, e.g. 8 am and 2 pm. Transdermal preparation should not be used continuously for more than 12 hours.

Isosorbide Dinitrate

This is available as 5 mg, 10 mg and 20 mg sustained release tablets, or 1.25 mg metered dose buccal spray.

Isosorbide 5 mononitrate tablets of 10 and 20 mg tablets and long acting tablets of 40, 50 and 60 mg are available. These are used for maintenance therapy and prevention of angina after the emergency is tided over.

Beta Adrenergic Blockers

Beta blockers relieve pain and reduce the need for analgesia in many patients and reduce infarct size. When used in the early hours of infarction, they limit infarct size, reduce the incidence of ventricular arrhythmias, atrial fibrillation and cardiac arrest. They reduce the incidence of recurrent ischemia and reinfarction within the first six weeks of initial MI.

In the acute phase, intravenous metoprolol is the drug of choice. If there are no contraindications, metoprolol is given IV in three boluses of 5 mg each at intervals of 2-5 minutes if the heart rate is >60/minute. If hemodynamic stability continues for 15 minutes after the last I.V dose, oral metoprolol 50 mg is given 6 hourly for two days and then changed to 100 mg b.i.d.

Contraindications for beta blockers include cardiac failure evidenced by the presence of rales heard over the lower parts of the chest 10 cm above the level of the diaphragm, hypotension (BP < 90), bradycardia (heart rate < 60/minute), prolonged PR interval > 0.24 second or third degree heart block. Other commonly used beta blockers include atenolol 50-100 mg daily, and bisoprolol 5 mg daily, given orally.

The ultra short acting drug esmolol can be used in an emergency in a dose of 500 mcg/kg/minute for 4 minutes IV.

THROMBOLYTIC THERAPY

Plaque rupture and thrombus formation play a major role in the genesis of acute coronary occlusion leading to acute myocardial infarction. The introduction of thrombolytic (fibrinolytic) therapy was a major advance in the treatment

of acute ST elevation myocardial infarction (STEMI) since over 90 percent of such patients have complete occlusion of the culprit artery. Early reperfusion of the ischemic myocardium has brought down the immediate post-MI mortality from 10-15 to 5-10%. Several randomised trials have upheld its benefit and safety. Whenever possible thrombolytic drugs should be given by the first attending physician; irrespective of the speciality, if the indications are clear.

Classification of Thrombolytic Agents

1. **First generation drugs:** Streptokinase, urokinase: These act on all sites where fibrin is formed. In addition to dissolution of the clots locally, they also produce generalised hemorrhagic state.
2. **Second generation:**
 TPA—tissue plasminogen activator. Single chain—alteplase and double chain—duteplase.
 APSAC—Anisoylated plasminogen streptokinase activator complex
 SCU-PA—Single chain urokinase type plasminogen activator.
 TCU-PA—Two chain urokinase type plasminogen activator.
 These are clot specific agents acting at the site of fibrin formation with very little or no generalized hemorrhagic tendency.
3. **Third generation:**
 - i. Reteplase (rPA)—recombinant TPA
 - ii. Tenecteplase (TNK – PA)
 Though several thrombolytic agents are available, the first generation drugs are the ones widely used in India on account of their free availability, effectiveness, safety and above all, the lowest cost. A course of streptokinase costs Rs. 3000, whereas urokinase costs Rs. 10000. All the others are several times more expensive and also are not freely available. Therefore, they are employed only under exceptional situations.

Indications

1. In those with S-T elevation in the ECG, more than 0.1 mV(1mm) in two or more contiguous leads within 12 hours of onset of symptoms.
2. In those with new onset or presumably new onset left bundle branch block within 12 hours of onset of symptoms.

Best results are obtained if thrombolysis is done within 6 hours of onset, earlier the better. Benefit may occur even up to 12 hours of onset, though in a smaller proportion.

Dosage and Administration

Streptokinase (SK) is available as lyophilised powder in vials containing 2,50,000, 7,50,000 or 15,00,000 units. It has to be stored at 15-25°C. The initial dose is 1.5 million units diluted in 100 mL normal saline and infused over one hour.

Occurrence of thrombolysis and reperfusion of the myocardium is evidenced by the following features.

1. Relief of chest pain
2. Resolution of the S-T segment elevation of >50% by 60-90 minutes.
3. Evidence of reperfusion phenomena such as
 - a. arrhythmias-VPCs, accelerated idioventricular rhythm or bradycardia
 - b. abrupt rise in serum creatine kinase activity
 - c. recanalisation of the coronary artery demonstrable by angiography.

Contraindications

- A. Absolute contraindications
 1. Previous hemorrhagic stroke at any time
 2. Ischemic stroke within 3 months
 3. Known intracranial neoplasm, structural cerebrovascular lesion (AV malformation)
 4. Suspected aortic dissection
 5. Active internal bleeding or bleeding diathesis (other than menstrual bleeding)
 6. Significant closed head or facial trauma within 3 months
- B. Relative contraindications
 1. Hypertension with BP > 180/110 mm Hg
 2. History of prior cerebrovascular accident or known intracerebral pathology
 3. Current use of anticoagulants in therapeutic doses and other known bleeding diatheses
 4. Recent trauma including head trauma or major surgery within 3 weeks
 5. Noncompressible vascular puncture
 6. Occurrence of internal bleeding within 2-4 weeks
 7. For streptokinase and anistreplase, previous history of use of the same drug within 5 days to 2 years, or history of allergic reaction
 8. Pregnancy
 9. Active peptic ulcer

Complications of Streptokinase Therapy

1. Allergic reactions such as angioneurotic edema, hypotension, bronchospasm, urticaria, rashes and fever may develop. Administration of 4 mg betamethasone IV helps to reduce the allergic reactions. Presence of antibodies to streptokinase reduces its therapeutic effects and increases allergic reactions.

2. Bleeding complications: Minor bleeding occurs in 3-4%. Major bleeding 0.4-1%. Intracranial bleed may occur in less than 0.6%.
3. Hemodynamic effects: Transient hypotension and bradycardia.
4. Reperfusion adverse effects: These are the effects of sudden reperfusion into areas of ischemic myocardium. They are caused partially by the effect of free radicals. Adverse effects include arrhythmias such as VPC, accelerated idioventricular rhythm, ventricular tachycardia, ventricular fibrillation and bradyarrhythmias. Cardiac rupture may occur due to further damage to infarcted myocardium and hemorrhage into it.
5. Coronary reocclusion: 15% of recanalised vessels undergo thrombotic occlusion within a few hours to 3 days.

OTHER THROMBOLYTIC AGENTS

Urokinase (UK)

Urokinase is a double chain glycoprotein which acts as a trypsin like protease and occurs in two molecular forms. It was first isolated from human urine and hence its name. It is also obtained by recombinant DNA technology from cultured human renal cells. It is nonantigenic. It is not fibrin specific and therefore it causes generalised bleeding tendency. Its half-life is 10 minutes. It produces less sustained systemic fibrinolysis. Dose for IV use is 3 million units given over 45 to 60 minutes. Different dosages of 1.5, 2 and 3 million units have been used in several trials. Patency at the end of 1 hour is 60%. Infusion is similar to that of streptokinase. Anaphylactic reactions are practically nil. It is more expensive than streptokinase and therefore it may be reserved for patients allergic to SK or who have received SK previously.

Since the other newer class of thrombolytic agents are seldom used in the Indian scene, only passing mention is made about them.

Tissue Plasminogen Activator (tPA)

TPA is a naturally occurring enzyme that binds to fibrin with greater affinity than streptokinase, without increasing generalized bleeding tendency. It has been in use since 1984. rtPA is produced by recombinant DNA technology. Several dosage schedules are in use.

Total dose should not exceed 100 mg. It should be accompanied by IV heparin 5000 units bolus followed by 1000 units/hour with the dose adjusted to keep the partial thromboplastin time (PTT) at 1.5-2 times the normal. This helps to prevent reocclusion of the coronary arteries.

APSAC, Anistreplase

APSAC is a preformed complex of SK and plasminogen, which is spontaneously activated after IV administration. Once activated it behaves identical to SK, except that it has a longer half-life. It has a spectrum of activity and incidence of complications similar to SK. It is easy to administer. Hence it is used for prehospital thrombolysis in AMI patients. Dose is 30 units IV over 2-5 minutes. The half-life is 30-90 minutes and it retains its effect for 4-6 hours.

Comparison of Thrombolytic Therapy

Several international trials (GISSI-2, ISIS-3 GUSTO-1) TIMI-IV have compared different modes of thrombolytic therapy. Based on their evidence, consensus on this form of therapy has been arrived at.

Choice of Agent

In patients presenting within 4 hours of onset of symptoms the speed of reperfusion of the occluded vessels is of paramount importance and a high intensity thrombolytic regimen such as TPA or APASC is the preferred treatment, except in those individuals in whom the risk of death is low.

For those patients presenting between 4 and 12 hours after the onset of chest discomfort, the speed of reperfusion of the occluded vessel is of lesser importance and therefore streptokinase and TPA are equivalent options. Cost is the main factor for choice.

Late Therapy

There is no definite reduction in mortality if thrombolytic drugs are routinely administered to patients presenting after 12 hours of onset. Still we consider it reasonable to give thrombolytic therapy in selected patients with persistent symptoms and ST elevation in ECG beyond 12 hours.

Since elderly patients are at increased risk of cardiac rupture if thrombolytic drugs are given later than 12 hours after the onset of symptoms, it is better to restrict late thrombolysis to patients younger than 65 years with ongoing ischemia, especially those with large anterior infarctions. Older patients with ongoing ischemic symptoms who come in after 12 hours of onset are probably better managed with PTCA than with thrombolytic therapy.

Percutaneous Transluminal Coronary Angioplasty (PTCA)

Several studies (PAMI, GUSTO IIB and others) have confirmed the advantages of this method in cases not amenable to drug therapy or even as a primary therapy.

Advantages include reduction of mortality, preventing re-infarction and a recanalization rate of > 90%.

Indications

1. As an alternative to thrombolytic therapy in patients with S-T segment elevation or new onset LBBB. PTCA can be done within 12 hours of onset of AMI or even later if symptoms persist. Success rate of PTCA depends upon the skill of the operator and facilities in the hospital.
2. Patients below the age of 75 years who present with shock within 36 hours onset of AMI should also be considered for PTCA.
3. In those presenting with severe congestive heart failure and/or pulmonary edema.

Calcium Channel Blockers

They have no role in the primary or secondary prevention of acute MI. Even the possibility of harm has been raised. In patients with first episode of non-Q infarction or first episode of acute inferior wall infarction without LV dysfunction, use of verapamil and diltiazem may reduce the incidence of reinfarction but they have no advantage over beta blockers and aspirin.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS (ACE INHIBITORS)

Indications

1. Patients seen within 24 hours of acute MI with S-T segment elevation, in the absence of contraindications.
2. In those patients with MI and clinical heart failure or left ventricular ejection fraction (LVEF) less than 40% during and after convalescence from AMI.

ACE inhibitors should generally be started within the first 24 hours, ideally after thrombolytic therapy has been completed and the blood pressure has stabilized, if there are no contraindications. Initially low doses such as 6.25 mg captopril or 5 mg lisinopril or equivalent doses of other ACE inhibitor should be started and later stepped up if necessary. They can be stopped if there is no evidence of symptomatic or asymptomatic left ventricular dysfunction by 4-6 weeks.

Lipid Lowering Agents

All patients recovering from AMI should be considered potential candidates for modification of their lipid profile. The target LDL cholesterol in patients with IHD is <100 mg/dl. Initial therapy should consist of dietary modification (<7 percent of total calories as saturated fat and cholesterol <200 mg/d). In patients with an LDL cholesterol level greater than 130 mg/dl on admission, it

is better to start lipid lowering drugs. HMG-CoA reductase inhibitors (statins) are the first line lipid lowering drugs.

Magnesium Salts

The available data suggests that routine use of intravenous magnesium in ST elevation myocardial infarction has no place in current practice. Magnesium is useful only in known or suspected hypomagnesemic states and especially when these are associated with severe ventricular arrhythmias or QT prolongation.

Anticoagulants

Heparin is used in the acute stage in those undergoing PTCA, those who have received tPA or rPA and those at high risk for systemic emboli (large or anterior MI, AF, LV thrombus). The dose is 5000 units given as IV bolus admission and followed by IV infusion at the rate of 800-1000 units/hour.

The indication for routine use of long-term anticoagulation after acute MI is not clear. It may be given for the following conditions:

1. Prevention of recurrence of MI in patients who cannot tolerate aspirin
2. Post MI patients in persistent atrial fibrillation
3. Presence of left ventricular thrombus (see Chapter 165).

General Measures

To reduce risk of vomiting early after infarction and reduce risk of aspiration, during the first 4-12 hours after admission patients should receive a clear liquid diet. Thereafter diet with 50-55% of calories derived from complex carbohydrates and up to 30% from mono and unsaturated fats should be given. The diet should contain fruits and vegetables which are rich in potassium and magnesium. The foods should be small in quantity and given at frequent intervals.

RESUMPTION OF PHYSICAL ACTIVITY

Graded and supervised physical activity is encouraged as early as the patient can tolerate. In the absence of complications such as shock, cardiac failure or serious arrhythmias, mobilization of the patient should be started on the second day itself.

Before allowing the patient to get up and walk, vital signs should be checked and safety of mobilization should be ensured.

Stage 1—First 2 Days

Use bed pan or commode for toilet purposes. The patient is allowed to feed from the food tray with arm and back supported. All joints are given active and passive

movements. The ankle joint is exercised actively. The patient may be allowed to sit in a chair for short periods.

Stage 2—Days 3-4

The patient is allowed to walk out of the room under supervision. The upper part of the body can be bathed with the patient sitting in a chair with back supported. Bed to chair transfer for 20-30 minutes may be allowed daily.

Stage 3—Days 5-7

Patient can walk up to 200 meters two or three times a day. Before the patient is discharged, an exercise tolerance test is performed so that the schedule of exercise at home can be advised.

Early ambulation reduces the risk of deep venous thrombosis, pulmonary embolism and prolonged invalidism, in addition to improving the morale of the patient.

APPENDIX: EVIDENCE BASED MEDICINE

The development of newer methods, newer drugs, surgical methods and newer equipment have necessitated large scale multinational studies to evaluate their advantages and cost effectiveness. The number of well known studies in this field, outnumber all other similar studies done in other branches of medicine. Based on these studies several consensus protocols have evolved. Further studies are in the pipeline. Evolution of the management strategy has drawn heavily from these trials and the present state of the art technology is a classic example of evidence based medicine.

A few of the trials are listed below

SAVE: Survival and ventricular enlargement (CAPTOPRIL)

SMILE: Survival of myocardial infarction long-term evaluation (ZOFENOPRIL)

AIRE: Acute infarction-ramipril efficacy

TIMI: Thrombolysis in myocardial infarction

CONSENSUS II: IV ENALAPRILAT

CHINESE CAPTOPRIL STUDY

ISIS: International study of infarct survival

LIMIT-2—Second Leicester intravenous magnesium intervention trial

MAGIC—Magnesium in coronary disease

GISSI—Gruppo Italiano per lo studio della streptochinasi nell'infarto miocardico

GUSTO I—Global use of strategies to open occluded coronary arteries

GUSTO III—Newer antiplatelet drugs

FTT: Fibrinolytic therapy trialist collaborative study

EMERAS: Studio Multicentrico Estreptoquinase Republican de America de Surcollaborative study

ISAM—Intravenous Streptokinase in acute MI

4S—Scandinavian simvastatin survival study

(S)MASH (Swiss)—Multicentre trial of angioplasty for shock

ASSET—Anglo-Scandinavian study of early thrombosis

Several subsequent trials organized on national and international levels have published their results. Further studies are going on at present and publishing their results from time-to-time.

CORONARY REVASCULARISATION

Percutaneous transluminal coronary angioplasty PTCA is a radiological intervention procedure undertaken by cardiologists in which the stenotic segment of the arteries are dilated by suitable balloons passed through catheters, percutaneously through the femoral artery, retrograde into the aorta and then into the coronary arteries. By inflating the balloon the atheroma is crushed and the arterial lumen is restored. The lumen is maintained patent by the use of different types of stents. The number of stents depend on the number of occlusions. Re-occlusion by thrombus is prevented by using antiplatelet drugs like aspirin and clopidogrel. In addition to aspirin and clopidogrel several newer drugs including glycoprotein IIb-IIIa receptor blocking agents are used. These agents have considerably improved the results of PTCA by maintaining luminal patency in much higher proportion of patients. In well equipped centers the success rate exceeds 90%. Even complicated lesions can be treated by angioplasty by skilled operators (Figs 124.5 and 124.6).

The original stents introduced in 1987 were simple metallic stents. In them the re-occlusion rate was 30% and above within 1 year. Subsequently drug eluting stents were introduced. These elute drugs such as sirolimus, paclitaxel and others which serve to inhibit re-occlusion. Drug eluting stents are considerably more expensive than the plain stents. The cost is Rs. 150000 to 300000 per procedure depending on the number of stents required.

In the early days of angioplasty the percutaneous interventions (PCIs) were done as elective procedures in stabilized and chronic patients. With the accumulation of experience and technology many cases of complex and acute myocardial infarction have been taken up for emergency angioplasty. PCIs are done as life-saving and myocardium-saving procedures. The results of such emergency procedures are often dramatic. The complication of re-stenosis following PCI has been treated by options such as further balloon angioplasty, intracoronary radiation therapy (brachy therapy) and implantation of further drug eluting stents.

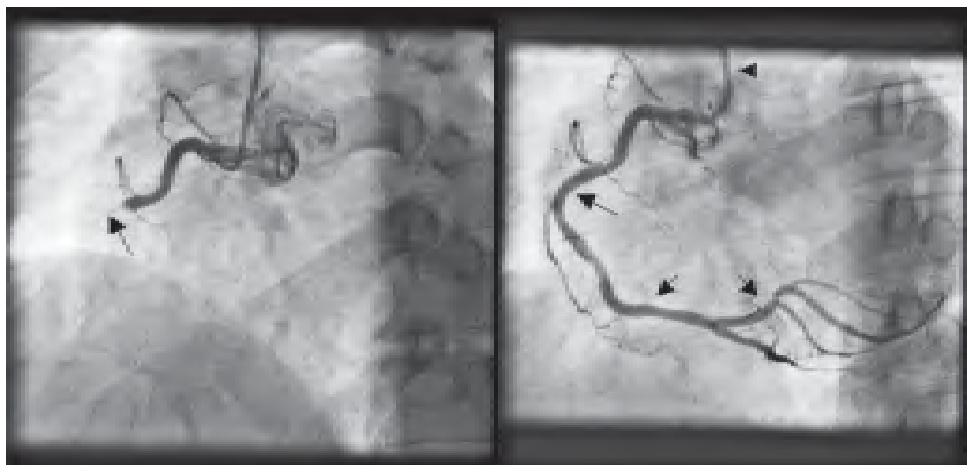


Fig. 124.5: Coronary angiogram in a patient with acute inferior wall myocardial infarction showing RCA. First picture: Before primary PTCA, RCA was totally occluded with thrombus.(arrow). Second picture: After primary PTCA, showing RCA with good flow and the branches (arrows)

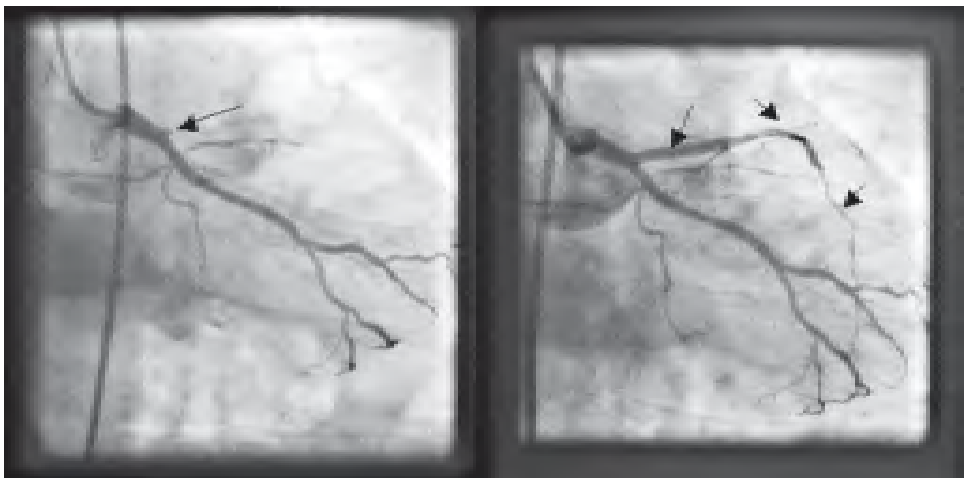


Fig. 124.6: Coronary angiogram in a patient with acute anterior wall myocardial infarction showing LAD. First picture: Before primary PTCA, LAD was totally occluded from ostium with thrombus and is not seen (arrow). Second picture: After primary PTCA, showing LAD with good flow and the branches (arrows)

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Coronary Artery Bypass Graft (CABG)

This operation is being done in India for about 30 years and many centers have gained considerable expertise and experience in the procedures. The intra- and perioperative mortality is around 2-3% in good large volume centres. Surgery is indicated for stenosis of left main stem, multivessel disease especially in presence of LV dysfunction, in which the clinical benefit and coronary disease-related mortality are significantly improved. Several grafts (3-5 or even more) are introduced at the same session, which connect the root of the aorta to the coronary artery distal to the occlusion.

Originally saphenous vein was used as the conduit. At present in addition to this vein, internal mammary artery and other arteries are also being employed. The results are better with arterial grafts. Several modifications

of the original technique have been introduced. Including keyhole surgery on the beating active heart.

Both bypass surgery and angioplasty may be complicated later by reocclusion. In case of stents the restenosis is due to smooth muscle proliferation. Several newer techniques are being experimented upon to prevent reocclusion of the stent. These include irradiation of the stented artery by gamma or beta radiations and impregnation of the stents with antiproliferative drugs like sirolimus, actinomycin D and paclitaxel (drug eluting stents) which prevent smooth muscle cell proliferation. All these innovations are being evaluated for their long-term results.

The procedure followed in most of the centers to pick up cases requiring revascularisation is to subject patients who have angina or who have suffered an acute

myocardial infarction (after 2-3 weeks of convalescence) to a stress test on the treadmill. Stress test is taken as positive if it provokes angina or produce ST segment depression in ECG of 1 mm or more from the baseline, which recovers on rest. Such patients with positive stress test are taken up for coronary angiography. Cases with limited number of stenosis are ideal for coronary angioplasty. Those with multiple vessel disease and multiple occlusions require bypass graft surgery.

Transmyocardial laser revascularisation is an operative treatment for refractory angina pectoris when CABG or PTCA are not feasible. This method may prove beneficial in those with no other treatment options.

Right Ventricular Infarction

The right coronary artery is the major source of blood flow, supplying the right atrium, right ventricle, inferior wall and posterior wall of left ventricle and posterior part of the interventricular septum. Right ventricle is supplied by the RV branches of the right coronary artery. The RV has a more favourable oxygen supply-demand ratio compared to the LV. In addition, the collateral circulation in the RV is also better.

RV infarction may occur in nearly half of all inferior myocardial infarctions, although only 10 to 15% of patients show classic hemodynamic abnormalities of clinically significant RV infarction. Right ventricular infarction with hemodynamic abnormalities accompanying inferior STEMI is associated with a significantly higher mortality (25% to 30%) than inferior MI alone.

RV infarction results from occlusion of right coronary artery proximal to the right ventricular branches. Majority of cases of RV infarction occurs in association with inferior wall infarction. Isolated RV infarction accounts for less than 2% of the total.

Physical findings: The diagnostic triad includes hypotension, clear lung fields and elevation of jugular venous pressure in the setting of an inferior wall infarction. Although this combination of findings is specific, it occurs only in less than a third of the cases.

ECG recorded with right precordial leads may show the features of RV infarction. Demonstration of 1 mm or more ST-segment elevation in lead V1 and in the right precordial leads V3R and V4R is the single most predictive ECG finding in patients with RV infarction (Fig. 124.7). The finding may be transient; half of patients show resolution of ST elevation within 10 hours of onset of symptoms. Echocardiography gives diagnostic findings. Right heart catheterization may be helpful in diagnosing RV infarction. Confirmation of the diagnosis can be made by radionuclide ventriculography. Complications include shock, which is uncommon but serious when it occurs, varying degrees of heart block, atrial fibrillation, atrioventricular asynchrony, septal rupture and development of right to left shunt through a patent foramen ovale.

Management: The principles of therapy include:

1. Maintenance of RV preload – maintenance of intravascular volume
2. Reduction of RV afterload – inotropes, and intra aortic balloon counter pulsation
3. Inotropic support to the failing myocardium, and
4. Early reperfusion – primary angioplasty or thrombolysis

Volume loading with IV normal saline helps to maintain RV preload. *Measures usually undertaken to treat LV infarction such as diuretics, nitrates and injection of morphine sulphate can reduce the RV preload and aggravate hypotension and shock.*

Inotropic support is given by infusion of dopamine or dobutamine in usual doses. If atrioventricular asynchrony occurs, it has to be corrected by A-V sequential pacing. Atrial fibrillation demands prompt cardioversion.

If there is concomitant LV failure the RV afterload is increased and this further depresses RV function. In such circumstances measures such as sodium nitroprusside infusion or an intra-aortic balloon counterpulsation which serves to improve LV function should be undertaken. Improvement in LV function automatically leads to fall in afterload as well.

Measures aimed at reperfusing the occluded coronary artery such as fibrinolytic therapy and emergency

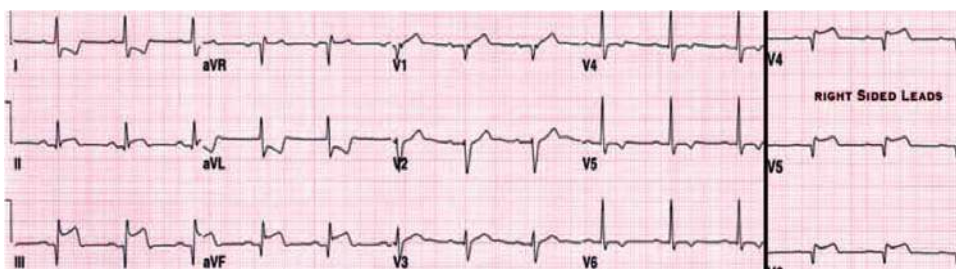


Fig. 124.7: ECG showing inferior MI with right ventricular MI. Note ST elevation in 2, 3, aVF, V1 and right chest leads. ST depression in I, aVL

angioplasty have been found to improve RV function early. Emergency revascularization by angioplasty improves survival.

Prognosis: When inferior myocardial infarction is complicated by RV infarction the mortality may go up to 30% compared to 6% in inferior infarction without involvement of the RV. In survivors of RV infarction generally the RV function recovers on follow-up.

**Stable Angina Pectoris
(Chronic Stable Angina)**

The term “angina pectoris” is used to denote the pain or discomfort produced by reversible myocardial ischemia brought on by exertion or emotion and relieved by rest. Coronary atherosclerosis is the most common cause. Other causes include aortic stenosis, aortic incompetence, syphilitic aortitis, polycythemia vera, rapidly developing anemia and others.

CLINICAL FEATURES

Ischemic cardiac pain starts and increases with exertion or emotion and forces the patient to stop activity. With rest the pain completely subsides within a few minutes. The quality of pain, its location and radiation are similar to that described under myocardial infarction, but it is milder. At times the manifestation may be only undue dyspnea or vague chest discomfort rather than clear cut pain.

Physical examination in between the attacks is unrewarding in most cases, but during the attacks of pain, elevation of blood pressure, a third or fourth heart sounds, and evidence of mitral incompetence due to papillary muscle dysfunction may be detectable.

Diagnosis: Angina pectoris should be diagnosed by history. Resting ECG may be normal in approximately half of patients with chronic stable angina. The most common ECG changes are non-specific ST –T wave changes with or without abnormal Q waves. During an episode of angina, ECG becomes abnormal in 50% or more patients with normal ECGs. Exercise ECG is helpful in those patients with chest pain and normal resting ECGs. The depression or elevation of the S-T segment during exercise are diagnostic of angina. The whole procedure has been quantitated by the treadmill test, in which the ECG response to graded exercise can be recorded. The pattern of ECG abnormality has been correlated with the severity of coronary artery occlusion. Myocardial perfusion imaging using radioactive isotopes and stress echocardiography are also useful in diagnosis of myocardial ischemia.

Prognosis: Annual mortality in patients managed by medical therapy is about 4%. The mortality is 3,7 and 11% with affection of one, two or three coronary arteries

respectively. Presence of resting ECG abnormalities and congestive cardiac failure worsen the prognosis.

MANAGEMENT

General measures include control of hypertension and diabetes, treatment of thyrotoxicosis and anemia, weight reduction, and avoidance of smoking and caffeine (coffee and tea in excess of 3 cups a day).

Drugs

Antiplatelet Agents

The use of aspirin is associated with a 33% reduction in the risk of adverse cardiovascular events. In the absence of contraindications, aspirin 75 to 150 mg daily should be used routinely in all patients with acute and chronic ischemic heart disease with or without manifest symptoms.

Lipid Lowering Agents

One percent reduction in total cholesterol would reduce coronary events by 2%. Continued treatment is associated with angiographically demonstrable arrest of progression, more stabilization and even regression of the plaque lesions and decreased incidence of clinical events. Both mortality rate and major coronary events are reduced by 30-35%. Lipid lowering therapy should be recommended even if the elevation of total cholesterol and LDL fraction is moderate. Statins (HMG – CoA reductase inhibitors) are the first choice drugs for the treatment of hyperlipidemia.

Anti-anginal and Anti-ischemia Therapy

Drugs in this group include mainly the beta adrenoreceptor blocking agents (beta blockers), calcium antagonists and nitrates. Other classes of drugs include: ACE inhibitors and metabolic agents.

Beta Blockers

Mechanism of action: Inhibition of beta-receptors cause decrease in heart rate, decrease in myocardial contractility and lowering of arterial pressure thus decreasing myocardial oxygen demand. Reduction in heart rate also increases diastolic interval thereby improving myocardial perfusion.

The beta blockers used commonly are:

Propranolol	20-80 mg twice daily
Metoprolol	50-200 mg twice daily
Atenolol	50-200 mg/day
Bisoprolol	5-20 mg/day

Other drugs such as nadolol, acebutalol, nebivolol are also available.

The goal is to reduce the resting heart rate to 50 to 60 per minute. Beta blockers reduce the rate of cardiac related

TABLE 124.2

Calcium antagonists		
<i>Dihydropyridine group</i>	<i>Dosage</i>	<i>Side effects</i>
1. Amlodipine	2.5-10 mg/d	Headache, edema of the legs and feet
2. Felodipine	2.5-10 mg/d	Headache, edema
3. Nicardipine	20-40 mg t.i.d	Headache, dizziness, flushing, edema
<i>Other groups of drugs</i>		
<i>Diltiazem</i>		
Immediate release	30-90 mg t.i.d	Hypotension
Slow release	60-180 mg b.i.d	Myocardial depression Bradycardia
<i>Verapamil</i>		
Immediate release	80-120 mg t.i.d	Myocardial depression
Slow release	120-480 mg/d	Bradycardia

TABLE 124.3

Commonly used nitrates		
1. Nitroglycerine	Sublingual tablets	0.3 to 0.6 mg upto 1.5 mg
	Buccal spray	400 µg as needed
	Transdermal	15 × 15 cm patch containing 7.5-40 mg
	Oral sustained release	2.5 mg-13 mg
	Buccal	1-3 mg 3 times daily
	Intravenous	5-20 µg/min
2. Isosorbide dinitrate	sublingual	2.5-15 mg
	Oral	5-80 mg, 2-3 times daily
	Buccal spray	1.25 mg metered doses
	Chewable tablets	5 mg
	Oral slow release	40 mg o.d or b.i.d
	Intravenous ointment	1.25-5 mg/h 100 mg/24 h
3. Isosorbide mononitrate	oral	20 mg twice daily 60-240 mg once daily

mortality, non fatal MI, and unstable angina. Beta blockers can be combined with nitrates. The advantages are:

1. Reflex tachycardia seen with nitrates is decreased
2. The increase in LV volume and diastolic pressure and wall tension associated with decreased heart rate caused by beta blockers is counteracted by concomitant use of nitroglycerin.

Side effects include fatigue, inability to perform exercise, lethargy, insomnia, nightmares, worsening of claudication and impotence.

Calcium Antagonists (Table 124.2)

Mechanism of action: Calcium antagonists inhibit calcium ion movement through slow channels in cardiac and smooth muscle membranes by noncompetitive blockade of voltage-sensitive L-type calcium channels. The three major classes of calcium antagonists are the dihydropyridines (nifedipine is the prototype), the phenylalkylamines (verapamil is the prototype), and the modified benzodiazepines (diltiazem is the prototype). All calcium antagonists exert a negative inotropic effect.

The newer second generation agents such as amlodipine, felodipine and others decrease coronary vascular resistance and increase coronary blood flow. They reduce myocardial oxygen demand primarily by reduction of systemic vascular resistance and arterial pressure. The negative inotropic effect of calcium antagonists like verapamil and diltiazem also decreases the myocardial oxygen requirement.

Hypotension, depression of cardiac function and worsening heart failure may occur during long-term treatment with all the calcium antagonists. Dependent edema may occur as a troublesome complication. This resolves on withdrawing the drug.

Nitrates

Clinical effects: In patients with chronic stable angina, nitrates improve exercise tolerance, time to onset of angina and ST segment depression during treadmill exercise test. Combination with beta blockers, or calcium antagonists enhance these beneficial effects (Table 124.3).

Contraindications: Nitroglycerine and nitrates are relatively contraindicated in hypertrophic obstructive cardiomyopathy because in these patients nitrates can increase LV outflow tract obstruction and can precipitate presyncope or syncope. It should also be avoided in cases of critical aortic stenosis.

Other Anti-anginal Agents

Nicorandil: A potassium channel activator, this has pharmacologic properties similar to those of nitrates and is effective in the treatment of stable angina.

Metabolic agents: Such as trimetazidine, ranolazine and carnitine have been observed to produce antianginal effects in some patients. They are still being investigated further.

Bradycardiac agents: Such as alinidine and zatabradin have been used for the treatment of stable angina. Other drugs such as ketanserin and ACE inhibitors have also been tried successfully.

Risk Factor Modification

1. Cessation of cigarette smoking
2. Management of hyperlipidemia
3. Control of hypertension
4. Control of diabetes mellitus

5. Treatment of obesity
6. Physical exercise—graded regimen
7. Relief of anxiety

Revascularisation procedures: Coronary revascularisation procedures like PCI and CABG are indicated when angina is refractory to medical management. They improve the quality of life and prolong survival.

Unstable Angina Pectoris

Introduction

Coronary artery disease presents a spectrum of conditions with acute transmural infarction at one end and non transmural infarction, unstable angina, chronic stable angina and silent ischemia at the other end. Unstable angina (previously also known as preinfarction angina, crescendo angina, acute coronary insufficiency and intermediate coronary syndrome) is at the centre of this spectrum.

Definition

The condition is diagnosed under the following circumstances:

1. Crescendo angina - angina that is more severe, prolonged or more frequent, superimposed on a pre-existing pattern of relatively stable exertion related angina pectoris.
2. Angina pectoris of new onset usually within one month
3. Angina pectoris at rest as well as with minimal exertion.

Classification

Based on the severity, clinical features, and response to treatment Braunwald *et al* have classified unstable angina as follows.

Based on Severity

Class I: New onset severe or accelerated angina

The duration is less than 2 months. Anginal attacks are more severe, more frequent occurring more than thrice a day and the threshold of exertion to cause angina is less. There is no rest angina.

Class II: Angina at rest—subacute

Patients with one or more episodes of angina at rest during the preceding month, but not within the preceding 48 hours.

Class III: Angina at rest—acute

Patients with one or more episodes of angina at rest within the preceding 48 hours.

Based on Clinical Circumstances

Class A: secondary unstable angina

This is a clearly distinct condition caused by extrinsic factors which worsen myocardial ischemia, e.g. anemia, infection, fever, hypotension, tachyarrhythmias, thyrotoxicosis, and hypoxemia secondary to respiratory failure.

Class B: Primary unstable angina

Class C: Post-infarction unstable angina. This occurs within 2 weeks of documented myocardial infarction

Based on Response to Intensity of Treatment

1. Absence of treatment or minimal treatment
2. Occurring in the presence of standard therapy with conventional dose of oral beta blockers, nitrates and calcium antagonists for chronic stable angina.
3. Occurring despite maximally tolerated doses of all three categories of oral therapy and intravenous nitroglycerine.

This classification can be correlated with the underlying disease. For example, class III patients are more likely to have intracoronary thrombus and heparin may be of greater value in such patients than in class I and II. A clinical score based upon this classification is available. It is an important predictor of intracoronary thrombus and complexity of the lesions.

Pathophysiology

The majority of patients with unstable angina have significant obstructive coronary atherosclerosis. Rupture or erosion of an atherosclerotic plaque with superimposed nonocclusive thrombus is by far the most common cause of unstable angina. The type of plaque that ruptures, the so-called vulnerable plaques, are usually lesions with less than 50 percent stenosis. A patient having a small increase in myocardial oxygen demand, in conjunction with a reduction in coronary blood flow due to the plaque rupture can lead to an episode of ischemia. Other important mechanisms contributing to aggravation of ischemia include platelet aggregation, thrombosis and coronary vasoconstriction.

Clinical and Laboratory Findings

Symptoms: The chest discomfort in unstable angina is similar in quality to that of classic effort induced angina, but it is more intense. There is an abrupt and progressive reduction in the threshold of physical activity required to provoke angina and this should be taken as a warning for the onset of unstable angina. Rest angina or nocturnal angina may occur in many cases. Radiation of pain to an additional site and onset of new associated features such as sweating, nausea, vomiting, palpitation and dyspnea should all be taken as suggestive symptoms.

Physical Examination

This may reveal non-specific findings such as transient third and fourth heart sounds, dyskinetic apical impulse suggesting left ventricular dysfunction, and transient murmur of mitral regurgitation during or immediately after an ischemic episode. Features of congestive cardiac failure may occur. There may be hypotension during the episodes of pain. These indicate adverse prognosis.

Electrocardiogram

In unstable angina, ST segment depression (or transient ST segment elevation) and T wave changes occur in up to 50 percent of patients. New ST segment deviation, even of only 0.05 mV, is a specific and important measure of ischemia and prognosis. T wave changes are sensitive but non-specific of acute ischemia. An unusual finding is the presence of transient inverted 'U' waves. Continuous ECG monitoring can be used for two purposes in unstable angina: (1) to detect arrhythmias in association with the acute episode and (2) to monitor the ST segment for evidence of recurrent ischemia.

Laboratory Parameters

- Cardiac troponin T and troponin I:
The degree of increase of troponins has prognostic implication in unstable angina.
- C-reactive protein: This is a sensitive indicator of inflammation and the level of this marker is correlated with adverse prognosis
- Serum amyloid A protein and
- Fibrinogen

Coronary Angiography

Three vessel disease is found in approximately 35%, two vessel disease in 25%, single vessel disease in about 25% and left main coronary artery disease in approximately 5-10%. Critical obstruction may not be demonstrable in any vessel in 15% of patients with unstable angina. Coronary angiogram demonstrating eccentric lesions with scalloped or overhanging edges are more characteristic of unstable angina.

Adverse Prognostic Factors

- Older age
- Continuing rest pain despite medical therapy
- Ischemia detected by Holter's monitoring
- Significant ST-T wave changes on electrocardiogram at initial presentation.
- Troponin -positive cases
- Levels of markers of inflammation such as C-reactive protein, serum amyloid A and fibrinogen
- Multivessel disease, presence of thrombus or complex coronary morphology at coronary angiography

Management

Comprehensive management of unstable angina or non-Q myocardial infarction (MI) include the following:

- Antithrombotic therapy including antiplatelet drug and anticoagulants
- Antianginal drugs
- Revascularization procedures
- Risk factor modification and pharmacologic measures to slow or halt progression of atherosclerosis.

Antiplatelet Agents

Aspirin is the drug of choice. It should be started in a dose of 162-325 mg given orally as early as possible. Maintenance dose of aspirin is 75-162 mg/day. Aspirin reduces the risk of myocardial infarction by 35% at 6 months and 40% at 1 year.

Clopidogrel is a thienopyridine derivative that inhibits platelet aggregation by inhibiting ADP action on platelet receptors. Recent studies have shown that addition of clopidogrel to aspirin in high risk unstable angina decreases the mortality and further cardiovascular events.

Other antiplatelet drugs are abciximab, eptifibatide and tirofiban which are inhibitors of glycoprotein IIb - IIIa receptors on platelets. Their indication is only under very special circumstances. These are highly expensive, and not freely available.

Anticoagulants

Heparin given in doses intended to keep the activated partial thromboplastin time at 1.5-2 times the normal value reduces the incidence of nonfatal MI from 1.9 to 1.2% and refractory angina from 22.9 to 9.6%. In the acute phase heparin is more effective than aspirin but a combination is even better. After the acute phase heparin is withdrawn and aspirin is continued. Low molecular weight heparin is found to be superior and easier to be administered than unfractionated heparin in unstable angina.

Direct thrombin inhibitors such as hirudin, hirulog and argatroban are effective anticoagulants which could be considered when heparin is contraindicated. These drugs are used only in limited situations at present.

Oral anticoagulants are not routinely used on a long-term basis. Thrombolysis is not indicated for patients with uncomplicated unstable angina. Combined prophylaxis with warfarin and antiplatelet drugs is more effective than using single drugs alone (see Chapter 165).

Antianginal Therapy

Nitrates, calcium channel blockers and beta blockers are used for this purpose.

Nitrates

They form the mainstay of therapy. Intravenous nitroglycerine controls the angina and prevents recurrence.

They also improve global and regional left ventricular function. Nitrates may be given sublingually, orally, topically or intravenously. Intravenous nitroglycerine is started in a dose at 5-10 µg/min by continuous infusion and increased by 10 µg /min every 5 to 10 minutes until relief of symptoms is achieved or limiting side effects appear. Headache, fall of systolic blood pressure below 90 mm Hg or more than 30% below the initial mean arterial pressure are indications for stopping the infusion. Patients controlled with intravenous nitroglycerine should be switched on to an oral or topical nitrate preparation when they are symptom-free for 24 hours. Tolerance to continuous intravenous nitroglycerine therapy develops within 24 to 48 hours.

Beta Adrenergic Blockers

These drugs are standard therapy for unstable angina. They reduce the risk of developing MI by 13%. For immediate effect intravenous esmolol or metoprolol can be used. This can be followed by oral drugs, the dose of which can be titrated to keep resting heart rate between 50 and 60/mt.

Calcium Channel Blockers

These drugs are as effective as beta blockers in relieving symptoms. They do not prevent the development of acute myocardial infarction or reduce mortality. Even an increased risk of MI has been reported if short acting nifedipine is used as monotherapy in unstable angina.

Diltiazem has been found to be effective in reducing reinfarction and post-infarction ischemia in non-Q MI. Calcium antagonists should be used as a second line therapy in patients with continued ischemia despite treatment with nitrates and beta blockers. Particular caution should be taken in adding a calcium antagonist to beta blocker in patients with left ventricular dysfunction.

The anti-anginal effects of nitrate, beta blockers and calcium channel blockers are often additive. Triple therapy is recommended in refractory unstable angina. Anti-thrombotic therapy is generally used concurrently.

Percutaneous Coronary Interventions

Patients with suspected unstable coronary syndromes should be assessed for the risk based on clinical history, physical examination and presenting electrocardiogram. Patients considered to be at low risk may be treated with nitrates, aspirin and beta blockers as outpatients. They can undergo stress testing after 48 hours and should undergo coronary angiogram if indicated. Medium and high risk patients should be admitted and treated aggressively with heparin, aspirin, clopidogrel, nitrates and beta blockers. Platelet receptor antagonists (GPIIb-IIIa) should be considered in higher risk groups. Cardiac catheterisation

and revascularisation should be performed early in the high and medium risk patients with elevated troponin levels. The sensitivity and specificity of diagnosis can be improved with addition of thallium imaging, SPECT imaging or stress echocardiography.

Role of Ventricular Assist Devices: Intra-aortic Balloon Pump (IABP)

This increases diastolic flow through the stenotic segment and this may prevent complete occlusion. It also improves ventricular function. IABP is extremely effective in controlling.

1. Recurrent ischemia, and
2. Complications in very high risk patients.

Upto 5% of patients may require IABP to control severe recurrent ischemia and to stabilize ventricular function.

Coronary Artery Bypass Grafting (CABG)

The subsets of patients in whom CABG offers better control of symptoms and survival benefits are those who have:-

1. Left main stem disease, and
2. 3-vessel disease with left ventricular dysfunction.

Risk Factor Modification and Pharmacological Measures

This includes cessation of smoking, control of hypertension and diabetes, lipid lowering, weight reduction and dietary modifications. Long-term treatment with aspirin, beta blockers and lipid lowering agents (statins) should be emphasized.

Measures to lower serum lipids should be undertaken in patients with dyslipidemias. Aim should be to keep LDL levels below 100 mg/dl. Drug therapy should be instituted also in marginally abnormal patients if other measures fail to control the lipid levels.

Statins are used more liberally in this group of patients. Statins have the additional benefit of stabilizing the plaques in the vessels.

Prinzmetal's Angina

(Syn) Variant Angina

In 1959 Prinzmetal *et al* described an unusual syndrome of cardiac pain secondary to myocardial ischemia that occurs almost exclusively at rest, not precipitated by physical exertion or emotional stress and also associated with ST segment elevation in the ECG. This is known as Prinzmetal or variant angina. It may be associated with acute myocardial infarction, severe cardiac arrhythmias including ventricular tachycardia and fibrillation as well as sudden death.

Pathogenesis

Angina is caused by spasm occurring in normal or diseased coronary arteries. Spasm is usually focal and involves a single site usually adjacent to an atheromatous plaque.

The possible mechanisms include

1. Hypercontractility of arterial wall associated with atherosclerotic process itself.
2. Endothelial injury.
3. Myocardial sympathetic dyssynergia.

Cigarette smoking, use of cocaine, hyperinsulinemia and insulin resistance are known risk factors. Anginal episodes show a circadian rhythm, peak attacks occurring during early morning hours between midnight and 8 am.

CLINICAL FEATURES

Patients with variant angina tend to be younger than patients with chronic stable angina or unstable angina and many do not exhibit classic coronary risk factors except that they are often heavy cigarette smokers. The anginal discomfort which is extremely severe may be accompanied by syncope, the latter presumably due to arrhythmias. Occasionally the angina is accompanied by other vasospastic disorders such as migraine and Raynaud's phenomenon.

Electrocardiogram

ECG changes are characteristic. The diagnostic feature is the elevation of ST segment during pain. A pattern of *alternating* ST segment elevation between the precordial and inferior leads is associated with angiographically documented multivessel spasm involving both the left anterior descending and right coronary systems. Conduction disturbances and ventricular arrhythmias may occur during the anginal attacks.

Arteriographic Studies

Spasm of a proximal coronary artery with resultant transmural ischemia and abnormalities in left ventricular function has been convincingly documented arteriographically and is the diagnostic hallmark of Prinzmetal angina. Significant fixed proximal coronary obstruction of at least one major vessel occurs in the majority of patients, and in these patients spasm usually occurs within 1 cm of the obstruction. The remainder has normal coronary arteries in the absence of ischemia.

Several provocative tests for coronary spasm have been developed.

1. Ergonovine test. This test has 100% sensitivity
2. Acetylcholine test, sensitivity 99%
3. Methacholine test

4. Miscellaneous: other provocative agents are exercise, cold pressor test and induction of alkalosis by hyperventilation.

Prognosis

Long-term survival is good. Survival at 5 years is 89-97%. The extent, severity and activity of coronary artery disease have adverse influence on prognosis for long-term survival and freedom from myocardial infarction. Nonfatal myocardial infarction occurs in up to 20% of patients and death in up to 10% during this period. Patients with variant angina are at a higher risk of sudden cardiac death.

Management

Drugs acting in Prinzmetal's angina bring about relief predominantly by the relief of coronary vasospasm

1. In Prinzmetal's angina nitrates are beneficial, the action being exclusively direct vasodilating effect of spastic coronaries.
2. Calcium antagonists are very effective in preventing the coronary artery spasm of variant angina and they should be used in maximally tolerated doses.

Calcium antagonists along with long and short acting nitrates are the mainstay of therapy. Even after surgical revascularisation procedures these drugs should be continued as maintenance therapy.

3. Beta blockers: Response to beta blockers is variable. They may even cause deterioration in Prinzmetal's angina.
4. Prazosin which is a selective alpha adrenoceptor blocker is beneficial in Prinzmetal's angina.
5. Aspirin in dose of 75 mg daily should be given. Larger doses of aspirin inhibit the synthesis of the naturally occurring coronary vasodilator prostacyclin. This may even increase the severity of ischemic episodes.
6. Coronary angioplasty and CABG are helpful in variant angina with discrete proximal fixed obstructive lesions. PTCA and CABG are contraindicated in patients with only isolated coronary artery spasm without accompanying fixed obstructive lesions.

ISCHEMIC CARDIOMYOPATHY

Multiple small infarcts and extensive diffuse fibrosis of the myocardium present a picture of cardiomegaly and congestive cardiomyopathy. There may be accompanying mitral incompetence. End stage ischemic cardiomyopathy is an indication for cardiac transplantation.

Asymptomatic Coronary Artery Disease

This is not uncommon even in apparently normal individuals. Routine stress testing may bring out the abnormality. Such cases may develop acute myocardial infarction or die suddenly as a result of ventricular fibrillation or cardiac arrest. Significant abnormalities in

the treadmill test are indications for coronary arteriography. Occlusion of the left main coronary artery or all the three vessels is an indication for early bypass surgery.

Prevention of coronary artery disease: Primary prevention can be achieved by:

1. proper dietary manipulation to avoid high intake of saturated fats, and overnutrition;
2. avoidance of smoking;
3. regular exercises; and
4. regular medical check-up.

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Diseases of the Myocardium

C.G. Bahuleyan, K. Suresh

Chapter Summary

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Endomyocardial Fibrosis	868

Myocarditis

ACUTE MYOCARDITIS

Myocarditis most commonly results from an infectious process, the most common being viral infection, specifically, Coxsackie B. Myocarditis can also be caused by radiation, chemicals, or hypersensitivity to drugs. In the majority of patients, active myocarditis remains unsuspected because the cardiac dysfunction is subclinical, asymptomatic, and self-limited.

Infection by cardiotropic viruses prompted the initial hypothesis that the viral infection was responsible for myocardial injury. However it was noted that cardiac dysfunction increased after the eradication of the infective agent and speculated that the pathogenesis may be due to the immunologic responses initiated by the virus. Demonstration of T-lymphocyte and macrophage infiltration, and a variety of cytokines known to depress myocardial contractility in endomyocardial biopsies of patients with active carditis strengthened the concept of immune-mediated injury. In addition to chronic inflammatory immune mechanism or persistent viral infection,

apoptotic cell death may be another mechanism by which myocarditis can result in cardiomyopathy. Several different viruses have been reported to be triggers for apoptosis.

Causes

1. Infectious:

Viruses

Coxsackie virus, adenovirus, echo virus, influenza virus, herpes simplex virus, varicella-zoster virus, hepatitis, Epstein-Barr virus, and cytomegalovirus, HIV, hepatitis (A and B), polio virus, mumps, rabies, respiratory syncytial virus, arbovirus.

Bacteria

Corynebacterium diphtheriae, Streptococcal and staphylococcal species, *Haemophilus influenzae*, *Bartonella*, *Brucella*, *Neisseria gonorrhoea*, *Actinomyces*, *Chlamydia spp*, *Treponema pallidum*, *Leptospira*, *Borrelia burgdorferi*.

Fungi

Candida spp, *Aspergillus spp*, Histoplasma, Blastomyces, Cryptococcus, Coccidioidomycetes.

Parasites

Trypanosoma cruzii, toxoplasma, schistosoma, trichinella.

2. Non infectious

Drugs causing hypersensitivity reactions

Antibiotics: sulfonamides, penicillins, chloramphenicol, tetracycline, amphotericin B.

Antituberculous: isoniazid, para-aminosalicylic acid

Anticonvulsants: phenytoin, carbamazepine

Anti-inflammatory: indomethacin, phenylbutazone

Diuretics: acetazolamide, chlorthalidone, hydrochlorothiazide, spironolactone

Others: lithium, doxorubicin, emetine, cocaine, numerous catecholamines, acetaminophen, zidovudine

Wasp, scorpion, spider stings

Radiation

Connective tissue disorders such as systemic lupus erythematosus (SLE), rheumatoid arthritis, dermatomyositis, Kawasaki disease, sarcoidosis, and giant cell arteritis.

Nutritional disorders: Deficiency of thiamine—beriberi.

CLINICAL FEATURES

Clinical manifestations of myocarditis are variable. Most patients have a self-limited disease, whereas others present in profound cardiogenic shock. The most obvious symptom suggesting myocarditis is an antecedent viral syndrome. Flu-like symptoms occur in approximately 60 percent of patients. Unexplained tachycardia, arrhythmias, hypotension, cardiomegaly, and evidence of cardiac failure occurring in the presence of any of the etiological disorders should suggest the possibility of myocardial damage. The disease process affects the impulse producing and conducting tissues and produces arrhythmias and varying grades of conduction defects. Sudden cardiac death can be the initial presentation of myocarditis in some patients, presumably from complete heart block or ventricular tachycardia. The ECG shows sinus tachycardia, non-specific changes in ST and T-waves, conduction defects, low voltage complexes and sometimes myocardial infarction pattern. X-ray may reveal cardiomegaly. Increase in CK-MB is observed in approximately 12 percent of patients. Troponin levels may also increase. Echocardiography can reveal left ventricular systolic dysfunction in patients with a normal-sized left ventricular cavity. Endomyocardial biopsy is the critical test to confirm the diagnosis.

Prognosis: Myocarditis is a serious condition associated with mortality. Death occurs as a result of sudden cardiac failure, heart block or fatal arrhythmias. The prognosis depends upon the extent of cardiac involvement and the underlying cause.

Management: The condition should be anticipated and early treatment instituted. The patient is put to absolute bed rest with cardiac monitoring in an intensive cardiac care facility. Complications such as cardiac failure, heart block, and arrhythmias are managed as they arise. Immunosuppressive therapy is not routinely recommended for infective myocarditis. Standard heart failure treatment remains the mainstay of therapy.

CHRONIC MYOCARDITIS

This condition may follow the acute condition or arise *de novo*. The clinical picture resembles one of cardiomyo-

pathy, but milder. Mainly it presents with cardiomegaly and congestive heart failure.

Cardiomyopathy

Cardiomyopathy is a primary disorder of the heart muscle that causes abnormal myocardial performance and is not the result of disease or dysfunction of other cardiac structures. Thus, the term *cardiomyopathy* excludes cases of myocardial failure due to myocardial infarction, systemic arterial hypertension, valvular stenosis or regurgitation and congenital heart disease.

The currently used clinical classification of cardiomyopathy was developed by the World Health Organization (WHO) and the International Society and Federation of Cardiology.

WHO Classification of Cardiomyopathy

Dilated cardiomyopathy This condition is characterized by dilatation and impaired contraction of the left or both ventricles.

Hypertrophic cardiomyopathy This condition is characterised by left and/or right ventricular hypertrophy, which is usually asymmetric and involves the interventricular septum. Typically, the left ventricular volume is normal or reduced. Mutations in sarcomeric contractile protein genes cause disease.

Restrictive cardiomyopathy This entity is characterised by restrictive filling and reduced diastolic volume of either or both ventricles with normal or near normal systolic function and wall thickness.

Arrhythmogenic right ventricular cardiomyopathy The disorder is characterised by progressive fibrofatty replacement of right ventricular myocytes.

Unclassified cardiomyopathies Unclassified cardiomyopathies include a few cases which do not fit readily with any group. e.g. fibroelastosis, systolic dysfunction with minimal dilatation, mitochondrial involvement, etc.

Specific cardiomyopathies

- Ischemic cardiomyopathy
- Valvular cardiomyopathy
- Hypertensive cardiomyopathy
- Inflammatory cardiomyopathy
- Metabolic cardiomyopathy
- General system disease
- Muscular dystrophies
- Neuromuscular disorders
- Sensitivity and toxic reactions
- Peripartal cardiomyopathy

Dilated Cardiomyopathy

Idiopathic dilated cardiomyopathy (IDC) is diagnosed by excluding significant coronary artery disease, valvular

abnormalities, and other causes. It is a relatively common cause of heart failure, with an estimated prevalence rate of 0.04 percent and incidence rates varying from 0.005 to 0.006 percent. The incidence increases with age, and males are afflicted at a higher rate than females. IDC may be familial in as many as 35 to 50 percent of the patients when first-degree relatives are carefully screened. Majority are autosomal dominant, due to mutations of the cardiac actin or desmin gene, but in the majority of cases the disease gene is still unknown.

CLINICAL FEATURES

Main symptoms are shortness of breath, orthopnea, dyspnea upon exertion, fatigue, palpitation and edema. Atrial fibrillation and ventricular dysrhythmias may be early signs of myocardial disease. Some patients may present with systemic embolism or stroke. On examination there may be tachycardia, narrow pulse pressure and jugular venous distension. There may be cardiomegaly, left ventricular third heart sound and murmurs of mitral and tricuspid regurgitation. ECG demonstrates sinus tachycardia or atrial fibrillation, varying degrees of ST-T wave changes and intraventricular conduction disturbances. Chest X-ray usually demonstrates left ventricular and left atrial enlargement. Echocardiography will show dilatation of left ventricle and left atrium and sometimes of right sided chambers, and left ventricular systolic dysfunction (Figs 125.1 and 125.2).

Management: In general, treatment consists of the use of ACE inhibitors in asymptomatic or symptomatic patients, the use of diuretics in volume-overloaded subjects, and the use of digoxin in subjects who remain symptomatic on the former medications. In mild to moderately symptomatic subjects, β -adrenergic blocking agents improve symptoms and reduce mortality. Adjunctive therapy includes anticoagulation in subjects

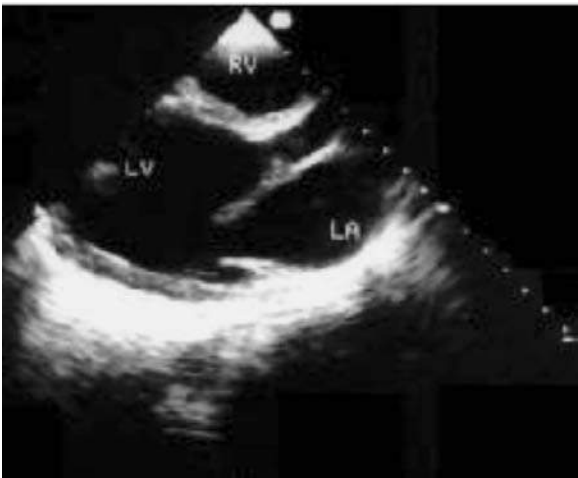


Fig. 125.2: 2D echo picture of a patient with dilated cardiomyopathy showing dilated left ventricle and left atrium LV – left ventricle, LA – left atrium, RV – right ventricle

with lower LV ejection fractions to prevent thrombo-embolic complications, amiodarone to treat symptomatic arrhythmias and maintaining potassium levels in the high normal (4.3-5.0 mEq/L) range. Those with malignant ventricular arrhythmias may benefit from implantable cardioverter defibrillator. Those who are resistant to medical therapy are candidates for cardiac transplantation.

Hypertrophic Cardiomyopathy (HCM)

K. Suresh

Known previously as idiopathic hypertrophic subaortic stenosis, HCM has a prevalence of 1/500 in the general population. HCM is genetically heterogeneous caused by mutations in any one of ten genes that encode contractile proteins of the cardiac sarcomere, involving thick filaments (beta-myosin heavy chains, and regulatory myosin light chains), thin filaments (cardiac troponin T, cardiac troponin I, ∞ - tropomyosin, and ∞ - actin), and cardiac myosin-binding protein C. More than 150 mutations involving the 10 genes have been reported. HCM has an autosomal dominant pattern of inheritance.

Location of genetic alterations and their relative frequency of occurrence in familial HCM.

Gene	Chromosome	Frequency (%)
B-Myosin heavy chain	14q1	35-45
Cardiac Troponin T	1q31	15
∞ - tropomyosin	15q2	5
Myosin binding protein C	11p 13-q 13	10

The clinical diagnosis of HCM is based on the most characteristic morphologic feature of the disease, i.e. thickening of the left ventricular wall associated with a



Fig. 125.1: Chest X-ray of a patient with dilated cardiomyopathy showing cardiomegaly, left and right atrial enlargement

non-dilated cavity in the absence of another cardiac or systemic disease capable of producing left ventricular hypertrophy (e.g. systemic hypertension or aortic stenosis). The most important features of HCM are (i) the heterogeneous nature of the left ventricular hypertrophy which predominantly involves the interventricular septum (IVS) and (ii) the dynamic left ventricular outflow tract obstruction caused by the systolic anterior motion of the anterior mitral leaflet.

Left ventricular hypertrophy is the gross anatomic marker of HCM. The distribution of hypertrophy is almost always asymmetric, with wall thickening dominantly involving the anterior interventricular septum (IVS). Dynamic obstruction to left ventricular systolic outflow develops. The main physiologic consequence is caused by the bulge of the asymmetric septal hypertrophy into the left ventricular outflow tract and the systolic anterior motion of the anterior mitral leaflet. In some patients the pattern of hypertrophy is diffuse, involving both septum and substantial portions of the lateral free wall. In some concentric left ventricular hypertrophy can be observed. In the generalized form the left and/or right ventricle show hypertrophy without obstructive features (Fig. 125.3).

The pathophysiological abnormalities determine the clinical outcome. These include:

1. LV diastolic dysfunction
2. LV dynamic outflow tract obstruction
3. Myocardial ischemia
4. Arrhythmias particularly AF, VT and sudden cardiac death.

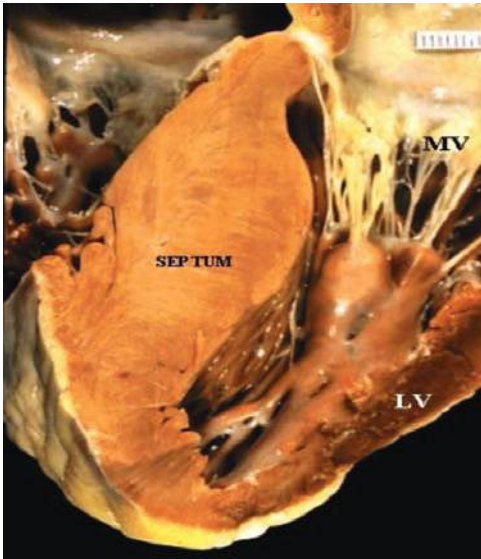


Fig. 125.3: Pathological specimen of hypertrophic cardiomyopathy showing asymmetric hypertrophy of IVS (ASH) and normal thickness LV free wall.

Septum – interventricular septum, LV–LV free wall, MV–mitral valve

Ref: J.P. Veinot: Cardiomyopathy and Pericardial diseases

Clinical Features

The onset of symptoms is often between 20 and 40 years of age, although they can become evident at any age. They include exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, fatigue, chest pain (which may be atypical of angina pectoris), and palpitation. Impaired consciousness including dizziness, near syncope, and syncope or sudden death may occasionally be the first manifestation.

Those with left ventricular outflow tract (LVOT) obstruction may have a brisk carotid pulse, double or triple apical impulse, fourth heart sound and the characteristic diamond shaped systolic murmur best heard at the lower left sternal border and apex.

Electrocardiogram shows left ventricular hypertrophy, ST-segment changes and T-wave inversion, left atrial enlargement, abnormally deep Q waves, and diminution or absence of R-waves in the right precordial leads. Chest X-ray may show cardiomegaly and pulmonary venous congestion.

Echocardiogram is the main diagnostic tool in HCM. The asymmetric hypertrophy of the septum (ASH) and the systolic anterior movement (SAM) of the anterior mitral leaflet can be visualized. In addition the dynamic LVOT obstruction can be quantified. Doppler echocardiography can assess the left ventricular outflow tract pressure gradient and values above 30 mm Hg across the aortic outlet are diagnostic.

Features which predict higher risk of major cardiovascular events in patients with HCM include the following:

1. Family history of sudden death
2. Specific mutations in sarcomeric proteins (e.g. Troponin T mutation)
3. History of resuscitation after cardiac arrest, recurrent syncope
4. Presence of ventricular tachycardia on Holter monitoring
5. Extreme left ventricular hypertrophy (>3 cm thick)
6. Rise in hemodynamic outflow pressure gradient >30 mm Hg
7. Fall in BP with exercise
8. Limitation of myocardial reserve and
9. Bridging of the left anterior descending coronary artery in children.

Prognosis

HCM may present with a fatal cardiac event as the first manifestation in an unsuspected case. A frequent cause for unexpected sudden death during competitive sports activities is HCM. In a low risk patient the overall annual mortality is <1%.

Management

Symptomatic patients with HCM may benefit by drugs such as beta-blockers, verapamil, and disopyramide. Judicious addition of diuretic agents in those with severe symptoms of heart failure despite treatment with beta blockers or verapamil leads to symptomatic improvement. Beta-adrenergic blocking agents or verapamil are usually efficacious in controlling heart rate in patients with chronic atrial fibrillation. If atrial fibrillation develops, anticoagulant therapy should be started and continued indefinitely. In those patients who are symptomatic despite medical management, septal ablation is one method which reduces the outflow gradient and the symptoms. This is a method to induce infarction of the hypertrophied septum by injecting alcohol into the septal artery. Surgical septal myomectomy may be required some patients (Morrow's operation). Infective endocarditis prophylaxis should be given to those with LVOT obstruction.

Competitive sports and strenuous, exertion should be avoided since sudden death may occur during these activities. All first degree relatives should be screened by echocardiography. In adolescents aged 12-16 years screening should be done annually. In those above 40 years screening can be done at longer intervals. Prophylactic measures include avoidance of dehydration and drug therapy using beta-adrenergic blockers.

Apical HCM

Hypertrophy confined to the left ventricular apex ("apical HCM") has been reported most commonly by Japanese investigators. It is characterized by isolated apical hypertrophy and is common in Japan where it constitutes 25% of all cases of HCM. Outside Japan it constitutes only 1-2% of cases. Clinical presentation is similar and patients experience chest pain, dyspnea, fatigue, and in rare instances, sudden death. The diagnosis is made by the typical electrocardiographic, echocardiographic and angiographic features. ECG shows giant negative T waves in precordial leads and LV hypertrophy. Echocardiogram shows localized hypertrophy in the distal left ventricle, increase in thickness in the apical region of at least 15mm, or a ratio of maximal apical to *postero basal* thickness greater than 1.5 and absence of outflow tract obstruction. LV angiogram shows spade like configuration of the LV cavity at the end of diastole, obliteration of apical LV cavity at the end of systole. Compared to the other forms of HCM prognosis is favourable. Treatment consists of β -blockers and calcium channel blockers.

Obliterative (Restrictive) Cardiomyopathy

The term *restrictive cardiomyopathy* refers to either an idiopathic or systemic myocardial disorder characterised

by impaired diastolic filling of ventricles, normal or reduced left ventricular (LV) and right ventricular (RV) volumes, and normal or nearly normal systolic (LV and RV) function. The hemodynamic and clinical manifestations may mimic those produced by constrictive pericarditis, which, in contrast to restrictive cardiomyopathy, is a surgically curable disorder.

Classification of Restrictive Cardiomyopathy

- **Idiopathic**
- **Specific heart muscle disease**
 - Endomyocardial fibrosis
 - Eosinophilic endomyocarditis
 - Infiltrative
 - ♦ Amyloidosis - common
 - ♦ Hemochromatosis (dilated left ventricle with restrictive physiology) – rare
 - ♦ Glycogen storage disease - rare
- **Iatrogenic**
 - ♦ Following heart transplantation
 - ♦ Following mediastinal radiation
- **Malignancy**
 - ♦ Metastatic endocardial and myocardial infiltration
 - ♦ Carcinoid heart disease

Endomyocardial Fibrosis

A particularly common form of this disorder is *endomyocardial fibrosis* (EMF), prevalent in Kerala, other states of India, Africa and Brazil. This condition is characterized by fibrosis and obliteration of the ventricular inflow tract and restriction to ventricular filling. Males are affected more, especially children and young adults and more among the poor. The etiological agent is not yet identified for certain, though several factors such as malnutrition, dietary deficiency of trace elements such as selenium, infection, filariasis, eosinophilic infiltration and an imbalance of trace elements (magnesium vs cerium) have been implicated. Pathologically the disease is characterized by fibrosis affecting the inflow tracts and apices of one or both ventricles; the endocardium and subjacent myocardium being affected. Combined right and left ventricular disease occurs in half of the cases, pure left ventricular involvement in 40% and pure right ventricular involvement in 10%.

Clinical Features

The onset is slow, and symptoms may be present for a few months to several years before presentation. Children and adolescents are affected more.

Left Ventricular EMF

Patients with left ventricular involvement present very early with varying grades of dyspnea and palpitation –

clinically they may resemble mitral incompetence. Physical examination reveals cardiomegaly, loud apical third heart sound and pansystolic murmur in the mitral area. Complications include pulmonary hypertension and left heart failure. ECG may reveal left ventricular hypertrophy. Myocardial calcification may develop and this may be detected by imaging studies. Echocardiography is diagnostic. The characteristic plastering of the posterior mitral leaflet to endocardium, the marked endocardial thickening, obliteration of cavity and sparing of outflow regions are typical of endomyocardial disease. Cardiac catheterization may reveal raised left ventricular end diastolic pressure and pulmonary hypertension.

Right Ventricular EMF

These cases develop features of right ventricular inflow tract obstruction resulting in back pressure in the right atrium which dilates to aneurysmal levels. Tricuspid incompetence may develop. The patients present with long duration of fatigue and abdominal distension due to



Fig. 125.4: 18 years old female with endomyocardial fibrosis



Fig. 125.5: X-ray chest in right ventricular EMF showing gross cardiomegaly and enlarged right atrium

hepatomegaly and ascites. Long standing cases may develop cardiac cirrhosis. Ascitic fluid shows high protein content. Physical examination reveals rise in JVP, loud third heart sound and features of tricuspid regurgitation. Atrial fibrillation, thromboembolism, pericardial effusion and cardiac cirrhosis may develop as complications (Fig. 125.4).

ECG may show qR pattern in right precordial leads, indicating right atrial enlargement. X-ray chest reveals gross cardiomegaly, mainly due to the aneurysmal right atrium (Fig. 125.5).

Echocardiography is diagnostic, with the RV cavity obliteration, dimpling of the apex, outflow dilation, and huge right atrial enlargement. Right ventricular end diastolic pressure is increased.

Differential diagnosis includes other forms of cardiomyopathy, pericardial diseases, infiltrative lesions of the myocardium and valvular heart disease. Biopsy studies help to exclude infiltrative diseases.

Treatment is symptomatic. Measures to control congestive heart failure using diuretics and inotropes help to relieve symptoms in early cases. Surgical excision of endocardium, valve replacement, etc. have been tried in selected cases.

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Diseases of
the Pericardium

C.G. Bahuleyan

Chapter Summary

Acute Pericarditis 870

Pericardial Effusion and Tamponade 871

Constrictive Pericarditis 872

The pericardium is the serous membrane covering the heart and the root of the great vessels. The visceral layer is closely apposed to the heart and the parietal layer encloses the pericardial space which contains a thin film of fluid which lubricates the surfaces. Function of the pericardium is to keep the heart in position and allow smooth and controlled movements within the thorax.

ACUTE PERICARDITIS

Acute fibrinous or dry pericarditis is a syndrome, resulting from pericardial inflammation of no more than 1 to 2 weeks duration and characterized by typical chest pain, a pathognomonic pericardial friction rub, and specific ECG changes. A variety of conditions are associated with acute pericarditis. However the majority of cases are idiopathic, i.e. no specific etiology could be identified with routine diagnostic testing. Most such cases are due to viral etiology.

Causes

1. **Idiopathic**
2. **Infections:**
 - a. Viral infections, e.g. Coxsackie B.
 - b. Bacterial infections, e.g. rheumatic fever, tuberculosis, pneumococci, staphylococci, streptococci, salmonellae, actinomyces, nocardia.
 - c. Protozoal, e.g. *E. histolytica*, toxoplasma. In tropical countries amebic liver abscess may give rise to pericarditis and effusion.
 - d. Fungal, e.g. histoplasmosis.
3. **Connective tissue disorders:**
 - a. Disseminated lupus erythematosus.
 - b. Rheumatoid disease.

- c. Scleroderma.
- d. Polyarteritis nodosa

4. **Myocardial infarction**
5. **Immune-mediated disorders:** Post-myocardial infarction and post-cardiotomy syndromes.
6. **Traumatic:** Blunt injury to chest, penetrating injuries, following paracentesis of pericardium.
7. **Metabolic disorders:** Uremia, myxedema.
8. **Malignancy:** Leukemias, lymphomas, secondary deposits from the primary tumours.
9. **Other causes:** Rupture of aortic aneurysm, dissecting aneurysm of the aorta, irradiation, cardiomyopathy.

CLINICAL FEATURES

Acute pericarditis typically produces sharp retrosternal pain that radiates to the trapezius ridge and is aggravated by lying down and relieved by sitting up; its onset frequently is heralded by a prodrome of fever, malaise, and myalgia. The pain of pericarditis is often worse with inspiration and is difficult to distinguish from pleurisy. The hallmark of acute pericarditis is the pericardial friction rub. It has a superficial, creaky, or scratchy character. It is usually heard between the lower left sternal edge and the cardiac apex with patient leaning forward. Pericardial rub usually has three components - during ventricular systole, during ventricular diastolic filling and during atrial systole, resulting in a triphasic rub. Sometimes it may be monophasic, with only the systolic component or it may be biphasic.

ECG is the most important diagnostic test in acute pericarditis. The ST-T wave changes in acute pericarditis are diffuse and have characteristic evolutionary changes. In the first stage, ST-segment elevations typically occur within a few hours of the onset of chest pain and persist for hours or days. In the second stage, the ST segments return to baseline and the T waves may appear normal or exhibit a loss of amplitude. In the third stage, tracings show inversion of T waves. The ECG normalizes in the fourth stage. In uncomplicated acute pericarditis, the chest radiograph is generally normal. An enlarged cardiac silhouette may occur because of a moderate or large

pericardial effusion. Echocardiographic identification of pericardial effusion confirms the clinical diagnosis of acute pericarditis, but a patient with purely fibrinous acute pericarditis often has a normal echocardiogram.

Treatment: Acute idiopathic pericarditis is a self-limiting disease in 70 to 90% of individuals. Symptomatic patients should be treated with NSAIDs. Aspirin 650 mg q3–4h or ibuprofen 600 to 800 mg q6h are the commonly used drugs. Narcotic analgesics may be required for severe pain. Those who do not respond to NSAIDs may require steroid therapy (prednisolone 60 to 80 mg/day) for a week to control pain, with the dose tapered rapidly thereafter. Patients in whom pericarditis is a manifestation of systemic illness, such as sepsis, uremia, connective tissue disease, or neoplasia, in addition to symptomatic treatment, therapy directed towards the primary disorder is required. If symptoms of pericardial tamponade develop, aspiration will be required.

PERICARDIAL EFFUSION AND TAMPONADE

Accumulation of transudate, exudate, or blood in the pericardial sac is a common complication of pericardial disease and should be sought in all patients with acute pericarditis. Idiopathic pericarditis and any infection, neoplasm, autoimmune diseases and radiation, which can cause acute pericarditis, can cause pericardial effusion. Effusions are common after cardiac surgery. Hydropericardium can occur in severe cardiac failure. Bleeding into the pericardial sac (hemopericardium) can occur following blunt or penetrating chest trauma and due to cardiac rupture in post – MI patients. Those effusions with high chance of progression to tamponade are caused by bacterial, fungal and HIV associated infections.

Clinical manifestations of pericardial effusion are highly dependent upon the rate of accumulation of fluid in the pericardial sac. Rapid accumulation of pericardial fluid may cause elevated intrapericardial pressures with as little as 80 cc of fluid, while slowly progressing effusions can grow to 2 liters without symptoms.

When sufficient amount of pericardial fluid accumulates, it can increase the intrapericardial pressure, cause obstruction to inflow of blood into the ventricles, fall in cardiac output and result in cardiac tamponade. In cases of trauma rapid accumulation of small quantity of blood can cause tamponade, while in cases of chronic effusions large quantity of fluid accumulates before tamponade develops.

Clinical Features

Many patients with pericardial effusion also have pericardial pain. However effusions do not by themselves cause symptoms unless tamponade is present. Patients with tamponade may develop dyspnea. They also have

chest tightness and dizziness. In the most severe cases, consciousness may be impaired, and except for the raised venous pressure, such patients appear to be in hypovolemic shock.

A careful general examination in case of pericardial effusion may give clue to the etiology. In effusions without tamponade CVS examination is normal, except in very large effusions where the cardiac impulse is difficult to palpate and heart sounds are muffled. If tamponade is present patient will be uncomfortable with dyspnea, tachypnea, diaphoresis, cold extremities, peripheral cyanosis and depressed sensorium, due to low cardiac output. Tachycardia is the rule. Hypotension is usually present. A paradoxical pulse is present in most cases. Paradoxical pulse is the exaggerated inspiratory fall in systolic blood pressure, often exceeding 10 mm Hg. Jugular venous pressure is markedly elevated and Y descent is absent. Normal decrease in venous pressure on inspiration is maintained. Physical examination reveals reduced force or absence of the apical impulse, enlargement of the area of cardiac dullness, muffled heart sounds and pericardial rub (Fig. 126.1).

ECG usually shows sinus tachycardia, reduced voltage and sometimes, electrical alternans of the QRS complex. In chest X-ray cardiac silhouette assumes a flask like appearance in moderate to large effusions. Echocardiography is the procedure of choice for the diagnosis of pericardial effusion. Pericardial effusion appears as an “echo-free” space between the visceral and parietal pericardium. Early diastolic collapse of right atrium and right ventricle seen in echo indicate presence of tamponade (Figs 126.2 and 126.3).

Management

In pericardial effusions without tamponade aim is to establish the etiology by a careful history including



Fig. 126.1: 14 years female with chronic pericardial effusion. The cotton seal is over the site of aspiration



Fig. 126.2: Chest X- ray in pericardial effusion showing flask shaped enlargement of heart and stenciled appearance of cardiac borders

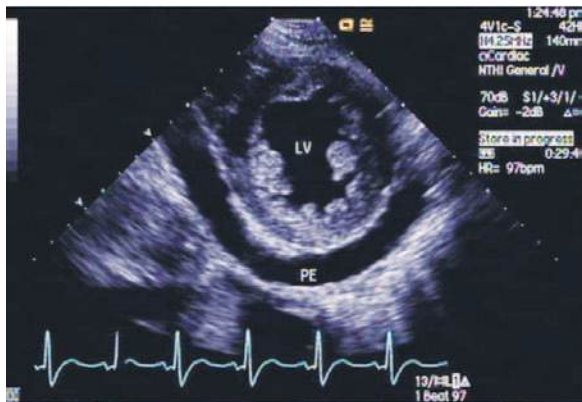


Fig. 126.3: 2D –Echocardiographic picture of pericardial effusion which is seen as echo free space behind the left ventricle. LV – left ventricle, PE – pericardial effusion

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medication review and radiation therapy, general physical examination and investigations. Depending on the circumstances, the investigations should include, skin testing for tuberculosis, screening for neoplastic and autoimmune diseases, infections and hypothyroidism. Drainage of the pericardial effusion is usually unnecessary unless purulent pericarditis is suspected or cardiac tamponade supervenes. If a definite etiology is not evident by non-invasive testing, pericardiocentesis is required.

Pericardial Aspiration

Those patients with tamponade should be considered as having a medical emergency. Volume expansion should be done with blood, plasma, dextran, or isotonic sodium chloride solution, as necessary to maintain adequate intravascular volume. Removal of pericardial fluid is the definitive therapy for tamponade. Removal of small amounts of pericardial fluid (~50 mL) produces consi-

derable symptomatic and hemodynamic improvement. Most commonly employed method for closed pericardiocentesis is the sub xiphoid approach. A 16- or 18-gauge needle is inserted at an angle of 30-45° to the skin, near the left xiphocostal angle, aiming towards the left shoulder. Surgical creation of a pericardial window, which involves the surgical opening of a communication between the pericardial space and the intrapleural space is sometimes required in recurrent effusions.

CONSTRUCTIVE PERICARDITIS

Constrictive pericarditis is a condition in which a thickened, scarred, and often, calcified pericardium forms a tough cover around the heart limiting diastolic filling of the ventricles. Although acute pericarditis from most causes may eventuate in constrictive pericarditis, the most common causes are idiopathic conditions, cardiac trauma and surgery, tuberculosis and other infectious diseases, neoplasms (particularly lung and breast), radiation therapy, renal failure, and connective tissue diseases. Rare causes include Dressler's syndrome, sarcoidosis, Whipple's disease, amyloidosis, methysergide therapy and dermatomyositis.

Patients generally complain of fatigue, dyspnea, weight gain, abdominal discomfort, nausea, increased abdominal girth, and edema. Physical findings include ascites, hepatosplenomegaly, edema, and, in long-standing cases, severe wasting. This general appearance often leads to an erroneous diagnosis of hepatic cirrhosis. Misdiagnosis is avoided through a careful examination of the neck veins. In constrictive pericarditis, the venous pressure is elevated and displays deep Y and often deep X descents. Kussmaul's sign is usually present. Often the heart is normal-sized. Infrequently a pericardial knock can be detected on auscultation infrequently.



Fig. 126.4: X- ray chest lateral view in constrictive pericarditis showing calcification around the cardiac silhouette (arrow)

Electrocardiogram will show atrial fibrillation in approximately one-third of cases. Low, QRS voltage, non-specific T-wave changes, and P mitrale are common. Chest X-ray usually shows normal or mildly enlarged cardiac silhouette. Pericardial calcification may be present, best seen in lateral view (Fig. 126.4). Echocardiographic findings of thickened pericardium, and abnormal Doppler flow patterns can point to the diagnosis of constriction. Computed tomography (CT) is a highly accurate method of evaluating pericardial thickness and therefore plays an essential role in the diagnosis and management of constrictive disease. Because of the close physiologic similarities of constrictive pericarditis and restrictive cardiomyopathy, increased pericardial thickness detected by CT scan is the most reliable means of distinguishing

between the two disorders, as normal pericardial thickness excludes most cases of constrictive pericarditis.

Treatment

Pericardiectomy is the definitive treatment for constrictive pericarditis. Surgery is not indicated in very early stages of constriction or in severe, advanced disease (functional class IV), when the risk of surgery is excessive. Medical therapy in constrictive pericarditis plays only a small role. In some patients, constrictive pericarditis resolves either spontaneously or in response to various combinations of nonsteroidal anti-inflammatory agents, antituberculous drugs, steroids, and antibiotics. Diuretics and, digoxin are useful in patients with atrial fibrillation who are not fit candidates for pericardiectomy.

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Cor Pulmonale

C.G. Bahuleyan

Chapter Summary

- Acute Cor Pulmonale 873
- Chronic Cor Pulmonale 873
- Pathophysiology 873
- Clinical Features 874
- Treatment 875

GENERAL CONSIDERATIONS

Cor pulmonale is the enlargement of the right ventricle secondary to diseases of the lung parenchyma, pulmonary circulation, thoracic cage or the mechanics of ventilation. Right-sided heart dysfunction secondary to left-sided heart failure, valvular dysfunction, or congenital heart disease is excluded in the definition of cor pulmonale. Cor pulmonale may be acute or chronic.

Refer also to Section: 14 : Chapter: 140

ACUTE COR PULMONALE

Acute cor pulmonale is acute dilatation of the right ventricle, RV will be dilated and its muscular wall is

stretched thin. This most often is the result of massive pulmonary embolism and this leads to right sided heart failure or shock.

Chronic Cor Pulmonale

Chronic cor pulmonale is defined as the occurrence of hypertrophy and dilatation of the right ventricle resulting from pulmonary hypertension, which occurs as a consequence of disease of the pulmonary parenchyma and/ or the blood vessels between the origin of the pulmonary artery and the termination of the pulmonary veins. Normally, the lung is perfused by the pulmonary arteries at a low pressure (10-20 mm Hg), this circulation serving the function of gas exchange. The bronchial arteries arising from the aorta supply blood at systemic arterial pressure to the lung parenchyma and air passages. Normally these two systems do not communicate directly.

PATHOPHYSIOLOGY

The final common pathophysiologic event that causes chronic cor pulmonale is pulmonary arterial hypertension,

that is, chronically increased resistance to blood flow through the pulmonary circulation. The increase in pulmonary vascular resistance can be caused by various mechanisms. The main pathophysiologic processes that cause elevation of pulmonary vascular resistance are:

1. Persistent vasoconstriction – due to global constriction of resistance vessels in pulmonary circulation due to persistent hypoxia as in conditions like high altitude dwelling, hypoventilation syndromes and chest deformities.
2. Loss of cross-sectional area of the vascular bed, which occurs in emphysema, lung resection, chronic thromboembolic disease, fibrotic lung diseases and cystic fibrosis.
3. Obstruction of large pulmonary vessels as a result of extrinsic compression of pulmonary arteries or veins by lymph nodes or tumours, fibrosing mediastinitis and pulmonary veno-occlusive disease.
4. Chronically increased blood flow through the lungs as in left to right shunts result in pulmonary hypertension, reversal of shunt and Eisenmenger's syndrome.
5. Pulmonary vascular remodeling, which occurs in primary pulmonary hypertension and collagen vascular diseases.

See also chapters 137 and 140.

Pathology: As a result of factors which clinically elevate pulmonary arterial tension the right ventricle dilates and hypertrophies. At some stage, the myocardium is unable to function at the high-pressure load, dilates, and fails. Any sudden rise in pulmonary tension resulting from factors like hypoxia tip the patient into right ventricular failure.

Dysfunction of the left ventricle occurs in some patients with cor pulmonale, but the evidence available indicates that cor pulmonale per se does not cause disease of the left side of the heart. Most likely left ventricular dysfunction coexisting with cor pulmonale results from other causes, such as coronary ischemia or systemic hypertension.

Chronic hypoxia gives rise to secondary polycythemia and increase in the viscosity of the blood. This causes further increase in the RV afterload. Hypercapnea and the resulting acidemia can directly depress the myocardium and can contribute to cardiac failure.

Causes

1. *Diseases of the lung parenchyma:*
 - a. Chronic obstructive pulmonary diseases—emphysema, chronic bronchitis, bronchial asthma.
 - b. Restrictive lung diseases—diffuse interstitial fibrosis, pulmonary hemosiderosis, radiation fibrosis, scleroderma.
 - c. Pneumoconiosis.
 - d. Bronchiectasis and cystic disease of the lungs.

2. *Diseases of the chest wall which restrict proper ventilation:* For example kyphoscoliosis, myopathies, myasthenia gravis, and extreme obesity.
3. *Diseases affecting the pulmonary arteries or veins:* Primary pulmonary hypertension, pulmonary arteritis, veno-occlusive disease, schistosomiasis, recurrent thromboembolism, sickle cell anemia.
4. *Diseases which depress the respiratory center resulting in diminution of the respiratory drive.*
5. *Chronic mountain sickness.*

CLINICAL FEATURES

Clinical manifestations of cor pulmonale are often obscured by the signs and symptoms of underlying disease and therefore are closely related to the pulmonary disease or disorder. There is no suggestive symptom, that is specific for cor pulmonale. Episodes of leg edema, atypical chest pain, dyspnea on exertion, exercise-induced peripheral cyanosis, prior respiratory failure, and excessive daytime somnolence are all historical clues suggesting the presence of cor pulmonale. Cough and complaints of easy fatigability are common. Some patients with nocturnal hypoventilation and sleep apnea may present with personality changes, mild systemic hypertension, and headache. Shortness of breath is nearly a universal symptom in cor pulmonale. Abdominal pain may result from liver and bowel congestion if RVF is present.

The patients are often cyanosed and the extremities are warm due to vasodilatation. In overt RVF, cardiac enlargement, distended neck veins, hepatomegaly, and peripheral edema are present. The earliest signs are those associated with long standing pulmonary hypertension. The most sensitive sign for pulmonary hypertension is a loud pulmonary component (P_2) of S_2 , and right parasternal heave may be present. Pulmonary ejection click and right ventricular S_3 gallop may be heard. With very high pulmonary artery pressures (PAP), characteristic diastolic and systolic murmurs of pulmonary regurgitation and tricuspid regurgitation may develop.

Investigations: Hemoglobin may be considerably increased due to secondary polycythemia. X-ray chest may reveal the pulmonary abnormality. There may be right ventricular and PA enlargement. Right descending PA diameter greater than 16 mm suggests severe pulmonary hypertension. ECG diagnosis of RVH in cor pulmonale is usually difficult due to hyperinflated lungs. Atrial fibrillation and multifocal atrial tachycardia may be seen particularly in those with COPD. Features of RVH may be present and include right axis deviation, P pulmonale, and tall R waves in V_1 and deep S waves in lead V_6 . Echocardiography is often difficult because of the hyperinflated lungs is a poor conductor of ultrasound. Echocardiogram will show dilated and hypertrophied right ventricle and dilated right atrium. Pulmonary artery

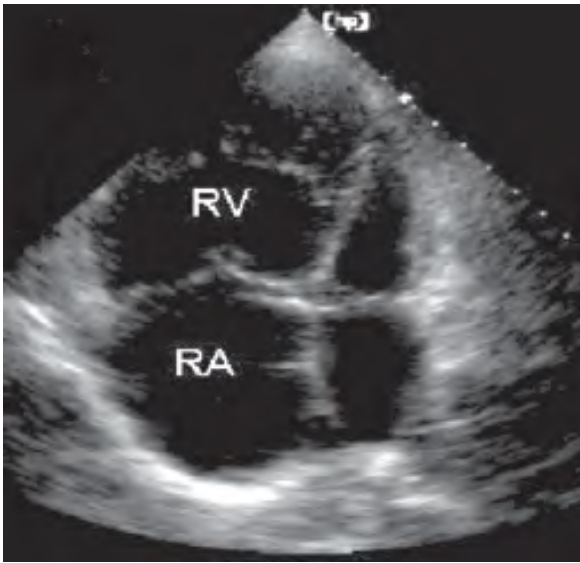


Fig. 127.1: 2D Echocardiogram in cor pulmonale showing dilated right ventricle and right atrium
RV – right ventricle, RA – right atrium

pressure can be measured using echo – Doppler studies (Fig. 127.1). Investigations to assess ventilatory function, diffusing capacity of the alveoli and pulmonary vasculature are indicated to determine the nature and extent of pulmonary lesion. Blood gas analysis, arterial oxygen and carbon dioxide and estimation of pH and plasma bicarbonate serve to determine the severity of anoxia, hypercarbia and respiratory acidosis.

Course and prognosis: Prognosis depends more on control of the underlying lung disease than on control of pulmonary hypertension in most cases. The pink puffers tend to live longer than the blue bloaters. Once right heart failure develops, prognosis is poor. Patients with COPD requiring oxygen supplementation have 2-year survival of 50%, but some patients survive for 5 to 8 years.

TREATMENT

Treatment of the underlying lung disease is the focus of therapy and is the best way to reduce the pulmonary hypertension. If right heart failure has not appeared, a major goal is to prevent its onset by treatment of lung disease.

Measures to Reduce Pulmonary Hypertension

Relief of hypoxia is of prime importance in reducing pulmonary hypertension, both to prevent and to treat cor pulmonale. This may be done in two ways: (1) treatment of the underlying disease and (2) O₂ administration.

In COPD, alveolar ventilation may be improved by measures such as bronchodilators for bronchospasm,

antibiotics to prevent or treat acute exacerbations of bronchitis, bronchial toilet for removal of secretions, and avoidance of airway irritants such as tobacco smoke. Corticosteroids may be helpful in some patients with interstitial lung disease and in patients with a bronchospastic component of COPD. Measures should be instituted to treat the systemic disease in which obliterative vascular disease is associated or to prevent further pulmonary emboli if this is the problem.

Most patients with chronic cor pulmonale have a component of hypoxic pulmonary vasoconstriction, and all patients should be treated with oxygen in amounts adequate to restore arterial O₂ tension to greater than 60 mm Hg.

Pulmonary vasodilators like prostacyclins and nitric oxide are efficacious in some patients with primary pulmonary hypertension but are of unproven value in cor pulmonale from COPD. Epoprostanol (prostacyclin), given I V as continuous infusion in a dose of 2.4 ng/kg bw per minute, reduces pulmonary artery pressure. This may be tried in severe cases. Epoprostanol is available as Flolan, Glaxo welcome research, Triangle Park NC (USA).

Endothelin receptor antagonists e.g. Bosentan, has been approved for use in severe PAH, especially PPH, because of the role of endothelin in producing pulmonary vasoconstriction. It can produce hepatic dysfunction. It has to be used on a long-term to produce the benefit. It is costly and not freely available. Long-term anticoagulation with warfarin has been reported to prolong survival, since this may slow the downhill course of the disease. Calcium channel blockers, especially nifedipine in doses of 10 mg bd or tid have been reported to be beneficial. Cardiac failure is controlled by the use of diuretics, aminophylline and digoxin.

Treatment of Heart Failure

While treatment of the lung disease and relief of hypoxia are necessary to reduce cardiac work, general principles of management of heart failure apply. Beneficial effects of digitalis are not as obvious as in LVF, and arrhythmias caused by digitalis may occur at relatively low serum levels in patients with hypoxia and acidosis. Nevertheless, studies have shown that digitalis improves right ventricular function in cor pulmonale, and it is an appropriate drug for treatment of RVF when given with care and at controlled dosage levels. Diuretics are effective in the treatment of RVF, and indications for their use are the same as in other forms of heart disease.

When the hematocrit is above 55 to 60 percent, phlebotomy may reduce pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR) and possibly improve right ventricular function. Phlebotomy should be done cautiously in small volumes (200-300 mL).

Surgical Treatment

Pulmonary embolectomy is extremely efficacious for unresolved pulmonary emboli causing chronic thrombotic pulmonary hypertension. Single-lung, double-lung, and heart-lung transplantations are all used for salvage in the terminal phase of several diseases complicated by cor

pulmonale. The diseases most commonly treated by lung transplantation are primary pulmonary hypertension, emphysema, idiopathic pulmonary fibrosis, and cystic fibrosis. Volume-reduction surgery for selected patients with emphysema improves ventilatory function and gas exchange, and the long-term benefit of this approach is under study.

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Diseases of the Aorta

C.G. Bahuleyan

Chapter Summary

- Takayasu's Arteritis 876
- Dissecting Aneurysm 877
- Aneurysms of the Aorta 879
- Cholesterol Crystal Embolism 880

Non-specific Aortoarteritis

13

An idiopathic inflammatory process involving the aorta and its major branches may occur as a primary abnormality as in Takayasu's arteritis or it may occur in association with conditions such as scleroderma, Hodgkin's disease or rheumatoid arthritis. It may produce stenosis of aorta and its major branches or dilatation of aortic root with aortic regurgitation or aneurysm of thoracic or abdominal aorta.

Takayasu's Arteritis

Syn: Pulseless disease, young female arteritis, or Harbitiz-Raedu syndrome

This condition is named after the Japanese ophthalmologist who first described changes in the central vessels of the retina in 1905. Women are affected 8 times more than men. More than half the patients are under 20 years of age. The disease is prevalent in India, Japan, south east Asia, south and east Africa, south America, and Mexico. Aorto-arteritis is the common form of large vessel

vasculitis seen in north Kerala. It is also a common cause of renovascular hypertension. Type III aorto arteritis was the most frequent form.

ref: Jacob BS and Krishnan R. abstract of IRACON 2002 JI. Ind Rhem. Asso. 10, suppl. Page 10.

Takayasu's disease is a chronic vasculitis mainly involving the aorta and its main branches such as the brachiocephalic, carotid, subclavian, vertebral and renal arteries as well as the coronary and pulmonary arteries. Chronic vasculitis involves the intima, media and adventitia. The etiology is not fully known. Symptoms are caused by stenotic lesions or thrombus formation. More acute progression leads to destruction of the media and consequent aneurysm formation and arterial rupture.

Pathology: The histological findings include panarteritis, fibrous scarring, intimal proliferation, thrombosis, and aneurysm resembling syphilitic aortitis, but there is no clinical or serologic evidence to suggest syphilitic etiology even remotely. Current thinking favours an autoimmune process to be operative.

In addition to the aorta, arteries of the neck, renal arteries and arteries of the lower limbs are also frequently affected. These may lead to strokes in the young, renal hypertension, limb ischemia and thromboembolic episodes. In India, renal artery involvement is one of the frequent causes of renal hypertension.

Clinical features: The early symptoms are non-specific. These include fever, myalgia, arthralgia and vague symptoms. The ESR and C-reactive protein levels are

raised in the early stages. Even at this stage MRI, CT, angiography or digital subtraction angiography may show lesions. Clinical presentation with arterial occlusion occurs later.

The presenting symptoms may be those associated with hypertension, viz. headache, giddiness, palpitation, congestive heart failure and pulmonary edema. Depending on the site of lesions, clinical manifestations may vary. When the arch and its vessels are involved, symptoms are due to ischemia to the brain and upper extremities. Pulse is absent in the upper limbs and there is hypertension in the lower extremities (reversed coarctation). Signs of aortic regurgitation may be present.

The middle aortic syndrome: This is the most prevalent type in India and is produced by involvement of the descending thoracic or abdominal aorta with or without stenosis of the renal arteries or left subclavian. This picture may mimic congenital coarctation but presence of abdominal, subclavian or carotid bruit, difference in blood pressure between the upper extremities, claudication in the lower limbs, and absence of collaterals around the scapula and rib notching suggest the diagnosis of aortoarteritis. Angina pectoris due to coronary arterial involvement, abdominal angina due to mesenteric involvement, and pulmonary artery involvement occur uncommonly. Early occurrence of unilateral cataract is more often seen in Indian patients.

Aortography is diagnostic. Hematological and serological investigations are not helpful in establishing the cause.

The clinical course is variable. In some the course is protracted, in the others it is self-limiting. Death is due to hypertensive complications or a cardiomyopathy-like picture.

Management: In established cases surgical treatment may have to be considered as a palliative measure, especially in localised lesions. Early institution of steroid therapy and low dose aspirin has been advocated. Immunosuppressant drugs are added on to the regimen in selected cases. The results are not uniformly predictable.

Dissecting Aneurysm of the Aorta

Definition: aortic dissection is a catastrophic illness characterized by dissection of blood between and along the laminar planes of the media, with formation of a blood filled channel within the aortic wall. This will lead to creation of a dissecting intramural hematoma. It will often rupture causing massive hemorrhage.

Causes

1. Hypertension: More than 90% of the patients suffer from chronic hypertension.

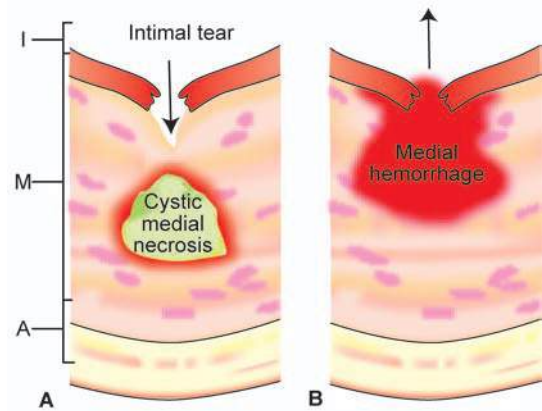


Fig. 128.1: Proposed mechanisms of initiation of dissection

2. Conditions that cause cystic medial necrosis, e.g. Marfan's syndrome, Ehlers-Danlos syndrome, pregnancy.
3. Other structural disorders of the aorta: coarctation of the aorta, aortic hypoplasia, aortic stenosis, bicuspid aortic valve, syphilitic aortitis, giant cell arteritis.
4. Trauma: Blunt trauma to the chest in automobile accidents, e.g. steering wheel injury, iatrogenic causes such as femoral artery cannulation. Men are affected twice as common as women.

Pathogenesis

Aortic dissection is believed to begin with the formation of a tear in the aortic intima that directly exposes an underlying diseased medial layer to the driving force of the intraluminal blood. This blood penetrates the diseased medial layer and cleaves the media longitudinally, there by dissecting the aortic wall (Fig. 128.1).

CLINICAL FEATURES

The symptoms start with sudden onset of severe pain in the chest, interscapular region, neck, mid-back, abdomen, sacral region, and lower limbs. The pain may be mistaken for myocardial infarction. Unlike the pain of acute myocardial infarction, the chest pain produced by aortic dissection is usually abrupt in onset, very severe from the start and unremitting. Rarely dissections involving ascending aorta will involve coronary artery ostium producing acute myocardial infarction. Several other manifestations may develop. These include syncope, blindness, dyspnea, nausea, vomiting, hematemesis, melena, oliguria, hematuria and paresis or paralysis of lower extremities.

Physical examination: The blood pressure may be elevated, or the patient may be in shock dissection flap can occlude the ostium of left subclavian artery and lead to absent pulse in left upper limb. Asymmetry of pulses and difference in blood pressure (anisophygmy) between two upper limbs helps to clinch the diagnosis. Aortic

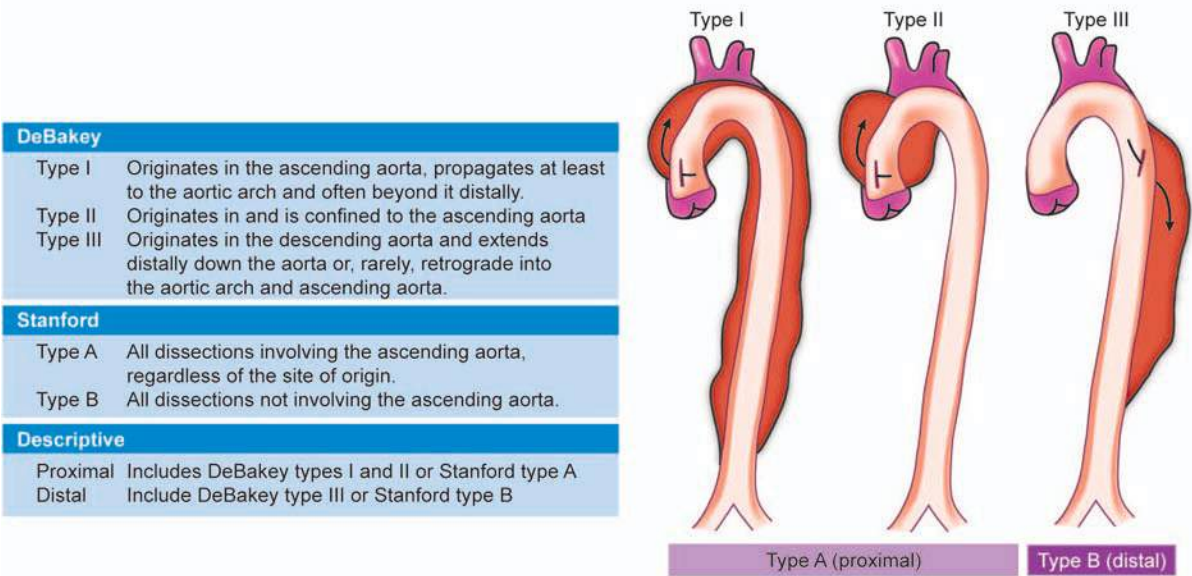


Fig. 128.2: Classification of dissecting aneurysms

regurgitation may develop giving rise to the characteristic early diastolic murmur in the aortic area. The jugular vein may be engorged unilaterally. Other features include leftsided hemothorax, cardiac tamponade, silent abdomen due to paresis of intestines, presence of arterial bruits and variable neurological deficits.

Diagnosis: Aortic dissection should be suspected in all cases of intense chest pain associated with signs of shock, especially if the clinical features and ECG do not suggest myocardial infarction. X-ray chest may show widening of mediastinal shadow (Figs 128.3 and 128.4). Trans-esophageal echocardiography is helpful to make a bedside

diagnosis. Contrast enhanced CT gives excellent resolution to clearly delineate the dissection. Dissecting aneurysms have been classified in different ways (Fig. 128.2).

Course and prognosis: In extensive dissection, death occurs due to shock or rupture into the pericardium and pericardial tamponade.

Treatment: Supportive care includes careful monitoring of blood pressure, maintenance of fluid intake and output, and control of the blood pressure with a negative inotropic agent such as trimethaphan or a combination of sodium nitroprusside and propranolol. Drugs like hydralazine which increase the velocity of ventricular ejection, favour

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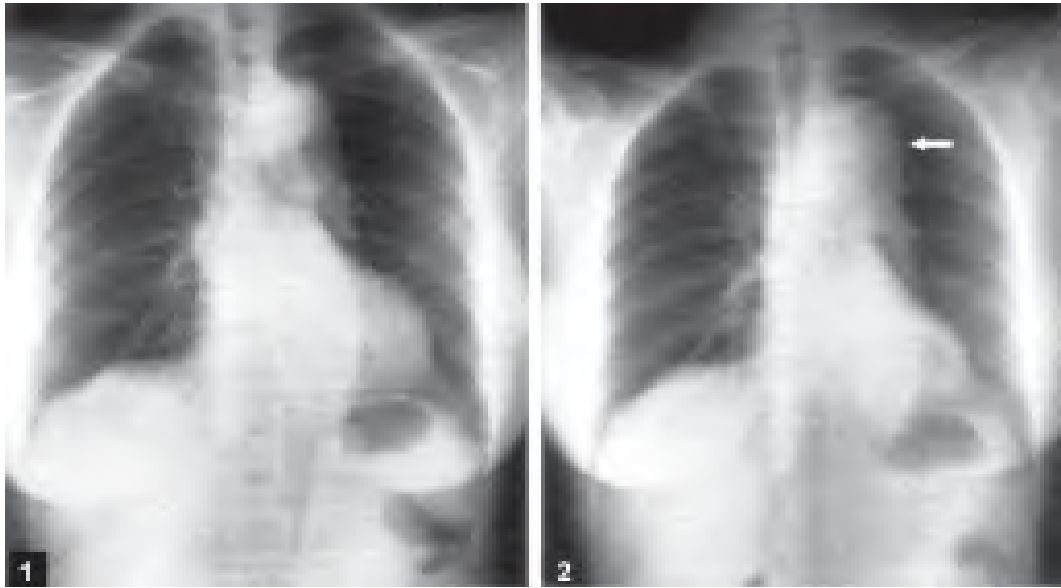


Fig. 128.3: Chest X-ray of patient with dissection of the aorta (1) Original X-ray taken 2 years previously (2) Note the widening of the aortic knuckle—arrow

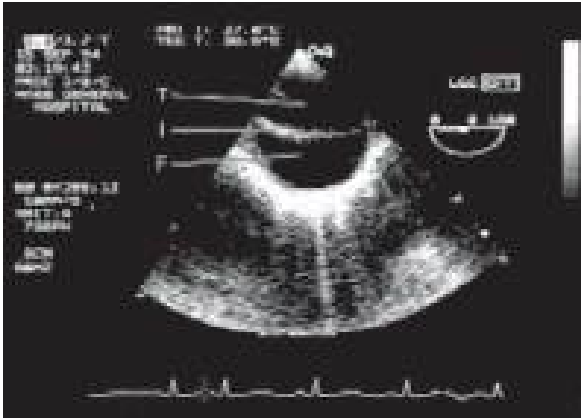


Fig. 128.4: Transesophageal echogram
Note: T—true lumen F—false lumen I—flap of intima

progression of dissection and, therefore, these should be avoided. Once the medical condition is stabilized, surgery (resection and prosthetic reconstruction of the aorta) is undertaken, but mortality remains high. If medical treatment fails to arrest progression, emergency surgery may be required.

Dissection of the ascending aorta, irrespective of whether it originates there or extends from other sites is most likely to be fatal due to rupture into the pericardium. Such patients should be taken up for immediate surgery. When the dissection is confined to the descending aorta close monitoring and medical therapy are indicated.

Aneurysms of the Aorta

Definition: The term *aortic aneurysm* refers to a pathological dilatation of the aortic lumen involving one or several segments. One useful criterion defines aortic aneurysm as a permanent dilatation of the aorta having a diameter at least 1.5 times that of expected normal diameter of that given aortic segment. Morphology of an aortic aneurysm is typically either fusiform, which is more common or saccular.

Seventy-five percent of all aneurysms involve the abdominal aorta and the commonest site is below the renal arteries. The vast majority are caused by arteriosclerosis. In 60% of cases there is associated hypertension. Next in frequency to be affected is the descending thoracic aorta. The causes include arteriosclerosis, traumatic false aneurysms, tertiary syphilis and mycotic aneurysms. The most frequent cause of aneurysms of the ascending aorta is cystic medial necrosis secondary to Marfan's syndrome. Other causes, include Ehlers-Danlos syndrome, hypertension and aging. Syphilis used to be a frequent cause when this disease was more prevalent. Aneurysms of the aortic arch are the least frequent, and they are caused by arteriosclerosis or tertiary syphilis.

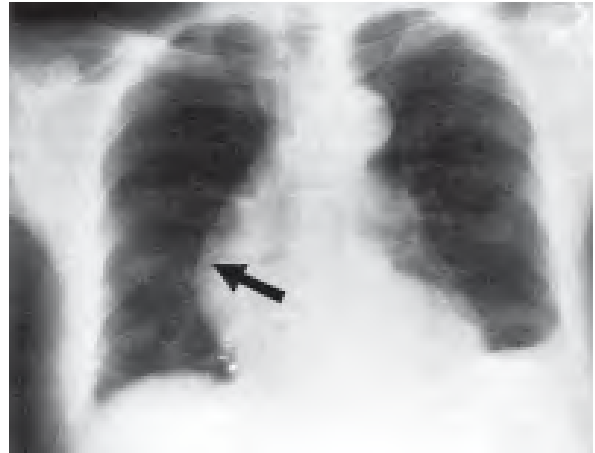


Fig. 128.5: CXR of a patient with aneurysm of ascending aorta. Note: bulge of the right cardiac border and widening of the upper part of the cardiac shadow (arrow)

Clinical features: Majority of aortic aneurysms, regardless of their location are asymptomatic. They are discovered accidentally when being evaluated for other diseases. When these aneurysms suddenly enlarge or rupture, they produce dramatic symptoms. Rapidly enlarging aneurysms produce severe pain depending on the location. On examination a pulsating mass is discovered. Thoracic aortic aneurysms produce pressure symptoms by impingement on other structures. It can produce compression of superior vena cava and produce SVC syndrome (non pulsatile engorgement of jugular veins with congestion), compression on recurrent laryngeal nerve can produce hoarseness of voice. Can cause traction on trachea and cause characteristic sign i.e. tracheal tug. Ruptured aneurysm should be suspected if the patient presents with severe pain followed by shock. Pulsating mass is no longer palpable. Rupture into esophagus will present as massive hematemesis, while rupture into pleural or peritoneal space would present as hemothorax or hemoperitoneum.

Investigations: CXR may show aneurysms and calcification along its margins (Fig. 128.5). Computerized tomography is the investigation of choice and it clearly delineates the extent, size and integrity of the aneurysm. Magnetic resonance angiography (MRA) is an alternative for the preoperative evaluation of aortic aneurysms. Aortography has several limitations and its use in the evaluation of aortic aneurysms have declined (Fig. 128.6).

Natural history: Rupture is the most frequent cause of death and occurs in 40-70%. Untreated, the 5-year survival rates for thoracic, thoraco-abdominal and abdominal aneurysms range from 13-39%. Aneurysms of the arch grow faster than those of the ascending and abdominal aorta. Aneurysms greater than 6 cm in diameter have faster growth rates and higher tendency to rupture. Coexistence of hypertension and cardiac ischemia worsen the prognosis.

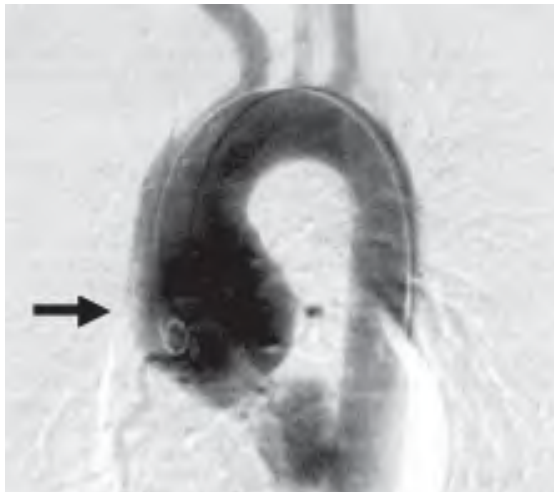


Fig. 128.6: Aortogram of a patient with aneurysm of ascending aorta. Note: the increase in diameter of the ascending aorta beyond the valve (arrow)

Treatment: Treatment depends on the site involved, size of the aneurysm and the propensity for rupture. All thoracic aneurysms larger than 6 cm and those producing symptoms should be repaired with Dacron graft. If patient

has Marfan's syndrome, then aneurysm should be repaired if it is ≥ 5 cm. Abdominal aortic aneurysms should be repaired if it produces symptoms or ≥ 5.5 cm in size. Surgery for ruptured aneurysms carry a high mortality.

Cholesterol Crystal Embolism

This occurs when cholesterol crystals derived from atheromatous plaques existing in the major arteries embolise. The precipitating events are vascular surgery, angiography, angioplasty or institution of anticoagulant therapy. Typical features include ischemic damage to the kidneys or livedo reticularis especially in the legs, gangrene of toes in the presence of normal arterial pulsations of the feet, hypertension and splinter hemorrhages. Blood counts show eosinophilia. Renal failure occurs in 50% and intestinal bleeding in 10%.

Less common features include ischemic pancreatitis, cholecystitis and localised polypoid lesions in the colon. Reported mortality is 60-80%. Morbidity is considerable. Biopsy of skin lesions is diagnostic in cholesterol crystal embolism. Treatment consists of supportive measure, cessation of anticoagulant therapy and institution of corticosteroids in selected cases.

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Cardiac Surgery

13

C.G. Bahuleyan

Chapter Summary

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At present cardiac surgery has reached a very high level of technical perfection. This has been made possible by advancements in anesthesia, maintenance of extracorporeal circulation by pumps and oxygenators, hypothermia,

methods to control cardiac arrhythmias, better methods of myocardial preservation, availability of newer prosthetic materials and progress in intensive postoperative care including circulatory assist devices.

Surgical treatment is available for the following conditions.

- Congenital heart diseases
- Acquired valvular diseases
- Ischemic heart disease
- Constrictive pericarditis
- Cardiac tumours
- Heart block and serious arrhythmias—pacemaker implantation.

- g. Correction of abnormal conducting tissues in the heart producing recurrent tachyarrhythmias e.g. WPW syndrome.
- h. Endomyocardial fibrosis
- i. Cardiac tamponade
- j. Cardiac aneurysms
- k. Cardiogenic shock not amenable to inotropic drugs—balloon counterpulsation, urgent revascularisation.
- l. Resistant and fatal cardiac failure — Transplantation.
- m. In addition, in several acute conditions such as rupture of valves or chordae, obstruction of aorta and pulmonary artery, traumatic lesions and infective endocarditis resistant to medical therapy, emergency surgical measures may be required.

Congenital Heart Disease

Most of the congenital heart diseases are amenable to surgical correction or palliation now, the present stress being on early detection and correction of congenital cardiac defects. Pediatric cardiac surgery, especially in infants and neonates has so progressed that defects like ventricular septal defects, Fallot's tetralogy, aortic stenosis, transposition of great arteries, tricuspid atresia and total anomalous pulmonary venous drainage are all operable in infancy or early childhood.

Life-saving palliative surgical procedures may be required in the neonates in the first few days of life in conditions which threaten life, e.g. transposition of great vessels, Hypoplastic left heart syndromes.

Definite corrective surgical treatment is undertaken at a later date. In many situations when functional two ventricular circulation can not be achieved, bypassing the right ventricle by anastomosing the vena cava to the pulmonary artery, i.e. total cavopulmonary connection (TCPC) is done. This achieves good functional capacity. Such circulation where in the right ventricular function is bypassed is called Fontan circulation.

Coronary Artery Surgery

The technique of coronary artery bypass using saphenous vein grafts was a epoch making discovery in the management of severe ischemic heart disease. At present coronary revascularization procedures include coronary angioplasty, and bypass surgery. In the surgical procedure, blood from the aorta is diverted through a conduit to the coronary artery distal to the occlusion. The common materials used are the saphenous vein, and the internal mammary artery. Synthetic prosthetic materials are also being tried upon. Revascularization procedures promptly relieve angina, reduce the extent of infarction and reinfarction, improve the quality of life and also prolong life compared to medical therapy in a selected subset. In good

centres, the intra and perioperative mortality is less than 3%.

Long-term results are good. Percutaneous angioplasty techniques are undergoing refinement and perfection. Except in a few situations, angioplasty is able to achieve effective revascularization. In complicated lesions, methods such as rotator atherectomy, laser atherectomy and stenting help to achieve success. The major disadvantage of angioplasty namely re-occlusion has been brought down to a great extent by the routine use of stents which help to retain the lumen patent for considerably longer periods. Use of newer antiplatelet drugs such as glycoprotein receptor antagonists have further reduced the occurrence of acute and delayed thrombotic occlusion of the stents. The newer interventions are highly successful but the escalation of cost is a deterrent. Irradiation of the coronary arteries after stenting, and impregnation of the stent with rapamycin or taxols help to reduce the incidence of re-occlusions.

At present the major surgical load in cardiovascular surgery is contributed by coronary revascularization procedures.

Surgery for Chronic Valvular Diseases

Hemodynamically significant valvular heart disease tends to progress with time in many cases and end up with cardiac failure if the valvular abnormality is not corrected. All the acquired and congenital valvular diseases are amenable to surgical correction. Stenotic lesions are corrected by valvotomy which can be done either by a closed or open heart procedure. Valve tissue which is not grossly damaged and which will lend itself to dilatation can be corrected by this method. Balloon valvotomy is a standard procedure for the management of pulmonary stenosis and mitral stenosis.

Valve replacement has to be undertaken for regurgitant lesions and when the valve tissue is grossly damaged. Prosthetic valves are in use for about forty years. The most commonly used valves are the Starr-Edward's ball in cage valve and Bjork-Shiley's tilting disc valve, though several others are also available. Tissue valves obtained from cadavers or from pig's aorta and valves made from tissues like dura mater, pericardium and fascia lata are also employed at times, depending on the individual circumstances. Each type of valve has its own advantages and problems. Main problems include thromboembolism, infective endocarditis, obstruction to the valve, valve degeneration and chronic hemolytic anemia. Patients with implanted valves have to take life-long anticoagulant therapy. This may pose an additional risk of bleeding in them. They all have to take prophylaxis against infective endocarditis.

From time-to-time there have been reports of failure of the different makes of valves. Indian made valves (Chitra valves) are available at lower costs than imported valves. The results are comparable to other valves, even though surgical experience is less, compared to the imported valves.

Reports of large series on valve surgery reveal that over 90% of them are well at five years and over 70% of them are well at ten years follow-up. Among those with implanted artificial valves 38% of deaths are valve problem related, 20% are due to other cardiac causes, which are not directly attributable to the valve. The remaining die of non-cardiac causes.

At present facilities for cardiac surgery are available in several centres in India. The bulk of the work is for the management of coronary artery disease, valvular heart disease and congenital heart disease.

Cardiac Assist Devices

Several attempts have been made from time-to-time to assist the failing ventricle to increase its output. From the early part of this decade, artificial hearts have been implanted into individuals suffering from irrecoverable congestive cardiac failure and the initial success in keeping such patients alive for weeks to months have encouraged the development of newer and newer devices.

Artificial hearts made of inert chemical substances are now available. Maximum clinical experience has been with Jarvik-7, developed by the cumulative efforts of William Kolft, Donald Olson and Robert Jarvik, and the surgical experience of William DeVries and his associates. This device has been used as a permanent cardiac replacement and life has been prolonged for twenty months or more, though complications are frequent. The main use of such artificial devices is to support a moribund patient with a definitely fatal cardiac failure till the time of cardiac transplantation.

Cardiac Transplantation

Cardiac transplantation has emerged as a definite therapeutic procedure with definite indications. At present several hundreds of cardiac transplantations are done in many centres in the world every year. The survival at the end of four years is above 75% in patients treated with the immunosuppressant drug cyclosporin A, tacrolimus, mycophenolate mofetil and others. Cardiac transplantation provides an advantage over implantation of an artificial heart in giving freedom from being tethered to an external support. In the United States alone there are more than sixty centres which undertake cardiac transplantation. Cardiac transplantation can be considered as a rational and socially acceptable therapy for a limited number of patients with irrecoverable cardiac failure under certain special conditions. The techniques of cardiac transplantation have improved progressively for the past twenty years. These advances include better definition of criteria for selection of patients, more effective immunosuppression, improved myocardial preservation and better surgical techniques. The introduction of cyclosporin A as an immunosuppressant has improved the 5-year survival of transplant recipients from 40% in 1984 to over 75% at present. Though a very effective immunosuppressant drug, cyclosporin A does produce grave complications. Newer immunosuppressants solve this problem partially. The excellent rehabilitation that follows heart transplantation returns over 80% of survivors to their previous occupations and earning capacity. The heavy cost (US \$ 70,000) is certainly a wise investment, if facilities permit. This technique is available in India in a few centres.

The first successful heart transplant was done at the All India Institute of Medical Sciences at New Delhi in September 1994. Since then more than 38 transplants have been done, 20 at AIIMS, 15 at Madras, 2 at Cochin and one at Bangalore.

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Hypertension 884

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Many cardiovascular disorders like ischemic heart disease, hypertension, rheumatic heart disease, congenital heart disease and cardiomyopathy are preventable to a great extent by therapeutic intervention and alteration in the lifestyle. The management of these diseases once established is at best only partly successful and associated with high cost. Therefore, the science of preventive cardiology has grown remarkably in the recent past.

Coronary Heart Disease

There are two approaches of prevention (1) Primary, and (2) Secondary. Primary prevention includes modification of atherogenic risk factors prior to the development of clinical evidence of the disease. Secondary prevention includes methods adopted to prevent recurrences or delay progression of the disease in patients with clinically manifest coronary heart disease.

Primary prevention: Modifiable risk factors: *Plasma lipids:* The relation of plasma cholesterol to the development of atherosclerotic coronary heart disease and to coronary mortality is already established. Higher levels of plasma cholesterol cause higher risk. The relationship between dietary cholesterol and the plasma cholesterol is also well established; the higher the dietary cholesterol content, greater the serum level of cholesterol. Adjustment in the total calorie intake and reduction of saturated fat content in the diet can lower serum level of cholesterol and thereby arrest the progression and also lead to regression of coronary atherosclerosis. It has been found that specific lipid subfractions are involved in the pathogenesis and is considered targets of treatment. Low density lipoprotein (LDL) is the primary lipoprotein which is associated with atherogenesis. High density lipoprotein

(HDL) which scavenges the cholesterol to liver is considered 'good cholesterol'. Adult treatment panel III (ATP III) has recommended guidelines for evaluation and treatment of hypercholesterolemia.

Detailed recommendations are available for the various risk categories regarding ideal levels of total cholesterol, LDL cholesterol and HDL cholesterol. These may be referred to, for further details. In general, total cholesterol < 200 mg/dL, LDL cholesterol total < 100 and HDL cholesterol above 50-60 are desirable.

Regular physical exercise also helps to reduce total serum cholesterol triglycerides and other lipid fractions. Increased consumption of fish and fish oils which contain eicosapentaenoic acid and docosa-hexaenoic acid help to lower low density lipoproteins (LDL) and elevate high density lipoproteins (HDL), in the plasma, thus reducing the atherogenic risk further.

First step in the management of high lipid levels would be to initiate therapeutic life style changes (TLC).

This includes the following.

- A. **Dietary modification:** Saturated fat < 7% of the total calories, cholesterol < 200 mg/day, soluble fiber 10-25 g/day
- B. **Weight reduction** by 5-8% and
- C. **Increased physical activity** walking 3 km/in 35-40 minutes daily or at least 5 session a week.

In selected cases where the general measures do not achieve the full target levels, drug prophylaxis should be started. Drugs used for this purpose include the statins, bile acid sequestrants, nicotinic acid and fibric acids. Details are given in Section: 10 Chapter: 93. The metabolic syndrome is a constellation of risk factors, which in concert increase the risk for atherogenesis. For details refer to Section: 10 Chapter: 93.

Metabolic syndrome: Metabolic syndrome is a constellation of risk factors which in concert increase the risk for atherogenesis: For further details refer to Section: 10 Chapter: 93.

Cigarette smoking: Smoking increases the risk of coronary heart disease. Cessation of smoking brings down the

incidence of myocardial infarction as well as sudden death. After smoking is discontinued the coronary risk is decreased by about 50% within one year. The risk approaches that of non-smokers within 2-10 years. The cessation of smoking also increases the HDL:LDL ratio. (see Chapter 26).

Hypertension

Elevated systolic or diastolic blood pressure is an independent contributor to coronary risk, especially in people with hypercholesterolemia. It is advisable to control hypertension along with modification of other risk factors to minimize progression of coronary atherosclerosis.

Reduction in dietary intake of salt and foods containing high content of saturated fat instituted from childhood may be useful in preventing the onset of hypertension. This becomes more important especially in predisposed individuals with positive family history. There is evidence of a direct relation between serum lipids and blood pressure, independent of other variables such as age and body mass index. In some families hypertension may be present in several siblings, who also show elevation of low density lipoproteins (LDL) and triglycerides. Many trials have shown that reduction of cholesterol by diet and/or drugs lead to 25% reduction in the incidence of hypertension and reduction in nonfatal myocardial infarction in men. Regular exercise programmes, treatment of obesity and moderation of alcohol consumption, help to lower the blood pressure and reduce its ill effects. Yogic exercises, transcendental meditation and participation in leisure activities are also helpful.

Secondary prevention: These methods are undertaken in patients who have already developed clinical ischemic heart disease. Methods to salvage the myocardium include the use of drugs like anti-platelet drugs and beta blockers or interventional treatment like coronary angioplasty and coronary artery bypass surgery. Since the mortality and morbidity from acute myocardial infarction depends mainly on the quantum of myocardial damage, all the methods adopted to reduce the infarct size such as thrombolytic therapy, angioplasty, or myocardial revascularization surgery undertaken in the acute stage also can be included under secondary prevention.

Other recently identified atherosclerotic risk factors include the following: Management of these is given in the appropriate sections.

- High level of CRP
- Increase in lipoprotein LP(a)
- Alterations in tissue plasminogen activator and Plasminogen activator inhibitor levels
- Low density lipoprotein
- Increase in fibrinogen levels
- Other risk factor are also being detected.

Cardiomyopathy

The preventive aspect assumes an important role in hypertrophic cardiomyopathy which is transmitted as autosomal dominant. Genetic counselling may help to reduce the birth of affected children.

Deficiency of nutritional factors such as selenium and probably infection has been implicated in the etiology of endomyocardial fibrosis. Further studies are in progress.

Respiratory System

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Respiratory System:
General Considerations

C. Sudheendra Ghosh, Ronald Win B

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General Considerations

INTRODUCTION

The main function of the respiratory organs is to provide a constant supply of oxygen to the tissues and to remove carbon dioxide from them through the lungs. Ultimately this gas exchange occurs between the alveolar air and mixed venous blood in the capillaries across the alveolocapillary membrane. The alveolocapillary membrane has a total area of 75 m² in an adult. Air is taken in through the air passages comprising the nose, pharynx, larynx, trachea, bronchi, and the bronchioles. The terminal portions of the air passages—the respiratory bronchioles and alveolar ducts—subserve the function of gas exchange. The part above the vocal cords is termed the upper respiratory tract and the parts below form the lower respiratory tract.

The trachea which is 11 cm long is kept permanently open by the presence of C-shaped cartilages on its wall. Several mucous glands present in the mucous membrane provide mucus which moistens the surface and facilitates ciliary action. The trachea divides into the right and left bronchi.

The bronchi are similar to the trachea in structure. The right main bronchus is 1-2.5 cm in length and it is in direct line with the trachea. This fact makes it more vulnerable for obstruction by foreign bodies entering through the trachea. The right main bronchus divides into branches which supply the right upper lobe, middle lobe, and lower lobe. The left main bronchus is longer (5 cm) and it forms an angle of 50°-100° with the right main bronchus. It divides into two branches which supply the upper and lower lobes. Further division of the lobar bronchi gives

rise to segmental bronchi which supply bronchopulmonary segments (Figs 131.1 and 131.2).

Bronchopulmonary segments: The bronchopulmonary segment is a wedge of lung tissue supplied by each bronchus along with the corresponding branches of the pulmonary artery and vein. The bronchopulmonary segments act as independent units and are separated by fibrous septa (Table 131.1).

Divisions of the bronchial tree: After 8-13 successive divisions the segmental bronchi break up into the smallest bronchi. They continue further as bronchioles. The bronchioles have no cartilage and mucous glands on their walls. The bronchioles divide further and the terminal

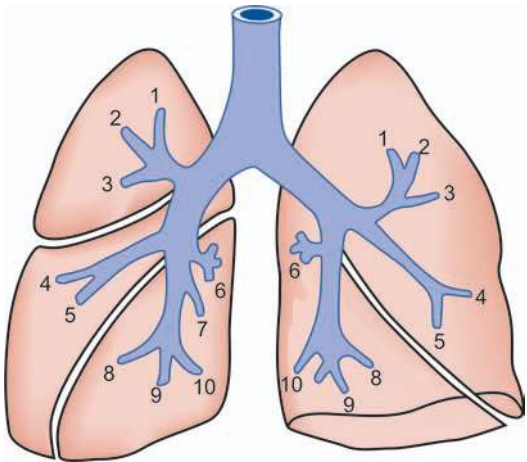
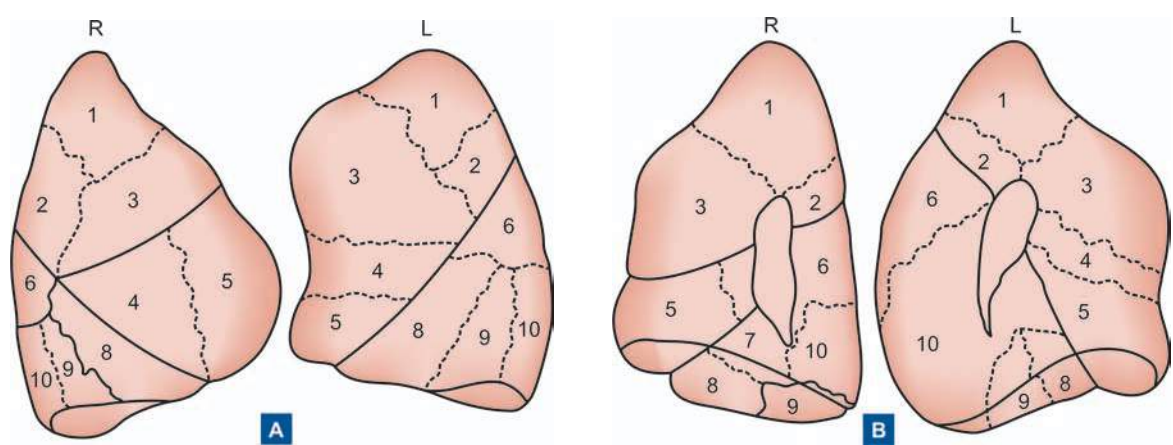


Fig. 131.1: Divisions of bronchi

Right upper lobe	Left upper lobe
1. Apical	1. Apical
2. Posterior	2. Posterior
3. Anterior	3. Anterior
Right middle lobe	Lingular lobe
4. Lateral	4. Superior
5. Medial	5. Inferior
Right lower lobe	Left lower lobe
6. Apical lower lobe	6. Apical lower lobe
7. Medial basal	—
8. Anterior basal	8. Anterior basal
9. Lateral basal	9. Lateral basal
10. Posterior basal	10. Posterior basal



Bronchopulmonary segments marked on the surfaces of the lungs

Fig. 131.2A: Lateral surfaces

Fig. 131.2B: Medial surfaces

- Right

 - 1. Apical
 - 2. Posterior
 - 3. Anterior
 - 4. Superior (of Lingula)
 - 5. Inferior (of Lingula)
 - 6. Apical lower lobe
 - 8. Anterior basal
 - 9. Lateral basal
 - 10. Posterior basal
- Left

 - 1. Apical
 - 2. Posterior
 - 3. Anterior
 - 4. Superior (of Lingula)
 - 5. Inferior (of Lingula)
 - 6. Apical lower lobe
 - 8. Anterior basal
 - 9. Lateral basal
 - 10. Posterior basal

Segmental bronchi and the named bronchopulmonary segments	
Right upper lobe	Left upper lobe
Apical	Apico-posterior
Posterior	Anterior
Anterior	
Right middle lobe	Lingula
Lateral	Superior
Medial	Inferior
Right lower lobe	Left lower lobe
Apical	Apical
Anterior basal	Anterior basal
Lateral basal	Lateral basal
Posterior basal	Posterior basal
Medial basal or cardiac	—

bronchioles are formed after the fourth division. The terminal bronchioles give rise to respiratory bronchioles. Alveoli begin to appear on the walls of the respiratory bronchioles. As the respiratory bronchioles divide further, the number of alveoli arising from them progressively increases. Normal adult lung contains about 300 million alveoli. Rapid division of the respiratory bronchioles results in enormous increase in surface area. The terminal portions of the respiratory bronchioles divide into alveolar ducts and sacs. Alveoli are 0.1-0.2 mm in diameter. Up to the respiratory bronchioles the airways only conduct

air passively, but beyond this they also take part in gaseous exchange. The part supplied by a single terminal bronchiole is called an “acinus”. An alveolar duct with its distal connections is called a “primary lobule”. A group of primary lobules separated by connective tissue septa form a “secondary lobule”.

Pores of Kohn and Canals of Lambert: Pores of Kohn are openings connecting alveoli, which allow communication between them and sometimes even between adjacent segments.

Canals of Lambert are short communications lined by epithelium which exist between distal bronchioles and some of the neighbouring alveoli. These take part in collateral ventilation between different regions of the lung. The lining of the trachea, bronchi, and bronchioles consists of ciliated columnar epithelium containing goblet cells. The respiratory bronchioles are lined by non-ciliated cuboidal epithelium. The lining epithelium of the alveoli is flattened and it comprises two types of cells—type I and type II pneumonocytes arranged on a basement membrane. Type I pneumonocytes are numerous and they cover most of the inner surface of the alveoli. Gas exchange occurs mainly across these cells. Type II pneumonocytes are smaller in number. They contain lamellated osmiophilic inclusion bodies which are thought to be of lysosomal nature. Surfactant is produced or stored in them.

Secretions of the airways and ciliary action: Mucus is secreted by the mucous glands and goblet cells. Mucous glands are seen all along from the trachea to the smallest bronchi. They are most numerous in the medium-sized bronchi and are absent from bronchioles. In the bronchioles there are only a few goblet cells. Vagus is secretomotor for the mucous glands. The goblet cells respond to direct irritation. The mucus contains acid and neutral polysaccharides mainly, and variable quantities of sodium, potassium, albumin, globulin, specific antibodies, lysozyme, and transferrin. In addition to its antibacterial action, the mucus provides a milieu for the cilia to function. Ciliary action helps to remove particulate matter. Each cell contains about 200 cilia, each being 6-7 μ long. By successive rhythmic movement, they produce a wave motion passing regularly from cell to cell. An optimum amount of mucus of the correct thickness (5 μ) and optimum viscosity is essential for proper ciliary function. Drying up of tracheal secretions, increase in thickness and viscosity of the mucus layer, inhalation of irritants, excessive intake of alcohol and drugs like cocaine impair ciliary function and predispose infection of the respiratory tract. Ciliary function is impaired in inherited disorders such as Kartagener's syndrome in which several other defects including loss of motility of the sperms are seen.

Surfactant: This is a substance produced by type II pneumonocytes from the 30th week of intrauterine life. It lines the alveoli. It contains an insoluble lipoprotein (dipalmitoyl lecithin) which forms a thin layer at the air-fluid interface and lowers surface tension. Pulmonary surfactant is a mixture of phospholipids and surfactant-specific proteins which reduce alveolar surface tension during respiration. Specific proteins (SP) A, B, C and D contribute to the biophysical properties of surfactant. SP-A, and SP-D also have antimicrobial properties. In infant respiratory distress syndrome surfactant is deficient from birth. In adult respiratory distress syndrome surfactant deficiency develops as an acquired defect caused by sepsis, pneumonia, traumatic damage and major surgery. Surfactant has beneficial therapeutic effects only if it contains the phospholipid as well as the specific proteins. Activated neutrophils clear the surfactant and lead to its dysfunction. Surfactant prevents the alveoli from collapsing by reducing surface tension within the alveoli. Absence of surfactant results in the collapse of small alveoli during expiration and hyperinflation of the larger alveoli during inspiration, in addition, increase in surface tension leads to transudation of fluid from capillaries into the alveoli. Absence of surfactant leads to the formation of hyaline membrane disease in the newborn. Impairment of pulmonary blood flow and prolonged administration of dry oxygen or air leads to reduction in surfactant.

Pleura: The lung is covered by visceral pleura on its surface and the thoracic cavity is lined by the parietal

pleura. The space between them contains 10-20 mL of serous fluid having a protein content of 1.77 g/dL. Pleural cavity is only a potential space. During inspiration the lung fills the pleural space. The pleural space is under negative pressure so that the lung is kept in apposition with the parietal pleura. At the end of a quiet expiration the pleural pressure is about -5 cm of water. The pressure inside the pleural cavity is not uniform throughout. The negative pressure is higher at the apices than at the bases. The pleural fluid is formed at the parietal pleura.

Pulmonary circulation: The main pulmonary artery divides into the right and the left pulmonary arteries which divide successively along with the bronchi. The proximal divisions of the artery contain muscular and prominent elastic coats but the branches corresponding to the bronchioles have more prominent muscular coats than elastic layers. The arterioles accompanying the terminal bronchioles and respiratory bronchioles are thin-walled and consist of an endothelial lining with elastic lamina, without the muscular layer. These end up as capillaries. The alveolar wall is supplied by a dense capillary network which provides a large perfusing area. The venous ends of the capillary bed join to form veins which traverse in the interlobar septa. They do not follow the bronchial tree. The veins end up finally as the four main pulmonary veins which drain into the left atrium.

Bronchial circulation: The bronchi and their branches derive their nutrition from the bronchial arteries which usually arise from the descending aorta, but they may arise from intercostal, subclavian or internal mammary arteries as well. The bronchial arteries and their branches supply only up to the level of the respiratory bronchioles. Beyond this the vascular supply is derived from the pulmonary vessels. Veins arising from the bronchial tree drain into the azygos veins, but some may also enter the pulmonary veins. Though the bronchial veins drain venous blood into the pulmonary vein, this is not significant in health. In conditions like bronchiectasis and lung abscess, these bronchial capillaries proliferate and larger volumes of venous blood may be added to pulmonary venous circulation.

Lymphatic drainage: The lungs and pleura are drained by three groups of lymphatics. These are: (1) Lymphatics arising from the visceral pleura and interlobular septa drain the peripheral portions of the lung. These lymphatics follow the pulmonary veins to the hilum. (2) Lymphatics draining the acini form the peribronchial lymphatics and pass to the hilum. (3) Anastomotic channels are formed between the two lymphatic systems. The lymphatics from the upper part of the left lung drain into the thoracic duct while those from the lower part of the left lung and the entire right lung drain into the right lymphatic duct.

Protective mechanisms of the airways: Apart from ciliary action, the cough, sneeze, and gag reflexes serve to protect the air passages.

1. **Cough reflex:** All irritating stimuli arising from the respiratory passages below the pharynx evoke cough. This reflex is triggered off by stimulation of the subepithelial receptors situated in the trachea and bronchi. Sequence of events during cough are: (1) Closure of the glottis, (2) muscular contraction to increase intrathoracic pressure, and (3) sudden release of air by opening of the glottis.
2. **Sneeze:** Irritant stimuli from the nose evoke sneeze. The mechanism is the same as for the cough reflex, but the air is expelled through the nose.
3. **The gag reflex:** This reflex prevents entry of materials into the trachea and this is associated with closure of the glottis.

Pulmonary Physiology

Gas exchange between the blood and the alveoli is brought about by different processes which include : (1) ventilation of the alveoli, (2) mixing of inspired air and alveolar air, and (3) diffusion of gases across the alveolar membrane. Under resting conditions, 5 litres of blood perfuse the pulmonary capillaries, and 6 litres of air enter and leave the lungs every minute. 250-300 mL of oxygen is taken by the pulmonary capillary blood to the tissues and 200-350 mL of carbon dioxide is released into the alveolar air. With exercise these go up considerably.

Control of Breathing

Nervous control of breathing: Respiration is controlled by the respiratory center situated in the medulla and pons. The respiratory center consists of inspiratory center, expiratory center and pneumotaxic center which control the rhythm, depth, and rate of respiration. Principal muscles of respiration are the diaphragm and intercostal muscles. When there is demand for increasing the ventilation or the effort for respiration is higher the accessory muscles of respiration come into play. These include the muscles attached to the thoracic inlet and the abdominal muscles.

Chemical control of breathing: Rise in carbon dioxide tension in the arterial blood is the strongest direct stimulus to the respiratory center to increase ventilation. Next in importance is hypoxia. Hypoxia stimulates the chemoreceptors of the carotid and aortic bodies attached to external carotid artery and ascending aorta respectively. A fall in pH stimulates breathing directly by its action on the respiratory center.

Types of Breathing

Cheyne-Stokes breathing: In this type of abnormal rhythm of respiration, there is increase in the rate and depth of respiration, which reach a maximum and then they come

down to reach a period of apnea. These cycles repeat. Cheyne-Stokes respiration is indicative of serious functional impairment of the respiratory centre. It is seen in cardiac failure, metabolic acidosis, increased intracranial tension, narcotic poisoning, and sometimes even during sleep (Fig. 131.3B).

Biot's breathing: This is a type of irregular breathing in which 3-4 respirations occur in clusters with apneic pauses. The respiration resembles sighs. This is commonly seen in meningitis and brain damage (Fig. 131.3C).

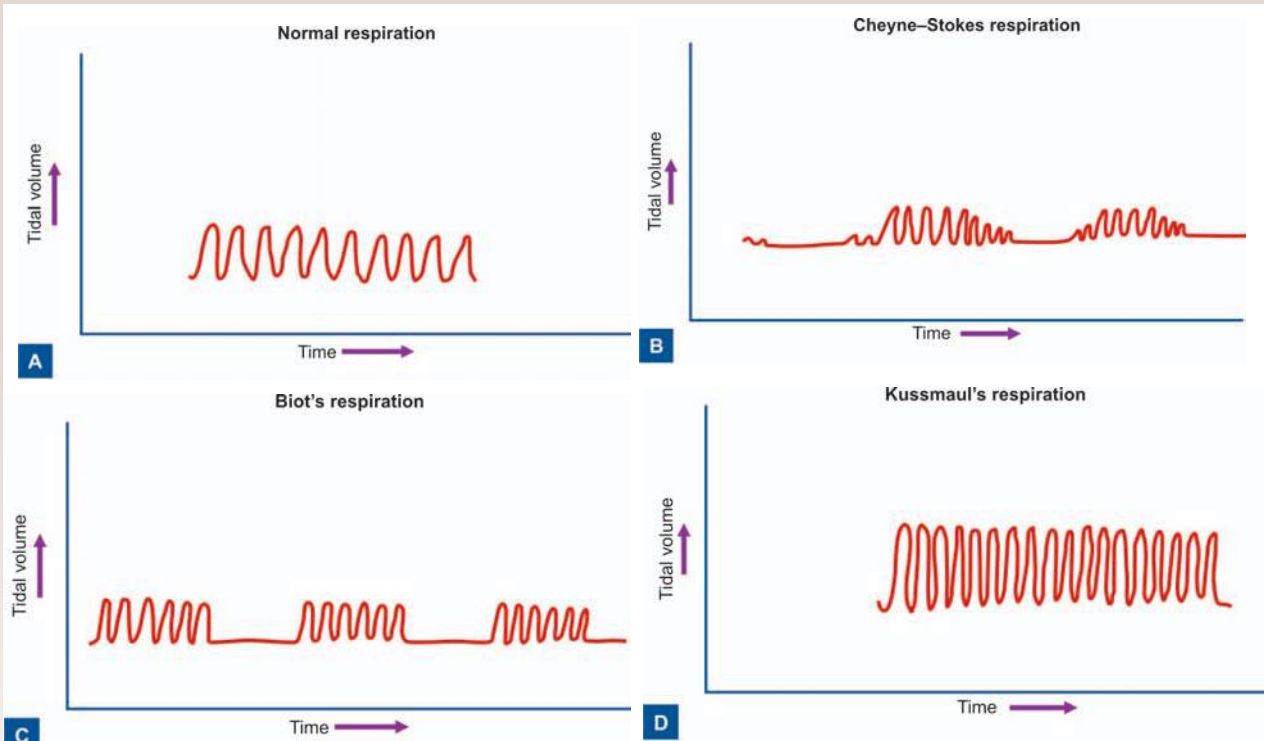
Kussmaul's breathing: In this type, the patient breathes with large tidal volume and so rapidly that there is virtually no pause between breaths. This is seen in all forms of metabolic acidosis, particularly diabetic ketoacidosis, renal failure and others (Fig. 131.3D).

Hyperventilation: The rate and depth of ventilation are increased. This occurs commonly in major pulmonary embolism, anxiety, neurocirculatory asthenia, meningitis, encephalitis, therapy with drugs like epinephrine, poisoning with salicylates or aspirin, hyperthyroidism, hypoxia, and acidosis. Hyperventilation results in excessive removal of CO₂ and consequent alkalosis. Kussmaul's respiration occurring in metabolic acidosis is a compensatory mechanism.

Causes of Alveolar Hypoventilation

1. **Obstruction to the airways**—both structural as in foreign body or secretion, and functional as in bronchospasm.
2. **Paralysis of respiratory muscles**—e.g., poliomyelitis, Guillain-Barré syndrome, or myasthenia gravis.
3. **Impairment of activity of respiratory centre**—e.g., narcotic poisoning, brainstem hemorrhage, coning of the brainstem.
4. **Alteration in the anatomy of the thoracic cage preventing effective ventilation** e.g., severe kyphoscoliosis, diaphragmatic paralysis, pectus excavatum, ankylosing spondylitis, flail chest injuries.
5. **Diseases which affect the lungs and pleura** e.g., pneumonias, atelectasis, pulmonary cysts, emphysema, acute pulmonary edema, malignant secondaries, pulmonary fibrosis, pleural effusion, pneumothorax.
6. **Conditions which interfere with movement of the thoracic cage and diaphragm** e.g., severe obesity, tense ascites.

Gas exchange in the alveoli: Air in the conducting airways is functionally inert and its volume is called the “*anatomical dead space*”. Functionally effective ventilation that the alveoli receive is called “*alveolar ventilation*”. When the alveoli are not perfused with blood, ventilation becomes ineffective. Ventilation occurring in alveoli which are not properly perfused with blood is called “*physiological dead*”



Figs 131.3A to D: (A) Normal respiration. Note the regular pattern—the tidal volume remains the same (B) Cheyne-Stokes respiration apnoeic spells interpose between episodes of waxing and waning respiratory movements (C) Biot's respiration. Apnoeic spells interpose between episodes of respiratory movements of similar amplitude (D) Kussmaul's respiration rapid and high volume respiratory movements occur continuously

space". In normal person, anatomical dead space is equal to physiological dead space. Dead space in typical adult male is equal to 150 mL.

Gas exchange in the alveoli is adversely affected by uneven ventilation, uneven perfusion or defective diffusion.

Ventilation perfusion abnormalities: Ventilation of unperfused alveoli leads to increase in dead space. Perfusion of unventilated alveoli results in the addition of unoxygenated blood to pulmonary venous blood. Taking effective minute ventilation to be 4 litres and pulmonary blood flow to be 5 litres, the normal ventilation perfusion ratio is 0.8.

Several conditions lead to imbalance in ventilation

1. **Normal variations:** The upper parts of the lungs receive less blood than the bases, the hydrostatic pressure of the blood being higher at the base. Though the perfusion is unequal in the different portions of the lung, ventilation is more or less uniform with only minor differences.
2. **Obstruction to pulmonary blood flow:** Pulmonary blood flow is obstructed in pulmonary embolism, vascular changes due to chronic inflammation, destructive lesions of the lung, pulmonary hypertension and vasoconstriction due to hypoxia. Since CO₂ is 20 times more easily diffusible than oxygen,

the ventilation perfusion imbalances lead to hypoxia from the beginning, only later hypercapnia develops.

Gas exchange by diffusion across the alveolar membrane: The alveolar membrane is 0.2 to 0.7 μ thick and it consists of a single layer of cells lining the alveoli, a thin basement membrane and the endothelial cells of the capillary. The alveolar capillaries contain mixed venous blood with high CO₂ and low O₂ tensions. Oxygen passes into the capillary and carbon dioxide passes into the alveoli within a few milliseconds. When the alveolar membrane is thickened, gas exchange is impaired. Diffusion of oxygen is affected early and, therefore, hypoxemia occurs first. Retention of CO₂ occurs only when the lesion is advanced. Several factors such as the structure of the alveolar membrane and ventilation perfusion abnormalities affect the diffusion capacity to a great extent. Hence, the term "transfer factor" is used instead of diffusion capacity.

BLOOD GASES

Both oxygen and carbon dioxide are carried by blood. Diffusion across the alveolar membrane depends upon the partial pressure of these gases on either side, and the diffusing capacity of these gases. Since carbon dioxide is much more readily diffusible than oxygen the level of CO₂ in blood closely follows the partial pressure of CO₂ in

alveolar air. The pattern of oxygen dissociation curve of hemoglobin is such that partial pressure of oxygen in arterial blood (PaO_2) does not fall significantly even when the partial pressure of oxygen in the alveoli falls from 100 mm Hg to 80 mm Hg. But when the alveolar PO_2 falls below 80 mm Hg arterial PO_2 falls steeply. The arterial PO_2 does not closely follow the alveolar PO_2 due to this phenomenon. Oxygen is carried by blood mainly in combination with hemoglobin (1.34 mL/g of Hb) and a small quantity as the dissolved form (0.003 mL/100 mL blood/mm Hg of oxygen tension). The oxygen content in blood can be expressed either as the percentage saturation (SaO_2) or the partial pressure (PaO_2). Arterial carbon dioxide level is expressed in terms of its partial pressure (PaCO_2). Alveolar gas concentrations are expressed in terms of their partial pressures.

Normal Blood Gas Values

Arterial oxygen saturation (SaO_2)	= 95-98%
Partial pressure of arterial oxygen (PaO_2)	= 80-100 mm Hg (11-14 kPa)
Partial pressure of arterial carbon dioxide (PaCO_2)	= 35-45 mm Hg (4.5-6 kPa)

Pulmonary mechanics – Work of breathing: The total work involved in moving the thoracic cage, expanding the lungs and moving the gases in and out is known as the work of breathing.

Pulmonary compliance: The elastic property of the lung is expressed in terms of pulmonary compliance. It is the distensibility of the lung per unit change in intrapleural pressure. Normal pulmonary compliance is about 0.2 litre per cm of water. In conditions like pulmonary fibrosis and pulmonary edema compliance is diminished. It is increased in emphysema.

Airway resistance: About 90% of resistance to flow of air is contributed by the larger air passages and 10% by the smaller airways. Airway resistance is expressed as cm H_2O /litre/second. Resistance to air flow offered by the air passages depends upon several factors like the caliber of the passage, driving pressure, rate of flow, type of flow (laminar or turbulent), density of the gas, and its viscosity. Airway resistance is calculated from values for atmospheric and alveolar pressures and the rate of air flow

Airway resistance =
$$\frac{\text{alveolar pressure} - \text{pressure at the airway opening}}{\text{rate of flow}}$$

In general, airway resistance is measured at a flow rate of 0.5 L/sec. In normals, during quiet breathing the airflow resistance varies between 1.5 to 3 cm water/L/sec. It reaches high values (above 10 cm of water/L/sec) in obstructive airway disease.

ASSESSMENT OF PULMONARY FUNCTION

Different aspects of respiratory function can be subjected to investigational study. These include:

- 1. Gas transport down the airways,
- 2. Gas mixing within alveoli,
- 3. Gas transfer across the alveolocapillary membrane, and
- 4. Lung perfusion.

1. Gas Transport Down the Airways

Entry of air down the airways and its return can be measured using static and dynamic spirometry. Body plethysmography is employed to measure lung compliance and airways resistance. Several parameters are used to determine the ventilatory capacity of the lung.

SPIROMETRY

Spirometry is a measure of air flow and lung volume during a forced expiratory maneuver from full inspiration. It is the simplest test of all respiratory functions. FEV_1 and VC which are the most important parameters to assess the ventilatory capacity, are estimated by spirometry (Fig. 131.4). Other clinical uses of spirometry include the following:

- Additional information to help to establish the *clinical diagnosis* in a patient
- Assess the *prognosis* in a patient
- Assess whether disease is present at an *early stage*, i.e. prior to overt clinical disease
- Assist in quantifying the *severity of airway disease*.
- Assess the *effect of therapy*
- Delineating *risk factors*, e.g. the odds of developing future respiratory disease, or operative risks
- Monitoring whether there is normal pattern of *lung growth or aging*.

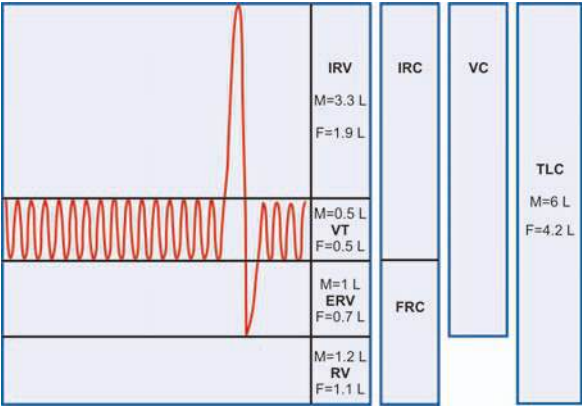


Fig. 131.4: Static lung volumes. IRV, inspiratory reserve volume; VT, tidal volume; ERV, expiratory reserve volume; RV, residual volume; IRC, inspiratory reserve capacity; FRC, functional reserve capacity; VC vital capacity; RLC, total lung capacity

1. Lung Volumes

Tidal volume (TV) is the volume of gas inspired or expired during each respiratory cycle. Normally it is 0.5 litre in men and women.

Inspiratory reserve volume (IRV) is the maximal volume of gas that can be inspired from the end of tidal inspiration. Normal value is 2-3 L in men.

Expiratory reserve volume (ERV) is the maximal volume of gas that can be expired from the end of tidal expiration. Normal value is 1.3 litres in men.

Residual volume (RV) is the volume of gas still remaining in the lungs after maximal expiration. Normal value is 1.6 litres in men. In women the values are slightly lower.

2. Lung Capacities

Total lung capacity (TLC) is the volume of gas contained in the lung at the end of maximal inspiration. Normal value is 5.4 litres.

Vital capacity (VC) is the maximal volume of gas that can be expelled from the lung by forceful effort after maximal inspiration. In health, vital capacity is influenced by factors such as age, sex, position, body frame and state of physical conditioning. Average normal value is 3.8 litres in men.

Inspiratory capacity (IC) is the maximal volume of gas that can be inspired from the resting expiratory level. Normal value is 2.5 litres in men.

Functional residual capacity (FRC) is the volume of gas remaining in the lung at the end of tidal expiration. Normal value is 2.9 litres in men.

Forced expiratory volume in one second (FEV₁) [timed vital capacity]: The volume of air expelled in the first one second of a forcible expiration following a full inspiration is called forced expiratory volume in one second (FEV₁). Normally FEV₁ is above 75% of the total vital capacity, FEV₂ is above 85%, and FEV₃ is above 95%. Airways obstruction is indicated by FEV₁ below 70% of normal. Volume time curve is a very useful

spirogram (Fig. 131.5A). FEV₁ is the most useful and reproducible measurement. It is the volume of air expelled in the first second of forced expiration after a full inspiration. FEV₁ depends on the effort made by the patient, the elastic recoil of the lungs and the positive thoracic pressure applied around them by the expiratory muscles. In patients with obstructive airway disease successive FEV₁ measurements yield reproducible results. FEV₁ reflects severity of airway obstruction and correlates approximately with maximal exercise capacity (Fig. 131.6). Rate of decline is influenced by tobacco smoke.

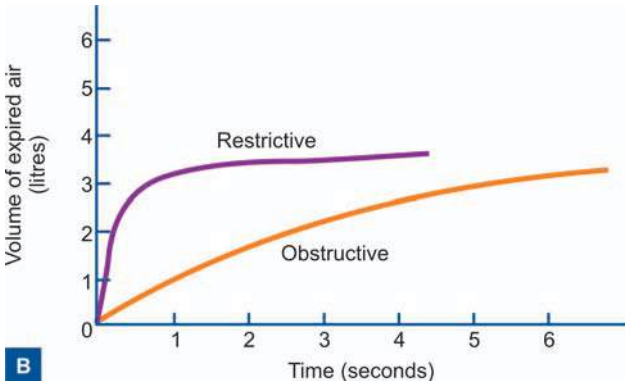
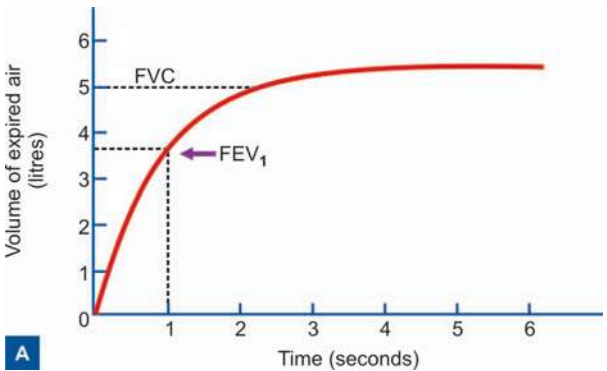
Chronic Bronchitis emphysema syndrome which is mainly due to narrowing of the airways is diagnosed when: FEV₁ is < 80% of the predicted value and the FEV₁/FVC or FEV₁/ vital capacity is < 70%. Improvement or reversibility of airflow obstruction is defined as an improvement in FEV₁ by more than 15% and more than 0.3 litres after administration of the β -adrenergic agonist, salbutamol, 200 μ g by inhalation.

Bronchial challenge studies are very useful in demonstrating airway hyper-reactivity which is characteristic of asthma. Patients with asthma characteristically react to small doses of pharmacological bronchoconstrictors, exhibiting transient decreases in FEV₁ and increases in airway resistance. The most commonly reported measurements are the dose of methacholine or histamine needed to provoke a 20% reduction of FEV₁(PD₂₀). Healthy non-asthmatic subjects require doses that are, on an average, several orders of magnitude greater.

Note: (Fig. 131.5B) Volume time relationship in obstructive and restrictive lung disease. It shows the percentage of reduction the volume of air during the 1st second.

Forced expiratory time (FET) is the total time taken for completing a forced expiration. Normally it is 4-6 sec.

Peak expiratory flow rate (PEFR): PEFR is the maximum rate that can be sustained during the first 10 millsec. of a sudden forced expiration after a full inspiration. The PEFR depends upon the height and surface area of the individual. Nomograms are available for reference. It is



Figs 131.5A and B: Volume-time curves obtained during forced expiration
(A) Normal (B) Restrictive and obstructive lung diseases

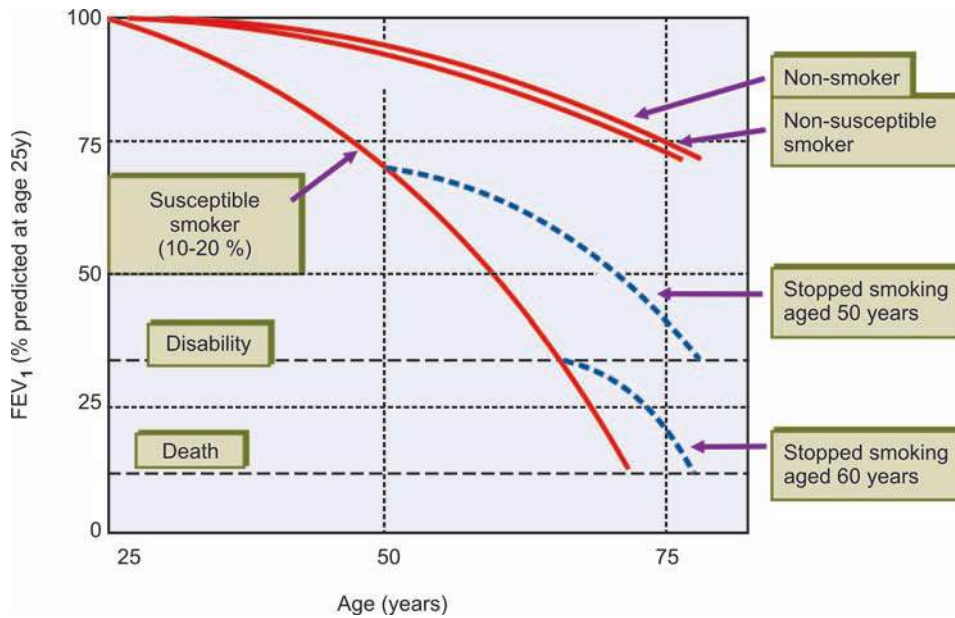


Fig. 131.6: Annual decline in lung function. Note the relation between decline in FEV_1 in the normals (non-smokers) and smokers. Rate of decline in FEV_1 is many times higher in smokers. Note also the improvement in FEV_1 on stopping smoking

measured using Wright's peak flow meter. This is an easy and convenient method to assess airways obstruction. Other methods to assess PEFR employ the peak flow gauge and the De Bono Whistle. Distribution of inspired air in different parts of the lungs is studied by single breath oxygen test.

Maximal expiratory flow rate (MEFR): This is the flow rate at a specified portion of a forced expiration after a maximal inspiration, e.g. MEFR 300-1300 denotes flow rate for 1 litre of expired gas after the first 300 mL has been breathed out.

Maximal inspiratory flow rate (MIFR): This is the flow rate at a specified portion of a forced inspiration.

Maximal mid-expiratory flow rate (MMFR): This is the velocity of air expressed as litres per second during the middle third of the total expired volume. It is also denoted as forced expiratory flow (FEF 25-75%). In normals the values vary with age and height of the individuals. Average values lie between 1.5 and 5.5 litres/sec in men. Determination of MMFR helps to detect borderline cases of airway obstruction.

Maximal voluntary ventilation (MVV), or maximal breathing capacity is the total volume of air breathed by a subject using maximum effort over a period of 1 min.

Air velocity index (AVI): The ratio of the percentage of predicted MVV to the percentage of the predicted vital capacity is called air velocity index. The normal range is from 0.8 to 1.2.

Diffusing capacity: This is the volume of a gas transported across the alveolocapillary membrane in 1 min for one

unit of pressure gradient. It is expressed as mL/min/mm of Hg difference in partial pressure.

Closing capacity: During inspiration the air enters different portions of the lung in a definite order. The upper portions fill first and then the middle and lower parts in order. During expiration air escapes in the reverse order, the basal portions emptying first and the apical regions being the last. As a result, the smaller airways at the bases start to close even while air from apices is escaping. The volume of air contained in the lungs at the point where the airways first start to close is called closing capacity.

Closing volume (CV): The difference between the closing capacity and the residual volume is termed closing volume. This is often expressed as a percentage of the vital capacity. In normal subjects below 40 years it is less than 20%. The CV increases with age. In many cases increases in closing volume may be the only detectable abnormality in impending airway obstruction.

Entry of air down the airways and its return can be measured using static and dynamic spirometry. Body plethysmography is employed to measure lung compliance and airways resistance. FEV_1 and VC which are the most important parameters to assess the ventilatory capacity, are estimated by spirometry.

The modern equipment used for estimating the respiratory parameters such as vital capacity, PEFR, TLC, FEV and MEFR which represent different functional aspects of lung function are computerised and the results are given as graphs or loops (e.g. flow volume loop), which can be easily interpreted. In normal individuals the maximal expiratory flow rate decreases steadily throughout forced expiration. Reduction in maximal expiratory flow during the middle of forced expiration is caused by

small- airways disease and can be an early sign of small-airway disease. When tracheobronchial collapse occurs in emphysema or rare disorders of bronchial cartilage, flow rate decreases early in expiration. In obstruction of the airway outside the thorax, flow tends to be constant throughout the first part of expiration rather than decelerating.

Instantaneous flow values are easily read off from such graphs. These can distinguish between obstruction at different levels in the respiratory tree.

2. Gas Mixing within Alveoli

These measurements demand rapid analysis of expired air. The measurement of alveolar and arterial carbon dioxide tension is the method employed for this purpose.

3. Gas Transfer Across the Alveolocapillary Membrane

Estimation of transfer factor is conducted by using carbon monoxide which has a very high diffusing capacity.

4. Lung Perfusion

It is studied by isotopic methods.

Cardiopulmonary Exercise Test (CPET)

Cardiopulmonary exercise testing (CPET) involves the measurement of oxygen uptake (VO_2), carbon dioxide output (VCO_2), minute ventilation $\dot{V}$ or VE , and other variables in addition to the monitoring of 12-lead electrocardiogram (ECG), blood pressure, and pulse oximetry during a maximal symptom-limited exercise test. When appropriate, the measurement of the arterial blood gases provides important information about pulmonary gas exchange. During standard cardiac stress testing the focus is primarily on ECG and blood pressure measurements, whereas in CPET the focus is on gas exchanges. CPET helps to distinguish between pulmonary and cardiac lesions.

During CPET several ventilatory variables such as tidal volume, respiratory rate, ventilation in one minute, breath-to-breath variation in oxygen and carbon dioxide levels in expired air can all be estimated.

Oximeters which can be fitted to the finger tips can give values of arterial oxygen saturation fairly accurately.

SYMPTOMATOLOGY IN RESPIRATORY DISEASES

Cough with or without expectoration, chest pain, dyspnea and hemoptysis are the most frequent respiratory symptoms.

Cough with expectoration is a prominent symptom in inflammatory lesions such as bronchitis and pneumonia or in irritative and allergic lesions of the respiratory tract. Pharyngitis, laryngitis, tracheitis, and early stages of bronchitis give rise to cough without expectoration. In some infections like *Bordetella pertussis*, *Klebsiella* and some

viruses, paroxysms of cough are followed by a long inspiratory whoop caused by laryngeal spasm. Cough elicited by change of posture (postural cough) is characteristic of bronchiectasis, lung abscess, and bronchopleural fistula. “*Bovine cough*” or “*gander cough*” is the term used to denote cough devoid of its explosive (tussive) phase. This occurs in bilateral adductor paralysis of the vocal cords. In asthma cough and dyspnea tend to recur regularly at night. In left sided heart failure with pulmonary edema, cough occurs in the recumbent posture. Development of a sudden and uncontrollable paroxysm of cough in an otherwise healthy person should suggest the possibility of an aspirated foreign body. The change in character of the cough may be an early clue to the development of complications or superimposition of fresh pathology.

Otogenic cough: This is reflex cough elicited by stimulation of the external auditory meatus, part of which is supplied by the auricular branch of the vagus (Arnold’s nerve). In a rare case, impacted wax in the ear or a foreign body in the meatus may elicit reflex cough. Otoscopic examination may reveal the cause. Other reflex symptoms include vomiting and syncope.

Cough is generally a protective reflex designed to keep the airway patent and clear the exudates. Sometimes irritant cough becomes troublesome, interfering with sleep causing severe annoyance. Other untoward effects of cough include syncope (cough syncope), pneumothorax, mediastinal and surgical emphysema and rib fractures (*cough fracture*). In children paroxysmal cough may lead to subconjunctival hemorrhage.

Sputum: The material expectorated from the respiratory tract is called sputum. In healthy individuals the secretion of the respiratory passages is just adequate to provide a protective lining, and there is no expectoration. Expectoration in excess of 10-25 mL of sputum in 24 h should raise the possibility of disease. Copious amounts in excess of 300 mL are seen in bronchiectasis and lung abscess. Character of the sputum often suggests the underlying pathology. Sputum is serosanguinous in pulmonary edema, mucoid and sticky in asthma and chronic bronchitis, thick and purulent in bronchiectasis and lung abscess, creamy yellow in pulmonary tuberculosis, bloodstained in carcinoma, tuberculosis, bronchiectasis, mitral stenosis and pulmonary infarction, rusty in pneumonia and black in coal worker’s pneumoconiosis lung abscess or gangrene of the lung. Copious watery sputum occurs in alveolar cell carcinoma, this is known as bronchorrhea. Sputum is chocolate coloured in hepatopulmonary amebiasis.

Hemoptysis

Presence of blood in the sputum is termed “*hemoptysis*”. In true hemoptysis blood is derived from the airways or the lungs. The quantity of blood may be small as in mitral stenosis or massive as in cavitary pulmonary tuberculosis

or neoplasms. Sometimes blood is derived from the upper respiratory passages or mouth and this is termed “*spurious hemoptysis*.” Hemoptysis before middle age brings to mind tuberculosis, pneumonia, bronchiectasis and mitral stenosis. After 40 to 45 years of age, bronchogenic carcinoma and tuberculosis top the list. Hemoptysis is a manifestation of serious underlying disease warranting full investigation. Though rare, massive hemoptysis results in considerable loss of blood demanding emergency management. Non-respiratory causes of hemoptysis include pulmonary hypertension occurring in mitral stenosis, acute pulmonary edema, pulmonary infarction, trauma and hemorrhagic diseases. Rarely massive and fatal hemoptysis may develop when an aortic aneurysm erodes into the trachea or a bronchus. *Spurious hemoptysis* is commonly resorted to by hysterical individuals to attract medical attention.

Management of hemoptysis: The patient should be hospitalised as an emergency and a rapid clinical examination is done to determine the cause. It is important to avoid percussion, which may worsen the hemoptysis.

The patient is kept in bed rest and sedated with diazepam 10 mg administered intramuscularly. Respiratory depressants such as morphine should be avoided since they impair expectoration. Blood loss and its effects are assessed by monitoring the volume of blood expectorated and the pulse, respiration and blood pressure. If the blood loss exceeds 200-300 mL in 24 hours and it is persistent, blood transfusion is indicated.

In the majority of cases the underlying cause can be made out by clinical examination and chest radiography. Specific treatment is instituted early (e.g. antituberculosis drugs in tuberculosis, antibiotics in pneumonia and lung abscess) in conditions where such treatment is available. Majority of cases subside with rest, sedation, and blood transfusion. In conditions like pulmonary neoplasms, bleeding tends to persist. In such cases emergency bronchoscopy is done to locate the lesion and decide upon further management. If the site of bleeding is located, bronchial artery embolisation is a very effective method to arrest the bleeding promptly.

Digital clubbing (Syn: Hippocratic fingers): This is caused by increase in the volume of soft tissue in and around the distal phalanges of the fingers and toes, especially the nailbeds. This leads to increased curvature of the nails. Severity of clubbing varies and this has been graded for clinical purposes.

Grade 1: Fluctuation of the nail can be elicited on the nailbed.

Grade 2: The normal angle between the nail and nailbed is lost.

Grade 3: The terminal portion of the phalanx and nail appears as a drumstick or a parrot beak.

Grade 4: In addition to digital clubbing, other regions show pulmonary osteoarthropathy.

Being highly subjective, the value of grading is at best minimal in borderline cases. More than the severity of clubbing, the period taken to develop the clubbing may be more important. Occurrence of clubbing within weeks should suggest conditions like lung abscess, bronchogenic carcinoma and infective endocarditis. In these conditions the nails are painful.

Causes

- Respiratory diseases**—Suppurative lesions like bronchiectasis, lung abscess, empyema, and infected cysts; advanced tuberculosis with bronchiectatic changes, bronchogenic carcinoma, pneumoconiosis, fibrosing alveolitis, and pleural fibroma.
- Cardiovascular disorders**—Cyanotic congenital heart diseases and infective endocarditis.
- Alimentary disorders**—Malabsorption states, ulcerative colitis, cirrhosis of the liver, hepatomas and amebic liver abscess.
- Miscellaneous groups**—Clubbing may develop in thyrotoxicosis. At times it may occur non-pathologically in several members of a family (familial clubbing). Repeated trauma to the finger tips as occurring in carpenters and blacksmiths leads to occupational clubbing.

In pachydermoperiostosis which is a rare familial disorder, clubbing occurs in association with thickening of the ends of long bones and coarse thickening of the skin over several regions.

Dyspnea: Difficulty in breathing or shortness of breath associated with marked awareness of the effort of respiration is called dyspnea. The severity of dyspnea can be graded and this gives clue to the severity of the disease and its progression.

Medical Research Council Grading

Grade 1: Troubled by shortness of breath when hurrying on level ground or walking up a slight hill.

Grade 2: Short of breath when walking with people of own age or on level ground.

Grade 3: Has to stop for breath when walking at own pace on level ground.

In left-sided heart failure and in hypoventilatory states, the patient becomes more dyspneic in the recumbent posture and considerable relief is obtained by sitting-up. This is referred to as *orthopnea*. Attacks of severe breathlessness occurring during sleep at night may awaken the patient and assumption of the erect posture gives relief. This is termed *paroxysmal nocturnal dyspnea*. This is also characteristic of left-sided heart failure.

Respiratory disorders that lead to dyspnea may fall into different groups.

- Central causes for dyspnea affect the respiratory center, e.g. encephalitis or cerebrovascular accidents.

2. Significant airways obstruction is a common cause for dyspnea. Obstruction to the airway may be mechanical as due to a foreign body or functional as due to spasm. Larger airways may be obstructed by aspirated foreign bodies, diphtheritic membrane, tumors, blood or secretions. Obstruction to the larynx produces inspiratory stridor and indrawing of the chest wall. Dyspnea is felt both during inspiration and expiration. Obstruction to the smaller airways occurs in asthma, emphysema, chronic bronchitis, and extensive bronchiectasis. In these conditions the difficulty is felt more for expiration and the characteristic expiratory wheeze may be heard.
3. Disorders that impair the process of gas exchange, e.g. massive pulmonary collapse, pulmonary embolism, respiratory distress syndrome, fibrosing alveolitis, pulmonary fibrosis and extensive parenchymal diseases such as tuberculosis, cystic disease and malignancy.
4. Diseases that prevent expansion of the lung, e.g. pneumothorax, pleural effusion, kyphoscoliosis, injury to the chest wall, paralysis of respiratory muscles.
5. Dyspnea is commonly the first symptom when the inspired air does not supply adequate amounts of oxygen to the individual. This happens when the oxygen tension is low as in high altitudes or in gas poisoning.
6. Hysterical hyperventilation may present as dyspnea. In this, the subject voluntarily hyperventilates. Other traits of the hysterical personality may be evident. Excessive removal of carbon dioxide due to overventilation leads to respiratory alkalosis and tetany.
7. In diseases like pneumonia and pleurisy, painful restriction of respiratory movements leads to hypoventilation and dyspnea.

Cyanosis: Bluish discolouration of the skin and mucous membranes due to the presence of excess of reduced hemoglobin in peripheral blood is called cyanosis. In

extensive diseases of the lungs central cyanosis occurs due to defective oxygenation of arterial blood or the development of functional arteriovenous shunts. In chronic bronchitis and emphysema the main defects are those of ventilation and perfusion. In fibrosing alveolitis, the defect is mainly one of diffusion. Differentiation between respiratory and cardiac causes of cyanosis can be made on clinical grounds in many cases. In respiratory diseases inhalation of oxygen clears the cyanosis, whereas this is not so in cardiac lesions with right to left shunts.

PHYSICAL EXAMINATION

Examination of the respiratory system should be preceded by a careful general examination. Dyspnea, cyanosis, digital clubbing and cervical or axillary lymphadenopathy may suggest a primary respiratory disorder.

For purposes of physical examination, chest is divided into different areas with a view to enable anatomical localization of the lesion. The anterior part is divided into supraclavicular, infraclavicular, mammary and inframammary regions. The lateral aspect is divided into the axillary and infra-axillary regions and the back is divided into suprascapular, interscapular and infrascapular regions (Table 131.2).

Physical examination is carried out sequentially from inspection to palpation, percussion and auscultation. Measurement of the chest for its expansion is a simple and reliable clinical method for assessing the ventilatory capacity. Normal expansion in an adult ranges from 6-8 cm.

Percussion: The note raised by percussion and the vibration felt by the pleximeter finger give valuable clues to the state of the underlying lung and pleura. By percussion it is possible to assess the relative proportion of air, solid tissue or fluid underlying the area.

Special forms of percussion include “*tidal percussion*” and the “*elicitation of shifting dullness*”. The former is employed to distinguish dullness caused by the

TABLE 131.2

Shows the relationship of the clinical areas with the underlying lung

Anterior:	1. Supraclavicular region and infraclavicular region (from the clavicle down to the third rib) 2. Mammary region (from the third to the sixth rib) 3. Inframammary region (from the sixth rib to the costal margin)	Correspond to the apical and anterior segments of the upper lobe respectively Correspond to the anterior surface of the middle lobe on the right and the lingula on the left Parts of the middle lobe on the right and lingula on the left and parts of the lower lobe on both sides
Lateral:	1. Axilla (from the apex of the axilla down to the sixth rib) 2. Infra-axillary region (from the sixth rib to the costal margin)	Major part of the lateral aspect of the upper lobe and part of the lower lobe Lateral segments of the lower lobe
Posterior:	1. Suprascapular region (above the spine of the scapula) 2. Interscapular region (second to seventh dorsal spines) 3. Infrascapular region (below the seventh dorsal spine)	Part of the apical segment and contiguous posterior segments of the upper lobe Apical segment of lower lobe and contiguous posterior portion of the upper lobe Posterior basal segments of the lower lobes on both sides

TABLE 131.3

Clinical significance of alteration in percussion note

Normal lung	Resonant normally
Hollow viscus, pneumo- thorax	Tympanitic
Moderate pneumothorax, emphysema, bullae	Hyper-resonant
Consolidation collapse, fibrothorax	Impaired resonance to moderate dullness
Pleural effusion, empyema, thick fibrothorax	Stony dullness

upper border of the liver from that caused by pleural fluid or consolidation of the lower portion of the lungs. Shifting dullness occurs when there is fluid which is free to move with changing positions of the patient. This occurs in hydropneumothorax or in a large cavity containing fluid and air (Table 131.3).

Auscultatory findings: Breath sounds, vocal resonance and whispering pectoriloquy are elicited by auscultation. Breath sounds are produced by oscillation set-up in the larger air passages (trachea and larger bronchi) by turbulent flow of air. Over the larger air passages the character of breath sounds is bronchial. In the lower regions of the lungs, the parenchyma acts as a low pass filter which filters off the higher frequency components (200 Hz and above) and this changes the character of the breath sounds to vesicular. When this filtering effect is lost, the sounds are directly transmitted to the chest wall and the breath sounds become bronchial. This occurs in consolidation of the lungs. This is the acoustic basis of bronchophony and whispering pectoriloquy as well. Adventitious sounds heard during auscultation may be “wheezes” (previously called “rhonchi”) and “crackles” (used to be known as “crepitations”).

Breath sounds: Normal breath sounds are vesicular. This is characterized by the phase of inspiration, closely followed by a short expiratory phase (one-third of the inspiration) and the quality being rustling. In bronchial breathing the expiratory and inspiratory phases are equal with a pause in between and the quality is guttural or aspirate. Normally bronchial breathing is heard over the trachea, when auscultated over the front and back of the neck. Pathological associations of the bronchial breathing include pulmonary consolidation, collapse adjoining a patent bronchus or rarely other conditions. Based on the pitch, bronchial breathing has been described as “tubular” (high pitched), “cavernous” (low pitched) and “amphoric” (low pitched breath sounds with high pitched overtones). “Tubular breathing” is heard over pneumonic consolidation, “cavernous breathing” over communicating cavities and large air passages, and “amphoric breathing” over open pneumothorax and large communicating cavities. “Bronchophony” (increased vocal resonance) occurs over

areas of consolidation. “Whispering pectoriloquy” (whispered sounds being heard distinctly on auscultating the chest) can be elicited over areas of bronchial breathing. When only high frequency sounds of a spoken voice are transmitted to the chest wall, the vocal resonance attains a nasal quality and this is termed “aegophony”. This may be elicited above the level of a pleural effusion.

Adventitious sounds may be continuous or interrupted. “Continuous adventitious sounds” include: (1) “stridor” occurring in laryngeal and bronchial obstruction, and (2) “wheezes” arising from narrowed air passages. Wheezes are musical lung sounds. When heard by auscultation, they are termed rhonchi. Interrupted adventitious sounds include crackles (which may be fine, medium or coarse), and pleural rubs. Crackles (crepitations) are produced by explosive equilibration of gas pressure between boluses of air in the air passage and the sequential opening up of airways during respiratory cycles. Coarse crepitations may be due to the presence of exudate in the larger air passages and these disappear with coughing and expectoration.

Pleural friction rub: This is a leather-creaking sound heard superficially in pleural diseases. It may be heard both during inspiration and expiration at the same part of the respiratory cycle. It is not altered by coughing.

Pleuropericardial sounds: These are better heard when the breath is held in full inspiration, as rubbing sounds. They suggest the presence of pleurisy and pericarditis.

Crunching sounds: These are heard when auscultating over areas of surgical emphysema and sometimes over pericarditis.

Knocks: These are sharp adventitious sounds heard in pneumothorax caused by the movement of the collapsed lung over the mediastinum.

Investigations in Respiratory Diseases

General investigations of importance which point to disease of the respiratory organs include peripheral blood picture, total and differential leukocyte counts and determination of ESR. Lymphocytosis is suggestive of chronic inflammatory diseases like tuberculosis whereas neutrophil leukocytosis occurs in acute infections like pneumonia. Increase in eosinophils above 10% calls for estimation of the absolute eosinophil count. Mild and moderate increase in eosinophils is very common in Indian subjects. This is caused by factors such as helminthiasis and external allergens. In susceptible subjects even moderate eosinophilia may present with symptoms of respiratory allergy. Higher eosinophil counts are found in bronchial asthma, hydatid disease and pulmonary eosinophilia. Chronic hypoxemia results in the development of secondary polycythemia. Elevation of ESR is a non-specific indicator of inflammatory and neoplastic lesions in the lungs. ESR is not specific for diagnosis,

but in the follow-up of chronic diseases like tuberculosis, ESR is a helpful parameter.

1. Sputum Examination

- a. Sputum should be examined macroscopically, microscopically after proper staining, and bacteriologically. Total quantity of sputum in 24 h, colour, consistency and other characteristics like odour and presence of blood are of great value in diagnosis. Presence of fungi in mycotic infections, asbestos bodies in asbestosis and motile amebae in pulmonary amebiasis can be detected by direct microscopy of fresh sputum. *Gram's stain* and *Ziehl-Neelsen stain* are employed to identify the bacterial and mycobacterial pathogens in the smear. Malignant cells can be detected by cytological examination. Wet preparations stained with methylene blue may suggest the presence of malignant cells. Staining with Leishman's stain helps to identify leukocytes in sputum. Presence of numerous neutrophils suggests infective basis whereas predominance of eosinophils suggests allergic etiology. This distinction is very helpful in the management of asthma. *Papanicolaou staining* technique helps to identify the malignant cells further. Giemsa stain reveals *Pneumocystis carinii*.
- b. *Bacteriological tests*: Sputum culture is done to identify the organisms and their sensitivity to various antibiotics. Proper collection of the specimen is essential for getting reliable results. Sputum should be taken directly into sterile receptacles. Contamination by oropharyngeal organisms leads to fallacious results on culture. Uncontaminated specimens of sputum can be obtained by transtracheal aspiration. Bronchial washings collected through a bronchoscope or smears collected by a brush during bronchoscopy are ideal specimens for cytological and microbiological studies, wherever facilities are available.

line at the level of the lower margin of the anterior end of the second rib separates the upper from middle zone, and a horizontal line passing through the lower margin of the anterior end of the fourth rib separates the middle from the lower zone. Chest radiographs give evidence of morphological lesions. In many instances, radiological appearances help to infer the etiology as well.

Radiological Appearances Caused by Physical Abnormalities in the Lungs

Consolidation: Presence of homogenous opacities with well defined margins indicate pulmonary consolidation. Radiological consolidation is characterised by presence of air bronchogram that is seen thorough the consolidated lung. Since there is no change in the volume of the lung the trachea and mediastinum are not shifted.

Collapse: Pulmonary collapse throws a homogenous opacity with clearcut concave margins. The trachea, mediastinum, and interlobar fissure are shifted towards the area of collapse. The dome of the diaphragm on the affected side is elevated. The unaffected portions of the lung shows hypertranslucency due to compensatory emphysema.

Fibrosis: Presence of streaky linear or reticular shadows with shift of trachea and mediastinum to the same side and compensatory emphysema of the unaffected regions is suggestive of fibrosis.

Pleural effusion: Presence of small quantities of fluid (less than 300 mL) in the pleura causes only obliteration of the costophrenic angle. As the quantity of fluid increases, more extensive homogenous opacity appears with obliteration of the costophrenic and cardiophrenic angles. The upper margin tends to be concave with its higher level towards the axilla and the lower level towards the mediastinum. Midline structures are shifted to the opposite side.

Presence of fluid and air (*hydropneumothorax*) is diagnosed by the presence of a horizontal level of fluid below, with hypertranslucency (due to air) above. The lung markings are not visible since the lung is collapsed towards the hilum.

Pneumothorax: Presence of air in the pleural cavity leads to hyperlucency and absence of lung markings on the affected side. The margin of the collapsed lung is seen towards the hilum. The midline structures are pushed to the opposite side.

Cavities: Cavities are seen as areas of central translucency within areas of consolidation or fibrosis.

Morphology of the cavities vary with different lesions. Tuberculous cavities are thin-walled and empty. Thick-walled cavities containing fluid and air suggest the possibility of lung abscess or neoplasms.

2. Radiological Studies

Plain X-ray chest-posteroanterior (PA) view: Radiographs are taken in full inspiration with the film placed in front of the chest and the source of X-ray kept 1.5-2 m behind the patient. In addition to PA views, lateral views are also taken with the affected side close to the film to locate the bronchopulmonary segment which is the seat of disease. In normal skiagrams the lungs appear as translucent zones in which bronchovascular markings are clearly detectable and can be traced almost to the periphery.

The trachea, mediastinum, costophrenic, and cardiophrenic angles and the level of the diaphragm are taken as landmarks in the interpretation of chest skiagram. On either side the lung fields are compared zone by zone. For purposes of description the lung fields are divided into the upper, middle, and the lower zones. A horizontal

Opacities in the lung: Opacities may be single or multiple. Depending on their size and distribution, multiple opacities are grouped as *miliary mottling* (1-2 mm size), *nodularity* (1 cm or above) and *cannon balls*. Their size, density, distribution, and number give clues to their pathological nature. The lungs are hypertranslucent in emphysema and less translucent in conditions such as interstitial fibrosis or pulmonary edema.

Lesions in the apices of the lungs are brought out better by taking lordotic views or penetrated views. By this method, parts concealed behind ribs are visualized. The exact spatial location of any lesion can be obtained by taking the PA and lateral views. Oblique views may be required for further localization. Radiographs taken in the lateral decubitus are necessary to detect conditions such as intrapulmonary effusions. In cases where X-ray pictures are not conclusive, more informative procedures like high resolution computed tomography are done.

Fluoroscopy: This procedure helps in assessing the respiratory movements and the movements of mediastinal structures. Due to the risk of the radiation and want of accuracy in diagnosis this procedure is seldom used at present.

Contrast radiography: The technique of visualizing the bronchial tree using radio-opaque dyes is called *bronchography*. This is the only reliable method to assess the total extent and type of bronchiectasis.

Pulmonary angiography: It is performed to study the pattern and distribution of the pulmonary arteries and their branches. Arteriography is the method of choice to demonstrate pulmonary embolism and arteriovenous malformations.

Ultrasonography: has become an important investigational modality in respiratory diseases. Pulmonary parenchymal lesions, mediastinal lesions, pleural fluid, pleural lesions, cardiac and pericardial lesions and several others can be diagnosed confidently. Ultrasound directed biopsies and aspiration are also more effective than blind procedure.

Radioisotopic investigations: Isotopic techniques have made it possible to obtain visual images as well as precise quantitative information about the regional distribution of ventilation and perfusion. These methods are generally non-invasive. New machines incorporating computer facilities are available.

Perfusion imaging: This is employed to study the state of the pulmonary vasculature. The main clinical uses are in the investigation of pulmonary embolism, atresia or hypoplasia of pulmonary artery, presence of right-to-left intracardiac shunts and pulmonary venous hypertension.

Ventilation imaging: This can be made by using ¹³³Xenon.

Aerosol inhalation studies: Aerosolised radioactive particles can be administered for inhalation. Commonly ^{99m}technetium-labelled phytate, lactose, albumin or sulphur colloid are used. The radioactive particles are distributed in the lungs depending upon the patency of the air passages. The concentration or radioactivity is diminished in areas of poor ventilation. Another use of labelled aerosol particles is to study the efficiency of mucociliary function. When mucociliary function is impaired, the clearance of radioactivity from the lung is delayed.

Using perfusion and ventilation imaging studies, valuable information can be obtained. In pulmonary embolism ventilation is normal, but perfusion is diminished, whereas both ventilation and perfusion are diminished in parenchymal, pleural or obstructive airway disease.

Isotopic localization of pulmonary tumours: Isotopes such as ⁵²Gallium citrate and ⁵⁷Cobalt-labelled bleomycin which are concentrated by tumours are used to study neoplastic lesions.

Computed tomography: This is employed to detect abnormalities in the pleura, lungs, major blood vessels and mediastinal structures. CT scan distinguishes between cysts, tumours and vascular lesions. It is very helpful to diagnose bronchiectasis. It is a valuable adjunct when skiagrams are not conclusive. CT has become a regular investigation modality in respiratory medicine. High resolution CT (HRCT) is more useful to detect pulmonary infiltrative diseases and bronchiectasis early.

Magnetic resonance imaging (MRI): is also very helpful to bring out structural lesions of intrathoracic organs. The advantages over CT are its capacity to give pictures in the sagittal, coronal and transverse planes with higher resolution. Lesions occurring at the apices of the lungs and thoraco-abdominal junctions are picked up better by MRI. It can also distinguish between vascular and nonvascular structures at the hilum even without contrast.

Endoscopic studies: Several endoscopic procedures are available to study respiratory disorders. These include laryngoscopy, bronchoscopy, mediastinoscopy, and thoracoscopy. Laryngoscopy visualizes the upper respiratory tract up to the larynx and the trachea.

Bronchoscopy: Bronchoscopy is the endoscopic procedure used to visualise the trachea, bronchi and their branches, aspirate secretions for investigations, obtain biopsy material, and remove obstructions. Clinical indications for bronchoscopy include bronchial obstruction, pulmonary neoplasms, unresolved pneumonia, lung abscess and recurrent hemoptysis. Broncho-alveolar lavage can be done during bronchoscopy and the specimen can be examined further.

Availability of flexible fiberoptic bronchoscopes with facilities for aspiration and biopsy procedures has increased their importance in diagnosis and therapy in recent years. Flexible bronchoscopes can reach up to the second or third division of the bronchi whereas rigid bronchoscopes reach only up to the first division.

Video bronchoscope gives better clarity of the lesion. Advances in bronchoscopy include trans bronchial biopsy to grade peripheral lung cancers, application of trans bronchial stents to relieve obstruction and auto-fluorescence bronchoscopy for early detection of lung cancer. Newer instruments incorporating ultrasound and high magnification equipments give better diagnostic results.

Mediastinoscopes are used to inspect the superior mediastinum and perform biopsy procedures under direct vision.

Thoracoscopy is inspection of the thoracic contents with a thoracoscope after producing a partial pneumothorax. Video assisted thoracoscopy (VATS) is useful for conducting procedures like lung volume reduction surgery.

Investigations using aspirated material: In the diagnosis of pleural diseases, the examination of pleural fluid is most important. So also examination of bronchial aspirates and material from other sites gives valuable diagnostic clues. Macroscopic appearance, microscopy, cytology, microbiological studies, and biochemical investigations are helpful in diagnosis.

Biopsy Studies

Lymph node biopsy: Biopsy of the appropriate scalene lymph node or palpable axillary or cervical lymph nodes helps to diagnose granulomatous and neoplastic lesions.

Lung biopsy: Lung tissue can be obtained by percutaneous biopsy, bronchoscopically, or by open biopsy under vision. Percutaneous biopsy using a Vim-Silverman needle or a trephine is performed to diagnose diffuse lesions and peripherally situated localised lesions. When the lesions are small and not accessible superficially, thoracotomy and open biopsy are preferable.

Pleural biopsy: This is resorted to when pleural lesions have to be diagnosed. *Cope's needle* or *Abram's pleural biopsy punch* is used for obtaining material from the parietal pleura. *Vim-Silverman needle* or *Menghini's needle* can be used in the absence of the specialized needles. Aspiration and biopsy can be done as ultrasound or CT guided procedures for greater diagnostic yield.

Broncho-alveolar lavage: This procedure is adopted to obtain material from the terminal portions of the respiratory tree and alveoli. The specimen is subjected to microscopy and cytological examination. Organisms such as *Pneumocystis carinii*, *CMV*, *legionella*, *fungi* and *mycobacteria* can be identified in the washings. Broncho-alveolar lavage has been used therapeutically to remove occluding plugs in cystic fibrosis and severe asthma. In alveolar proteinosis lavage using heparin and acetyl cysteine helps to remove the proteinaceous material.

132

Respiratory Failure

14

C. Sudheendra Ghosh, Ronald Win B

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General Considerations

The state in which the lungs cannot perform the function of gas exchange adequately during rest and exercise is called respiratory failure. In this condition the resting PaO_2 falls below 60 mm Hg (60 torr or 8 kPa) and/or the PaCO_2 rises above 49 mm Hg (49 torr or 7 kPa), when breathing room air at sea level. Lowered PaO_2 alone is not adequate to make the diagnosis of respiratory failure. In right to

TABLE 132.1

Causes of respiratory failure

1. <i>Interference with the mechanics of the chest wall</i>	Severe kyphoscoliosis, obesity, flail chest injury with multiple rib fractures, paralysis of the chest wall muscles and diaphragm, immobility of the chest wall as in progressive systemic sclerosis
2. <i>Pleural disorders</i>	Large collection of pleural fluid, tension pneumothorax, gross thickening of the pleura and others
3. <i>Diseases of the airways</i>	Severe asthma, advanced chronic bronchitis and emphysema, laryngeal edema, mechanical obstruction of air passages
4. <i>Pulmonary diseases</i>	Pulmonary interstitial fibrosis, neonatal and adult respiratory distress syndrome, allergic alveolitis, extensive malignancy, bilateral pneumonia
5. <i>Diseases of pulmonary vasculature</i>	Primary pulmonary hypertension, polyarteritis nodosa, repeated pulmonary embolism
6. <i>Metabolic</i>	Metabolic alkalosis
7. <i>Depression of the respiratory centre</i>	Injury to brainstem, raised intracranial tension and narcotic poisoning lead to central respiratory failure

left shunt lesions the PaO₂ may be lowered without respiratory failure. Causes of respiratory failure are many. Interference with any of the major processes-ventilation, perfusion or diffusion-may result in respiratory failure (Table 132.1).

The clinical picture depends on the speed of onset, cause and severity. Acute respiratory failure produces more dramatic symptoms whereas chronic respiratory failure may even remain asymptomatic. Respiratory failure may or may not be associated with dyspnea. Though in the early stages CO₂ retention causes dyspnea, with the passage of time the respiratory centre becomes adapted and unresponsive to elevated level of CO₂. At this stage the lowered PaO₂ (60 mm Hg or below) is the effective stimulus for respiration. There is no direct correlation between the blood gas levels and severity of dyspnea.

In the majority of cases the patient has a longstanding respiratory problem such as chronic obstructive airway disease and respiratory failure is precipitated by infection. The increased secretions and mucosal edema caused by infection aggravate the airway obstruction and this results in alveolar hypoventilation. As a result hypoxia and hypercapnia (rise in level of arterial carbon dioxide) develop. As the respiratory failure progresses the PaO₂ falls from 60 mm Hg (mild) to 20 mm Hg (severe).

Type I-respiratory failure: This type is characterized by lowered PaO₂ and normal or low PaCO₂. This is usually the result of conditions in which ventilation is normal, but there is defective diffusion or ventilation-perfusion imbalance. Conditions like pulmonary edema, respiratory distress syndrome, extrinsic allergic alveolitis and interstitial pulmonary fibrosis lead to type I respiratory failure.

Type II-respiratory failure: In this condition PaO₂ is reduced and PaCO₂ is elevated. Hypoxia is the more prominent feature. This results from conditions characterized by defective ventilation occurring along with ventilation-perfusion imbalance. Alveolar hypoventilation occurs in chronic bronchitis, emphysema, asthma and respiratory paralysis. Hypercapnia develops only when the FEV₁ goes down below 1.2 litres. With higher values of FEV₁, hypercapnia is rare. If the respiratory failure is of acute onset, retention of carbon dioxide leads to acidosis and fall of pH. If the respiratory failure becomes chronic, compensatory mechanisms come into play. Renal conservation of bicarbonate restores the pH to near-normal.

CLINICAL FEATURES

Respiratory failure may be acute or chronic. In the latter exacerbating factors lead to acute manifestations. The main biochemical factors are hypoxia and hypercapnia which in turn give rise to various other abnormalities in acid-base balance and electrolyte disturbances. The manifestations of hypoxia and hypercapnia vary from each other.

Manifestations of hypoxia: Hypoxia is more harmful to tissues than hypercapnia. Vital organs such as the brain, heart, liver and kidney, and the pulmonary vessels are adversely affected. Neurological symptoms include headache, irritability, insomnia, drowsiness, mental confusion, and coma. Objective evidence of cerebral dysfunction can be demonstrated by the electroencephalogram. If hypoxia is severe, fatty change, tissue necrosis, and focal hemorrhages develop in the myocardium. Cardiac arrhythmias are precipitated.

Constriction of pulmonary arteries leads to pulmonary hypertension and this may precipitate right sided heart failure. Liver cells become edematous and necrosed. In chronic hypoxia the liver shows fatty change and fibrosis. Severe hypoxia may give rise to renal tubular damage. Secondary polycythemia develops in chronic hypoxic states.

Manifestations of hypercapnia: In the initial stages hypercapnia stimulates the respiratory center and the resultant hyperventilation helps to lower the PaCO_2 to normal levels. In established hypercapnia the respiratory center becomes insensitive to raised PaCO_2 . In such cases the stimulus for the respiratory centre is hypoxia. In judicious administration of oxygen may abolish this hypoxic stimulus and this may give rise to further depression of respiration and carbon dioxide narcosis. Hypercapnia causes cerebral vasodilatation, headache, and rise in intracranial tension. As a result, papilledema may occur in severe cases. Peripheral vasodilatation develops and this gives rise to warm extremities, flushing, and rapid high volume pulse. When PaCO_2 levels exceed 50 mm Hg, drowsiness, confusion, muscle twitching, and flapping tremors develop. The deep tendon reflexes become sluggish. The patient lapses into coma when PaCO_2 rises above 80 mm Hg.

Management of Acute Respiratory Failure (ARF)

This should be managed as an emergency in an intensive respiratory care unit if facilities are available. Proper monitoring includes the record of heart rate, respiratory rate, blood pressure, temperature, serum electrolytes and blood gas levels. In addition to general supportive care, special attention should be paid to the airways and proper oxygenation.

Maintenance of the airway: Irrespective of the cause, in all cases of respiratory failure, the upper air passages should be fully inspected and foreign bodies and secretions should be removed. In the recumbent comatose patient, the chin should be pulled up to prevent the tongue from falling back and obstructing the pharynx. If the patient cannot expectorate freely, secretions should be aspirated. If the patient can cooperate, removal of secretions should be aided by postural coughing, gentle tapping on the chest, steam inhalation and administration of drugs like bromhexine hydrochloride. Bromhexine hydrochloride can be administered orally in a dose of 8 mg thrice daily. Mucolytic agents can be administered as aerosols, e.g., acetylcysteine. Adequate hydration is necessary, since it helps to loosen the secretions for easy expectoration. If bronchospasm is present, it can be relieved by drugs like salbutamol given 2-4 mg orally or

0.5 mg intramuscularly. Parenteral corticosteroids (betamethasone 4 mg) may have to be given if bronchospasm is not relieved by simple measures. Salbutamol and beclomethasone can also be given as metered aerosols. Tracheostomy may be required in some cases where the tidal volume is low.

Antibiotics: Since infection is a very common precipitating factor, antibiotic therapy is indicated. Preliminary assessment of the infecting agent can be made by Gram-staining and culture of the sputum and the suitable antibiotic can be started. In the acute case crystalline penicillin and in the chronic case a broad-spectrum antibiotic such as ampicillin or amoxicillin may be required. Antibiotic therapy may have to be reviewed when microbiological results are obtained.

Correction of hypoxia: This is the mainstay in the management of respiratory failure. Oxygen is administered with nasal catheter, or by more effective methods such as masks or tents. If given by nasal catheter, the rate is 2-3 litres per minute and the catheter tip should be located 15 cm from the nostril. The *venturi mask* which delivers oxygen at a preset low concentration is ideal if available. The concentration of oxygen can be adjusted at 24, 28 or 35% by giving oxygen at rates ranging from 4-8 litres/min. It is desirable to bring the PaO_2 level above 50 mm Hg and pH above 7.25. In chronic respiratory failure administration of oxygen should be closely supervised to avoid the development of carbon dioxide narcosis. Once the emergency has been tided over, the patient is weaned off from oxygen gradually.

Supportive measures: Administration of fluid and electrolytes, preferably with monitoring of central venous pressure (CVP) and maintenance of nutrition are important.

Assistance to ventilation: Mechanical assistance should be considered when the patient's own effort is inadequate to maintain oxygenation. If the PaO_2 remains below 60 mm of Hg and PaCO_2 remains above 55 mm Hg while receiving oxygen therapy, respiratory assistance is indicated.

The decision to assist ventilation should be individualised depending on several factors. Non invasive positive pressure ventilation (NIPPV) is delivery of mechanical ventilation to the lungs without an invasive (endotracheal) airway. This can be delivered with the use of either negative pressure ventilators or non-invasive positive pressure ventilators. Intubation is indicated when NIPPV has failed or contraindicated. Contraindications include inability to protect the airway, patient intolerance, and hemodynamic instability or cardiac arrest.

Different types of ventilators are available. Volume cycled ventilators are superior since these are more efficient and safe. If the patient's respiratory mechanism is active, it is desirable to assist it (assisted ventilation).

On the other hand, in patients in whom spontaneous respiration is abolished, controlled ventilation using a preset volume and rate is employed. Modern respirators are designed to assist respiration when the patient's own respiratory effort goes down and they are reciprocally inhibited when the patient's breathing recovers.

Positive end expiratory pressure (PEEP): One of the problems encountered in patients with respiratory failure maintained on assisted respiration is premature closure of the terminal airways during expiration, giving rise to air trapping. This is prevented by maintaining a positive end expiratory pressure. In addition, it helps to reopen bronchioles and alveoli which remain closed. The tidal respiration is improved. Positive end expiratory pressure also helps to reduce the functional intrapulmonary shunts, thereby increasing the PaO_2 . The disadvantage of PEEP is reduction in venous return to the heart due to increased intrathoracic pressure and consequent cardiac failure. Assistance to ventilation should be carried out by specially trained teams. As the patient improves, he is gradually weaned off the ventilator under supervision. Ventilatory support is a highly skilled job, which has to be undertaken by a team trained to establish the airway, activate the machines and monitor the progress of the patient clinically and from blood gases and acid-base values. In many centres this is done under the supervision of the anesthetist, intensivist and pulmonologist.

Extracorporeal membrane oxygenators are being employed in the management of severe hypoxemic respiratory failure when conventional methods fail. Solutions containing perfluorocarbon which dissolve oxygen and deliver it to tissues are also being introduced into the management of respiratory failure. As the patient improves, he is encouraged to undertake mild exercises. Respiratory exercises are advised to increase the tidal volume and help expectoration. He is also instructed on methods to avoid the precipitating factors. Incurable cases should be considered for lung transplantation which facility is still not available in India.

Chronic Respiratory Failure

Some patients with progressive respiratory disease eventually enter a state in which the arterial oxygen and carbon dioxide are persistently abnormal. Acute respiratory infection tips them into severe respiratory failure. In such cases prompt treatment of infections, bronchodilators and management of respiratory failure help to tide over the crisis. In irreversible chronic ventilatory failure, provision of continuous oxygen in the house is very beneficial in giving symptomatic relief. Lung transplantation is available in many countries, but not yet in India. This has to be considered when the chances of functional recovery sufficient to sustain life is improbable.

Acute Respiratory Distress Syndrome (ARDS)

(Syn. Shock lung, Wet lung)

The ARDS was first formally described by Ashbaugh and colleagues in 1967.

This is a syndrome characterised by a fairly acute onset of severe respiratory distress in adults who have normal pulmonary functions. Clinically it resembles respiratory distress syndrome of the newborn (RDS) but in the latter, changes in surfactant are the primary mechanisms for disease. This is not so in adults.

Diagnostic Criteria

1. Acute onset of respiratory failure
2. $\text{PaO}_2/\text{FIO}_2$: <300 mm Hg = acute lung injury (ALI),
3. $\text{PaO}_2/\text{FIO}_2$: <200 mm Hg = acute respiratory distress syndrome (ARDS)
4. Chest radiograph: Bilateral alveolar infiltrates consistent with pulmonary edema
5. Pulmonary capillary wedge pressure <18 mm Hg.

Etiology: Many factors contribute to the picture of ARDS. ARDS may follow several unrelated pathological conditions. These include prolonged shock, cardiopulmonary bypass surgery, severe infections like septicemia, viral, bacterial, fungal or pneumocystis pneumonia, inhalation of irritant fumes, drugs like nitrofurantoin, methadone and morphine, trauma to chest including major surgery, acute pancreatitis, fat embolism, massive blood transfusions, prolonged administration of oxygen in high concentrations, and immunological disorders like Goodpasture's syndrome.

Pathogenesis: The initiating factor is damage to the pulmonary capillaries leading to extravasation of fluid into the interstitium and alveoli. This results in ventilation-perfusion imbalance. Work required for respiration increases since the edematous lung is less compliant. Disseminated intravascular coagulation which may occur in shock favours the development of ARDS. Other pathogenetic mechanisms include microemboli produced from extracorporeal circulation, immune complexes and presence of excess of catecholamines. The lungs are airless, congested, hemorrhagic and edematous. In the acute phase interstitial and alveolar edema is present. Unlike as in left heart failure where pulmonary capillary pressure is high, it is normal in ARDS. Type I pneumocytes desquamate and are replaced by hyaline membrane. Type II, pneumocytes suffer damage resulting in the depletion of surfactant. This results in widespread microatelectasis. Vascular damage leads to interstitial edema. If the condition persists for more than ten days the epithelium undergoes cuboidal transformation and progressive interstitial fibrosis. This may be manifested functionally as alveolocapillary defects.



Fig. 132.1: X-ray chest shows bilateral alveolar infiltrate consistent with pulmonary oedema

Clinical features: ARDS sets in on a background of any of the various clinical conditions mentioned earlier. Early features include tachypnea and dyspnea. Auscultation may reveal diffuse wheezes and crackles. The arterial oxygen saturation falls progressively. Arterial CO_2 is maintained normal for considerable periods by hyperventilation. The chest X-ray shows progressive haziness of lung fields due to increasing quantity of fluid (Fig. 132.1). The fully established picture is one of severe respiratory failure which may be fatal. Prognosis depends upon the underlying condition and the stage at which respiratory support is given. The mortality used to be 50-60%, but with modern treatment it has come down. Those who recover do so without sequelae. Rarely emphysema may result.

Management: Prompt treatment of the predisposing factors like shock and infection may help to prevent the development of ARDS, and if already established, to prevent deterioration. The general management is the same as for respiratory failure. Fluid therapy should be carefully controlled as the lungs are already edematous. Administration of salt-free albumin along with frusemide has been beneficial. Institution of positive end expiratory pressure (PEEP) ventilation and more efficient cardiovascular support help to reduce mortality. PEEP serves to increase the lung volume, reduce intrapulmonary shunting and collapse of alveoli. Extracorporeal membrane oxygenation (ECMO) is life-saving in selected cases.

Inhalation of nitric oxide as a pulmonary vasodilator is under trial. Corticosteroids are indicated in cases where the primary disorder is immune-mediated.

Respiratory Distress Syndrome (RDS) of Newborn

This is a syndrome characterized by tachypnea, expiratory grunt and cyanosis caused by the lack of surfactant and often with a fatal outcome seen most frequently in premature babies below 38 weeks gestation. Fetal causes include neonatal asphyxia, acidosis and hypothermia. Antepartum hemorrhage, uncontrolled diabetic state in the mother, hypoxia, gross anemia and caesarean section done for fetal distress are the maternal causes associated with higher incidence of RDS.

Pathogenesis: The level of surfactant in the alveoli is reduced. This results in atelectasis of the alveoli. In addition to the reduction in surfactant, other abnormalities such as alterations in the pulmonary and systemic circulation, coagulopathy, fibrinolysis, interstitial edema, decreased plasma proteins and disordered pulmonary mechanics are important contributory factors leading to the final picture. The effort required to distend the alveoli during inspiration is greater. Reduction in compliance leads to rapid shallow breathing, inspiratory indrawing of intercostal spaces and cyanosis. Histopathologically there is extensive alveolar atelectasis, dilatation of alveolar ducts, interstitial edema and the presence of a hyaline membrane covering the respiratory bronchioles, alveolar ducts and alveoli. The hyaline membrane is formed by desquamated epithelial cell debris and fibrin.

Clinically the baby has tachypnea, grunting expirations, indrawing of the intercostal, subcostal and suprasternal spaces and cyanosis. Untreated, the mortality is very high. Children who survive RDS are predisposed to various chronic respiratory problems in later life.

Treatment: Neonatal intensive care units have reduced the mortality from RDS. The airway is maintained patent by careful suction of secretion and physiotherapy. Controlled administration of oxygen, positive end expiratory pressure respiration (PEEP), correction of acidosis and maintenance of normal body temperature (36.5°C skin temperature) are the important supportive measures. Antibiotics are indicated in the presence of infection. Corticosteroids have been employed, based on subjective observations.

Surfactant therapy: Instillation of surfactant directly into the airways helps to relieve the condition. EXOSURF NEONATAL (Burroughs Wellcome) is a protein free synthetic lung surfactant. The contents of a vial is reconstituted with 8 mL preservative-free sterile water. This solution contains 13.5 mg of dipalmitoyl phosphatidyl choline. Surfactant should be administered only in centres where facilities for assisted ventilation and

respiratory monitoring are available. The dose is 5 mL/kg body weight, repeated after 12 hours.

The baby is put on endotracheal ventilation and the surfactant solution is delivered into the infant's trachea through the sideport of the endotracheal tube, taking several minutes for the administration. The first dose should be administered as early as possible on diagnosing RDS.

Prenatal estimation of the lecithin: sphingomyelin ratio in amniotic fluid (obtained by amniocentesis) is useful to predict the chances of developing RDS. If L:S ratio is less than 1.5 the risk is high. If L:S ratio is over 2 the risk of RDS is minimal.

Administration of corticosteroids to mothers who go into premature labour helps to reduce the chances of RDS in the newborn.

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Diseases of the Upper Respiratory Tract

K.E. Rajan

Chapter Summary

- Rhinitis 905
- Epistaxis 905
- Pharyngitis 906
- Acute Tonsillitis 906
- Sinusitis 907
- Acute Laryngitis 908
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- Laryngeal Paralysis 908
- Obstruction to the Respiratory Tract 908**
 - Acute Laryngeal Obstruction 908
 - Tracheal Obstruction 909
 - Bronchial Obstruction 909

TABLE 133.1

Treatment of allergic rhinitis			
Drug	Dose	Route	Frequency
Antihistamines			
Loratidine	5 mg	PO	Daily
Desloratidine	10 mg	PO	Daily
Cetirizine	10 mg	PO	Daily
Sodium cromoglycate	2% solution, metered dose	Nasal spray	4-6 hourly
Topical steroids			
Beclomethazone	2 doses of	Nasal spray	12 hourly
Budesonide	50 µg		
Mometazone			
<i>Prevention:</i> An attempt must be made to avoid known allergens or agents as far as possible.			

RHINITIS

Inflammation of the nasal mucosa is called rhinitis. The most frequent cause is allergy to inhaled substances such as pollen, dust, hair or animal dander. An immediate hypersensitivity reaction occurring on the nasal mucous membrane leads to sneezing, nasal obstruction, and watery nasal discharge. Ingested allergens may also lead to rhinitis. Rhinitis may be a predominant symptom in coryza and other respiratory viral infections. Edema of the mucosa occurring in rhinitis may lead to obstruction and infection of the paranasal sinuses.

Similar symptoms can be produced by physical irritants such as cold air, dry atmosphere or chemicals such

as strong perfumes. This condition is called ‘*vasomotor rhinitis*’.

Treatment: Allergic rhinitis responds to antihistamines, cromones and topical steroids. Vasoconstrictor nasal drops (xylometazoline 0.1%) may also be used. Continued use of nasal drops containing sodium cromoglycate may help to desensitize the nasal mucosa (Table 133.1).

EPISTAXIS

Epistaxis is bleeding from the nose. Usually bleeding occurs from the blood vessels over the anterior part of the nasal septum and anterior nares, areas easily examined

TABLE 133.2

Causes of epistaxis

Local causes:

Rhinitis, foreign bodies, sinusitis, carcinoma, trauma, rhinosporidiosis.

Systemic causes:

Infections: Influenza, typhoid, pertussis, malaria and rheumatic fever.

Other systemic diseases: Hypertension, hemorrhagic disorders and cirrhosis liver with hepatic failure.

by a nasal speculum. Epistaxis may result from local or systemic causes (Table 133.2).

Epistaxis is a frightening symptom. In majority of cases, it is self-limiting. *Treatment* consists of sedation, rest in bed and packing the nose with gauze soaked in adrenaline solution. Local vasoconstriction arrests the bleeding. If bleeding tends to be recurrent, the bleeding spot must be cauterized. In all cases of epistaxis, look for an underlying systemic disorder. Management of the systemic disorder is very important.

PHARYNGITIS

Pharyngitis is the most common cause of simple “sore throat”. In agranulocytosis and acute leukemia, necrotic ulceration of the tonsils and pharynx may be the presenting symptom. Excessive smoking, noxious fumes, corrosives and unaccustomed spicy foods are common irritants. Pharyngitis may also be caused by allergy to inhaled or ingested allergens (Table 133.3).

Clinical features: Pharyngitis gives rise to sore throat and dysphagia. The posterior and upper cervical lymph nodes may be enlarged and tender. Redness and edema over the

pharynx and adjoining areas may be seen. Pharyngitis may form part of the clinical picture of several systemic infections.

Treatment: Appropriate antimicrobial drugs are indicated in pharyngitis due to bacterial infections. Most cases respond to penicillin. Rest, steam inhalation, and analgesics give rapid symptomatic improvement. Throat lozenges containing menthol or eucalyptus oil give considerable relief to the pain and discomfort.

Acute Tonsillitis

Inflammation of the tonsils is more common during childhood. However, all age groups can be affected. *Hemolytic streptococcus-Lancefield group A* is the most common agent. Other pathogens causing pharyngitis may affect the tonsils as well. Tonsillitis is more common in poorer socioeconomic groups, where chances for cross infection are high.

Clinical features: Symptoms start with sore throat, pain over region of the tonsils, high fever, and dysphagia. Examination of the throat with a tongue depressor reveals enlarged, red tonsils covered with yellowish pus in the crypts on one or both sides. The exudate can be easily removed by a swab and the underlying mucosa does not bleed. Tonsillar and adjoining lymph nodes are moderately enlarged and tender. There is moderate neutrophilic leukocytosis.

Even if untreated, the acute symptoms and the tonsillar inflammation partially may subside in 7-10 days. In many patients, the streptococci persist within the crypts and give rise to recurrence of symptoms over several years. This is referred to as “chronic tonsillitis”.

TABLE 133.3

Common microbial causes of acute pharyngitis

Infective agent	Disease produced	Frequency (%)
VIRUSES		
1. Rhinovirus	Common cold	10
2. Coronavirus	-do-	10
3. Adenovirus	Pharyngoconjunctival fever	5
4. Herpes simplex	Gingivitis, stomatitis, pharyngitis	4
5. Parainfluenza	Common cold, croup	1
BACTERIA		
1. <i>S. pyogenes</i>	Pharyngitis, tonsillitis	15-30
2. Mixed aerobic infection	Gingivitis, stomatitis (Vincent's angina), peritonsillitis, peritonsillar abscess	1
3. <i>N. gonorrhoeae</i>	Pharyngitis	1
4. <i>C. diphtheriae</i>	Diphtheria	1
5. <i>M. pneumoniae</i>	Pneumonia, tracheobronchitis, pharyngitis	1
FUNGI		
<i>C. albicans</i>	Thrush	5

TABLE 133.4

Complications of tonsillitis

1. Extension of infection due to contiguity: Pharyngitis, laryngitis, tracheobronchitis, pneumonia, sinusitis, eustachian catarrh and suppurative otitis media
2. Systemic spread of infection: Septicemia, pyemia
3. Local complications: Chronic tonsillitis, peritonsillar abscess
4. Immunological complications: Rheumatic fever and glomerulonephritis

Complications: Acute tonsillitis may lead to several complications (Table 133.4).

In India and other neighbouring countries, acute streptococcal tonsillitis is the most common cause of rheumatic fever.

Diagnosis: Acute tonsillitis is diagnosed from the characteristic appearance of the tonsils, acute febrile onset, and neutrophilic leukocytosis. Confirmation and isolation of the organism must be attempted by culture of the pus taken before antibiotic therapy.

Acute tonsillitis has to be differentiated from faucial diphtheria. In neutropenic states, necrotic ulceration of the throat may also develop.

Treatment: Aspirin relieves the pain and fever. Drug of choice is penicillin. Crystalline penicillin G sodium is given in a dose of 1.0 mega unit every 6 hours intravenously. Erythromycin, ampicillin or cotrimoxazole may be given in appropriate doses as alternate therapies. It is important to administer the full course of treatment and repeat bacteriological study at the end of the course to ensure that organisms are eradicated. Indications for tonsillectomy include recurrent exacerbations of tonsillitis (more than four times in one year), or where chronic tonsillitis is complicated by otitis media.

Sinusitis

Sinusitis is the acute or chronic inflammation of the paranasal sinuses. Maxillary sinusitis is the most common type of sinusitis. The ethmoid, frontal and sphenoid sinuses are affected less frequently.

Sinusitis is caused by a variety of bacteria such as streptococci, staphylococci, pneumococci *Haemophilus influenzae* and anaerobic bacteria. Viruses such as the influenza and the parainfluenza virus and less commonly fungi such as aspergillus also may produce sinusitis (Table 133.5).

Anatomical abnormalities interfering with the normal draining mechanisms predispose to infection. Often the disease starts as an acute respiratory infection. It may follow dental procedures or swimming in contaminated water.

Infection reaches the sinuses from the nose, mouth, tonsils, nasopharynx, and the upper canines or molars. The

TABLE 133.5

Causative organisms in acute maxillary sinusitis

Organism	Frequency (%)
<i>S. pneumoniae</i>	30
<i>H. influenzae</i>	25
Anaerobic bacteria	6
<i>S. aureus</i>	4
<i>S. pyogenes</i>	2
<i>B. catarrhalis</i>	2
Gram-negative bacteria	9

lining mucosa of the nose and sinuses is inflamed. Obstruction of the opening of the sinus leads to accumulation of secretion, which may get infected. Sinuses may become filled with pus.

Clinical Features: Malaise, fever, frontal headache, and nasal discharge are the presenting symptoms. In maxillary sinusitis, pain may be felt in the maxillary area of the face. Frontal sinusitis causes pain around the eyebrows. Ethmoid sinusitis causes pain behind the eyes and frontal headache. Sphenoid sinusitis causes pain in the occipital region. Tenderness may be elicited over the sinuses. Pus may be seen pouring from the opening of the affected sinus on speculum examination.

Chronic sinusitis leads to recurrent headache, which shows a diurnal periodicity. The headache starts in the morning and worsens by mid-day, and subsides by evening. Foul-smelling purulent nasal discharge may occur. Once established, the condition persists for months or even years. Table 133.6 gives the complications.

Diagnosis: History of chronic headache and the demonstration of purulent discharge from the nose coupled with tenderness over the sinuses should suggest the clinical diagnosis. Trans-illumination of the involved sinus produces a dark shadow while the normal one produces a light shadow. X-ray examination of the paranasal sinuses shows haziness or opacities in the region of the infected sinuses. CT scan may be required for

TABLE 133.6

Complications of sinusitis

1. Intracranial infection: Meningitis, thrombophlebitis of the intracranial veins, thrombosis of the cavernous sinus and sagittal sinus, extradural abscesses.
2. Infection of the eye socket: Orbital cellulitis
3. Infection of ethmoid sinus: Third nerve palsy
4. Frontal sinusitis: Osteomyelitis of the frontal bone and edema over the region (*Pott's puffy tumor*)
5. Respiratory tract: Aspiration of pus into the respiratory tract leading to recurrent bronchitis, aspiration pneumonia, bronchiectasis, and lung abscess.

confirmation. The discharge from the sinus on culture isolates the causative organism. Fungal scrapings and smears as well as fungal cultures are done if a fungal aetiology is suspected.

Treatment

Medical: Specific therapy is to administer antibiotics depending on bacteriological results. In the acute stage, one of the newer generation cephalosporins is effective. Decongestant nasal drops, nasal sprays and steam inhalations help to reduce nasal mucosal edema and thus favour drainage of pus. Aspirin gives symptomatic relief.

Surgical: In chronic sinusitis, if conservative measures fail to clear the infection, pus has to be removed by irrigation and drainage. Caldwell-Luc procedure for chronic maxillary sinusitis may be employed. Ethmoidectomy may be required for ethmoid sinusitis.

Acute Laryngitis

Inflammation of the larynx may result from bacterial or viral infection or inhalation of irritant gases. It often results as a complication of acute coryza. Unaccustomed overuse of the voice leads to edema of the vocal cords. Laryngitis is characterized by hoarseness or loss of voice and pain during attempted speech. Irritant nonproductive cough may be present. In children, acute laryngitis manifests as ‘croup’ secondary to partial obstruction of the small larynx.

Treatment consists of rest to the voice, steam inhalations, avoidance of smoking, and administration of analgesics (paracetamol 0.5g 6 hourly). In many cases the condition is self-limiting with rest and analgesics. Antibiotics are indicated only if bacterial infection is present. Rarely complications do occur, leading to chronic laryngitis, tracheitis, bronchitis or pneumonia.

Chronic Laryngitis

Chronic laryngitis is characterized by hoarseness of voice or aphonia in association with throat irritation and dry cough. This may result from repeated attacks of acute laryngitis, excessive use of voice, tobacco smoking or chronic sinusitis. Laryngoscopy is a must to exclude local tumours or vocal cord palsy. Treatment consists of absolute voice rest, abstinence from smoking and steam inhalations.

Laryngeal Paralysis

Paralysis of the vocal cords may be organic or functional. The abductors and the adductors are supplied by the recurrent laryngeal nerves, which are branches of the vagus nerves. In organic paralysis the abductors, the

tensors and the adductors are affected in the order of sequence. The completely paralysed vocal cord lies immobile midway between abduction and adduction (*cadaveric position*). Abductor paralysis is always organic in nature and it may be unilateral or bilateral. On the other hand pure adductor paralysis is always bilateral and it is functional in nature. This is frequently seen in hysteria.

Causes of organic laryngeal paralysis: Involvement of the left recurrent laryngeal nerve is common in mediastinal tumours, aortic aneurysm and enlargement of the left atrium occurring in mitral stenosis. One or other of the recurrent laryngeal nerves may be affected in the neck by enlargement of the cervical lymph nodes, goiter or other surgical causes.

Paralysis of the vagus may occur in infective polyneuritis, fractures of the base of the skull, space occupying lesions in the posterior fossa or diphtheria.

Vagal nuclei are affected in brainstem lesions. These include basilar artery insufficiency, bulbar poliomyelitis, motoneurone disease, syringobulbia and tumours.

Clinical features: Usual symptoms are hoarseness of voice, cough, dyspnea, and alteration in the quality of the cough. Organic paralysis is accompanied by cough, whereas hysterical paralysis is not. In bilateral abductor paralysis, the cough loses its explosive phase (*“Bovine cough”*). In unilateral vocal cord paralysis the hoarseness and loss of voice may disappear with time, since the opposite vocal cord crosses the midline and restores the vocal aperture. Laryngeal paralysis is confirmed by laryngoscopy.

Treatment: Treatment of the cause of the laryngeal paralysis must be instituted wherever possible. Otherwise management is symptomatic. Bilateral abductor paralysis results in obstruction of glottis and it is fatal if the airway is not established by tracheostomy or intubation. *Persons with laryngeal paralysis should avoid swimming and diving, since they cannot hold breath and, therefore, they run the risk of drowning.*

OBSTRUCTION TO THE RESPIRATORY TRACT

Acute Laryngeal Obstruction (Table 133.7)

Acute laryngeal obstruction may present as a life-threatening emergency.

Foreign bodies may get impacted in the larynx. This may include dentures or large chunks of meat. Obstruction by bolus of food is more common under alcohol intoxication. This is called *‘Café Coronary’*.

Clinical features: Stridor, aphonia, and dyspnea are the hallmarks of laryngeal obstruction. Acute obstruction in children leads to cyanosis and inspiratory in-drawing of the trachea. The movement of a foreign body within the

TABLE 133.7

Causes of laryngeal obstruction

1. Foreign body
2. Inflammatory or allergic edema (including angio-neurotic edema due to food, irritant fumes, corrosives or insect stings)
3. Acute laryngitis and epiglottitis (especially in infants)
4. Exudates
5. Laryngeal muscle spasm
6. Inhaled blood clot/vomit in the unconscious
7. Tumors: Chronic progressive obstruction – especially carcinoma
8. Bilateral vocal cord paralysis

larynx may be palpable during respiratory efforts. When obstruction due to large bolus of food occurs at the table, the victim becomes anxious, restless, and cyanosed. He tries to cry, but the voice is lost. If the obstruction is not relieved immediately, he falls unconscious and death may occur within minutes.

Diagnosis: Acute laryngeal obstruction should be suspected when an otherwise healthy individual suddenly becomes choked and cyanotic with loss of voice.

Management: First aid consists of the removal of the foreign body manually or with a pair of tongs. The impacted foreign body can be dislodged by a sudden forcible thud on the chest with the head lowered.

Heimlich maneuver: This effective method is to be learnt by all first aid teams. The patient is hugged from behind with the rescuer's hands crossing each other over the patient's epigastrium and the chest is compressed suddenly. This helps in dislodging the obstruction (Fig. 133.1).

If the above attempt fails, the airway should be made patent by tracheostomy or by inserting a few large-bore hypodermic needles into the trachea. The patient is transported to hospital for further management.

Management of chronic obstruction depends upon the cause.

Tracheal Obstruction

Total tracheal obstruction is rare but may be caused by a foreign body. More often it is partial and is caused by external pressure due to mediastinal masses, goiter, mediastinitis, mediastinal fibrosis or aortic arch aneurysm. New growths, especially adenomas or polyps arising from the wall cause intermittent obstruction.

Tracheal obstruction leads to stridor, viz. noisy breathing with a harsh crowing sound mainly during



Fig. 133.1: Heimlich maneuver. Application of sudden pressure over the abdomino-thoracic region may dislodge the laryngeal foreign body

inspiration, and dyspnea. In the case of pedunculated growths the obstruction may be postural. Tracheal obstruction has to be distinguished from asthma and other causes of dyspnea. *Treatment* is surgical, after confirmation by bronchoscopy.

Bronchial Obstruction

Bronchial obstruction can occur in the larger bronchi or in the bronchioles and may be acute or chronic. The clinical manifestations vary accordingly. Acute obstruction is mostly intraluminal. It may be caused by aspiration of vomitus, blood, pus, mucus plugs, foreign bodies, or edema and exudates from the inflamed bronchial wall itself. Chronic obstruction is due to extraneous pressure from glands or intraluminal adenoma or bronchogenic carcinoma. Bronchial obstruction leads to collapse of the lung with subsequent infection of the distal parenchyma, bronchiectasis and fibrosis.

Treatment: Put the patient with head low so as to drain any fluid that may be present. Gentle tapping on the chest helps drainage. Aspiration of the tracheobronchial tree is needed if secretions are copious.

Endoscopic examination with removal of the obstruction should be done without delay. Surgery may be required if the condition does not clear with endoscopic aspiration.

134

Pneumonias

C. Sudheendra Ghosh, Ronald Win B

Chapter Summary

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- Klebsiella Pneumonia 911
- Mycoplasma Pneumonia 912
- Aspiration Pneumonia 912
- Hypostatic Pneumonia 913
- Bronchopneumonia 913

Introduction

Pneumonia is the sixth leading cause of death in the world today. It is also the major cause of death from infectious diseases. The mortality resulting from severe pneumonia varies from 20-40%. Mortality is more common among the elderly, and patients with comorbidities like diabetes mellitus, chronic obstructive pulmonary diseases, congestive heart failure, coronary artery disease, interstitial lung disease and carcinoma. Depending on the severity of the disease, the average cost of treatment varies from small to very large amounts.

Refer also chapter 37. Pneumococcal infection

Definition

Inflammation of the lung is called pneumonia. Community Acquired Pneumonia (CAP) is defined as an infection that begins outside of the hospital or is diagnosed within 48 hours after admission to the hospital in a patient who has not resided in a long-term facility for 14 days or more before the onset of symptoms. Up to 20% of patients with CAP require hospitalisation (Figs 134.1 to 134.3).

Hospital Acquired Pneumonia (HAP) is defined as infection of lung parenchyma occurring more than 48 hours after admission to a hospital. When HAP occurs the subset of patients receiving mechanical ventilation it is termed **Ventilator-Associated Pneumonia (VAP)**. VAP usually occurs at 48 to 72 hours following intubation.

Health Care Facility Associated Pneumonia (HCAP) is defined as pneumonia following admission to an acute



Fig. 134.1: X-ray chest showing lobar pneumonia Note: the consolidation of the upper zone right lung uniform opacity with clearcut margins, midline structures not shifted

care hospital on two occasions during the previous 90 days or residence in a long-term care facility or recent intravenous antibiotic therapy.

HAP is a common nosocomial infection with a rate between 5 and 10 cases per 1000 hospital admissions. The incidence in patients who require mechanical ventilation is 6 to 20 times higher. HAP is the leading cause of death from hospital acquired infections.

Pneumonias may be caused by specific pathogens like *Pneumococcus* or *Klebsiella* or by mixed flora which reach the lungs due to aspiration of infected material from the upper respiratory passages, stomach or exterior. The latter group is called aspiration pneumonia (Table 134.1).

Till a decade ago invariably the organism causing pneumonia sporadically in the community used to be pneumococcus. There has been a change in the pattern of causative organisms more recently. Due to the increase in number of immunosuppressed individuals in the community and more opportunities for cross infection between hospitalized patients and their home contacts the organismal pattern has changed even for community acquired pneumonias.

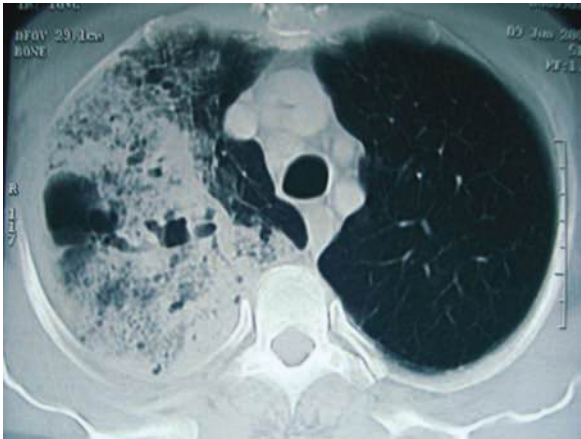
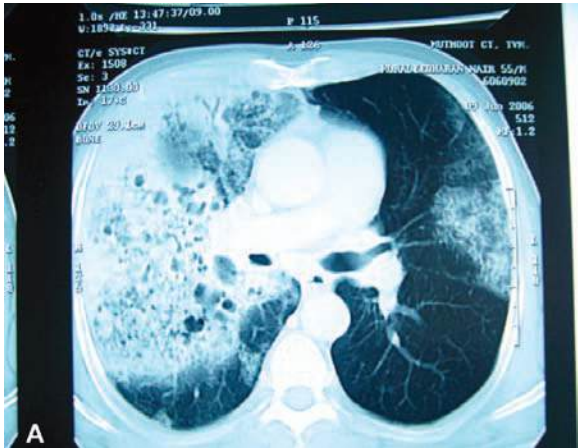


Fig. 134.2: HRCT Pneumococcal Pneumonia
Note the dense consolidation and air spaces in between



Figs 134.3A and B: Double pneumonia HRCT: Upper figure shows massive pneumonia right and smaller lesions left: Lower figure shows cavitation (abscess formation)

Other Organisms Causing Pneumonia

STAPHYLOCOCCAL PNEUMONIA

This is more frequently seen in debilitated subjects and in hospitalized patients. Respiratory viral infections

TABLE 134.1		
Causes of community acquired pneumonia		
Organism	Frequency %	
1. Pneumococcus	50-80	
2. Aerobic gram-negative bacilli	3-11	
3. <i>Kl. pneumoniae</i>	2-6	
4. <i>Staph.aureus</i>	1-10	
5. Mixed anaerobes	2-12	
6. <i>Mycoplasma pneumoniae</i>	3-44	
	(in young adults)	
7. <i>Haemophilus influenzae</i>	2.5-15	
8. Viral-influenza A and B, parainfluenza, adenovirus,	1-16	
9. <i>Strep. pyogenes</i>	1	
Pneumococcal pneumonia is described in Chapter 37.		

predispose to staphylococcal pneumonia. This is a dreaded complication in children with cystic fibrosis and in patients receiving immunosuppressant therapy. The organisms reach the lung through the bloodstream (pyemia) or along the respiratory passages.

Clinical features: The onset is with mild symptoms, but soon the condition worsens to produce grave toxemia, purulent and blood stained sputum and cyanosis. The lesions are generally multiple, giving rise to thin walled abscesses. It may frequently spread to the pleura to produce empyema or pyopneumothorax. Signs of lobar consolidation may not be evident. Diagnosis should be suspected from the clinical setting and the presence of toxemia far out of proportion to the pulmonary signs. Gram staining of sputum and culture reveal the organisms. Mortality varies from 20-25%.

Treatment: At present most strains of hospital-acquired staphylococci produce penicillinase. Hence penicillinase-resistant drugs such as cephalothin, cloxacillin or vancomycin may be necessary.

- Cloxacillin0.25-0.5 g oral, intramuscular or intravenous 6 h
- Cephalothin2 g 6 h.
- Vancomycin0.5 g 6 h.
- or Nafcillin1-1.5 g 6 h
- Early diagnosis and prompt treatment ensures cure.

KLEBSIELLA PNEUMONIA
Syn: Friedlander's Pneumonia

This is a grave illness seen in patients above the age of 40 years. Debilitating diseases, alcoholism, and malnutrition predispose this condition. Common site of involvement is the posterior segment of the upper lobe. The right lung is involved more frequently. The condition sets in with sudden chills, rigors, fever, dyspnea and cough



Fig. 134.4: Klebsiella pneumonia X-ray chest showing lobar consolidation with abscess formation right and pneumonitis left. Note: the bulging fissure

with gelatinous thick sputum streaked with blood. The course may be subacute or fulminant and fatal. Abscess formation is a common complication (Fig. 134.4). Mortality is high, ranging around 30%.

Treatment: Once the condition is suspected urgent treatment with cephalexin 1 g 6 h I M should be started. Gentamicin in a dose of 5-8 mg/kg may be added as a second antibiotic. Treatment may have to be continued for 2 weeks or more to ensure cure.

MYCOPLASMA PNEUMONIA

Syn: Primary atypical pneumonia, Eaton-agent pneumonia, Cold-agglutinin-positive pneumonia. This is caused by *Mycoplasma pneumoniae* which is a bacterium devoid of cell wall. It spreads in closed communities and in families through the respiratory secretions. Clinically it may present as (1) tracheobronchitis, or (2) pneumonia (in 30%). The disease starts insidiously with lassitude, headache, myalgia, and chest pain. Expectoration is scanty. Hemoptysis may occur. Physical examination of the chest may reveal only minimal findings. The skiagram shows extensive lesions, not made out clinically. Over 50% of patients develop cold agglutinins in their serum in a dilution of 1:32 or more by the second week. These non-specific antibodies agglutinate human O group erythrocytes at 4°C. These antibodies may be present for long periods. Complement fixation tests help to demonstrate specific antibodies. Tetracycline and erythromycin are effective against this organism.

Haemophilus influenzae pneumonia occurs principally in patients with underlying chest diseases such as chronic bronchitis emphysema syndrome, bronchiectasis and others. The organisms show resistance to aminopenicillins. Combination with co-amoxyclav is effective. Pneumonitis is a part of the general picture of infections by chlamydia, rickettsiae, several viruses including AIDS and systemic fungal infections.

ASPIRATION PNEUMONIA (NONSPECIFIC PNEUMONIA)

Infective material may be aspirated into the trachea and bronchi.

Causes Predisposing to Aspiration

1. Conditions which suppress the cough reflex, e.g. coma, alcoholic intoxication, general anesthesia.
2. Spill over of pus or gastric contents into the respiratory tract, e.g. sinusitis, tonsillitis, achalasia cardia, pharyngeal paralysis, tracheo-oesophageal fistula.
3. Violent contraction of abdominal muscles forcing gastric contents into the respiratory tract, e.g. epilepsy, tetanus
4. Aspiration from outside, e.g. drowning

The microbial flora is mixed, depending on the source of infection. The pulmonary lesion may be a localized massive pneumonia or a bronchopneumonia.

Clinical features: Aspiration of large volumes presents as pulmonary collapse or as pneumonia. In the presence of any of the predisposing factors, aspiration pneumonia should be suspected. Right lower lobe is more often affected because of the disposition of its bronchus. The upper lobe is also not infrequently involved in alcoholics and comatose subjects. If the obstruction is not removed by coughing or by other means the consolidation tends to persist and proceed to lung abscess. So also, aspiration pneumonia tends to recur if the primary cause is not removed.

Treatment: The general principles of treatment of pneumonia are applicable. In addition, prompt attention should be given to clear the respiratory passages of obstructing material. This can be achieved by postural drainage, physiotherapy to the chest to encourage coughing, suction using a mechanical sucker, or by bronchoscopic aspiration.

General Guidelines to Start Initial Antibiotic Regimens

Empirical selection of antimicrobial agents for treating patients with community acquired pneumonia is recommended as follows:

Outpatients: Generally preferred antimicrobial drugs are (not in any particular order) doxycycline, macrolides, or fluoroquinolones.

Selection considerations: These agents have activity against the most likely pathogens in this setting, which include *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*. Selection should be influenced by regional antibiotic susceptibility patterns for *S. pneumoniae* and the presence of other risk factors for drug-resistant *S. pneumoniae*. Penicillin-resistant pneumococci may be resistant to macrolides and/or doxycycline. For older patients or those with underlying disease, a fluoroquinolone may be a preferred choice; some authorities prefer to reserve fluoroquinolones for such patients.

For hospitalized patients, an extended spectrum cephalosporin combined with a macrolide or a β -lactam/ β -lactamase inhibitor combined with a macrolide or a fluoroquinolone (alone) are generally preferred.

For intensive care unit, an extended-spectrum cephalosporin or β -lactam/ β -lactamase inhibitor plus either fluoroquinolone or macrolide are generally preferred.

In patients with structural lung disease the preferred choice include: antipseudomonal agents (piperacillin, piperacillin-tazobactam, carbapenem, or cefepime) plus a fluoroquinolone (including high-dose ciprofloxacin). In patients, allergic to β -lactam, the preferred agents include fluoroquinolone or clindamycin. For suspected aspiration pneumonia, fluoroquinolone with clindamycin or metronidazole are the drugs of choices.

HYPOSTATIC PNEUMONIA

This is seen in elderly debilitated persons who are bed-ridden. It is a form of aspiration pneumonia. Inadequate cough reflex, excessive respiratory secretions and pulmonary congestion favour the development of hypostatic pneumonia. Microbial flora is derived from the upper respiratory secretions. The lesion is a bronchopneumonia. Hypostatic pneumonia acts as a preterminal event in many elderly debilitated individuals. Avoidance of prolonged recumbency, frequent change of posture (once in 2 h) in comatose and debilitated subjects and regular breathing exercises help to prevent this condition.

BRONCHOPNEUMONIA

Syn: *Acute lobular pneumonia, diffuse pneumonia*

Inflammation of the bronchial wall and the pulmonary parenchyma is the essential lesion in bronchopneumonia. This leads to patchy consolidation of the lung. The disease is more common during infancy and old age.

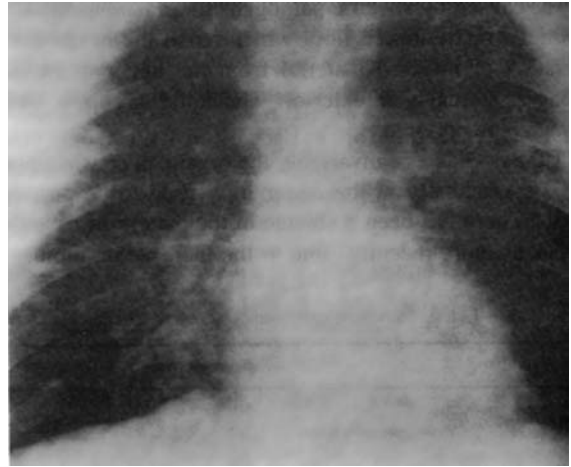


Fig. 134.5: Chest X-ray bronchopneumonia.
Note: Patchy opacities with indistinct margins

Causes: Bronchopneumonia may occur as a complication of several diseases such as whooping cough, measles and other viral infections in children. Chronic bronchitis, emphysema, and viral infections of the respiratory tract may be complicated by bronchopneumonia. Rarely bronchopneumonia may occur as the primary lesion.

Pathology: The common organisms are *staphylococci*, *streptococci*, *pneumococci*, and *H. influenzae*. Rarely *rickettsiae*, viruses and fungi may cause bronchopneumonia. The inflammatory lesions are widespread and patchy over both lungs, more in the lower lobes. The terminal bronchioles are affected initially and the alveoli are involved secondarily. There is collapse and consolidation in the affected lobule. Confluence of lesions may give rise to larger areas of consolidation. The exudate shows neutrophils and fibrin. Interstitial edema develops. There is compensatory emphysema around the collapsed alveoli.

Clinical features: The extent of pulmonary involvement and the virulence of the infective agent determine the clinical picture. Generally the onset is insidious. In the majority of cases bronchopneumonia follows the primary illness after a period of apparent improvement. The temperature goes up and tachypnea and cough may develop. The child may be cyanosed. Unlike as in lobar pneumonia, pleural involvement and herpes labialis are rare. Physical examination of the chest reveals widespread rales. Signs of extensive consolidation are rare. X-ray shows bilateral irregular and patchy shadows, more in the lower zones (Fig. 134.5).

Rarely bronchopneumonia may lead to bronchiectasis, pulmonary fibrosis, lung abscess or empyema. Mortality is higher in patients with chronic respiratory or cardiovascular disease.

Treatment: Prompt use of the appropriate antibiotic brings down the fever and helps in resolution of the lesions. In children suffering from measles and other viral infections, occurrence of bronchopneumonia should be anticipated

and early therapy started. In underdeveloped communities respiratory infections lead to severe setback in the growth and development of children and also predispose to prolonged morbidity and malnutrition.

135

Lung Abscess and
Pleuropulmonary Amebiasis

C. Sudheendra Ghosh, Dinesa Prabhu V.

Chapter Summary

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Lung Abscess

Localized suppurative lesion in the lung is called lung abscess. Tuberculous and cystic cavities, though secondarily infected by pyogenic organisms, are not usually included under this term.

Causes

1. Aspiration pneumonia: Aspiration of gastric contents or materials from the upper respiratory tract occurs during coma, anesthesia or deep sleep.
2. Other types of pneumonias.
3. Systemic pyemia.
4. Secondary infection of pulmonary infarcts.
5. Necrosis and infection of bronchogenic carcinoma.
6. Spread of amebic liver abscess and primary pulmonary amebiasis.
7. Bronchial obstruction leads to abscess formation distally.

Impairment of cough due to painful conditions in the chest or during postoperative period and conditions which impair ciliary function (heavy smoking or bronchitis) predispose to abscess formation. Right lower lobe is a common site for aspiration and suppuration. In the supine comatose patient, the posterior segment of the right upper lobe and apical segment of the right lower lobe being the

most dependent parts suffer more frequently. Next in frequency are the corresponding segments on the left.

Factors Predisposing to Lung Abscess

1. Aspiration of material occurring in dental sepsis: depressed consciousness, alcoholic bouts, epilepsy, head injury, coma, disturbances of swallowing, oesophageal stricture, bulbar palsy, achalasia cardia, and pharyngeal pouch
2. Necrotizing pneumonias
3. Hematogenous spread
4. Pre-existing lung disease: bronchiectasis, cystic disease, bronchial obstruction
5. Immunodeficiency

Pathology: Suppuration and necrosis of lung tissue constitute the basic pathological process. The abscess is lined by granulation tissue which limits the spread of infection. Common organisms are those derived from the upper respiratory tract and mouth. These include *aerobic* and *anaerobic streptococci*, *staphylococci*, *pneumococci* and *spirochetes*. Less commonly *E. coli*, *clostridia* and *B. proteus* may be present. When the abscess ruptures into a bronchus, pus is expectorated. The cavity contains pus and air. The wall is thick and ragged compared to tuberculous cavity or cyst. Chronic abscesses may be multiloculated. When the contents are discharged, healing occurs by fibrosis.

Clinical features: Early symptoms are those of pneumonia with fever, cough, rigor, malaise and pleuritic chest pain. Initially cough may be unproductive. Hemoptysis is not uncommon. When the abscess ruptures into a bronchus the cough become postural. The sputum is large in volume

(300-500 mL/day), purulent, blood stained and foul smelling. Systemic symptoms depend on the virulence of the organisms and general condition of the patient. In a moderately severe case the patient is febrile, toxic, and dyspneic. Painful clubbing of the fingers and toes develops in a few weeks.

Physical examination may reveal the presence of consolidation due to the surrounding pneumonic process. Pleural rub may be heard. Once the abscess opens into a bronchus, the auscultatory signs of cavitation are found. The breath sounds are cavernous and coarse. Post-tussive crepitations are heard.

Laboratory Findings

Neutrophil leukocytosis is present in most cases. *Sputum*: Once the abscess starts discharging pus, the sputum is large in volume, purulent, foul-smelling and blood-stained. On allowing it to stand in a conical glass the sputum settles into the typical three layers (froth above, serous portion in the middle and thick nummular particles below). The organisms can be identified by Gram staining and culture.

X-ray chest reveals consolidation with clearance in its center. A partially drained abscess is seen as a cavity containing fluid and air. Both posteroanterior and lateral views are necessary to locate the abscess (Figs 135.1 to 135.3).

Diagnosis: Clinical diagnosis is made from the history, physical signs of consolidation and cavitation and the presence of copious amounts of purulent sputum. X-ray chest confirms the diagnosis in almost all cases. Location of the abscess can be made by taking the lateral view skiagram as well. Microbial flora can be determined by sputum examination and microbiological tests. In the vast



Fig. 135.1: Pyogenic abscess. X-ray chest lung abscess right upper zone: Note the abscess cavity containing air and fluid



Fig. 135.2: X-ray chest tuberculous abscess with secondary infection

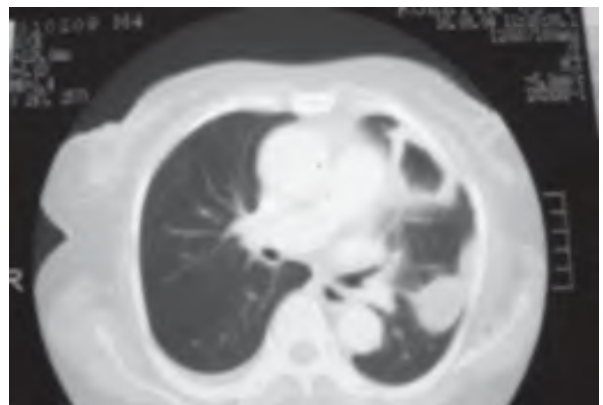


Fig. 135.3: HRCT Pulmonary abscess left upper lobe: Note the abscess cavity with the area of consolidation around

majority of cases these are sufficient to institute treatment and follow-up the case to recovery.

Bronchoscopy is indicated if there is likelihood of bronchial obstruction and malignancy or doubt about the etiology. Bronchoscopy will help to remove obstruction, drain the pus, collect the secretions for microbiological studies and also for biopsy.

Further investigations such as CT scan or MRI will be required in a few cases which do not run true to type.

Complications

Pulmonary: (a) Severe hemoptysis; (b) extension to other parts of the lung and to the other side; (c) pleurisy, empyema, and pyopneumothorax; and (d) local fibrosis and bronchiectatic changes.

Extrapulmonary complications: Brain abscess may develop due to metastases of septic emboli from the lung

which reach the cerebral circulation through the vertebral system of the veins (Batson's system).

Other complications include pulmonary osteoarthritis, emaciation and cachexia due to loss of large amounts of proteins (in the form of purulent sputum) and infection. If left untreated, lung abscess proves fatal.

Differential diagnosis: Lung abscess has to be differentiated from bronchiectasis, bronchogenic carcinoma, pulmonary tuberculosis, fungal infection, pulmonary cysts, and secondary neoplasms. Bronchiectasis is more chronic and usually bilateral. A cavitating bronchogenic carcinoma may resemble an abscess clinically and radiologically. Carcinoma is more common in smokers. The sputum is seldom profuse or purulent. It is more often blood stained with necrotic tissue being expectorated at times. Presence of hilar lymphadenopathy is suggestive of carcinoma. In cavitary pulmonary tuberculosis the sputum is mucoid and often not foul-smelling. Digital clubbing is less common. Tuberculosis affects the upper lobes more often, whereas abscess usually occupies the lower lobes. X-ray reveals thin walled cavities, without free fluid level.

In endemic areas, lung abscesses should be investigated for fungal pathogens by sputum tests and immunological studies. Cystic disease of the lung is often bilateral and present from early life. Radiologically the cysts appear thin-walled. Rarely cysts may be solitary. Digital clubbing is less marked in cystic disease of the lung.

Treatment: Principles of therapy include antimicrobial drugs, drainage of the abscess cavity and surgery in intractable cases.

Antibiotics: A properly collected sputum uncontaminated by oropharyngeal microbes should be sent for culture and sensitivity studies and the antibacterial drugs should be given in appropriate dosage till radiological clearance is complete. In most of the cases recovery is full in 4-6 weeks. Anaerobic infection has to be treated with metronidazole 500 mg given intravenously every eight hours. Drainage of the abscess is achieved by postural drainage and gentle tapotement over the chest. Respiratory physiotherapy to stimulate cough and help expectoration is instituted early. If clearance of the abscess is unsatisfactory, bronchoscopic aspiration may help. With proper medical treatment majority get cure.

Surgery: It is indicated in circumstances such as failure of medical treatment, residual fibrosis with bronchiectatic changes, suspicion of bronchogenic carcinoma, severe hemoptysis and pleural suppuration. If a reasonable course of medical treatment fails to bring about recovery, surgical resection of the abscess should be considered without undue delay. Risks of surgery are greater if the general condition of the patient has deteriorated.

Prevention of lung abscess: Lung abscess is largely preventable disease by preventing aspiration pneumonia. Other measures include prompt removal of bronchial obstruction, complete treatment of pneumonia, and early diagnosis of pulmonary suppuration.

Pleuropulmonary Amebiasis

Involvement of pleura and the lung are common complications of amebic liver abscess. Though primary metastatic infection of the lung can occur rarely, in over 90% of cases the infection is transdiaphragmatic. Direct spread from liver through transdiaphragmatic lymphatics results in pleural and pulmonary amebiasis. The common lesions are mild pleurisy, pleural effusion, empyema, consolidation, abscess formation, bronchopleural fistula and rarely bronchobiliary fistula. The empyema shows a tendency for encystment.

Clinical features: Pleuropulmonary amebiasis is commonly seen in the age group of 20-40 years and is more common in men, especially alcoholics. The initial symptomatology is that of liver abscess with fever, chills and pain over the right hypochondrium. The liver is enlarged, acutely tender and there is intercostal tenderness. Bulging and edema of the chest wall are also occasionally seen. Pleural and pulmonary involvement are accompanied by pleuritic pain, dyspnea, chocolate coloured sputum and hemoptysis. When there is a bronchobiliary fistula, the sputum is bile stained. Examination of the chest reveals signs of pleural effusion or consolidation depending on the lesion.

Diagnosis: This diagnosis should be suspected in right lower lobe lesions and right sided pleural effusions. Liver enlargement is present in most cases. Trophozoites of *Entameba histolytica* can be demonstrated in 20% of cases in the sputum or pleural fluid. X-ray shows elevated right hemidiaphragm with pleural effusion or pulmonary consolidation or abscess formation. Ultrasound examination is most helpful to reveal the abscess in the liver and other lesions in the abdomen. CT scan will reveal the lesion accurately.

Treatment: Systemic therapy with metronidazole and chloroquine helps to localize the lesion and full resolution in mild or even moderate cases. Secondary infection is to be treated with appropriate antibiotics. Presence of secondary infection can be assumed by examination of the aspirated pus.

In a few cases medical treatment suffices to clear the lesions. In moderate and large collections of pus and in the presence of high fever and toxemia suggestive of secondary infection, pleural aspiration or aspiration of the liver abscess is indicated.

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Allergic Disorders of the Lung

K.E. Rajan

Chapter Summary

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Extrinsic Allergic Alveolitis 917

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Clinical Features 919

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Bronchial Asthma

The term ‘asthma’ in Greek means ‘breathless’ or ‘breathe with open mouth.’

Asthma is a common chronic inflammatory condition of the airways whose mechanism is not completely understood yet. Epidemiological studies suggest that multiple genetic and environmental factors contribute to the causation of asthma, a clinical condition that is viewed as a cluster of related disorders. Genetic factors contribute to the variability with regard to age of onset, sensitivity of environmental causes and response to treatment. One study has identified a metalloprotein ADAM-33 that may have a role in inflammatory response to smooth muscle hypertrophy or hypersensitivity.

Airway inflammation is associated with airway hyper-responsiveness, airflow limitation, and respiratory symptoms. Airway inflammation leads to limitation of airflow by acute bronchoconstriction, edema of the airway wall, formation of mucus plugs, and airway remodelling.

Around 0.5-2% of the population suffers from asthma. The tracheobronchial tree reveals increased responsiveness to immunological and non-immunological factors. Several organic dusts, fumes, and chemicals precipitate immunological mechanisms. Non-immunological stimuli include thermal, chemical or psychological factors.

Bronchial asthma used to be classified into the *extrinsic (atopic)* and *intrinsic (cryptogenic)* types. In the former an external precipitating factor is identifiable, whereas in the latter, it is not. The antigens include ingested, inhaled or parenterally administered substances. The serum of such individuals may show elevated levels of specific antibodies belonging to the IgE and sometimes IgG classes. Persons developing extrinsic asthma have other atopic manifestations like eczema. The dermatological and respiratory manifestations show a see-saw relationship. In many cases family history of bronchial asthma may be present. Extrinsic asthma generally sets in by the age of 10-15 years. This type has a better prognosis from the point of response to therapy and mortality.

The age of onset for intrinsic asthma is after 30 years. Precipitating causes or raised antibody levels are not evident but these patients show a higher frequency of eosinophilia, aspirin sensitivity, and nasal polyposis.

Common stimuli which precipitate extrinsic asthma are inhaled allergens like house dust, pollens, fungi, animal hairs, insect scales and industrial fumes, and foods and drugs which are consumed in day-to-day life. Once sensitization occurs, these antigens release chemical mediators from the mast cells by interacting with the IgE molecules on their surface. Type I hypersensitivity reaction ensues. Asthma can also be caused by Type III (delayed) hypersensitivity mechanism mediated by IgG. In some individuals both Type I and Type III reactions occur, the former leading to an immediate asthmatic paroxysm and the latter leading to a delayed episode.

Exercise-induced asthma is a problem in children and young adults, in which bronchoconstriction is provoked by various forms of exercise such as running or climbing stairs, but others such as swimming may not do so. Provocation of bronchoconstriction by cold inspired air is a possibility in such cases. In many cases the attacks are brought on straight by the exercise, but in the others asthma sets in several hours after the exercise. The mechanism is a Type I hypersensitivity reaction. Short

acting β_2 -agonists are used to prevent exercise- induced asthma. Inhaled steroids are indicated and are useful. Systemic steroids are seldom necessary.

Respiratory infection and psychological stress play important roles in precipitating asthmatic paroxysms in both types. Both viral and bacterial infections may trigger off a paroxysm and the episodes tend to recur as long as the infections persist. In children, asthma may be the presenting symptom in primary tuberculosis. In adults, asthma may be aggravated by co-existent pulmonary tuberculosis. Cigarette-smoking and air pollution act as aggravating factors. The role of psychological stress is more in perpetuating the asthma than initiating the condition.

Many cases show familial predisposition. The atopic background may be inherited. Members of such families show asthma, eczema, hay fever and similar manifestations. The genetic locus for IgE, which is a mediator of Type I anaphylaxis is situated in the long arm of chromosome 11q. Obesity worsens asthma.

Extrinsic Allergic Alveolitis

This is a group of disorders caused by the inhalation of organic dusts. These organic substances induce a diffuse immune complex reaction in the walls of alveoli and bronchioles, leading to bronchioloalveolitis.

Clinically all these disorders cause dyspnea and systemic disturbances such as headache, muscle pain, fever and malaise within a few hours of exposure to the antigen (Table 136.1). Physical examination may reveal wheeze and end-inspiratory crepitations. X-ray of the chest may reveal diffuse small nodular shadows, predominantly involving the upper lobes (Fig. 136.1). High resolution CT thorax shows bilateral consolidation (Fig. 136.2). Pulmonary function studies show restrictive ventilatory defect with normal FEV₁/FVC ratio. Avoidance of the allergen causes relief of symptoms and recovery in the early stages, but in advanced cases the symptoms continue. Diffuse pulmonary interstitial fibrosis develops in those cases where exposure to the antigen



Fig. 136.1: X-ray chest: Extrinsic allergic alveolitis
Note: Bilateral diffuse opacities lower zones

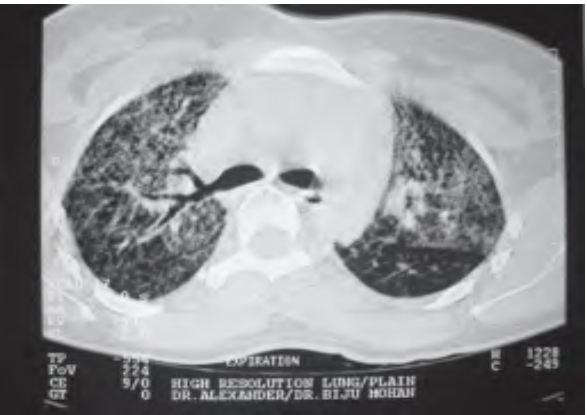


Fig. 136.2: HRCT extrinsic allergic alveolitis. Note: The diffuse thickening of the interalveolar septa and honeycombing

continues. Further complications include pulmonary hypertension and cor pulmonale.

Treatment consists of avoidance of the allergen and bronchodilators. In acute cases oral prednisolone 40 mg per day is indicated for 3-4 weeks, along with oxygen supplementation for hypoxemic patients.

Apart from these well-defined conditions, several forms of extrinsic allergic alveolitis occur in different occupational groups e.g. coir workers, cashew workers, workers in godowns and others.

PATHOLOGY

Inflammation of the airways is brought on by several factors. Eosinophils, T-lymphocytes (CD4+), macrophages and mast cells infiltrate the bronchial wall. The epithelium is vacuolated and the ciliated cells desquamate. Several cellular factors play their roles in the inflammatory process. Neuropeptides such as bradykinins, substance P and neurotensin A lead to bronchoconstriction and excessive secretion of mucus.

TABLE 136.1

Some common types of bronchioloalveolitis

Condition	Source
Farmer's lung	Mouldy hay, straw, grain dust
Bagassosis	Sugarcane dust
Byssinosis	Cotton dust
Mushroom worker's lung	Mushroom compost
Malt-worker's lung	Mouldy barley, malt dust
Maple bark stripper's lung	Mouldy bark
Bird fanciers' lung	Bird's droppings
Cheese worker's lung	Mouldy cheese

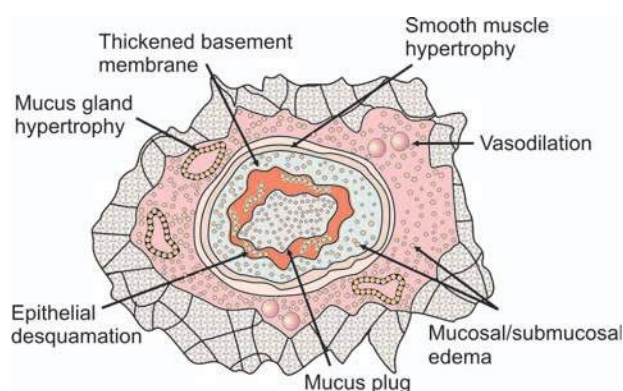


Fig. 136.3: Pathological features of asthma

Mast cells initiate the response on exposure to allergens, excessive osmotic changes and variations in temperature. Macrophages produce cytokines, which are either bronchoconstrictor or bronchodilator. Presence of eosinophils in the inflammatory exudate is characteristic of asthma. Eosinophils are derived from bloodstream. Major basic proteins and cationic proteins of eosinophils lead to destruction of mucosal surface. T-lymphocytes, especially CD4⁺ produce cytokines IL-3, IL-4, IL-5 and GM-CSF which modify the inflammation. TNF which is an inflammatory cytokine is expressed in greater amounts by mast cells. The broncho-alveolar secretions contain higher levels of TNF. Possibly platelet derived humoral factors also modify the inflammation.

The main chemical transmitters, which alter the airways, are histamine, prostaglandin and leukotrienes. These lead to contraction of bronchial muscle, increase in vascular permeability and excessive secretion of abnormal mucus (Fig. 136.3).

Airway inflammation persists for several years. Its severity correlates with the severity of asthma. Hyper-responsiveness of the inflamed airways is aggravated by autonomic and neural mechanisms. **The final result is obstruction of the small and medium sized airways brought about by mucosal edema, tenacious mucus and bronchoconstriction.**

CLINICAL FEATURES

The attacks start with dyspnea (often at rest), expiratory wheeze, and cough. The onset is abrupt in most cases. These attacks may occur seasonally or during all times of the year (perennial asthma). The attacks may last for several hours if untreated. Severity of the paroxysm varies. In the moderately severe case the patient is orthopneic and cyanosed, and the accessory muscles of respiration are active. There may be ineffective cough with only very scanty and tenacious mucoid expectoration. The asthmatic paroxysm in many individuals is ushered in by a bout of coughing and sneezing on exposure to the allergen. The pulse is rapid. Blood pressure is normal or elevated. In

severe cases pulsus paradoxus may occur. Expansion of the chest is considerably diminished, often to less than 2 cm during the attack. The diagnostic feature of bronchial asthma is the presence of expiratory wheeze heard all over the chest.

Once asthma occurs, the tendency is for the condition to persist for varying periods, even life-long, with remissions and exacerbations. About 50-60% of patients get cure or very considerable relief by altering their lifestyle such as change of residence, change of jobs, exercise programs including yoga exercises, changes of diet and others. Appropriate medication may improve the quality of life in the vast majority. 20-30% of patients are not free from asthma. However, attacks can be suppressed considerably by drugs. About 10% have severe disability despite active treatment. Allergic bronchopulmonary aspergillosis (ABPA) may develop in some asthmatic individuals.

Laboratory findings: These are often non-specific and they help to identify the coexisting disease. Some cases show moderate eosinophilia (10-15%). Examination of feces may reveal helminths, which may also contribute to the allergic reaction and increase in eosinophils. Sputum may reveal numerous eosinophils, mucus plugs and Curschmann's spirals (casts of smaller airways). Purulent sputum is indicative of respiratory infection. Culture reveals the infecting organisms. A simple method to infer whether infective or allergic causes trigger off paroxysm is to examine a Leishman's stain preparation of the sputum smear. Predominance of neutrophils suggests an infective cause whereas predominance of eosinophils suggests allergic etiology.

Identification of the allergen: Several tests have been introduced to identify the precipitating allergen. Intradermal tests are performed using a battery of antigens prepared from the common allergens prevalent in the area. In many instances the causative agent can be detected by the positive skin tests. These tests are of help in long-term management after tiding over the paroxysm.

Respiratory function tests reveal marked airway obstruction, which is relieved by the administration of bronchodilators.

Skiagram taken during the acute attack may show hypertranslucency due to emphysema but there may be no abnormality in between the attacks. It should be remembered that the radiological appearances and clinical severity show wide disparity in bronchial asthma.

Diagnosis

Diagnosis of bronchial asthma is clinical. The history of sudden attack of paroxysmal dyspnea, cough, and the auscultatory hallmark of expiratory wheeze heard all over the chest are diagnostic. Long duration of complaints,

history of allergy, and positive family history are other helpful clinical points.

Objective assessment of the severity of airways obstruction and response to bronchodilator therapy can be made by use of **bedside peak flow meter**. Respiratory function tests reveal gross reduction in FEV_1 , FEV_1/FVC ratio and peak expiratory flow rate (PEFR) and increase in the time taken for forced expiration. It is important to assess the severity of airways obstruction.

Confirmation of the diagnosis of asthma is usually achieved by serial peak expiratory flow rate (PEFR) monitoring. PEFR in the majority of cases shows a diurnal variation of more than 15% and improvement with therapy.

When it is necessary to investigate for provocative factors bronchial challenge testing or bronchial provocation testing (BPT) may be desirable.

Clinical features which indicate severe ventilatory impairment are given in the box.

1. Inability to narrate history continuously or severe distress even on mild exertion,
2. Cyanosis, flapping tremors,
3. Mental confusion,
4. Respiratory rate above 25/minute,
5. Heart rate persistently above 110/minute.
6. Inspiratory fall in blood pressure exceeds 16 mm Hg,
7. PEFR less than 40% of predicted value, and
8. Feeble breath sounds.

Differential diagnosis: Bronchial asthma has to be differentiated from other causes of paroxysmal dyspnea. These include chronic bronchitis emphysema syndrome (CBES), acute left-sided heart failure, acute bronchitis, tropical pulmonary eosinophilia, metabolic acidosis, and tracheal obstruction by foreign bodies or tumours.

It is important to distinguish left-sided heart failure (cardiac asthma) from bronchial asthma. Left-sided heart failure complicates valvular heart disease, systemic hypertension or ischemic heart disease. It causes paroxysmal dyspnea in the first half of the night whereas bronchial asthma is more common in the early hours of the morning. In bronchial asthma there is generalized wheeze all over the chest, whereas in cardiac failure, basal crepitations are more prominent, though generalized bronchospasm may also be evident at times. In heart failure, gallop rhythm may be evident. Careful search for the underlying disease may reveal the etiology.

TREATMENT

Treatment may be described under three heads: (1) treatment of the acute attack; (2) treatment in between attacks; and (3) treatment of acute severe asthma. Goals of asthma treatment are given in the box.

1. Prevent death (acute exacerbations of asthma)
2. Achieve and maintain symptom relief
3. Restore lung function and prevent relapse
4. Reduce the side effects of treatment
5. Control cost of management
6. Avoid complications

TREATMENT OF THE ACUTE ATTACK

At present the drugs of choice employed to stop an acute **attack are beta 2-agonist drugs**. They act mainly on the bronchial muscle as relaxants without much effect on the cardiovascular system. These include salbutamol, terbutaline, salmeterol, bambuterol and others. These can be given orally, as inhalations (aerosol or powder) or parenterally. The oral dose is effective within 15-20 minutes and the action lasts for 4-6 hours. The oral dose is; salbutamol 2-4 mg, terbutaline 2-4 mg and bambuterol 10-20 mg. These drugs can be given as metered dose inhalers. The usual dose ranges from 25-200 µg. Salmeterol is given as inhaled dose of 25-50 µg. These drugs are also usual components of cough syrup. Since larger doses of drugs are required for oral use, adverse side effects such as palpitation and tremours may occur in about 50% of patients. Aerosols are available as canisters of metered dose inhalers (MDIs) containing 100-200 doses. Each dose delivers 50-100µg of drug per puff. Good co-ordination of inhalation and pressure-actuation of canister is necessary for proper drug delivery. These have to be used prophylactically and therapeutically at the slightest warning of an impending attack. The dose being small, adverse side effects are minimal. The effect is immediate to set in and it may last for 4-6 hours. To avoid the chance of inadequate inhalation using aerosol sprays, spacers are available. The metered dose can be sprayed into the spacer, from which the patient can inhale it comfortably. Dry powder inhaler devices are delivery systems which provide the dose in powder form (rotahalers, acuhalers turbohalers and diskhalers). Dry powder devices are easier to operate as no co-ordination is required. Irrespective of type of delivery system, the patient has to be instructed and demonstrated the proper method of usage of the device. In any case the drug has to reach the lower airways, in order to be optimally effective.

Nebulizers, which can be carried by the patient or operated in the emergency room, are available for administration of these drugs. These can deliver larger doses as required. The drug solution is nebulized by passing oxygen or air under pressure through it.

Parenteral preparations of beta-adrenergic agonists are helpful when the paroxysm is severe and immediate relief is required.

Short acting β_2 -agonists (called 'relief medications') have no significant effect on the inflammatory response. Over-dependence on these agents has been established as one of the causes for fatal or near-fatal asthma attacks.

TABLE 136.2

Comparative daily dosage of commonly used inhaled steroids (in µg)						
Drug	Low daily dose		Medium daily dose		High daily dose	
	Adult	Child	Adult	Child	Adult	Child
Beclomethazone	200-500	100-250	500-1000	250-500	>1000	>500
Budesonide	200-600	100-200	600-1000	200-600	>1000	>600
Fluticazone	100-250	100-200	250-500	200-400	>500	>400

Corticosteroids: Glucocorticosteroids are currently the most effective anti-inflammatory medications for the treatment of asthma. They effectively improve lung function, decrease airway hyper-responsiveness, reduce symptoms, reduce frequency and severity of exacerbations, and improve quality of life. Inhaled corticosteroids are the preferred treatment for patients with asthma of all levels of severity. Patients requiring short acting β_2 -agonists more than 2 to 3 times a day should be treated with inhaled steroids. It is recommended that a starting dose of 400 µg/day for adults and 200 µg/day for children be employed. The dose must be titrated to the lowest dose, which maintains effective control of asthma. Parenteral, oral or nebulized steroids may be used in acute severe asthma. Often steroids are life-saving.

Table 136.2 gives comparative dosage of commonly used inhaled steroids.

Ill-effects of inhaled corticosteroids include oropharyngeal candidiasis and dysphonia. Systemic side effects develop, though this is less common than with oral preparations. Cataract may develop in some.

Indications for Short-course Oral Corticosteroid Therapy

- 1. Symptoms and PEFr deteriorate day by day (All acute forms of asthma).
- 2. PEFr less than 60% of the patient’s best PEFr.
- 3. Insomnia due to asthma.
- 4. Morning wheeze persists up to mid-day or even beyond.
- 5. Other treatments fail.

Sympathomimetic drugs: Acute asthma readily responds to sympathomimetic drugs. The time-honored drug, **adrenaline, 0.5 to 1 ml of 1:1000 aqueous solution** given subcutaneously relieves bronchospasm and terminates the paroxysm in minutes. Adverse effects include rise in BP, tachycardia, palpitation and precipitation of angina, especially in the elderly. Hurst’s method of administration is to deliver adrenaline subcutaneously in a dose of 1 drop every minute till the bronchospasm is relieved. With the advent of safer drugs, the use of adrenaline has been reduced but still in some cases where other drugs fail, adrenaline may give immediate relief.

Ephedrine used to be given widely in doses of 25 mg/ daily oral. Due to its adverse side effects, this drug is not

commonly used at present even though several anti-asthmatic preparations containing ephedrine are still in vogue.

Sympathomimetic drugs should be used with caution in hypertensives and elderly subjects with coronary artery disease or urinary obstruction. Fatal arrhythmias may be precipitated by repeated doses of these drugs.

Methyl xanthines: The common preparations include theophylline and etophylline. They can be given orally or as IV injections, singly or in combination.

Dose IV-combination vials of etophylline 169.4 mg and theophylline 50.6 mg to be given as slow IV injections or as IV drip in glucose 2-3 times daily. Tablets containing etophylline 77 mg and theophylline 23 mg are available for oral use to be taken 3-4 times daily. Sustained release tablets containing etophylline 150 mg and theophylline 35 mg are available to be taken 2-3 times daily.

Their beneficial effects include bronchodilation, synergistic action on the movement of the diaphragm, stimulation of the respiratory center and mild diuresis. When combined with β_2 -agonists they act synergistically.

Sustained-release preparations are preferred for oral therapy. Long-term treatment with sustained-release theophylline is effective in controlling asthma symptoms and improving lung function. Sustained-release theophylline is useful in the control of nocturnal symptoms and as an additional bronchodilator in patients with severe asthma. Theophylline may be used in patients with milder disease and as an add-on therapy to low or high doses of inhaled corticosteroids where further asthma control is needed.

Some patients with severe asthma attacks may benefit from intravenous aminophylline. For those who were not previously on oral xanthines, 5 mg/kg body weight is administered over 20 minutes, followed by an infusion at the rate of 0.5 to 0.7 mg/kg/h. Higher incidence of side effects such as palpitation, vomiting and arrhythmias is met with in some cases receiving intravenous aminophylline. Sometimes sudden vasomotor collapse or allergic manifestations may develop.

Anticholinergic agents: Since vagal tone accounts for bronchial muscle tone, anticholinergic drugs have been found to be beneficial in asthma. Inhaled ipratropium bromide and oxitropium bromide are bronchodilators that block the effect of acetylcholine released from cholinergic

nerves in the airways. These agents produce bronchodilation by reducing intrinsic vagal cholinergic tone to the airways. They also block reflex bronchoconstriction caused by inhaled irritants. They have no effect on airway inflammation. They are less potent bronchodilators than inhaled β_2 -agonists. They have a slower onset of action (30 to 60 minutes to maximum effect), but the effect is more sustained in duration.

Ipratropium bromide has an additive effect when nebulized together with rapid-acting β_2 -agonists for exacerbations of asthma. Usual dose is 0.25 to 0.5 mg by nebulizer every 4-6 hours or 20-40 μ g from a metered dose inhaler. It is useful as an alternative bronchodilator for patients who experience adverse effects of tachycardia, arrhythmia, or tremors from rapid-acting β_2 -agonists. Inhalation of ipratropium or oxitropium may cause a dryness of the mouth and a bitter taste. Unlike atropine, they do not cause mucociliary dysfunction, bladder neck obstruction or rise in intraocular pressure. Tiotropium bromide which is similar to ipratropium is available as rotacaps for inhalation- The dose is 18 μ g/inhalation, to be given once daily.

Complications of asthma: Though mortality is low, severe asthma may result in respiratory failure and death even in the most unexpected situation. Other complications include frequent respiratory infections, pulmonary collapse due to obstruction by viscid secretions, pneumothorax, mediastinal emphysema and cough fractures (fractures of ribs due to violent coughing). Children with asthma may show retardation of growth, especially if treated with systemic corticosteroids on a long-term basis. Longstanding bronchial asthma, punctuated with frequent respiratory infections may lead on to emphysema and chronic cor pulmonale.

Prevention of Recurrence

It is important to avoid known allergens, which can be identified. In the case of some allergens like house dust and pollen, desensitization can be achieved by repeated challenges.

Inhaled corticosteroids 200-800 μ g per day has been recommended as the treatment of choice for regular preventive therapy of asthma.

Long-acting inhaled β_2 -agonists (LABA) include formoterol and salmeterol. Their duration of action lasts for 12 hours or more. They relax airway smooth muscle, enhance mucociliary clearance, decrease vascular permeability, and may modulate mediator release from mast cells and basophils. LABA are indicated when initial doses of inhaled corticosteroids fail to achieve control of asthma. LABA must be combined with inhaled corticosteroids to control airway inflammation. Addition of LABA to inhaled corticosteroids improves symptoms, decreases nocturnal asthma, improves lung function, decreases the use of rapid-acting inhaled β_2 -agonists and reduces the number of exacerbations.

Cromones are a group of nonsteroidal anti-inflammatory medications. Administered as an inhalation they prevent the IgE-mediated mediator release from the mast cells. Sodium cromoglycate or nedocromil sodium may be used as preventive therapy in mild persistent asthma. Administered prophylactically, these medications inhibit allergen-induced airflow limitation after exposure to exercise, cold dry air, and sulfur dioxide. Therapy has to be continued for 4-6 weeks to determine its efficacy in individual patient. Usual dose of sodium cromoglycate is 20 mg every 6 hours. This drug should not be used during an acute attack since it may cause aggravation of the symptoms.

Anti-IgE: Binding of specific allergens to receptor-bound IgE on mast cells and basophils signals these cells to release preformed mediators (e.g. histamine) and synthesize other proinflammatory molecules (e.g. leukotrienes, cytokines, and chemokines). Subcutaneously administered anti-IgE blocks such a pathway in patients with moderate to severe asthma with an allergic component. It allows for reduction of oral/inhaled corticosteroids, and improves asthma control. Anti-IgE appears to be safe as add-on therapy and may reduce features of airway inflammation. It is an expensive modality of treatment.

Leukotriene receptor antagonist (Montelukast) is indicated as add-on therapy in mild to moderate asthma, which is not adequately controlled with an inhaled corticosteroid and a short acting beta-2 stimulant used as required. It reduces the dose of inhaled steroids in moderate to severe asthma. It may also be used to prevent exercise or drug induced asthma (e.g. aspirin-sensitive asthma). It is less effective than long-acting inhaled β_2 -agonists as add on therapy. Montelukast is given in a dose of 10 mg at bed time daily. These receptor analogues block the effects of cysteinyl leukotriene.

Anti-allergic H_1 -antagonists have mast-cell stabilizing properties. **Ketotifen**, when given in a dose of 1 mg twice a day as oral tablets on a long-term basis it reduces asthmatic paroxysms due to its inhibitory effects on the allergic response. It also helps to reduce the severity of allergic diseases of the eyes, nose and lungs. Its effects are fully established only when the drug is given regularly for 2 months or more. Sedation and weight gain are the prominent side effects of ketotifen.

Systemic steroid-sparing therapies: Steroid-sparing therapies include immunomodulators and macrolides. Examples include troleandomycin, methotrexate, cyclosporin, and gold. Their potential steroid-sparing effect may not outweigh the risk of serious side effects. Intravenous immunoglobulin has been shown to have some steroid-sparing effect, but this treatment is very expensive and has a high frequency of adverse effects.

Respiratory and other systemic infections should receive prompt attention. The appropriate antibiotic should be selected, based on microbiological tests. Tranquilizers,

TABLE 136.3 Levels of severity of acute asthma exacerbations	
Brittle asthma	– Wide PEF variability despite intense therapy. Sudden severe attacks on a background of well controlled asthma
Moderate asthma exacerbation	– Increasing symptoms – PEF >50-75% of best predicted value – None of the features of acute severe asthma
Acute severe asthma	Any one of the following: – PEF 33-50% of best/predicted – Respiratory rate ≥ 25/min – Heart rate ≥ 110/min – Inability to complete sentences in one breath
Life-threatening asthma	Any of the following in a patient with acute severe asthma – PEF < 33% of best/predicted, PEF not recordable – SPO ₂ < 92% – Central cyanosis – PaO ₂ < 8 kPa (60 mm Hg), especially on oxygen – Pa CO ₂ Normal (4.6-6.0 kPa) – Low pH – Silent chest, bradycardia, feeble respiratory efforts, dysrrhythmia, hypotension, exhaustion, confusion and coma
Near fatal asthma	– Raised PaCO ₂ and / or requiring mechanical ventilation

psychotherapy or suggestion under hypnosis may be useful adjuncts in persons with prominent emotional overlay.

Yoga and controlled breathing exercises are of considerable benefit in allaying the paroxysms.

Levels of severity of acute asthma exacerbations: Based on the severity of symptoms and signs, the Global Initiative. Against Asthma (GINA) has classified acute asthma exacerbations into 5 levels of severity, as detailed in Table 136.3.

ACUTE SEVERE ASTHMA

Acute severe asthma is a life-threatening emergency that places the patient at risk of developing respiratory failure. Patients are severely dyspneic, cyanosed, and often moribund. At this stage many of them are unresponsive to the ordinary bronchodilators. Dehydration may be evident.

Any patient of asthma may develop acute severe asthma as a complication. It may be precipitated by infection, allergic factors or psychological stress. Even in mild cases such paroxysms may supervene without warning. The attacks usher in either as progressive worsening of an existing paroxysm or sudden onset of severe dyspnea and air-hunger in a mild or moderate asthmatic. The attack may be so severe that the patient may not even be able to cry for help. Unless emergency care is given many of such patients may die of respiratory failure (Table 136.4).

MANAGEMENT OF ACUTE SEVERE ASTHMA

This is a medical emergency. This condition is generally unresponsive to conventional drugs administered in the

TABLE 136.4 Common risk factors for acute severe asthma	
• Use of more than 2 canisters per month of inhaled short-acting β₂-agonist • Two or more hospitalizations for asthma in the previous year • Past history of sudden severe exacerbations • Prior admission for asthma to an ICU • Prior intubation and ventilation for asthma • Current use of/or recent withdrawal from systemic corticosteroids • Co-morbidity such as cardiovascular diseases or chronic obstructive pulmonary disease • Serious psychiatric disease or psychosocial problems	

usual manner. Clinical assessment of the severity can be made from the intensity of dyspnea, cyanosis and inability of the patient to speak uninterruptedly. Estimation of peak expiratory flow rate gives an objective assessment of the condition.

GENERAL MEASURES

These involve (1) putting the patient to bed rest propped up with a back-rest, and (2) starting an intravenous infusion of normal saline. This aids in the administration of drugs and fluid replacement is essential to correct dehydration.

Emergency management: Patients should be hospitalized and managed in acute care facility as an emergency.

1. **Start oxygen** inhalation at the maximum possible concentration.

2. **Give rapid acting β_2 -agonists** inhalation in high doses immediately. Salbutamol (5.0 mg) or levosalbutamol (2.5 mg) is given, preferably using an oxygen-driven nebuliser. This dose may be repeated thrice at 15-30 minutes intervals. Four to six puffs of a metered dose inhaler administered using a large-volume spacer can be equally effective. Next choice is to give ipratropium bromide given either as nebulisation (0.5 mg) or as aerosol in a dose of 20-40 μ g, repeated at 4-6 hourly intervals. If inhalational therapy is not reliable, give salbutamol 500 μ g intravenously. Intravenous salbutamol helps to build up the blood level rapidly. For children the IV dose is 15 μ g/kg body weight.
3. **Hydrocortisone 200 mg or any** equipotent analogue (betamethasone 8 mg, dexamethasone 8 mg or methyl prednisolone 80 mg) is given as an intravenous push. Nebulised budesonide 0.5 mg every 12 hours may be of help to many patients. Prednisolone 10-15 mg is started simultaneously and repeated 6 hourly. Continue prednisolone 40-50 mg daily for at least 5 days.
4. **Intravenous aminophylline drip** may be started for maintenance therapy, if the patient is not on theophylline drugs already.
5. **Intravenous magnesium sulphate** (1.2-2.0 g given as IV infusion over 20 minutes) is a safe and effective treatment for those patients without good initial response to treatment.
6. Routine prescription of antibiotics is not indicated for acute asthma.

Sudden death may occur any time within 3-5 days of the acute episode and, therefore, such patients should be under surveillance for this period.

Ventilatory Assistance

If the condition does not respond to treatment or the respiratory embarrassment is increasing, ventilation should be assisted. If the secretions are tenacious and difficult to be expectorated, throat suction or bronchoscopic aspiration and bronchoalveolar lavage may be required. The indications are summarized in the box.

1. Pulses paradoxus
2. Central cyanosis despite O_2 inhalation
3. Deterioration of arterial blood gases despite treatment
 - a. $PaO_2 < 60$ mm Hg (8 kPa) and falling
 - b. $PaCO_2 > 40$ mm Hg (6 kPa) and rising
 - c. pH of 7.3 and falling
4. Extreme physical exhaustion
5. Clouding of consciousness, confusion, drowsiness
6. Coma, and
7. Respiratory arrest

Points to remember

Bronchial asthma is a very common disease. It may be mistaken for cardiac failure, hysterical hyperventilation or metabolic acidosis. Correct diagnosis and institution of emergency management in acute severe asthma is absolutely essential to save life. The common mistake committed by patients and doctors is to overlook the seriousness and emergency that can be caused by acute severe asthma.

Tropical Pulmonary Eosinophilia (TPE)

Syn: Weingarten's syndrome, pulmonary eosinophilosis

This common disease of the tropics is an immune hyper-response to filarial infection. It is characterized by an absolute eosinophil count of $2000/mm^3$ or more in peripheral blood, pulmonary symptoms and radiological changes, fever, dyspnea, and loss of weight. The disease is prevalent in India, Sri Lanka, Malaysia, Pakistan, Bangladesh, and several other tropical countries.

Etiology: Current evidence suggests that eosinophilia is an allergic reaction to helminthic parasites, particularly filarial worms. It is considered to be an immunologically mediated response to lymphatic filariasis in India. The role of filarial worms in the causation of tropical eosinophilia is suggested by several epidemiological, histopathological, and serological studies (See also section 6 chapter 70).

A constant and characteristic feature of TPE is peripheral blood eosinophilia ($2,000-50,000$ cells/ mm^3) in the presence of circulating filarial antibodies. A rapid response to diethylcarbamazine or positive serology will be diagnostic. If TPE goes untreated, there may be progression to chronic pulmonary fibrosis.

Pathology: Microscopically the lesion consists of inflammatory cell infiltration of several tissues. Lymphocytes and histiocytes are the initial invaders, later to be replaced by eosinophils. Lung biopsy shows an eosinophilic bronchitis and bronchopneumonia, with multiple small granulomas and areas of necrosis. Foreign body giant cells form tubercle-like nodules, surrounded by mononuclear cells. The extent of lesion is related to the duration of the disorder. While intact microfilariae are not generally seen, there may be fragments in the granulomas. The histological changes are not pathognomonic for tropical eosinophilia, since similar lesions may result from allergy to several other allergens.

CLINICAL FEATURES

The onset is insidious and the patients may come for treatment with several months' history. Males are affected more than females. The severity of symptoms does not correlate with the eosinophil counts. Many patients with

high eosinophil counts may remain asymptomatic. In some cases the onset may be acute resembling influenza, bronchial asthma or gastrointestinal disturbances. Patients may present with severe breathlessness, and nocturnal paroxysmal cough, accompanied by little sputum production. There is often a low-grade fever with occasional hemoptysis. Extrapulmonary manifestations occur in about 15% of patients and include splenomegaly, hepatomegaly, and lymphadenopathy. Blood samples show eosinophilia. No microfilaria is seen in peripheral blood. High IgE levels, seropositivity to filarial antibody, and rapid clinical improvement with administration of diethylcarbamazine are the hall marks of TPE.

The chronic form may present with exertional dyspnea, vague ill-health or asthmatic symptoms. Auscultation over the chest may show rhonchi with crepitations. Some cases present with fever, loss of weight, generalized lymphadenopathy, splenomegaly, and bleeding tendencies. The absolute eosinophil count ranges from 2000-10,000/mm³. In some cases the total leukocyte count may go as high as 30-40,000/mm³ and the eosinophils may form 70-90% of the total. All of them are mature eosinophils. The bone marrow shows infiltration by eosinophils and their precursors. If TPE goes untreated, there may be progression to chronic pulmonary fibrosis. Vast majority of cases are self-limiting and symptoms subside.

Skiagram of the chest reveals diffuse fine mottling with nodules 2-3 mm in size bilaterally in about 50% of cases. Miliary nodules or non-segmental, patchy opacities may be seen. Rarely the radiological features may be unilateral.

Diagnosis: Tropical eosinophilia should be suspected in all cases of respiratory disorders presenting with asthmatic symptoms of short duration. An absolute eosinophil count above 2000/mm³ is essential for making the diagnosis. Many patients show impaired lung function with reduction of vital capacity, total lung function, and residual volume. Some show combination of restrictive and obstructive features.

Tropical eosinophilia has to be distinguished from other parasitic infections, which cause lower degrees of eosinophilia, Loeffler's syndrome, aspergillosis, allergic alveolitis, bronchial asthma, and pulmonary tuberculosis. In bronchial asthma too, the eosinophils may be increased but the counts seldom reach the levels seen in tropical eosinophilia. Helminthic infections also cause moderate eosinophilia. These may be associated with respiratory symptoms. In these cases, eosinophilia clears up with de-worming. Loeffler's syndrome is the allergic respiratory features occurring during larval migration.

The course of tropical eosinophilia is benign with remission and exacerbation extending over several months or years. Death is rare, though a few cases have been reported.

Treatment: Drug of choice is diethylcarbamazine in a dose of 4-12 mg/kg/day for 10-14 days. In most of the cases the eosinophil count and symptoms subside promptly. Side effects are mild. These include headache, joint pains, anorexia, nausea, and vomiting. In a few cases there may be slight aggravation of respiratory symptoms at the start of treatment. Such cases respond to bronchodilators or corticosteroids. Prolonged follow-up is necessary, since the condition is likely to recur. Relapses also respond promptly to diethylcarbamazine.

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Chapter Summary

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Acute Bronchitis

This is acute inflammation of the bronchi and its ramifications. This is characterized by cough, discomfort behind the sternum, scanty expectoration to start with, later developing productive cough. In healthy individuals,

the infective agents are viral to start with, later bacteriae such as pneumococcus or *H. influenzae* may complicate the picture. At this time the sputum becomes purulent. In patients with underlying disease such as chronic bronchitis and emphysema, and in heavy smokers bacterial superinfection is the rule. Physical examination of the chest reveals wheeze and at times scattered crepitations.

In otherwise healthy subjects the disease subsides in 1-2 weeks with simple therapy with analgesics, expectorants and simple antibiotics such as ampicillin or cotrimoxazole. In those with underlying parenchymal diseases the primary condition is exacerbated and recovery is much slower.

Chronic Bronchitis

Chronic bronchitis is defined as a disease characterized by hypersecretion of mucus sufficient to cause cough and sputum on most days for at least three months in a year for two or more consecutive years. This happens in the absence of any other specific respiratory or cardiovascular disease.

In the initial stages the inflammation of the bronchi is intermittent and recurrent, later it becomes established. The larger air passages are affected during the early part of the disease, later obstructive features set in when the smaller airways are also affected. Infection leads to periodic aggravation of the symptoms and the sputum, which is mucoid, becomes purulent during these episodes. As the airways obstruction progresses, emphysema sets in. These two processes become established in the majority of cases so that the condition is termed **chronic bronchitis emphysema syndrome (CBES)**. The disease is more common in damp, cold, and dusty regions. Atmospheric pollution is accompanied by a higher incidence of CBES.

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of chronic morbidity and mortality throughout the world. The Global Initiative for Chronic Obstructive Lung Disease was created to increase awareness of COPD among health professionals, public health authorities, and the general public, and to improve prevention and management through a concerted worldwide effort. Chronic Obstructive Pulmonary Disease (COPD) is a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.

The most important risk factor for COPD is cigarette smoking. Pipe, cigar and other types of tobacco smoking popular in many countries are also risk factors for COPD. Passive exposure to cigarette smoke also contributes to respiratory symptoms and COPD.

Other documented causes of COPD include occupational dusts and chemicals (vapours, irritants, and fumes) when the exposures are sufficiently intense or prolonged.

Indoor air pollution from biomass fuel used for cooking and heating in poorly ventilated dwellings. Outdoor air pollution, which adds to the lungs total burden of inhaled particles, although its specific role in causing COPD is not well understood.

Symptoms of COPD include:

Cough

Sputum production

Dyspnea on exertion

Episodes of acute worsening of these symptoms often occur. Chronic cough and sputum production often precede the development of airflow limitation by many years, although not all individuals with cough and sputum production go on to develop COPD.

Pathogenesis

Chronic obstructive pulmonary disease (COPD) is a descriptive term given to the syndrome seen mostly in the elderly, who have airflow obstruction, not completely relieved by therapy. At least three distinct pathological processes may occur concurrently or separately in different subjects lead to COPD.

These are:

1. Emphysema which is due to destruction of alveolar walls
2. Chronic bronchitis with hypersecretion of mucus, and
3. Asthma with airway remodeling.

COPD encompasses chronic obstructive bronchitis with obstruction of small airways and emphysema with enlargement of air spaces, destruction of lung parenchyma, loss of lung elasticity and closure of small airways.

The inflammatory process in COPD differs from that in asthma in several ways. The type of inflammatory cells, inflammatory mediators, final outcome and response to treatment are different. In COPD the inflammation affects the peripheral airways-the bronchioles. The cells are macrophages, CD₈ lymphocytes and neutrophils. The lung parenchyma is affected. Unlike as in asthma there is no preponderance of eosinophils.

Oxidative stress also plays a significant role in the pathogenesis. Even though the lungs bear the main brunt of the disease, systemic effects also occur. Muscle weakness and wasting may develop as part of the systemic disorder.

Pathology: The bronchial mucosa shows hypertrophy and increase of the mucous glands and goblet cells with consequent overproduction of viscid mucus. The distal airways show narrowing of lumen caused by increased height of the epithelium and increased thickness of the muscle and connective tissue. The mucosa becomes ulcerated and when the ulcers heal, fibrosis occurs resulting in distortion of the lumen with stenosis and dilatation.

Distortion of the airways leads to permanent obstruction. Secondary infection occurs in the later stages. The ciliary movement is further impaired by the abnormally viscid mucus. This aggravates infection and a vicious cycle is established.

Severe recurrent infections cause the development of microabscesses in the bronchial wall. These heal with fibrosis. Squamous metaplasia occurs. Distortion and obstruction of the bronchial lumen result in air trapping and emphysema of the alveoli, some show collapse and fibrosis. The main pathological process can be summarized as follows:

- 1. Inflammation of the bronchi with enlargement of mucous glands and smooth muscle hyperplasia, all leading to wall thickening
- 2. Acinar distension due to the destruction of lung parenchyma probably mediated by imbalance of protease-antiprotease (alpha-1 antitrypsin) enzymes causing loss of support of small airways
- 3. Fibrosis and narrowing of the airways leading to increase in airway resistance.

The capillary bed is distorted and truncated and this aggravates the progression of pulmonary arterial hypertension. The pulmonary arteries become distended and atheromatous. Pulmonary hypertension gives rise to right ventricular hypertrophy and dilatation. Chronic cor pulmonale supervenes as time passes.

CLINICAL FEATURES

The clinical picture is varied depending on the severity and duration. The most frequent early symptom is cough recurring year after year, especially so in winter months. Later the cough becomes constant. Expectoration is mucoid and the sputum is tenacious, especially on waking up in the morning. Main complaint is the feeling of tightness of the chest. Physical examination reveals mild wheeze which disappears as the patient clears the bronchi by expectoration. Variable degrees of bilateral rhonchi and coarse crepitations are heard as adventitious sounds. Initially acute infections give rise to fever and purulent sputum. As the infection becomes established, fever and other general symptoms come down. At this stage the quantity and character of the sputum are more reliable indicators of infection. The sputum becomes copious in amount when bronchiectatic changes develop.

With the development of emphysema the chest assumes the inspiratory position and the respiratory excursions are considerably diminished. At this stage dyspnea is far out of proportion to the physical findings in the chest.

Key Indicators for Considering the Diagnosis of COPD

Chronic cough: Present intermittently or every day. Often present throughout the day; seldom only nocturnal

Chronic sputum production: Any pattern of chronic sputum production may indicate COPD
Acute bronchitis: Repeated episodes
Dyspnea that is: Progressive (worsens over time)
Persistent (present every day)
Worse on exercise
Worse during respiratory infections
History of exposure to risk factors: Tobacco smoke (including popular local preparations)
Occupational dusts and chemicals and smoke from home cooking and heating fuel.

DIAGNOSIS

Chronic bronchitis should be diagnosed from the history of recurrent cough extending over several years, mucopurulent sputum and the physical findings of bronchial obstruction and emphysema. X-ray is normal in the early stages but the features of emphysema may be evident later. X-ray may be helpful in identifying precipitating conditions like pneumonia, pneumothorax during the time of an exacerbation. HRCT is useful in quantifying the severity of emphysematous changes and locating areas with bronchiectatic changes.

Lung function tests show reduction in vital capacity, increase in the closing volume and features of airway obstruction (Fig. 137.1). Based on the spirometry values severity of obstruction can be categorised as mild, moderate severe and very severe.

Differential diagnosis: Chronic bronchitis has to be distinguished from asthma. Differentiation is easy in the early stages but there is considerable overlap of symptoms and signs in the advanced stages, and, therefore, the clinical assessment is difficult.

Other conditions like pulmonary tuberculosis, bronchiectasis, heart failure and bronchogenic carcinoma, obliterative bronchiolitis, diffuse pan bronchiolitis have to be ruled out in atypical cases.

Course and prognosis: Established chronic bronchitis is incurable. Over several years the condition progresses to

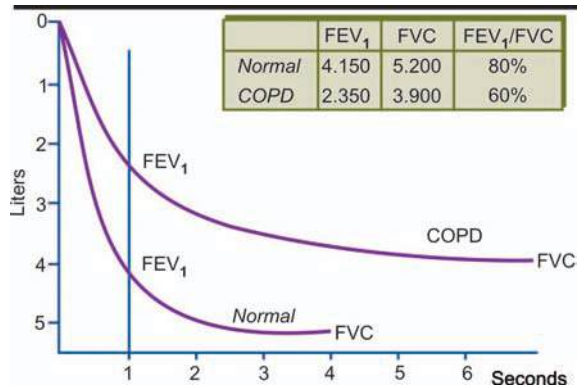


Fig. 137.1: Example of spirometric tracings and calculation of FEV₁, FEV₁/FVC ratio in normal and COPD

produce complications and death. Each infective exacerbation leads to further deterioration in lung function and precipitates the development of respiratory failure and cor pulmonale. Exacerbation can occur as a result of bacterial infection of the lower respiratory passages, viral infections of the respiratory tract or due to non-infective causes such as environmental allergens and pollutants.

Complications: These include:

- 1. Frequent respiratory infections,
- 2. Respiratory failure, and
- 3. Right-sided heart failure (cor pulmonale).

MANAGEMENT

General measures: Most effective single step to prevent deterioration is to stop smoking. This single measure itself affords considerable relief of symptoms. Environmental allergens and pollutants must be avoided by the patient.

Other general measures include improvement in general health, regular exercise, deep-breathing exercises, adequate sleep, treatment of obesity, and eradication of foci of sepsis in the throat, nose and paranasal sinuses. If these measures are started during the early phase of the disease, further progression can be arrested.

Drugs: Apart from the general measures, no active treatment is indicated in the early stages.

Treatment

Treatment of infective episodes: A broad spectrum antibiotic should be employed for 7-10 days during an

infective episode. Tetracycline or ampicillin may be started initially. Depending on the microbiological tests, the antibiotic may have to be changed.

Bronchospasm has to be relieved by the use of bronchodilators such as aminophylline, salbutamol or any other β -agonist. Ipratropium bromide is an anticholinergic muscarine receptor blocker, which blocks vagal reflexes responsible for bronchoconstriction. It is indicated when bronchospasm is troublesome (see box).

Ipratropium bromide delivered by a metered dose inhaler in a dose of 40-80 μ g helps to relieve bronchospasm without appreciable side effects. In COPD response of the airways to ipratropium is excellent. Tiotropium is a newer analogue which is equally effective.

Inhibitors of inflammatory response: Since inflammation plays a major role in the pathogenesis of COPD newer pharmacological agents are under trial. These include mediator antagonists which are capable of counteracting the effects of leukotrienes, lipooxygenases, interleukin B, tumor necrosis factor and the like. Protease inhibitors which inhibit neutrophil elastases, cathepsin and anti-inflammatory agents such as phosphodiesterase inhibitors are all in the process of development.

Several newer drugs especially phosphodiesterase-4 inhibitors are under trial. Roflumilast is a drug of this class given in a dose of 250 or 500 mg orally daily for 24 weeks. Results are encouraging.

Use of N-acetyl cysteine or bromhexine hydrochloride 8 mg thrice daily orally helps to liquefy the sputum. Steam inhalations help to improve vital capacity, relieve

TABLE 137.1

Therapy at each stage of COPD					
Old	0: At Risk	I: Mild	II: Moderate		III: Severe
			IIA	IIB	
New	0: At Risk	I: Mild	II: Moderate	III: Severe	IV: Very Severe
Characteristics	• Chronic symptoms • Exposure to risk factors • Normal spirometry	• FEV₁/FVC <70% • FEV₁ $\geq$ 80% • With or without symptoms	• FEV₁/FVC <70% • 50% $\leq$ FEV₁ <80% • With or without symptoms	• FEV₁/FVC <70% • 30% $\leq$ FEV₁ <50% • With or without symptoms	• FEV₁/FVC <70% • FEV₁ < 30% or FEV₁ <50% predicted plus chronic respiratory failure
Avoidance of risk factor(s); influenza vaccination					
Add short-acting bronchodilator when needed					
Add regular treatment with one or more long-acting bronchodilator, Rehabilitation					
Add inhaled glucocorticosteroids if repeated exacerbations					
Add long-term oxygen if chronic respiratory failure. Consider surgical treatments					

Commonly Used Formulations of Bronchodilator Drugs				
Drug	Metered dose inhaler (µg)	Nebulizer (mg)	Oral (mg)	Duration of action (hrs)
β₂-agonists				
Fenoterol	100-200	0.5-2.0	-	4-6
Salbutamol (albuterol)	100-200	2.5-5.0	4	4-6
Terbutaline	250-500	5-10	5	4-6
Formoterol	12-24		-	12+
Salmeterol	50-100		-	12+
Anticholinergics				
Tiotropium	18			
Ipratropium bromide	40-80	0.25-0.5	-	6-8
Oxipropium bromide	200		-	7-9
Methylxanthines				
Aminophylline (SR)	-	-	225-450	Variable, up to 24
Theophylline (SR)	-	-	100-400	Variable, up to 24

emphysema and open up the airways by expectorating the sputum.

Nonpharmacological measures: Noninvasive positive pressure ventilation and oxygen therapy at home using a simple nasal mask which eliminates the need for endotracheal intubation is beneficial. Long-term oxygen therapy has shown improved survival with better quality of life.

Pulmonary rehabilitation: Structured programme of education and exercises is very effective. Blowing into an air pillow repeatedly for 10-15 times twice a day and bending over a pillow held firmly on to the abdomen, in order to push the diaphragm up during expiration are simple maneuvers which can be practised at home.

Management of chronic respiratory failure: When hypoxemia becomes severe, i.e. PaO₂ below 55 mm Hg or SaO₂ below 80% at rest, continuous oxygen inhalation may have to be instituted for at least 18 hours a day. Oxygen therapy helps to reduce pulmonary arterial tension and allay cor pulmonale. In intractable cases lung transplantation may have to be considered.

Lung volume reduction surgery (LVRS): This has been found to be useful in selected cases. The rationale for this technique is to reduce the volume of over inflated emphysematous lung by 20-30%, in order to improve the elastic recoil of the lungs, to improve the configuration of the diaphragm, chest wall mechanics and gas exchange.

Lung transplantation: This procedure is in vogue for more than a decade in advanced countries, it is still not available in India. Transplantation of a single lung or both heart and lungs as a whole is possible. Transplantation

should be considered if the recipient is below 55 years of age, and is free from underlying conditions such as advanced diabetes, malignancy, hepatic or renal failure and conditions which impair mechanics of the chest wall.

The donor should be ABO and HLA compatible with normal lungs, preferably between 12 and 50 years of age and with normal cardiopulmonary anatomy. Usually cadaver lungs are used for transplantation. Complications may occur as in the case of any other major organ transplantation.

Indications

- 1. Incurable respiratory failure—chronic or acute due to pulmonary causes
- 2. Irreversible structural and functional abnormalities in the lung such as fibrosis, extensive bronchiectasis, cystic disease, emphysema and others.

Appendix

Standard guidelines have been laid down by several National Societies for management of COPD. Tables 137.1 to 137.3 give the recommendations of the British Thoracic Society.

ACUTE EXACERBATIONS OF COPD

Tables 137.2 to 137.4.

Assessment of Bronchodilator Response

If there is an increase of at least 15% of the baseline FEV₁ or at least 200 mL it is considered beneficial (British Thoracic Society).

TABLE 137.2

Indications for hospital assessment or admission for acute exacerbation of COPD

- Marked increase in intensity of symptoms, such as sudden development of resting dyspnea.
- Severe background COPD.
- Onset of new physical signs (e.g. cyanosis, peripheral edema).
- Failure of exacerbation to respond to initial medical management.
- Significant co-morbidities.
- Newly occurring arrhythmias.
- Diagnostic uncertainty.
- Older age.
- Insufficient home support.

TABLE 137.3

Medical Research Council modified dyspnea scale for breathlessness during daily activities

Grade 0	No breathlessness.
Grade 1	Breathless with strenuous exercise.
Grade 2	Short of breath when hurrying on the level or walking up a slight hill.
Grade 3	Walks slower than people of the same age on the level or stops for breathe while walking at own pace on the level.
Grade 4	Stops for breath after walking about 100 yards.
Grade 5	Too breathless to leave the house or breathless when dressing or undressing.

TABLE 137.4

Hospital discharge criteria for patients with acute exacerbations of COPD

- Inhaled β_2 -agonist therapy is required no more frequently than every four hours.
- Patient, if previously ambulatory, is able to walk across the room.
- Patient is able to eat and sleep without frequent awakening by dyspnea.
- Patients have been clinically stable for 12-24 hrs.
- Arterial blood gases have been stable for 12-24 hrs.
- Patient (or home caregiver) fully understands correct use of medications
- Follow-up and home care arrangements have been complemented (e.g. visiting nurse, oxygen delivery and meal provisions).
- Patients, family and physician are confident patient can manage successfully.

Bronchiectasis

Permanent dilatation and distortion of the bronchi is called bronchiectasis.

Etiology and pathogenesis: Most of the cases of bronchiectasis result from acquired causes.

1. Obstruction to the bronchus due to any cause leads to distal collapse of the pulmonary segment. The pull on the bronchi by the collapsed alveoli leads to dilatation of the bronchi. In the initial stages this is reversible and the bronchi regain their normal size when the lung expands. If the obstruction persists, accumulation of mucus occurs distally, infection supervenes and the bronchial wall is destroyed permanently. This results in permanent dilatation. The infective organisms are streptococci, pneumococci, klebsiella, and anaerobes.
2. Bronchiectasis may follow several viral infections without passing through the obstructive phase.
3. Congenital defects in the bronchial wall lead to bronchiectasis. The classical example is *Kartagener's syndrome*, which is characterized by dextrocardia, situs inversus, sinusitis, and defects of ciliary function in the bronchi and non-motile sperms.
4. Middle lobe bronchiectasis is a sequel to pulmonary tuberculosis. This is caused by obstruction to the middle lobe bronchus by tuberculous glands. This is called "**middle lobe syndrome**" or "**Brock's syndrome**".

Pathophysiology

Bronchiectasis is primarily a disease of bronchi and bronchioles involving a vicious circle of transmural infection and inflammation with mediator release. Bronchial mucosa shows infiltration by neutrophils and T lymphocytes. The expectorated sputum has higher content of elastase and chemoatracants – interleukin – 8, TNF α , and prostanoids. The lesions may be localized or diffuse and generalized.

CLINICAL FEATURES

The clinical picture is very chronic, extending over several years. The common site of lesion is the left lower lobe. Though children may be affected, usually symptoms manifest in early adulthood or middle age. Males are affected more than females. Digital clubbing is a prominent sign, sometimes being associated with hypertrophic pulmonary osteoarthropathy.

Postural cough with the production of large quantities of purulent and foul smelling sputum is the presenting complaint in most cases. On standing the sputum settles into 3 layers as described under lung abscess. Hemoptysis may occur frequently. This may be mild or severe. Recurrent infections such as pneumonia may develop. Repeated affection of the same lobe or segment should suggest the possibility of underlying bronchiectasis.

Bronchiectasis sicca is the condition in which bronchiectasis presents with mild or severe hemoptysis without purulent sputum.

Physical examination may reveal impairment of the percussion note and diminution of respiratory sounds over



Fig. 137.2: Cystic bronchiectasis. Note: The cystic areas in both lower zones

the affected area. The diagnostic finding is the presence of coarse, persistent leathery rales.

Complications

At times bronchiectasis may present with one of its complications. These include massive hemoptysis, recurrent pneumonia, emphysema, septicemia, brain abscess, and cor pulmonale. Anemia develops in long-standing cases due to chronic sepsis and recurrent hemoptysis. In untreated cases secondary amyloidosis may develop.

Diagnosis: Bronchiectasis should be diagnosed by the long history, presence of clubbing, postural cough, coarse leathery rales over the affected part and reasonably normal general health. Once established, bronchiectasis is not curable by medical treatment.

Differential diagnosis: Bronchiectasis should be distinguished from chronic bronchitis and emphysema, lung abscess, tuberculosis, congenital cystic disease of the lung, pulmonary sequestration and malignancy.

Lung abscess generally develops acutely. The right lower lobe is affected more often and the signs are localised. Tuberculosis is more common in the upper lobes, and clubbing is not prominent in uncomplicated cases. Features like digital clubbing and copious sputum are seen in tuberculous bronchiectasis. Cystic disease is not uncommon. All age groups are affected. A long history of recurrent respiratory disease is present in the majority of cases. Clubbing is not prominent. The cysts may be localized or generalized. Clinical distinction from bronchiectasis is difficult. Presence of cysts in other organs like the kidneys, liver, etc. suggests the probability of congenital cystic disease of the lung. X-ray reveals the presence of soap bubble-like or ring shadows (Fig. 137.2).

Pulmonary sequestration is a developmental anomaly where a portion of the lung receives aberrant blood supply



Fig. 137.3: Pulmonary sequestration HRCT. Note: The vascular anomaly at the site of sequestration

usually from the abdominal aorta. Patient may present with recurrent hemoptysis and other features of bronchiectasis (Figs 137.3 and 137.4).

Diagnosis can be confirmed by bronchography which helps to determine the extent and type of bronchiectasis. The lesion may be sacular, fusiform or cylindrical. Plain X-ray of the chest is not a reliable investigation to assess the site and extent of bronchiectasis. High resolution computed tomography (HRCT) has become the investigation of choice to assess the lesions in bronchiectasis. Availability of HRCT has eliminated the need for bronchography.

Management: General measures include high protein diet, treatment of intercurrent infections, and removal of focal sepsis from the upper respiratory tract.

Principles of specific therapy include postural drainage, administration of antibiotics, respiratory exercises and in selected cases, surgical excision. Postural drainage helps to clear the bronchi and bring about relief. The patient should be instructed to practise postural drainage



Fig. 137.4: Pulmonary sequestration: Aortogram showing aberrant arterial supply from thoracic aorta

regularly. This gives relief of cough and also the foul smell. The fetid odor of the breath can be controlled by administering steam inhalations containing tincture benzoin co. or eucalyptus oil. The choice of antibiotic is determined by microbiological studies. Intermittent antibiotic therapy is required to clear infection and prevent exacerbation. The site of lesion may have to be excised if medical treatment fails.

Indications for Surgery

1. The disease is localized to one lung or one segment and is not amenable to medical therapy;
2. Socioeconomic factors such as noncompliance by the patient;
3. Uncontrollable hemoptysis in which the site of origin of blood may be detected by emergency bronchoscopy and surgical resection has to be planned;
4. To reduce the area of infection. Even in bilateral disease sometimes surgical resection may have to be done on the more affected side, with a view to reduce the surface area of infection; and
5. To remove an obstructive lesion which tends to perpetuate the condition e.g., bronchial growth or bronchostenosis.

Emphysema

Definition: Emphysema is defined as a pathological increase in the size of airspaces distal to the terminal bronchioles, with destruction of the alveolar walls. The term hyperinflation is used to denote non-pathological overdistension.

Etiology

Diseases of the airways: Chronic bronchitis, prolonged exposure to irritants and dusts (heavy cigarette smoking), and chronic partial bronchial obstruction.

Conditions associated with alpha-1 antitrypsin deficiency: Persons who have alpha-1 antitrypsin deficiency develop emphysema by the third or fourth decade of life.

Chronic bronchial asthma leads on to emphysema as a sequel. Persons who have to hold breath for prolonged periods for diving under water for collecting shells, clay and the like develop emphysema over a period of 15-20 years. *Bidi* or cigarette smoking and repeated respiratory infections accelerate the process.

Several pneumoconioses give rise to emphysema as part of the pathological process or as compensatory mechanism, e.g. coal worker's pneumoconiosis, silicosis.

Occupational causes: Several occupations which require forced expiratory effort as seen in furnace blowers, goldsmiths, and users of wind instruments predispose to the development of emphysema in susceptible subjects.

Exposure to cadmium leads to the development of emphysema and pulmonary fibrosis.

Pathology: The lungs are in the inflated position occupying the whole of the pleural cavity. Since the elastic tissue is damaged, the lungs lose their elasticity and they fail to collapse when the chest is opened during autopsy. The diaphragm is depressed and respiratory excursions are diminished. The alveoli are overdistended. The septa rupture and neighbouring alveoli coalesce to form air cysts. The pulmonary vascular bed is progressively diminished and pulmonary arterial hypertension results. Reduction of alveolar surface area leads to impairment of gas exchange. Right ventricular hypertrophy and cor pulmonale may develop. Emphysematous bullae may rupture to produce spontaneous pneumothorax.

CLINICAL FEATURES

The main symptom is exertional dyspnea. As the condition progresses, even ordinary activity like talking, eating or lying flat may cause dyspnea. The chest is distended in the position of full inspiration. Expansion is diminished and the accessory muscles of respiration are active. Expiration becomes an active process due to loss of elasticity of the lung. Infective episodes occur frequently.

Physical examination reveals barrel-shaped chest with diminished expansion, hyper-resonance on percussion, obliteration of cardiac and liver dullness and diminished breath sounds with prolonged expiration. Due to increased intrathoracic pressure especially during expiration, the neck veins become distended during expiration and collapse during inspiration. The apex beat is felt feebly because of interposition of the distended lung. Right ventricular hypertrophy produces a heaving impulse in the epigastrium and subxiphoid region. Left parasternal heave may not be evident on account of the inflated lung covering the heart (Fig. 137.5).

Special Forms of Emphysema

Compensatory emphysema: This is the condition in which the normal lung tissue undergoes hypertrophy to compensate for extensive damage to the other lung or other parts of the same lung. Being a compensatory phenomenon, this is asymptomatic. The respiratory excursion of the normal lung is increased in this case.

Atrophic emphysema: This condition is the result of senile atrophy of inter-alveolar septa. The total lung volume is not increased.

Bullous emphysema: In this condition air spaces exceeding 1 cm in diameter develop either congenitally or as a part of acquired generalized emphysema. With passage of time these bullae enlarge and become giant bullous emphysema. They may rupture to produce

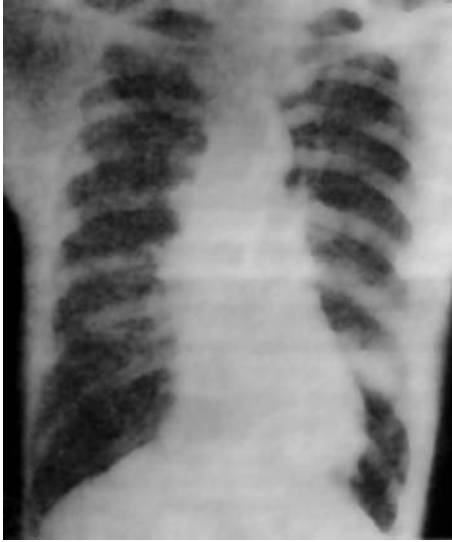


Fig. 137.5: X-ray chest—Emphysema. Note: The inflated position of the rib cage, lower level of the diaphragm and hypertranslucent lung fields



Fig. 137.6: Multiple bullae-infected. Note: Large thin walled cystic spaces on the right and abscess containing air and fluid in the left lung

pneumothorax. At times the bullae may get infected to produce abscesses (Fig. 137.6).

Alpha-1 Antitrypsin Deficiency

Alpha-1 antitrypsin (AAT) is one among the serine protein inhibitors which occurs in the plasma. It is an inhibitor of neutrophil elastase. It has also got anti-inflammatory properties. AAT is a glycoprotein normally secreted by the liver and circulating in blood. It moves with the alpha-I band on serum protein electrophoresis. 90% of the trypsin-inhibitory activity of serum is attributable to AAT.

From the plasma, AAT diffuses into lung tissues, where it acts as an anti-elastase, the elastase being secreted

by neutrophils. Elastase is capable of destroying the connective tissue framework of alveolar walls. Excessive destruction of alveolar walls may lead to emphysema. Cigarette smoking which predisposes to accumulation of neutrophils in the lung aggravates the destructive process. Cigarette smoke also inhibits AAT directly. AAT deficiency may be congenital or acquired. The gene frequency of the defect occurs in 1 in 2000 to 1 in 5000 of the population. In the congenital form it is transmitted as an autosomal recessive. More than 75 alleles of AAT gene are known. In the inherited form the hepatic production of AAT is less than 15% of normal.

Patients with AAT deficiency develop panacinar emphysema by the third or fourth decade of life. The congenital form may also be associated with hepatitis and jaundice in the newborn and cirrhosis liver in adults. Such patients show accumulation of abnormal AAT in hepatocytes.

AAT deficiency can be treated by replacing AAT by IV infusion weekly or monthly to individuals whose serum AAT levels are below 1 mmol/L and who have abnormal lung functions. AAT for therapeutic purposes is obtained from pooled plasma. AAT can also be administered as an aerosol.

Pulmonary Collapse

When a portion of the lung becomes airless it is termed collapse or atelectasis. Collapse may be present from birth, when a portion of the lung fails to expand. Acquired collapse is more common and this is caused by absorption of air from a previously normal lung.

Causes

Obstruction to the air passages: The air passages may be obstructed by intraluminal or extraluminal causes.

1. Foreign bodies which may be inhaled accidentally or aspirated by comatose patient.
2. Tumours of the bronchus: Carcinoma, adenoma, bronchial stenosis.
3. Copious secretions and thick plugs of mucus.
4. Extrinsic pressure on the bronchus by lymph nodes, tumours, etc., e.g. middle lobe syndrome in pulmonary tuberculosis.
5. Pneumothorax and pleural effusion.

In bronchial obstruction the air already present in the alveoli is absorbed. The lobe or segment shrinks due to its inherent elastic recoil. Functional impairment depends upon the extent of lung tissue affected.

CLINICAL FEATURES

Symptoms depend upon the extent of collapse and its onset. Acute lesions are more symptomatic than chronic ones. Small areas of atelectasis may be asymptomatic. Massive collapse gives rise to dyspnea with or without



Fig. 137.7: X-ray chest. Pulmonary collapse. Note: 1. The uniform opacity with clearcut concave margins. 2. Shift of trachea to the affected side

cyanosis. The movement of the affected side is reduced and the chest is flattened. Trachea and cardiac apex are shifted to the same side. Percussion note over the affected

side is diminished. Breath sounds are absent or diminished. Adventitious sounds are usually absent.

Investigations

1. *Radiology:* Skiagrams show the collapsed portion as homogenous opacities with sharp concave borders. Both the posteroanterior and lateral views are required for proper localization (Fig. 137.7).
2. *Bronchoscopy:* It is necessary to visualize the affected bronchi.
3. *Bronchography:* It reveals the actual site and nature of the block.

Complications and sequelae: Pulmonary collapse leads on to infection, abscess formation, and fibrosis of the affected segment. Bronchiectasis may develop as a late sequel.

Management: Emergency measures include removal of the obstructive cause and physiotherapy to expand the lung. Antibiotic therapy should be started to prevent aspiration pneumonia. Pleural diseases must be treated promptly to prevent permanent damage to the lungs.

Prevention: Proper physiotherapy and measures to protect the respiratory tract from aspiration of gastric contents go a long way to prevent pulmonary collapse.

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Occupational Lung Diseases
Syn: Pneumoconiosis

Chapter Summary

- General Considerations 934
- Silicosis 935
- Coal Worker's Pneumoconiosis 936
- Asbestosis 936
- Byssinosis 936

General Considerations

934 The term pneumoconiosis was coined by Zenker in 1866 to define a group of diseases caused by inhalation of dusts-

organic or inorganic. Inorganic dusts such as silica, asbestos or coal dust and organic dusts such as mouldy hay, cotton dust or sugarcane dust may lead on to pneumoconiosis. At present several occupations are known to be associated with this risk. More and more entities are likely to be recognized with the expansion of industry (Table 138.1).

Development of the pathological lesions depends upon several factors such as the nature of the substance inhaled, the concentration in the atmosphere, duration of exposure, particle size, and responsiveness of the individual. Particles below 10 µm in size reach the alveoli.

TABLE 138.1

Common causes of pneumoconiosis in India	
Condition	Industry
1. Silicosis	Mining, ceramics, potteries, foundries, metal grinding, stone crushing, agate grinding, slate pencil industry.
2. Coal workers' pneumoconiosis	Coal mining
3. Asbestosis	Asbestos cement, asbestos textile, asbestos mining and milling.
4. Byssinosis	Cotton textile industry

Alveolar macrophages carry them to the interstitial space where inflammatory reaction sets in. The process continues over the years and leads to gross functional and structural changes resulting in severe morbidity.

Lesions caused by inorganic dusts range from minimal inflammatory reaction around the dust particle to more marked changes like focal emphysema, interstitial fibrosis and calcification. Some dusts like asbestos are carcinogenic. In some disorders such as silicosis, the host's immune mechanism is altered making them more susceptible to develop tuberculosis.

Several organic dusts are widely distributed in the agricultural belts of India. They exert deleterious effects by local irritation, sensitization to the components of the dust or sensitization to fungal contaminants. They cause damage principally on the alveolar ducts to produce extrinsic allergic alveolitis.

The factors which lead to the final picture depend upon the substances inhaled. In general, they are:

1. Mechanical blockage,
2. Chemical irritation of the airways, chlorine and acid fumes,
3. Direct toxicity to the lung parenchyma, e.g. phosgene, methyl isocyanate,
4. Fibrosis, e.g. silica,
5. Sensitization, e.g. dander of animals, fungi, cotton dust,
6. Chronic granulomatous processes, e.g. beryllium toxicity
7. Predisposition to secondary infection, e.g. silicosis predisposes to tuberculosis, and
8. Neoplasia, e.g. asbestos.

Genetic factors modify the susceptibility to develop pneumoconiosis. On exposure, susceptible persons show early signs of ill-health, whereas the others are relatively immune. Other factors such as tobacco smoking, nutrition, and infections also may have roles in determining the final outcome in individual subjects. Industrial legislation requires adequate protective steps to be undertaken by establishments to safeguard against the development of pneumoconiosis amongst the workers.

SILICOSIS

Silicosis is the irreversible fibrosis of the lungs caused by inhalation of free silica dust (silicone dioxide). Over 3 million people working in various types of mines, ceramics, potteries, foundries, metal grinding, stone crushing, agate grinding, slate pencil industry, etc. are occupationally exposed to free silica dust and are at potential risk of developing silicosis. Silicosis may occur in combination with anthracosis. This is a major cause of permanent disability and mortality. In India it was first reported from Kolar gold mines, Karnataka in 1947.

The silica particles are ingested by the phagocytes, which accumulate and block the lymphatic channels. The lesions produced by silica dust are similar to those produced by coal dust, but the lesions are larger. In addition, silicosis also gives rise to pleural thickening and adhesions. Sometimes silicosis produces acute respiratory manifestations with dyspnea and impairment of gas exchange in the alveoli.

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In the acute form the disease manifests with dyspnea, cyanosis and constitutional disturbances. In the chronic form the prominent manifestations are cough and hemoptysis. Physical signs may be those of bronchitis, emphysema, and pleural thickening. Silicosis predisposes to the development of tuberculosis and the two diseases may coexist (silicotuberculosis). The functional impairment is a combination of restrictive and obstructive features. Immunological abnormalities such as the presence of rheumatoid factor may develop in 50% of cases.

Radiology: Diffuse miliary or nodular lesions are found in simple silicosis. Chest radiograph may show snow-storm pattern. Development of progressive massive fibrosis leads to the presence of dense shadows in the upper zones and this is termed "complicated silicosis". Hilar lymph nodes may show peripheral calcification. Occasionally patients with silicosis develop scleroderma.

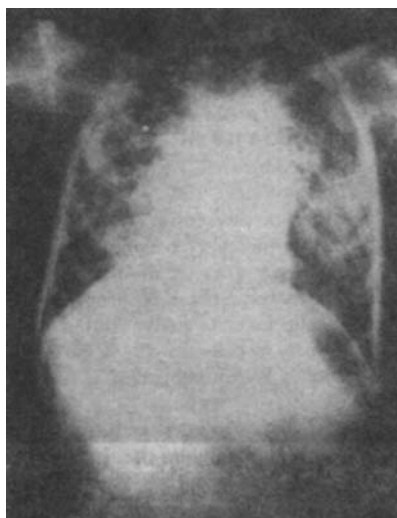


Fig. 138.1: X-ray chest—progressive massive fibrosis

COAL WORKER'S PNEUMOCONIOSIS

Syn: Anthracosis

Prolonged exposure to coal dust causes anthracosis among miners. These particles give a black colour to the lesions. Coal particles reaching the alveoli are ingested by the alveolar macrophages. The phagocytes are activated by the presence of substances like silica. Fibrosis develops at these regions. The affected lobules undergo centri-lobular emphysema. On prolonged exposure, progressive massive fibrosis (PMF) develops and this is the characteristic lesion in complicated pneumoconiosis. Radiologically the lesions of progressive massive fibrosis appear as sausage-shaped densities exceeding 1 cm in diameter, in the upper and mid zones of both lung fields (Fig. 138.1). Further complications such as chronic bronchitis, bronchiectasis, ischemic necrosis, thrombosis of pulmonary veins, pulmonary hypertension, cor pulmonale, or lymphatic obstruction may supervene.

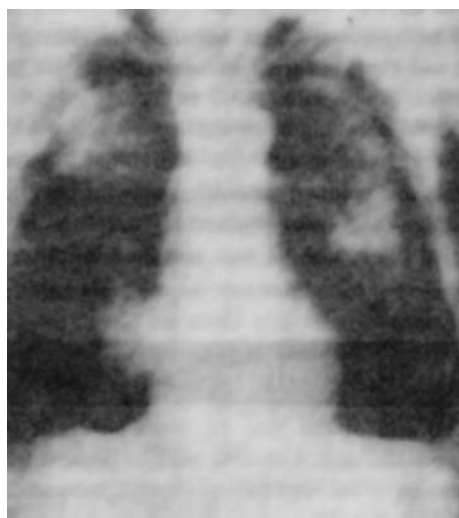


Fig. 138.2: X-ray chest—Caplan's syndrome.
Note: The large nodular shadows

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CLINICAL FEATURES

Gradual onset of dyspnea and cough with purulent expectoration mark the onset of the disease. Expectoration is more copious when bronchiectasis is also present. Dyspnea worsens when progressive massive fibrosis supervenes. Cavitation of these lesions gives rise to expectoration of huge amounts of black sputum. Large nodular lesions develop in the lungs in subjects with rheumatoid disease who develop pneumoconiosis. These lesions are 1-5 cm in diameter and detectable radiologically (Caplan's syndrome) (Fig. 138.2).

Asbestosis

Inhalation of asbestos dust leads to asbestosis. It is a complex silicate containing silicon, oxygen, hydrogen and

metals like calcium, magnesium, and iron. The raw material is obtained by mining. Different varieties of asbestos such as chrysotile, crocidolite, amosite and anthrophyllite are obtained from different regions.

Asbestos particles are needle-shaped and on account of this shape these preferentially settle in the lower lobes. They may reach the alveoli or may be arrested at the small air passages. They give rise to alveolar epithelial hyperplasia and interstitial fibrosis. Eventually fibrosis develops around the asbestos particles and this obliterates the alveoli. Fibrosis in asbestosis is due to mechanical irritation and it is peribronchial and diffuse in character.

Asbestos bodies are seen on histology of the lesions. These consist of asbestos fibers coated by proteinaceous material and ferritin granules derived from macrophages. Asbestos bodies may be demonstrable in the sputum. Mere presence of asbestos bodies in sputum is not sufficient to diagnose asbestosis. Asbestos fibers occur in two forms. The long thin fibers are called amphiboles (blue asbestos). The other one is the feathery form known as chrysotile or white asbestos. Both are carcinogenic, the former is more so. The pathogenesis of mesothelioma in the pleura involves four steps. These are (1) irritation of tissue (2) damage to mitotic spindle (3) generation of iron-related reactive oxygen molecules and damage to DNA and (4) phosphorylation of kinases. Pleural mesothelioma is an aggressive tumour of the serosal surface of the pleura. Widespread exposure to asbestos has increased the incidence of pleural and peritoneal mesotheliomas.

Asbestosis predisposes to bronchogenic carcinoma (especially in smokers) and mesothelioma of the pleura and peritoneum. It also predisposes to pulmonary tuberculosis. Malignancies of distant organs such as kidneys and breasts are more common in subjects with asbestosis.

Clinical features: The symptoms start with increasing dyspnea on exertion, cough, malaise, and weight loss. As the condition proceeds, cyanosis and digital clubbing supervene. The pulmonary functional defect is one of restrictive defect and impairment of diffusion. The clinical picture differs from case-to-case, depending on the extent of the lesion and presence of other coexistent conditions such as emphysema, bronchiectasis, tuberculosis, malignancy or pleural disease.

Radiologically, fine mottling and prominent streaky fibrosis are seen in the middle and lower zones. Pleural thickening, pleural effusion, and calcification may be evident in some cases.

Byssinosis

Pulmonary disease caused by exposure to cotton dust, flax or hemp is termed byssinosis. In the early stages the symptoms are tightness of the chest and wheeze usually felt by the patient when he resumes work after the weekly holiday. Later on cough and dyspnea become more prominent and persistent. Some subjects develop chronic obstructive airways disease. Persons employed in the carding section suffer more than those employed in other areas.

Cotton dust stimulates histamine release from mast cells in the lung. Pure cotton such as surgical cotton does not provoke the symptoms. The occurrence of dyspnea and cough at the beginning of the week and its subsidence during the working week is attributed to depletion of the mast cells of their histamine.

Radiological findings are non-specific. Treatment consists of withdrawal of susceptible persons from the environment and symptomatic measures.

Numerous other disorders have also been recognized as resulting from occupational exposure to different

TABLE 138.2	
Criteria for diagnosis of occupational lung disease	
1.	There should be an exposure to known, documented, hazardous agent
2.	The timing of exposure and onset of symptoms should be appropriate.
3.	The clinical syndrome should be consistent with the syndrome related to exposure.
4.	There should be no other more likely explanation for the signs and symptoms.

materials. It is beyond the scope of this text to describe all of them. Industrial medicine has assumed the importance of a sub-specialty, which includes occupational health hazards, trauma, exposure to toxins, effects of physical agents on health and legal problems arising out of these.

Management: Once established, pneumoconiosis is treated symptomatically since specific therapy is lacking.

Prevention: Workers who are employed in industry should be recruited only after proper pre-employment medical examination. Persons with family history of allergic respiratory disorders and those who have features of obstructive airway disease are more likely to develop permanent ill effects. Periodic examination of the workers to facilitate early detection and removal from the harmful environment is required by legislation. Industrial establishments where the risk of pneumoconiosis is present have to follow specifications intended to reduce the concentration of dust in the environment and also for giving protection to the workers. Many of the pneumoconiosis attributable to occupational exposure are eligible for compensation from the employers. Table 138.2 gives the general criteria for diagnosis.

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Pulmonary Fibrosis

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C. Sudheendra Ghosh, Dinesa Prabhu V.

Chapter Summary

- Replacement Fibrosis 938
- Interstitial Fibrosis 938

Definition: The term describes the abnormal formation of fibre like scar tissue in the lungs. There are over 140 known causes or associations with PF. The lung reacts to the insult by inflammation and subsequent fibrosis.

TABLE 139.1

Gives the causes of pulmonary fibrosis

Type of fibrosis	Causes
1. Replacement fibrosis	Pulmonary tuberculosis Bronchiectasis Lung abscess Pneumonias Fungal infections Pulmonary infarction Atelectasis Chronic pleural effusion Empyema Lipoid pneumonia Irradiation of lung
2. Focal fibrosis	Pneumoconiosis
3. Interstitial fibrosis	Fibrosing alveolitis Allergic alveolitis Connective tissue diseases 1. Progressive systemic sclerosis 2. Rheumatoid lung Asbestosis Sarcoidosis Radiation injury Pulmonary hemosiderosis Chronic pulmonary edema of long standing

Lung parenchyma has no power of regeneration. Hence destructive lesions lead on to fibrosis. Fibrosis of the lung parenchyma may take three forms—*replacement fibrosis*, *focal fibrosis*, and *interstitial fibrosis* (Table 139.1).

Replacement Fibrosis

In this form fibrous tissue is laid down over areas of lung destruction. The fibrosis is often localized and its extent depends on the extent of parenchymal destruction. The most common cause in India is pulmonary tuberculosis. The upper lobes are affected more frequently.

Clinical Features

The chest is asymmetrical with flattening of the affected side, drooping of the shoulder and diminution of movement. Trachea and mediastinal structures are pulled towards the same side, unless they were already fixed by pre-existing disease. The percussion note is diminished. Vocal fremitus and vocal resonance depend upon the severity of fibrosis. In extensive fibrosis they are reduced. If a major bronchus lies subjacent to the fibrotic area the vocal fremitus and resonance are increased and breath sounds become bronchial. In extensive fibrosis, especially fibrothorax, the breath sounds are considerably diminished.

Adventitious sounds may be heard and these are variable. Symptoms and hemodynamic disturbances depend upon the extent of pulmonary lesions and the cause.

Replacement fibrosis has to be distinguished from pulmonary collapse in which there may be ipsilateral shift of midline structures. Pulmonary collapse is usually of shorter duration and the underlying cause may be evident

Focal Fibrosis

This is seen in pneumoconiosis such as silicosis. The extent of fibrosis may vary from small nodular lesions to extensive areas (*progressive massive fibrosis*).

Interstitial Fibrosis

This is the end result of interstitial lung diseases. Interstitial fibrosis may result from allergic alveolitis, connective tissue disorders such as progressive systemic sclerosis and rheumatoid disease, cryptogenic fibrosing alveolitis, radiation injury to the lung, sarcoidosis, asbestosis, chronic pulmonary edema (occurring in mitral stenosis), and idiopathic pulmonary hemosiderosis.

Pulmonary fibrosis where the aetiology is unknown is termed as **Idiopathic Pulmonary Fibrosis (IPF)**. A common pathogenetic sequence occurs in most of the conditions leading to interstitial fibrosis, regardless of the etiology. The development of fibrosis follows injury to the alveolar walls that results from noxious agents which reach the alveolar walls either through vasculature or the airways. Studies show that the process begins with injury to alveolar wall and activation of coagulation cascade. Following injury, there is an influx of inflammatory and immunologically active cells which lead to alveolitis. The inflammatory cells and the mediators which are released produce oxidants resulting in continuous injury. This may induce connective tissue proliferation and remodeling in the lung by increase in the fibroblast. When alveolitis persists and progresses, this can result in partial or complete effacement of the alveolar capillary gas exchange apparatus. The resulting derangement of alveolar and interstitial architecture leads to functional and circulatory disturbances.

Clinical Features

The symptoms are those of ventilatory and diffusion defects, predominantly characterized by dyspnea, cyanosis, frequent respiratory infections, and chronic cor pulmonale. Physical examination may reveal gross clubbing, tachypnea, cyanosis, and diminished respiratory movements. Since these changes affect both lungs, there is no marked shift of midline structures. Breath sounds are diminished. Diffuse rales (crackles) which persist after coughing are characteristic. *The classical end inspiratory velcro crackles are present in IPF*. X-ray of the chest may show generalized loss of translucency and increased reticulation. Pulmonary function test will show restrictive pattern, usually decreased vital capacity. Earliest change



Fig. 139.1: HRCT of pulmonary interstitial fibrosis.
Note: The thickening of interalveolar septa

may be reduction in diffusion capacity. HRCT is very useful in assessing the nature of the lesion, extent of disease, and monitoring progress (Fig. 139.1). In advanced cases, traction bronchiectasis and subpleural honeycombing may be seen. Lung biopsy is useful for confirmation.

Cardiac findings include right ventricular enlargement and hypertrophy, and loud pulmonic second sound indicating pulmonary hypertension.

Course and prognosis: Replacement fibrosis does not usually progress further. The course of the disease and longevity depend on the extent of the lesion, occurrence of secondary infections and the development of cor pulmonale. In general, with reasonable care, localized fibrosis is compatible with prolonged survival. Diffuse interstitial fibrosis is progressive in most cases and life is considerably shortened. Death is due to respiratory failure or cardiac failure.

Management: General measures include the avoidance of smoking, treatment of intercurrent infections, reduction of weight and respiratory exercises. No definite treatment is available. Various drugs which block collagen synthesis and inhibitors of fibrogenic cytokines are under trial. Corticosteroids and immuno-suppressants are the main stay of treatment. But less than 20% of IPF patients respond to corticosteroids. High dose N-acetyl cysteine 600 mg tds orally added to the standard therapy – prednisolone and azathioprine preserves the vital capacity and improve the diffusion capacity. Long-term results are awaited. Fibrinolytic agents like pirfenidone are also being tried.

Cardiac complications are treated suitably. Lung transplantation is the only answer to those who do not respond to medical therapy.

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Circulatory Disturbances in Lungs

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14

Chapter Summary

Pulmonary Edema 939

Pulmonary Thromboembolism 940

Pulmonary Edema

ACUTE PULMONARY EDEMA

Acute pulmonary edema is a common medical emergency which can be brought about by diverse causes. There is accumulation of extravascular fluid within the lung. The mechanisms include rise in the pulmonary wedge pressure, changes in the dynamics of flow of fluids and

protein through the capillary walls and changes in the interstitium. Fluid may accumulate in the interstitium or in the alveoli.

Common Causes

1. Left-sided heart failure, e.g. acute myocardial infarction, hypertensive cardiac failure or mitral stenosis.
2. Aspiration of gastric contents (Mendelson's syndrome).
3. Neurogenic disorders such as subarachnoid hemorrhage, meningitis, encephalitis or brainstem injury with resultant depression of respiratory center

4. Fluid overload, e.g. overtransfusion of fluids, acute nephritic syndrome.
5. Drug hypersensitivity, e.g. hexamethonium, nitrofurantoin, busulphan.
6. Change in permeability of capillary wall, e.g. acute glomerulonephritis.
7. Narcotic poisoning with depression of respiratory center.
8. Irritant gases, e.g. phosgene, chlorine, acid fumes
9. Other forms of poisoning like paraquat, weedicides, organophosphorus.
10. Pulmonary embolism.
11. Uremia, aspiration of pleural effusion.

Rarer causes: Hanging, high altitude pulmonary edema, hypoproteinemia, disseminated intravascular coagulation, falciparum malaria, near-drowning, and pneumothorax.

Clinical features: Acute pulmonary edema ushers in with intense dyspnea, anxiety, and sweating. At its early phase the only obvious abnormality may be tachypnea. When fluid collects in the alveoli, the patient expectorates copious amounts of white or pink frothy sputum. Auscultation reveals widespread rales and occasional rhonchi. Initially the lower lobes are affected. Cyanosis may develop and it becomes deeper. Death occurs due to respiratory failure. Examination of the heart may reveal evidence of left-sided heart failure such as gallop rhythm or the presence of valvular lesions. See also chapter 116.

Management: Emergency management is indicated to save life. Cardiac causes have to be treated as for acute left-sided heart failure. The main steps in treatment include the administration of oxygen, frusemide, digitalis, aminophylline and vasodilator drugs. Physiological or open venesection may be required as an emergency rarely. The underlying cause should be attended to, after instituting the life-saving emergency measures. When pulmonary edema follows the inhalation of irritant fumes, massive doses of corticosteroids may be beneficial. In narcotic poisoning use of antidotes such as naloxone may help in bringing about dramatic improvement. Artificial ventilation is indicated in cases where respiratory failure develops. In addition, all the general principles of management of poisoning have to be adopted.

CHRONIC PULMONARY EDEMA

This occurs in chronic heart failure caused by mitral stenosis or left ventricular cardiomyopathy. The lungs are edematous, congested and brown on section (*brown induration*). Hemosiderosis may occur in long-standing cases. X-ray shows signs of chronic pulmonary venous congestion. Dilated interlobar septal lymphatics (Kerley's B lines) are seen. When pulmonary hemosiderosis develops, miliary shadows are seen in the radiograph. Treatment of cardiac failure clears the pulmonary edema as well in early cases.

Hypostatic congestion: This condition may develop in chronically bed-ridden patients due to diminished circulation, local anoxia, and infection. Hypostatic congestion can be prevented by early ambulation, respiratory physiotherapy, and adequate treatment of infection.

Pulmonary Thromboembolism

(See also Chapter 127)

Occlusion of the pulmonary artery or its branches by emboli constitutes pulmonary embolism. The emboli reaching the lungs usually originate from thrombosis of peripheral veins—particularly the calf vein and pelvic veins. It occurs in persons who are seriously ill due to other primary diseases. Pulmonary embolism may be acute and massive or recurrent and multiple.

Incidence: Acute pulmonary thromboembolism is detectable in 2-15% of all autopsy cases. The incidence reported from the West is very high (above 60%). Pulmonary embolism is more commonly associated with severe infection and dehydration. Probably there is a lower incidence of venous thrombosis and embolism in Asians and Africans compared to those in the West. It is possible that many cases are missed during life.

Conditions which predispose to pulmonary embolism:

1. Prolonged immobilization resulting from medical ailments and surgery or trauma, particularly involving the pelvis, abdomen and legs,
2. Diseases of veins of the lower extremities,
3. Congestive cardiac failure,
4. Pregnancy, contraceptive pills containing estrogens, and postpartum state,
5. Obesity,
6. Systemic malignancy, especially if widespread,
7. Hematological disorders such as polycythemia vera and chronic myeloid leukemia, and thrombophilic states
8. Miscellaneous conditions such as heat stroke, massive burns, and shock.

The widespread use of oral contraceptive pills has led to increase in the incidence of pulmonary thromboembolism in women, particularly in the age group 34-44 years. Women with previous episodes of thrombophlebitis or embolism are especially at risk. Pulmonary embolism tends to recur in survivors of the initial episode in up to 40%. Though the source of the embolus is not always evident, it is likely that in most of the cases veins of the legs and pelvis are the primary sources.

Clinical manifestations: The clinical features of pulmonary thromboembolism may be non-specific and vague in many cases. In some cases low grade fever may be caused by venous thrombosis. The intensity of

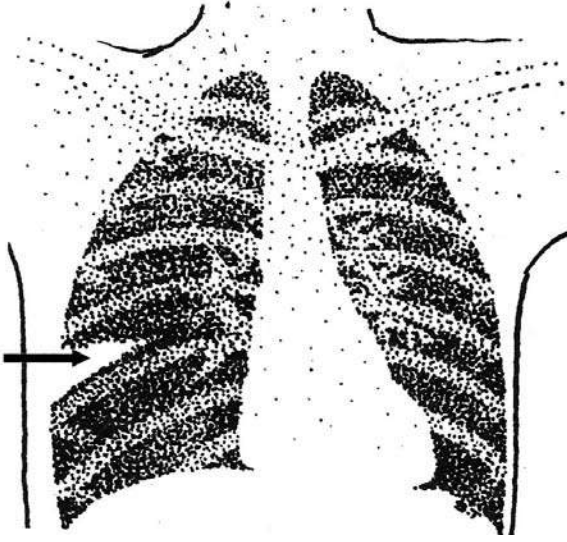


Fig. 140.1: X-ray chest: Pulmonary infarct. Note: The triangular opacity with the base towards the pleura

symptoms depends on the extent of pulmonary vascular obstruction and the development of pulmonary infarction.

Acute massive pulmonary embolism: This occurs as a grave medical emergency. In this condition more than 50% of the cross-sectional area of the pulmonary arterial tree is occluded. It manifests with sudden dyspnea, anginal pain, hemoptysis and circulatory collapse in a patient who is apparently well and progressing from other underlying disorders. The patient becomes cyanosed, convulsive and comatose. Cardiac auscultation reveals loud pulmonary second sound. Some cases present with signs of acute right ventricular failure with raised jugular venous pressure and hepatomegaly. If not relieved in time, a massive pulmonary embolus is rapidly fatal within minutes. Clinically acute massive pulmonary embolism may mimic acute myocardial infarction or dissecting aneurysm of the aorta. In acute myocardial infarction and dissecting aneurysm, hemoptysis is uncommon except when acute pulmonary edema develops. Electrocardiogram shows evidence of right ventricular strain and in a patient who had normal ECG, sudden development of right ventricular strain should raise the possibility of massive pulmonary embolism.

Examination of the lower limb may show edema or tenderness along the veins in some cases. *Homan's sign* may be elicitable in a few. In many, there may be no local signs to suggest venous thrombosis.

Submassive pulmonary embolism: This presents with the classic triad of symptoms consisting of cough, pleuritic pain, and hemoptysis. The patient may be dyspneic if the lesion is extensive. Physical examination reveals the presence of pleural rub and signs of consolidation. This classic clinical picture of pulmonary infarction usually

takes 3 to 5 days to develop. Infarction occurs only in 10-20% of cases. Fever may result from tissue necrosis and this may be mistaken for an infective episode. About 50% of those with infarction develop hemorrhagic pleural effusion.

Radiological features: The radiological features are not constant and they do not bear any direct correlation with the extent of arterial occlusion. Radiological abnormalities include elevation of the ipsilateral hemidiaphragm, pleural effusion, and linear opacities suggestive of atelectasis. 'Westermark' sign is the presence of diminution of vascular markings in a localised area which is seen in some cases. The main pulmonary artery may be distended. Pulmonary infarct produces a triangular opacity with the base of the triangle towards the pleura and its apex towards the hilum (Hampton's hump) (Fig. 140.1).

Symptoms and Signs of Pulmonary Embolism

Symptoms	Signs
Dyspnea	Tachycardia
Cough	Tachypnea
Substernal chest pain	Crackles
Sweating	Wheezes
Syncope	JVP elevated
Hemoptysis	Right ventricular gallop
Later pleuritic pain	Loud pulmonic second sound

Electrocardiogram: Classic ECG abnormalities develop only in a few cases. These include:

1. Prominent S-wave in leads I and II with the development of Q-wave and T-wave inversion in lead III;
2. T-wave inversion in V_1 - V_4 ;
3. Evidence of right bundle branch block in some cases;
4. Tall-peaked P-waves which reflect right atrial hypertrophy as a result of pulmonary hypertension; and
5. Arrhythmias such as tachycardias, ectopics and atrial fibrillation.

The acute electrocardiographic changes usually subside within a week.

Pulmonary angiography: This is the most specific method which unequivocally demonstrates pulmonary arterial obstruction. The common findings include abrupt "cut off" or amputation of lobar or segmental arteries and intraluminal filling defects.

Lung scan findings: Isotope lung scan is a useful investigation to demonstrate segmental perfusion defects (Fig. 140.2).

Course: The pulmonary vascular obstruction starts resolving within hours of its onset. Recovery depends upon several factors such as presence of collateral circulation, underlying pulmonary disease and the general

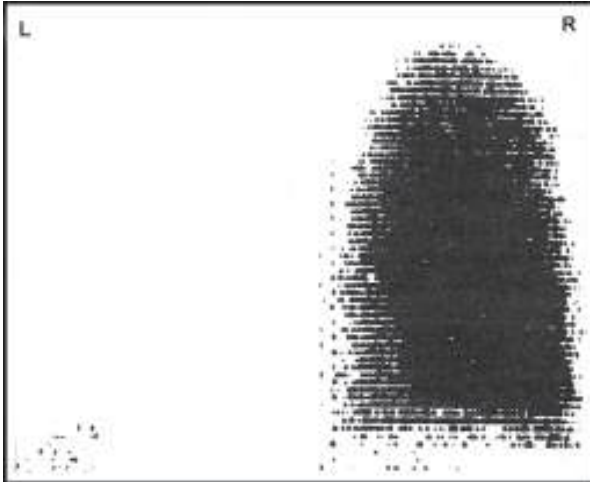


Fig. 140.2: Scintiscan pulmonary embolism. Note: The isotope does not reach the affected side (left side)

condition. About 25% of patients with mild embolism recover completely within two weeks.

MANAGEMENT

Emergency management: The patient is put to bed. Oxygen is administered and closed chest cardiac massage is started. An effective closed chest cardiac massage, in addition to restoring cardiac output, may help in fragmenting the thrombus and driving it into peripheral branches. If shock ensues, this should receive prompt attention. All cases should be assessed for thrombolytic therapy, early in the disease. In many cases this is a life-saving measures.

The patient should be transported rapidly to a centre where thrombolysis can be undertaken.

Thrombolytic therapy: This is employed to dissolve the clots already formed and recanalize occluded vessels. The most widely used enzymes are streptokinase, urokinase and tissue plasminogen activator (tPA). All are very effective in dissolving the clot. Streptokinase, is given in a dose of 1.2 mega units in 200 mL of dextrose in the first 1-2 h and then 100,000 units/hour for 24-48 h for maintenance. Urokinase is given IV in a dose of 4400 IU/kg over 10 minutes, followed by 4400 IU/kg hourly for 24 hours.

Recombinant human tissue type plasminogen activator (rtPA) acts locally at the site of clot formation with only less of generalized effect. 50 mg is given as IV bolus, repeated after 3 minutes, the total dose being 100 mg. The cost of 100 mg exceeds Rs.50,000. Once thrombolysis is achieved heparinization has to be continued. Thrombolytic agents can be given systemically IV or locally into the obstructed artery. Details of thrombolytic therapy are given in Chapter 124.

Anticoagulant therapy: Anticoagulant therapy is intended to prevent thrombosis and extension of the clot which is formed. It has no action on clot which has already been formed.

Heparin: Heparin is a very effective and widely used anticoagulant given parenterally. The usual dose is 10000-15000 units initially and maintenance dose is 5000 units/6 h. The drug is given intravenously or deep intramuscularly. The optimum effect is maintained by adjusting the dose by doing activated partial thromboplastin time (APTT) which is maintained at 1.5-2 times the normal control value. Low molecular weight heparin (LMWH) is effective, safer, and more frequently used at present despite its higher cost.

Oral anticoagulants: These are required as follow-up therapy in those who have peripheral venous thrombosis and those with conditions which predispose to thromboembolism. Warfarin or phenindione is given in appropriate doses to maintain the INR between 2.5 and 3 for periods varying from 6 months to several months.

Newer anticoagulant drugs: For acute anticoagulation several newer drugs have been introduced. These include fondaparinux which is a Factor X inhibitor. The direct thrombin inhibitors lepirudin, hirudin, and argatroban are currently available for use in heparin induced thrombocytopenia or thrombosis when heparin is contraindicated. Danaparoid is also available. Therapeutics of these anticoagulants is given in section 15 chapter 165.

Surgical therapy: Emergency removal of clots from the pulmonary artery is a heroic measure which is successful at times.

Surgical Prophylaxis

Since the veins of the pelvis and the lower limbs are the sources of pulmonary embolism, inferior venacaval ligation has been accepted as a procedure of choice to prevent recurrent pulmonary thromboembolism. Other elegant methods include the implantation of an umbrella device in the inferior vena cava which filters off emboli from travelling centripetally. Definite indication for surgical thrombectomy is recurrent thromboembolic pulmonary hypertension from an identified focus, especially when thrombolysis is contraindicated.

Prophylaxis: In all situations where confinement to bed is essential, regular physiotherapy to the lower limbs and breathing exercises help to prevent venous thrombosis. Heparin given in a dose of 5000 units subcutaneously 2 hours prior to surgery, and thereafter 5000 units 12 h until the patient is ambulant has been advocated in high risk patients. A combination of anticoagulant with compressive pneumatic stocking is found to yield better results.

Patients with single attack of venous thrombosis without any predisposing factor should receive anticoagulant therapy for 6 weeks, those with recurrence should receive medication for 12 months to indefinite periods.

Chronic Thromboembolic Pulmonary Hypertension

See also Chapter 127.
This is the result of multiple and recurrent microemboli obstructing the pulmonary vasculature. Patients who have thrombophilia and those with sources for recurrent emboli are possible candidates. The clinical picture may resemble that of primary pulmonary hypertension from which this condition has to be differentiated. The pulmonary artery pressures are elevated. Pulmonary angiography may help to delineate the vascular lesion in some cases, but not in the majority. Isotope scans and right heart catheterisation help to determine the extent and severity of the lesions. ECG helps to demonstrate the degree of enlargement and hypertrophy of the right sided cardiac chambers. Echocardiography can be used to estimate the pulmonary artery pressure and for serial follow-up.

Pulmonary Arterial Hypertension

It is a disease of the small pulmonary arteries that is characterized by vascular proliferation and remodeling. It leads to progressive rise in pulmonary vascular resistance and ultimately to right ventricular failure and death. It is of 2 types: primary and secondary. The pulmonary vascular bed is a high-flow, low pressure circuit that has the capacity to dilate and recruit unused vasculature in order to accomodate increase in blood flow. In pulmonary hypertension this capacity is lost resulting in elevation of pulmonary artery pressure at rest and further elevation during exercise. The pathological processes include proliferation of vascular smooth muscle cells and asymmetric neo-intimal hyperplasia in small pulmonary arteries and arterioles.

Causes

- 1. Increased pulmonary vascular resistance:

Obstructive	Hypoxic
Primary pulmonary hypertension	Chronic airway obstruction
Collagen vascular diseases	Restrictive lung diseases
Thromboembolism	High altitude
Tumour embolism	Chronic alveolar hypoventilation
Sickle cell disease	
Drug induced: fenfluramine, phenformin	

- 2. Increased pulmonary venous pressure
Mitral valve disease

- Left ventricular failure (LVF)
- Dilated cardiomyopathy
- Left atrial myxoma
- 3. Increased pulmonary blood flow:
 - Atrial septal defect (ASD)
 - Ventricular septal defect (VSD) and
 - Patent ductus arteriosus (PDA)

Primary Pulmonary Hypertension

This is a less common condition seen more frequently in women of child bearing age, and children. The etiology is not clear. Microembolisation of the pulmonary arterioles and capillary bed, and adverse reaction to drugs such as appetite suppressants, may very closely mimic primary pulmonary hypertension. The normal pulmonary artery pressure in health is 18-25 mm Hg/6-10 mm Hg. In pulmonary artery hypertension the mean pressure > is 30/20 mm Hg.

Pathological features include medial hypertrophy, fibrinoid necrosis and occlusion of the pulmonary arterial bed. This leads to rise in pulmonary artery pressure, right ventricular hypertrophy and cardiac failure.

Symptoms are vague until the lesion is advanced. Dyspnea of varying severity and signs of right heart failure develop. Anoxemia develops on exertion and this can be demonstrated by arterial oxygen studies.

Functional Classification of Pulmonary Hypertension

(Modified After the New York Heart Association Functional Classification According to the World Health Organization 1998)

- A. Class I—Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain or near syncope.
- B. Class II—Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.
- C. Class III—Patients with pulmonary hypertension resulting in pronounced limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain or near syncope.
- D. Class IV—Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

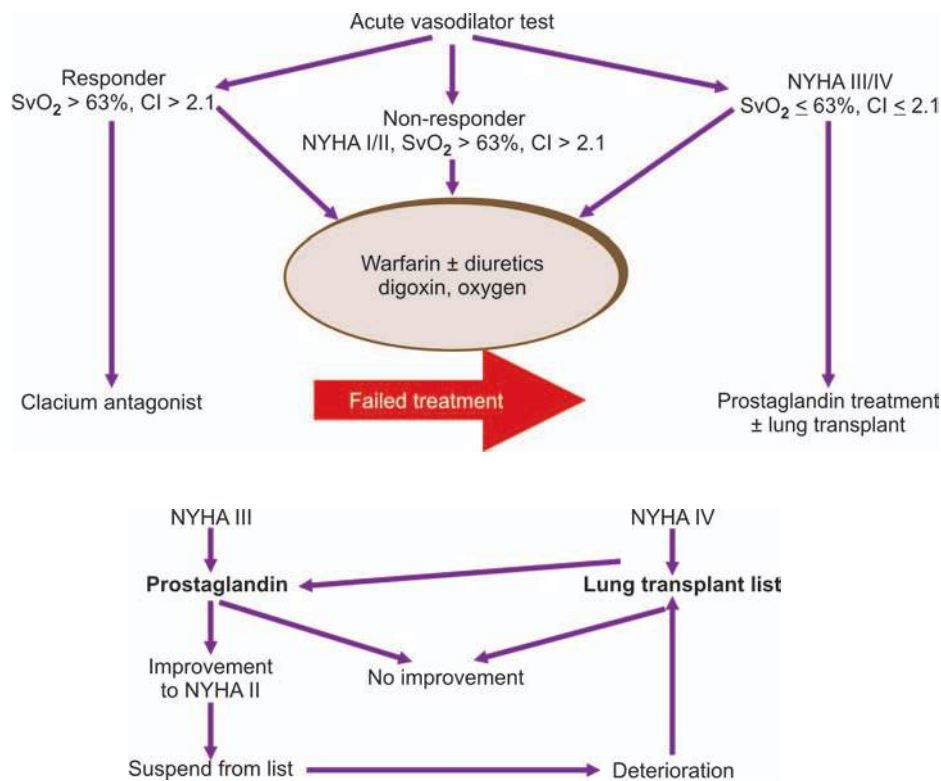


Fig. 140.3: Management of pulmonary arterial hypertension. CI—cardiac index; SvO₂, pulmonary arterial oxygen saturation; NYHA—New York Heart Association

A flow chart useful for institution of prostacyclin therapy is given above (Fig. 140.3):

Prognosis for recovery is poor. Majority die within 2-3 years of onset of symptoms. Symptomatic treatment includes the use of anticoagulants, vasodilators, nitrous oxide and calcium channel blockers such as nifedipine and diltiazem and oxygen therapy. When facilities permit, early lung transplantation may be of help.

Treatment

General measures including oxygen therapy.

Calcium Channel Blockers

Patients responding to first line vasodilators such as nitric oxide, prostacyclin or adenosine do respond to calcium channel blockers.

Prostacyclin: causes relaxation of vascular smooth muscles and inhibits growth of smooth muscle cells. It also inhibits platelet aggregation.

Side effects include: joint pain, headache, flushing, diarrhea. The drug is expensive.

Endothelin Receptor Antagonists

Bosentan: It is an orally active dual endothelin receptor blocker.

Dose: 62.5 mg BD for 1 month, then 125 mg BD thereafter.

Sildenafil: When given orally in doses of 25-50 mg orally repeatedly, it causes pulmonary vasodilatation. This drug is being used more frequently.

Neoplasms of the Lung

C. Sudheendra Ghosh, Ronald Win B

Chapter Summary

Benign Tumours 945

Bronchogenic Carcinoma 945

Pulmonary tumours may be benign or malignant, the latter may be primary or secondary. Malignant tumours far outnumber the benign ones.

Benign Tumours

The benign lesions include hamartoma, chondroma arising from the bronchi, bronchial adenoma, fibroma, neurofibroma, myxoma, and lipoma. Sclerosing angiomas, lymph cysts, histiocytomas, and endometriosis may be seen rarely. Hamartomas are tumours in which normal components of the lungs are combined in a disorganized manner.

BRONCHIAL ADENOMA

These constitute 1-6% of all pulmonary neoplasms. Females are affected more than males and the age group is lower than that of bronchogenic carcinoma. There is an association between bronchial adenomas and multiple endocrine neoplasia. Histologically, the tumours may be carcinoids, cylindromata, mucoepidermoid tumours or mixed tumours which resemble mixed parotid tumours.

Adenomas occur in the larger bronchi. They may be silent, or they produce symptoms such as cough, hemoptysis, bronchial obstruction and recurrent pneumonia. Hemoptysis may be massive and intractable.

The diagnosis should be suspected in any healthy young individual presenting with recurrent and massive hemoptysis and confirmed by bronchoscopy. Treatment is surgical excision.

Malignant Tumours of the Lung

Primary carcinomas are fairly common all over the world. The main types are, carcinoma of the bronchus and alveolar cell carcinoma (*bronchiolar carcinoma, pulmonary adenomatosis*).

The lungs are commonly the seat of secondary deposits from malignant tumours arising from many organs. Carcinomas of the breast, kidney, liver, gastrointestinal tract, testes, prostate, female genital tract and thyroid, and sarcomas from bone and soft tissues may all produce extensive metastases in the lungs.

Bronchogenic Carcinoma

This tumour originates from the basal cell layer of the bronchial wall. Bronchogenic carcinoma is the most common cause of cancer related mortality in the world.

Epidemiology: The disease is more common in the western world and the highest prevalence has been reported from Scotland. In India also the number of cases reported is steadily increasing and bronchogenic carcinoma accounts for 0.14-0.15% of all medical admissions in the major general hospitals. Incidence in males is 10-15 times more than that in females. The disease is most frequent in the fifth and sixth decades.

The role of external factors such as carcinogens derived from cigarette smoke, and from atmospheric pollution in the pathogenesis has been established by several epidemiological studies. In addition to cigarette smoke, exposure to several substances such as 3,4 benzpyrene from automobile smokes, asbestos, nickel chromate, arsenic, vinyl chloride, uranium and radioactive materials increase the risk of developing pulmonary cancer (Fig. 141.1). Among these the most widely investigated factor is cigarette smoking. **15% of male smokers develop lung cancer. Following cessation of smoking, risk of developing cancer decreases even by 10-20 years, the risk is still 2.5 times that of nonsmokers.**

Cigarettes and to a less extent bidis, considerably increase the risk of developing bronchogenic carcinoma, especially the squamous and small cell types. Adenocarcinoma and large cell carcinomas do not show this direct relationship. Smoking more than 20 cigarettes daily for 20 years or more, increases the risk of developing bronchogenic carcinoma 8-20 times above that of nonsmokers. Cigar and pipe-smoking is less harmful. Many substances present in tobacco, and the components

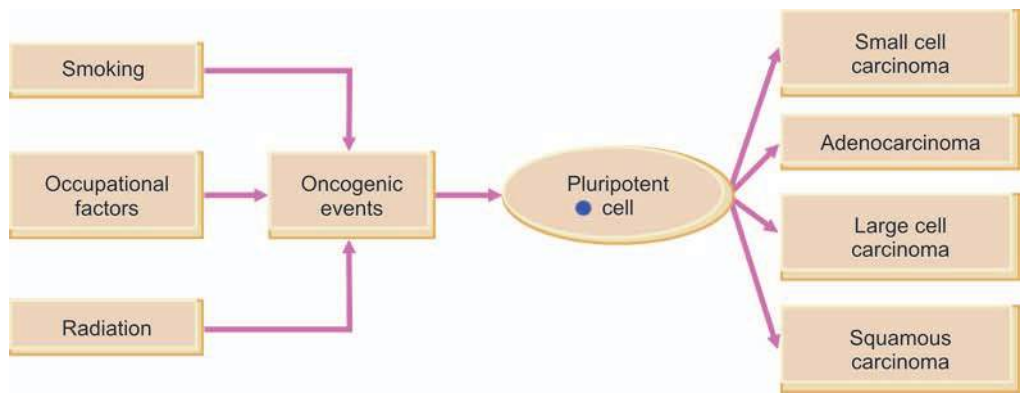


Fig. 141.1: Hypothesis for the development of different histological type of lung cancer from a single cell

of the paper have been found to increase the risk cumulatively. Both direct smoking and passive smoking, i.e. inhalation of smoke exhaled by others in a closed environment, are found to be harmful.

Histological classification: Histologically the tumours are classified into small cell type—otherwise known as oat cell carcinoma, and non-small type which includes squamous cell carcinoma, adenocarcinoma and large cell carcinoma. Oat cell carcinomas are invariably disseminated at the time of presentation. In contrast, large cell carcinomas which are detected early may be localised and hence amenable to surgical resection. One variety of adenocarcinoma is bronchiolo-alveolar cell carcinoma. In some tumours both epidermoid and adenocarcinomatous patterns are seen. Around 50% of tumours are situated centrally proximal to a segmental bronchus, and the rest are peripheral. Site of predilection is the right upper lobe. In some cases adenocarcinoma may supervene on areas of infarction or scars of tuberculosis. Lung tumours have been staged, taking into account the size, location, local effects, local lymphadenopathy and distant metastases.

Squamous cell or epidermoid carcinoma arises from the central bronchi in over 80% of cases. Among superior sulcus tumours it forms 30% or more. These tumours undergo cavitation readily. Metastasis occurs later in the disease.

Small cell carcinoma (SCLC) also known as oat-cell carcinoma is made up of cells containing large nuclei in relation to their cytoplasm. These are also seen more centrally in the lungs. Compared to squamous cell carcinoma the evolution of the disease is more rapid and metastasis occurs earlier.

Adenocarcinomas are more commonly associated with previous scars in the lungs. They form acinar and glandular patterns. They are situated more peripherally. Metastasis occurs early. Bronchioloalveolar carcinoma is a variant of adenocarcinoma, forming about 5% of the total primary malignant tumours. It may arise from the mucin-secreting bronchial epithelial cell, nonciliated secretory bronchiolar cells or type 2 alveolar epithelial cells. It is more common in women. Local spread throughout the airspaces occurs early. In many cases the origin may be multicentric.

Large cell carcinoma These consist of anaplastic large cells without squamous or glandular differentiation. They also occur more peripherally. Local spread and metastasis occurs early. These tumours tend to cavitate. Though distinct histological patterns can be identified in most cases, some may show overlap in cell types e.g. adeno-squamous carcinoma.

Several cytogenetic abnormalities are being elucidated. Oncogenes play a role in malignant transformation. Several tumours produce autocrine secretions which enable them to proliferate autonomously.

CLINICAL FEATURES

In many cases a long latent period may elapse before the tumour produces symptoms. Sometimes the radiological abnormality may be the finding that draws attention. In some cases metastases are the first to produce symptoms.

World Health Organisation (WHO) classification of malignant tumours of the lungs

Type	Frequency
Squamous cell (epidermoid)	30%
Small cell carcinoma	20
Adenocarcinoma	25
Large cell carcinoma (anaplastic)	10-15
Adenosquamous carcinoma	
Carcinoid tumour	
Bronchial gland tumours	
Others	

The incidence of squamous cell carcinoma is coming down and that of adenocarcinoma is going up.

Over 90% of the total number is constituted by squamous cell carcinoma, adenocarcinoma, small cell carcinoma and anaplastic large cell type. Histological diagnosis is important since the different types have different biological behaviour.

Clinical features may be described as (1) intrathoracic manifestations, (2) symptoms due to metastases, and (3) paraneoplastic syndromes. General symptomatology includes non-specific manifestations such as tiredness, anorexia, weight loss, clubbing of fingers and toes, fever, and pulmonary osteoarthropathy.

Pulmonary manifestations: Cough due to irritation of the bronchus may be troublesome, interfering with sleep. In the chronic smoker this is likely to be mistaken for cough due to excessive smoking. Hemoptysis occurs in many cases. Bleeding may be from the tumour or from other pulmonary complications. The tumour may block the bronchus and lead to obstructive symptoms like unilateral or localized wheezing, atelectasis, recurrent pneumonia or lung abscess. Further complications like pleurisy or empyema may be evident. At times the obstruction to the bronchus becomes valvular and the affected segment undergoes localised emphysema.

In some cases, a peripheral tumour undergoes central liquefaction and abscess formation.

Tumours of the apical region of the lung may invade the pleura, the brachial plexus and the cervical sympathetic chain. In most cases the tumour is a squamous cell carcinoma and this is called '*Pancoast's tumour*' or **superior sulcus tumour**. Involvement of the brachial plexus leads to intense neuralgic pain along the arm. Paralysis of the sympathetic chain gives rise to ipsilateral Horner's syndrome.

Pancoast's syndrome is a constellation of characteristic symptoms and signs that include pain over the shoulder and arm along the distribution of the C₈, T₁ and T₂ nerve roots, *Horner's syndrome*, weakness and atrophy of muscles of the hand, most commonly caused by extension of an apical lung tumour at the thoracic inlet.

Malignant pleural effusion may develop due to spread to the pleura. At times, the tumour may grow along the pleural surface resulting in pleural thickening. The hilar lymph nodes are enlarged. Mediastinal glands may be affected and enlargement of these structures gives rise to mediastinal syndrome. Compression of the phrenic nerve gives rise to diaphragmatic paralysis. Malignant pericardial effusion may develop. Direct spread to the ribs may lead to their destruction.

PHYSICAL EXAMINATION

Physical examination of the chest may reveal signs of consolidation, cavitation, atelectasis, or pleural effusion. Enlargement of pretracheal and scalene lymph nodes and recent onset of finger clubbing should suggest the possibility of malignancy.

Extrathoracic manifestations: Widespread secondaries may occur in the liver, bone, adrenal glands, brain, kidney, spleen, peritoneum, skin, and other organs. Manifestations caused by metastases may be the presenting features in many. For example, late onset seizures or a pathological

fracture may be the first evidence of a bronchogenic neoplasm.

Non metastatic metabolic or neuromuscular manifestation of lung cancer is known as paraneoplastic manifestation.

DIAGNOSIS

Bronchogenic carcinoma should be considered in the diagnosis of all respiratory disorders. Malignancy can mimic virtually all common pulmonary diseases such as tuberculosis, pneumonia, lung abscess, atelectasis, localized emphysema and pleural effusion.

The term *lymphangitis carcinomatosa* is given to the condition where the cancer has spread extensively through the lymphatics into the adjacent part of the lung giving rise to a picture of pneumonia or bronchopneumonia. X-ray shows characteristic streaky shadowing possibly representing the lymphatic spread.

When a solitary pulmonary nodule ('coin' shadow) is detected and diagnosis is not evident, the patient should be followed up to see the progress of the lesion. In general, malignant lesions have a doubling time of 20 to 400 days. More rapid growth is suggestive of inflammatory lesions. Calcification is in favour of non-malignant lesions.

INVESTIGATIONS

Radiological findings: Radiological findings may be varied. The presence of a circular or irregular shadow in an asymptomatic patient may be the only finding. The classic circular shadow is called "*coin*" lesion. In more advanced cases the lesion may be more extensive. Hilar glands are enlarged. The growth may undergo central cavitation and the resulting abscess shows thick and ragged walls. The presence of hilar adenopathy should suggest the malignant nature of the lesion. Presence of diaphragmatic paralysis along with a hilar mass should strongly suggest the possibility of bronchogenic carcinoma. Other features like collapse, consolidation, localized emphysema, and pleural and pericardial effusion may also be present (Figs 141.2 to 141.8).

Golden 'S' sign This is a radiological sign seen in central bronchogenic carcinoma obstructing the upper lobe bronchus. This produces collapse. The margin of the collapse segment produces the inward curve of 'S' and the mass will produce the outward curve of the 'S' in the lower part. Radiologically this is characteristic of upper lobe carcinoma (Fig. 141.6).

CT scans and MRI give good delineation of the tumour and its extensions in the thoracic cavity and thoracic cage. PET scans improve the rate of detection of local and distant metastases, especially in patients with non-small cell lung cancer. Positron emission tomography scan using 18F fluorodeoxy glucose, a new investigative modality to detect mediastinal and distant metastases in non-small cell lung cancer is superior to CT scan.



Fig. 141.2: X-ray chest. Bronchogenic carcinoma. Note: Tumour with bilateral massive lymph node metastases



Fig. 141.3: Non-small cell carcinoma lung

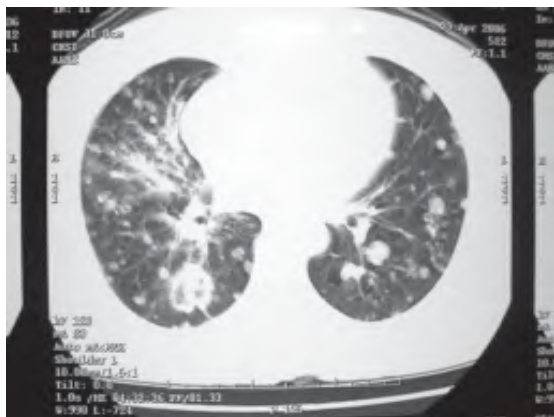


Fig. 141.4: HRCT: Metastases

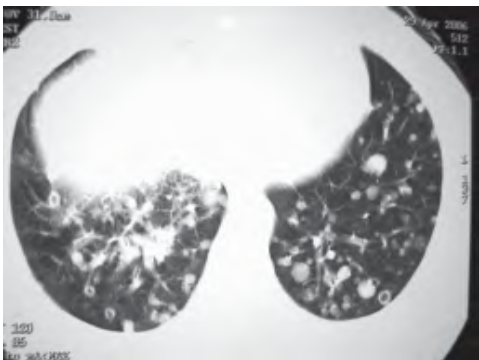


Fig. 141.5: HRCT cavitating metastasis



Fig. 141.6: Golden 'S' sign

Other diagnostic procedures include bronchoscopy, needle biopsy of peripherally placed tumours, biopsy of palpable lymph nodes in the neck and axilla and **scalene fat pad biopsy**. The right scalene node should be biopsied in cases of lesions of the right lung and the left lower lobe. The left scalene node should be biopsied for left upper lobe neoplasms. Mediastinoscopy and biopsy of nodes is a more rewarding procedure. Fluorescent bronchoscopy is a specialized form of bronchoscopy in which the malignant tissue emits fluorescence. This enables more easy detection of the lesions and helps to make more accurate biopsy.

Modern ultrathin fiberoptic bronchoscopes which can reach beyond the eighth generation bronchi are available. These help to diagnose peripheral lesions. When the nature of the lesion cannot be confirmed by the common investigation PET scan allows precise diagnosis and risk stratification. Measurement of tumour markers will also helps in the diagnosis of carcinoma lung.

Special Tests to Stage the Diseases

1. Staging-Correct staging of patients with lung cancer is crucial in determining the proper therapeutic approach. One of the most important parts of staging is a thorough

Sputum examination: Hemoptysis is present in many cases and the sputum is typically described as “currant jelly”. Malignant cells may be detected in the sputum by examining a wet preparation with methylene blue staining and this can be confirmed by *Papanicolaou’s method*.

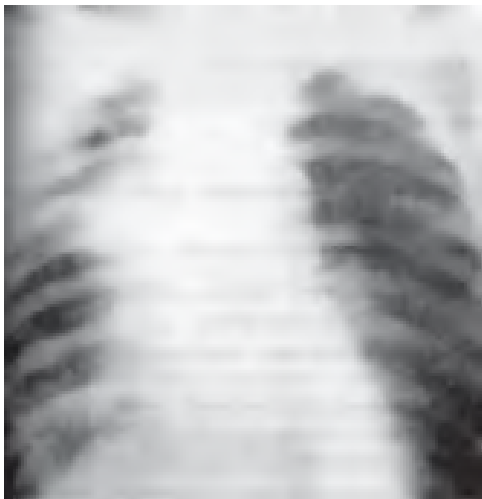


Fig. 141.7: X-ray chest—carcinoma lung. Note: The mass with hazy margins extending outwards from the right border of the mediastinum



Fig. 141.8: Pancoast's tumour. Note: The rounded opacity in the right upper region—arrowhead

history and physical examination. All patients need serum electrolyte estimation, liver function tests [including alkaline phosphatase and lactate dehydrogenase (LDH)], and chest X-ray. Elevated alkaline phosphatase suggests bone metastases. In the past, patients routinely had head CTs and radionuclide bone scans as part of the diagnostic workup, but large studies have shown that these tests should be ordered only if the patient's signs and symptoms indicate their necessity. For example, CNS symptoms or an abnormal neurological examination necessitate a brain CT with contrast.

NSCLC and SCLC are staged differently. Due to the high incidence of micrometastases early in the disease state, SCLC is divided into two stages: limited disease (25-30%), in which the tumor is limited to ipsilateral hemithorax (including contralateral mediastinal nodes), and extensive disease (70-75%), in which the tumor extends beyond the hemithorax (including pleural effusions). SCLC is treated with chemotherapy and radiation therapy. NSCLC is staged using the TNM staging system (T is tumor size, N is nodal involvement, and M is presence or absence of metastases).

TNM Descriptors and Staging for Lung Cancer

TNM Descriptors

T (primary tumor)

- T₀ No evidence of primary tumor
- T_x Tumor proven by presence of malignant cells in bronchopulmonary secretions
- T_{is} carcinoma *in situ*
- T₁ Tumor <3 cm (not in mainstem bronchus)
- T₂ Tumor >3 cm or present in mainstem bronchus but not within 2 cm of carina, invasion of visceral pleura, associated atelectasis or pneumonitis extending to hilar region.

- T₃ Tumour of any size that invades the chest wall, diaphragm, mediastinal pleura and parietal pericardium; tumor <2 cm from carina, associated atelectasis or pneumonitis of entire lung.
- T₄ Tumor of any size with invasion of mediastinum, heart, great vessels, trachea, esophagus, vertebral body, or carina; malignant pleural or pericardial effusion; satellite tumor nodules in the same lobe.

N (nodal Status)

- N₀ no nodal involvement
- N₁ metastases to ipsilateral peribronchial or ipsilateral hilar region (including direct extension)
- N₂ metastases to ipsilateral mediastinal and/or sub carinal lymph nodes
- N₃ metastases to supraclavicular or contralateral mediastinal, hilar, or scalene nodes

M (distant metastases)

- M₀ no distant metastasis
- M₁ distant metastasis

Staging of Bronchogenic Carcinoma

Stage	TNM Descriptor
Occult carcinoma	Tx N ₀ M ₀
0	Tis (carcinoma <i>in situ</i>)
IA	T ₁ N ₀ M ₀
IB	T ₂ N ₀ M ₀
IIA	T ₁ N ₁ M ₀
IIB	T ₂ N ₁ M ₀ or T ₁ N ₂ M ₀
IIIA	T ₁ N ₁ M ₀ or T ₁₋₃ N ₂ M ₀ (N ₂ disease)
IIIB	AnyT ₃ N ₃ M ₀ or T ₄ , any N ₀
IV	Any T, anyN, M ₁

PROGNOSIS

Since most of the cases are diagnosed late in the disease, overall prognosis in bronchogenic carcinoma is poor. Asymptomatic subjects detected by investigations have the best prognosis. Next in line are subjects with symptoms referable to the primary tumour with duration of less than six months. Metastases in CNS and liver confer a poor outcome. Small cell carcinomas have a poor prognosis since metastases develop early. In the majority of patients only palliative therapy is possible. Five-year survival figures for squamous cell carcinoma vary from 40-50% for stage 1 to less than 10% for stages III and above.

TREATMENT

Management depends on the stage of the tumour on diagnosis, histological type, and presence of complications. Treatment may consist of surgery, irradiation, and chemotherapy.

Surgery: When the primary is small and is detected before clinical manifestations develop and there are no metastases, surgical treatment is ideal. Contraindications for surgery include infiltration of the trachea, carina, superior vena cava, recurrent laryngeal nerve paralysis and pleural effusion. Involvement of the mediastinal nodes precludes the chance of resection in non-small carcinoma. Staging of the tumour by the presence of mediastinal lymph node involvement is absolutely essential for deciding on surgery. Stage I with N_0 (i.e.) no lymph node involvement and stage II with N_1 (i.e.) only ipsilateral mediastinal or bronchopulmonary node is present, are amenable to surgical resection which is the treatment of first choice. Surgical results are less satisfactory in those cases which have developed symptoms, and those with small cell carcinoma.

Radiotherapy: Radical radiotherapy is preferred in selected cases. In practice, in the majority of cases radiotherapy is given as a palliative measure in inoperable cases with local spread or distant metastases. Several recent advances in radiotherapy techniques such as split dose radiotherapy, use of radiosensitizers, and the availability of radiation equipment like linear accelerator, betatron, neutron beams and meson beams have made radiotherapy more effective with less of hazard. In some centers radiotherapy is also used prophylactically to the brain to prevent the development of metastases.

Chemotherapy: It is indicated in 90% of patients with bronchogenic carcinoma. The choice of drugs is based on the tumour histology, facilities for supportive therapy, and tolerance by the patient. Chemotherapy may be used as the sole modality of treatment in advanced cases or as an adjuvant to surgery and radiotherapy. Commonly used chemotherapeutic agents are methotrexate, cyclophosphamide, vincristine, CCNU, adriamycin, etoposide and cisplatin. Small cell cancer responds well whereas the others do not.

Other modalities of treatment are laser therapy which is employed in order to reduce the tumour mass and relieve obstructive symptoms. Incurable cases should receive terminal care which includes the provision of comfort, analgesics to relieve pain, management of symptoms, maintenance of nutrition, treatment of infection and proper attention by friends and family members. Preoperative radiotherapy followed by in en-bloc surgical resection is the most common treatment used for Pancoast's tumour.

SMALL CELL LUNG CANCER (SCLC)

It forms 20% of all primary lung cancers. It is associated with smoking. It is characterized by very rapid local and metastatic spread.

Paraneoplastic syndromes are more common with this subtype. Possibly SCLC is a tumour of neuroendocrine cells.

Mechanism of paraneoplastic syndromes:

1. Inappropriate secretion of hormones or other peptides such as growth factors, cytokines and prostaglandins by the tumour.
2. Immunological cross-reaction of antitumour antibodies with normal tissues.

In SCLC the genes encoding these hormones and humoral agents are not mutated, but they are deregulated, so that secretion goes on without feedback inhibition. Moreover, biologically inactive forms of hormones may result from aberrant processing of the RNA peptide.

Hormonal abnormalities: Syndrome of inappropriate antidiuretic hormone (SIADH) occurs in 10% cases.

Peptide Hormones Produced by SCLC

Atrial natriuretic peptide, corticotrophin, beta endorphin, beta human chorionic gonadotrophin, calcitonin, granulocyte colony stimulating factor, erythropoietin, gastrin releasing peptide, glucagon, growth hormone, interleukin-10, melanocyte stimulating hormone, neurone specific enolase, neurophysin, neurotensin, parathyroid hormone, physalemin, somatostatin, vasoactive intestinal peptide, vasopressin and others.

Immunologically Mediated Paraneoplastic Neurological Syndromes

These result from the cross-reaction of anti-tumour antibodies with antigens present in neural tissue, neuromuscular junction or muscle e.g., Lambert-Eaton myasthenic syndrome occurs in 6% of SCLC cases, and Myasthenia gravis may also occur rarely.

Myasthenia results from autoantibody mediated functional blockade of the calcium channels involved in the release of acetylcholine at nerve terminals. Polymyositis/dermatomyositis.

Peripheral Nervous System

1. Autonomic neuropathy
2. Intestinal pseudo-obstruction

Sensorimotor Peripheral Neuropathy

1. Subacute motor neuropathy
2. Subacute sensory neuropathy

Central Nervous System

Angioendotheliosis, dementia, encephalomyelitis—(brainstem encephalitis, limbic encephalitis), myoclonus-opsoclonus, optic neuritis, cancer-associated retinopathy, subacute cerebellar degeneration, subacute necrotizing myelopathy.

Cachexia

The most common paraneoplastic phenomenon is cachexia which is a complex metabolic syndrome probably resulting from a host response to tumour.

TREATMENT OF SCLC

Chemotherapy is the first line of treatment. The common regimens are:

- A – Adriamycin (doxorubicin),.
 - C – Cyclophosphamide,
 - E – Etoposide
- and A – Adriamycin

C – Cyclophosphamide

V – Vincristine

70-90% get effective symptom relief. SCLC is highly radiosensitive but relapse occurs frequently and rapidly. Combination of chemotherapy and radiotherapy is more useful. SCLC is common to produce brain metastasis and, therefore, PCI (prophylactic cranial irradiation) may help to prevent intracranial metastases. Still life is not prolonged since metastases at other sites prove fatal. At the time of diagnoses, brain metastases are seen in 10%, liver metastases in 25% and bone metastases in 20%.

Two year survival rate is about 30% in the cases with limited spread whereas it is below 10% in more advanced cases. *SCLC- the median survival without treatment is 6 to 8 weeks for limited disease*

At presentation less than 30% have limited disease.

Prophylaxis: Bronchogenic carcinoma is at least partially preventable by avoidance of smoking. The risk of cancer comes down quantitatively with the reduction in the number of cigarettes smoked and in those who give up smoking completely the increased risk of cancer comes down after a period of a few years.

Occupational exposure to asbestos, environmental pollutants and radioactive materials should be reduced to the minimum and persons engaged in these industries should receive protection.

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Pulmonary Cysts

C. Sudheendra Ghosh

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Chapter Summary

Congenital Cysts 951

Acquired Cysts 952

Cysts of the lung may be congenital or acquired.

Congenital Cysts

These cysts are of three varieties:

1. *bronchogenic*—these may be solitary or multiple;

2. *alveolar cell types*—these also may be solitary or multiple; and

3. *mixed types* having elements of both bronchogenic and alveolar cysts.

These vary in size and may be unilateral or bilateral. They may be located anywhere in the lung. They are filled with fluid at birth, but air enters the cavity later when bronchial communications develop. The cysts may be thick-or thin-walled.

Cystic disease of the lung: This may occur in association with fibrocystic disease of the pancreas. This is common in western countries, but is rare in India.

Acquired Cysts

These may present as bullous emphysema, subpleural cysts or parasitic cysts, which include hydatid disease and paragonimiasis.

Clinical features: The severity of symptoms is determined by the extent, size, time of diagnosis, and presence of complications. When the lung parenchyma is grossly reduced, respiratory embarrassment and respiratory failure may develop. Superadded infection is common and this is characterized by fever, cough, purulent sputum, and even hemoptysis. Though pulmonary osteoarthropathy may occur, it is a late feature. This is in contrast to bronchiectasis, in which clubbing is an early feature. Potential complications are infection, hemoptysis, pneumothorax, fibrosis, and cor pulmonale.

Diagnosis: Cystic disease has to be suspected when a child presents with recurrent respiratory infections. Presence of other congenital abnormalities should strengthen this suspicion. X-ray shows thin-walled cysts, which may be single or multiple. HRCT is very useful in locating the lesion and confirming the diagnosis. Tuberculosis, bronchiectasis, and lung abscess have to be differentiated.

In congenital cystic lung bronchography delineates the lesions. In the case of single non-communicating cysts the dye does not enter the cavity.

Treatment: A large single cyst producing respiratory embarrassment from infancy has to be excised. Video assisted thoracoscopy is used at present for the surgical excision of cysts. When the cysts are too numerous, surgery is contraindicated. Medical management is on the same lines as for bronchiectasis.

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Pulmonary Involvement in Systemic Diseases

C. Sudheendra Ghosh, Dinesa Prabhu V.

Chapter Summary

Collagen Diseases 952

Ankylosing Spondylitis 953

Sarcoidosis 953

Wegener's Granulomatosis 954

Goodpasture's Syndrome 954

Collagen Diseases

Systemic lupus erythematosus, dermatomyositis, progressive systemic sclerosis, rheumatoid arthritis, polyarteritis nodosa and Sjögren's syndrome involve the lung in varying degrees. Of these rheumatoid arthritis is most common.

Rheumatoid arthritis: Pleurisy, nodular intrapulmonary lesions, diffuse interstitial fibrosis, rheumatoid pneumoconiosis (Caplan's syndrome) and pulmonary hypertension are the common manifestations. Diagnosis depends on the total clinical picture and laboratory tests.

Systemic lupus erythematosus: Pleurisy with or without effusion which may be unilateral or bilateral, lupus pneumonia, diffuse interstitial fibrosis, and pulmonary hypertension are the usual manifestations. Diagnosis is based on other clinical features and demonstration of anti-nuclear antibodies.

Polyarteritis nodosa: In this there is a necrotizing vasculitis affecting the systemic arteries. In addition it may affect the pulmonary arteries as well, producing pulmonary hypertension. This condition has to be distinguished from Goodpasture's syndrome. X-ray shows patchy infiltrates or nodular type of lesions and pleural effusions. Steroids are the mainstay in the management.

Progressive systemic sclerosis: Pulmonary fibrosis starts in the lower lobes and is seen as a honeycomb pattern of the lungs in the skiagram. Spontaneous pneumothorax is a common complication. Alveolar cell carcinoma may develop in some.

Dermatomyositis: Lung involvement is rare. The early lesions are in the form of a lymphocytic interstitial

pneumonia of the lower lobes which gradually leads on to interstitial fibrosis.

Sjögren’s syndrome: Pulmonary lesions are in the nature of lymphocytic interstitial pneumonia leading on to interstitial fibrosis. Secondary bacterial pneumonias and later bronchiectasis occur. Infections are more common due to drying up of the secretions.

Ankylosing Spondylitis

Here the upper lobes are involved. The initial lesion is consolidation which progresses to cavitation and fibrosis. The lesions are considered to be part of the disease process itself.

Sarcoidosis

This is a granulomatous disease of unknown etiology which may involve several organ system in the body. Though common in western countries, this disease is less commonly seen in India. Several reports of this disease have appeared from all parts of India.

Sarcoidosis is characterized by several immunological abnormalities. These include relative deficiency of cell mediated immunity along with an enhanced B lymphocyte mediated humoral immune response. Several MHC alleles confer susceptibility to sarcoidosis, e.g. DR 11, 12, 14, 15, 17. Some alleles are protective, e.g. DR1, DR4 and DQ. Histologically the lesions of sarcoid show granuloma formation with large closely packed epithelioid cells and a few multinucleated giant cells. Some of these giant cells show cytoplasmic inclusion bodies. Hypercalcemia caused by increased intestinal absorption of calcium is a common finding. Sarcoidosis affects several organs and therefore the presentation is protean (Table 143.1). The commonest presentation of the disease is as bilateral hilar lymphadenopathy with associated fever and erythema nodosum (Figs 143.1 and 143.2).

Course and prognosis: This disease follows a chronic recurrent course extending over several years. A few may recover completely. The pulmonary lesions may progress to fibrosis, emphysema and cor pulmonale. Prognosis is best in those who present with hilar adenopathy, without pulmonary parenchymal involvement.

Diagnosis: Sarcoidosis should be considered in the differential diagnosis, of other pulmonary lesions, hilar lymphadenopathy, erythema nodosum and other systemic illnesses presenting with hypergammaglobulinemia or hypercalcemia. Skiagram of the chest reveals hilar adenopathy and the pulmonary lesions (Fig. 143.1). Tuberculin test is usually negative or only weakly positive (anergy). The gamma globulins are considerably elevated. Hypercalcemia occurs in 20% of cases. The *Kveim-Siltzback test* is an intradermal test using the material

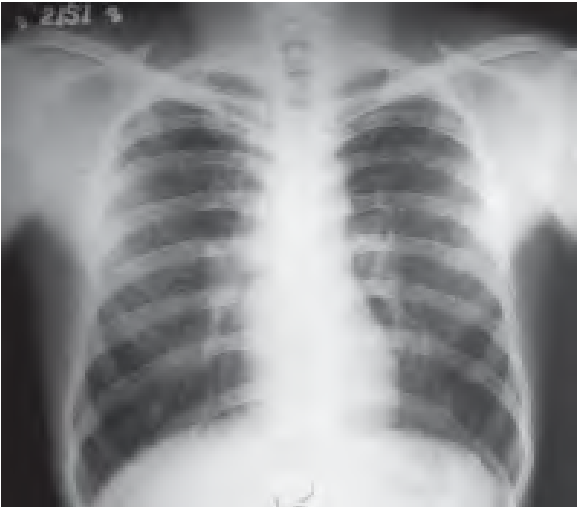


Fig. 143.1: X-ray chest sacoidosis.
Note: Bilateral hilaradenopathy with miliary lesions

TABLE 143.1	
Sarcoidosis—clinical manifestations	
General symptoms	Fever, lymphadenopathy, uveoparotid fever (a picture resembling atypical mumps) hypercalcemia, renal calculi.
Respiratory system	Hilar lymphadenopathy, diffuse pulmonary lesions which may be miliary, nodular or linear infiltrations, cavitation, confluent lesions, diffuse fibrosis, nasal granuloma, laryngeal plaques.
Eyes	Anterior and posterior uveitis, non-specific and phlyctenular conjunctivitis, glaucoma, enlarged lachrymal glands, Sjögren's syndrome.
Nervous system	Peripheral neuropathy, meningitis, cranial nerve palsies, intracranial space occupying lesions, transverse myelitis.
Endocrine	Diabetes insipidus-due to lesion in the posterior pituitary
Bones and joints	Polyarthralgia, cysts seen especially in terminal phalanges, and subcutaneous tissue swellings.
Abdomen	Hepatosplenomegaly
Skin	Erythema nodosum, lupus pernio (violaceous lesions at the tip of the nose), plaques, papules, nodules and scars
Cardiovascular	Myocarditis, congestive heart failure, conduction disorders, cor pulmonale.

obtained from sarcoid lesions and this is positive in over 80% of cases. This test is seldom done now due to the risk of transmission. Sarcoidosis should be differentiated from tuberculosis, lymphoma, metastatic malignancy and berylliosis. Distinction from tuberculosis can be quite difficult in some cases. Histologically presence of caseation in biopsy specimen is very suggestive of



Fig. 143.2: HRCT sarcoidosis. Note: Hilar lymph nodes

tuberculosis. In sarcoidosis caseation is absent. Serum angiotensin converting enzyme (ACE) is elevated in sarcoidosis. Similar elevation may occur in other diseases as well, so that this is not a specific diagnostic test. Gallium⁶⁷ scan reveals increased uptake in sarcoid granulomas occurring in the hilar lymph nodes and parenchymal tissues. Gallium⁶⁷ scan when considered along with raised serum levels of ACE gives a high degree of diagnostic specificity. Examination of material obtained by bronchoalveolar lavage is of value in the diagnosis of pulmonary sarcoidosis. In active lesions the proportion of lymphocytes is high. This also is not a specific test. Fiberoptic bronchoscopy with transbronchial biopsy is the confirmatory test to prove pulmonary sarcoidosis.

TREATMENT

Corticosteroids are indicated in life-threatening situations arising out of vital organ involvement. The other indications for steroids include lesions of the eyes, nervous system, cardiovascular system and hypercalcemia. Prednisolone has to be started in a dose of 20-60 mg/day initially and tapered off as the condition improves. Maintenance dose has to be given for 3-6 months. Other drugs which are also beneficial include chloroquine, hydroxychloroquine, methotrexate, azathioprine, cyclophosphamide and TNF α receptors blockers such as pentoxifylline, thalidomide and the monoclonal antibody infliximab.

Wegener's Granulomatosis

Friedrich Wegener a German Physician described the condition in 1939. This is characterized by necrotizing vasculitis and granulomatous inflammation affecting mainly the upper and lower respiratory tract and the kidneys. The exact etiology is unknown but the lesions are due to a hypersensitivity reaction. Both granuloma and necrotizing vasculitis should be evident for making the histological diagnosis. Most commonly lesions are seen in the paranasal sinuses, lungs, skin and kidneys. Indian

experience is that 82-100% get upper respiratory passage lesions, 40-50% get pulmonary lesions and 65-70% get renal lesions.

Clinical features: It may manifest at any age, the mean age of onset is 40 years and males are more affected. Initial symptoms are headache, sinusitis, rhinorrhea and vague general ill-health. Cough and hemoptysis may occur. Pulmonary manifestations are pneumonitis, hemoptysis, pleurisy, pneumothorax or cavitation. Acute glomerulonephritis syndrome may occur. Renal biopsy shows focal glomerulonephritis, rapidly progressive glomerulonephritis, or necrotizing and proliferative lesions.

The eyes are involved, leading to iritis, scleritis and conjunctivitis. Intraorbital granulomas may occur. Cardiac lesions include coronary arteritis and pericarditis. Mononeuritis multiplex or cranial nerve palsies may be seen. Skin shows purpura, vesicles and necrotic ulceration.

The ESR is raised. Leucocytosis and thrombocytosis are seen in many cases. The condition has to be distinguished from systemic lupus erythematosus, polyarteritis nodosa, Goodpasture's syndrome, and midline granuloma. Circulating anti-neutrophil cytoplasmic antibodies are demonstrable in patients having pulmonary and renal lesions. Measurement of cANCA (anti-neutrophil cytoplasmic antibodies with cytoplasmic staining) has good specificity for the diagnosis of Wegener's granulomatosis from other forms of vasculitis such as microscopic polyangiitis and Churg Strauss' syndrome. Confirmation of diagnosis is by biopsy of the lung lesion or lesions elsewhere. Untreated, the mortality is 82% at the end of one year.

Treatment: Corticosteroids and immunosuppressant drugs like cyclophosphamide and azathioprine are effective. 50% get full remission, 30% get partial remission and 10-20% may die of the disease. Therapy with cotrimoxazole (160 mg trimethoprim and 800 mg of sulphamethoxazole) b.d for 24 months has been found useful to reduce the frequency of relapses.

Pulmonary Involvement in Goodpasture's Syndrome

(Syn: Lung purpura, Idiopathic pulmonary hemosiderosis)

This is a rare disease characterized by hemorrhage into the alveoli leading to hemoptysis and in some cases associated with proliferative glomerulonephritis. The pulmonary lesion shows degeneration, excessive shedding, and hyperplasia of the alveolar epithelium and cytoplasmic vesiculation. Antibodies to basement membrane antigens are often demonstrable and there is cross reactivity with glomerular and alveolar capillary basement membrane. The disease starts in childhood

below the age of 7 years. If it starts above the age of 15, renal lesions are also found. There is recurrent hemoptysis of varying severity with hemosiderin-laden macrophages in the sputum. Iron deficiency anemia occurs due to blood loss. Occasionally enlargement of liver, spleen and lymph nodes and clubbing of fingers occur. After recurrent episodes extending over several years, radiological lesions develop in the form of micronodular shadows. There is no fibrosis. The course is variable. In a third, death occurs

within three years and in another third the disease becomes inactive. Renal lesion is progressive and death occurs due to renal failure (see Section 16, Chapter 170).

Treatment is with moderate to high doses of corticosteroids. Oral iron should be given to correct the anemia.

Pulmonary involvement in mucoviscidosis (see section 9 chapter 89).

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Diseases of Pleura

C. Sudheendra Ghosh, Dinesa Prabhu V.

Chapter Summary

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Both visceral and parietal pleura have a single layer of mesothelial cells. Mesothelial cells contain abundant microvilli that are present diffusely over the entire pleural surfaces. They are 0.1 μm in diameter and about 1.5 μm length. They produce collagen, elastin, fibronectin and laminin. The visceral pleura can be considered to consist of three layers. The endopleura, which is the continuous mesothelial layer; then the external elastic lamina; and the third layer the vascular layer consisting of connective tissue containing lymphatics and blood vessels. This lies over the internal elastic lamina. In health the surfaces of the pleural cavity are coated with a thin layer of pleural fluid that allows frictionless apposition of visceral and parietal pleura during each respiratory cycle. Pleural fluid is formed as ultrafiltrate of plasma just enough to wet the pleural surfaces. The rate of production of pleural fluid is 0.01 ml/kg/hr and it maintains a balance between

production by the systemic vessels of the parietal pleura and removal by the parietal pleural lymphatics. Pleural fluid does not enter the visceral pleural lymphatics. The pressures vary during the entire respiratory cycle from $-5 \text{ cm H}_2\text{O}$ at mid chest at full expiration to $-30 \text{ cm H}_2\text{O}$ at mid chest at full inspiration.

Pleurisy

Inflammation of the pleura is called pleurisy. In dry pleurisy, the pleural surfaces are inflamed without fluid in between them. In many cases pleurisy is associated with effusion. Both dry pleurisy and pleural effusion may develop at different stages of the same disease process.

Dry or fibrinous pleurisy: In this condition the lesion in the underlying lung spreads to the pleura. Trauma to the chest may also lead to pleurisy. The suggestive symptom is the catching pain felt acutely over the affected area by inspiratory movements brought about by deep breathing, coughing or sneezing.

Etiology of Pleurisy

1. Pulmonary tuberculosis,
2. Pneumonia, lung abscess, bronchiectasis,
3. Bronchogenic carcinoma with secondaries,
4. Pulmonary infarction,
5. Connective tissue disorders such as systemic lupus erythematosus, polyarteritis nodosa, and rheumatoid disease,

6. Rheumatic fever,
7. Viral infections, especially Coxsackie (Bornholm's disease),
8. Hepatopulmonary amebiasis,
9. Uremia,
10. Pleural malignancy-mesothelioma,
11. Secondaries from other malignancies,
12. Lymphomas,
13. Lymphatic obstruction, especially filariasis,
14. Trauma to chest wall,
15. Complication of surgery in the abdomen or thorax, and
16. Pleural effusion in association with tense ascites.
17. Pancreatitis.

PLEURAL EFFUSION

In this condition fluid accumulates between the two layers of the pleura. Normally pleural cavity contains only a small amount of fluid. Movements of the lung favour the movement of the fluid in and out of the pleural space.

Normal composition of pleural fluid

Volume:	0.1 to 0.2 ml/kg
Cells per cmm:	1000 to 5000
%Mesothelial cells	3-70
%Monocytes:	30-70
%Lymphocytes:	2-30
%Granulocytes:	10
Protein:	1-2 gm%
%Albumin:	50-70
LDH:	<50% of plasma LDH
pH:	7.6

In most of the disease states, absorption of the fluid is reduced. The fluid may be contained in the general pleural space or it may be loculated in the interlobar fissure, intrapulmonary space or may remain adjacent to the mediastinum. The fluid progressively compresses the adjacent lung which undergoes collapse.

CLINICAL FEATURES

The development of symptoms depends upon the speed of accumulation of fluid and its quantity. Common symptoms include dyspnea, pleuritic pain, or symptoms of the underlying disorder. High fever may occur in acute pyogenic infections. Tuberculosis may be associated with low grade fever.

Physical examination: Physical examination reveals diminution of movement on the affected side and the presence of pleural friction rub on auscultation. Pleural rub has a superficial grating quality. The rub is heard better by gentle pressure of the chest piece of the stethoscope on the chest wall. Unlike rales it is not altered by coughing. With the development of pleural effusion, the rub may disappear in many cases. Pleural rub has to be distinguished from crepitations and sounds arising from movements of the chest wall. Other painful conditions like

pneumonia, myocardial infarction, and herpes zoster have to be differentiated from pleurisy.

Pleural fluid is clinically detectable only when it is about 500 mL in volume but radiologically it may be detected even when the volume is 300 mL. A fully developed moderate or massive effusion reveals fullness of the intercostal spaces and restriction of respiratory movements on the same side. Midline structures are shifted to the opposite side. Percussion elicits stony dullness with the highest level in the axilla and lower levels in front and back (*S-shaped curve of Ellis*). This is the most constant physical sign. The Traube's space which is the area overlying the gas bubble of the stomach, is obliterated in left-sided effusions. Breath sounds, vocal fremitus and vocal resonance are diminished or absent. Aegophony may be present above the level of effusion. At times bronchial breathing may be heard over a pleural effusion.

Complications: These include: (1) Respiratory embarrassment, (2) massive bilateral effusions which may be fatal due to respiratory failure, (3) secondary infection of the pleural fluid which converts it into empyema, (4) organization of fibrin from the fluid on the surface of the collapsed lung (*cortication*) that (*prevents re-expansion*), and (5) fibrosis of the pleura and obliteration of the pleural space (*fibrothorax*) which develop as a sequel to long standing pleural effusions.

Characteristics of Uncomplicated and Complicated effusion		
	Uncomplicated	Complicated
Appearance	Clear fluid	Cloudy/turbid
pH	>7.30	7.1 – 7.29
Glucose mmol/L	>2.2	<2.2
LDH IU/L	<1000	≥1000
Organism	–ve	–ve/+ve

Radiographic appearances: If the fluid volume is small only the costophrenic angles are obliterated. As the fluid accumulates further, it throws a triangular lateral opacity obscuring the hemidiaphragm. Large pleural effusions shift the midline structures to the opposite side (Fig. 144.1). An interlobar effusion in the oblique fissure produces an elongated cigar-shaped shadow seen well in the lateral view. Fluid in the horizontal fissure throws a rounded shadow seen in the PA view. The term “*vanishing pulmonary tumour*” has been used for interlobar effusions since they clear up with treatment.

Character of the fluid may be transudate or exudate. The light criteria help to identify exudates.

Light criteria
• Pl. fluid/Serum protein ratio >0.5
• Pl. fluid LDH >200U/Lit
• Pl. fluid/Serum LDH >0.6



Fig. 144.1: X-ray pleural effusion-right side Note: The homogenous opacity on the right hemithorax with highest level in the axilla. Costophrenic and cardiophrenic angles are obliterated

Types of Pleural Effusion – Transudate and Exudate	
Cause of Transudate Pleural Effusion	Cause of Exudate Pleural Effusion
LVF	Tuberculosis
Cirrhosis	Parapneumonic
Nephrotic syndrome	Malignancy (primary and metastatic)
Hypoalbuminemia	Collagen vascular diseases
Hypothyroidism	RHD disease, SLE, Churg-Strauss syndrome
Pulmonary embolism	Post-myocardial infarction syndrome
Meig's syndrome	Pulmonary infarction
Peritoneal dialysis	Pancreatitis
	Pseudopancreatic cyst
	Esophageal rupture
	Drugs
	Chylothorax, Pseudochylothorax

Tuberculous effusion is straw-coloured. The fluid is hemorrhagic in malignancy and infarction and it is chylous (milky) in lymphatic obstruction due to filariasis and lymphomas. Collection of purulent fluid in the pleura is called *empyema*.

Microscopy: In acute bacterial infections, neutrophils predominate, while lymphocytes predominate in tuberculosis. Eosinophils may predominate in dyscollagenoses and pulmonary infarction.

Examination of a wet preparation stained by methylene blue reveals malignant cells in over 90% of cases of malignant effusions. Identification of the nature

of the malignant cells is done by *Papanicolaou's technique*. The nature of chylous fluid is confirmed by demonstrating the presence of fat. Elevated amylase levels are suggestive of acute pancreatitis (500 units/mL or higher). Levels of LDH are raised in exudates. Gram-staining, Ziehl-Neelsen staining, and culture help to identify the causative microbes. When the diagnosis is not arrived at by these investigations, pleural biopsy may be attempted. Biopsy is done with a *Cope's needle* or *Abrams' needle*. Though a positive biopsy is diagnostic, a negative biopsy does not exclude pleural malignancy.

MANAGEMENT

Pleural effusion may rarely present as an emergency with respiratory embarrassment. In such cases emergency measures are required to give relief especially if the effusion is massive or bilateral.

Emergency aspiration: Aspiration is done to get a specimen of fluid for diagnostic tests and to relieve distress.

The fluid is aspirated by thoracentesis done in the eighth or ninth intercostal space in the posterior axillary line after anesthetizing the part. Sufficient fluid is removed to relieve the distress. Whenever pleural fluid is aspirated, it is also subjected to diagnostic investigations.

Elective aspiration: Medical therapy is instituted depending on clinical features and pleural fluid analysis. It is ideal to aspirate the fluid after instituting specific drug therapy for 3-4 days.

Indications for aspiration: (1) to make the diagnosis, (2) to relieve distress, and (3) to remove the exudate so as to hasten full recovery of the pleura and avoid complications. It is generally advisable to restrict the volume of fluid removed at one sitting to 1 litre or less in order to avoid pulmonary edema. Aspiration has to be repeated at times. Two or three aspirations will be adequate in most of the cases of tuberculous effusion. In malignant pleural effusion and pulmonary infarction the pleural fluid tends to reaccumulate even after repeated aspirations. Sometimes aspiration of the pleural cavity may give rise to complications. These include pleural shock, anaphylactic shock due to anesthetic, bleeding into the pleural cavity, pulmonary edema, infection, and accidental introduction of air into the pleura.

Pleural shock: The patient develops vasomotor collapse on puncturing the pleura. Inadequate local anesthesia may be a predisposing factor. Urgent resuscitatory measures include the injection of adrenaline, parenteral steroids, and intravenous fluids. Pleural shock may be fatal, if not recognized in time.

Bleeding into the pleural cavity is from vessels on the pleural surface. Bleeding should be suspected when the

aspirated fluid becomes progressively blood-stained. In severe cases hypovolemic shock may ensue. When bleeding is evident, it is advisable to stop the procedure.

Entry of air inadvertently during aspiration converts a simple pleural effusion into hydropneumothorax. Rarely subcutaneous emphysema or air embolism may develop.

Pulmonary edema occurs in some cases of chronic effusion when the lung expands on removal of the fluid. Slow aspiration and limiting the volume of fluid aspirated at one sitting to 1 litre helps to reduce these complications. Onset of pulmonary edema is heralded by troublesome cough with frothy expectoration. Auscultation reveals the presence of rales. Onset of pulmonary edema is an indication for stopping aspiration.

Pleural effusion which is a part of generalised edema, clears up when the underlying condition is treated. Unless there is respiratory embarrassment, thoracentesis is required only for diagnostic purposes.

Tuberculous Pleural Effusion

Tuberculosis is perhaps the most common cause of pleurisy occurring in young adults in India. The pleura may be directly involved by the tuberculous process. In most cases it spreads from an underlying pulmonary focus and the effusion is almost always on the side of the pulmonary lesion. Sometimes a caseous subpleural focus may rupture into the pleural cavity or the pleura may be the seat of miliary lesions. In the majority of cases the classic adolescent pleural effusion is a postprimary tuberculous phenomenon though rarely it may occur in primary tuberculosis. The effusion may develop rapidly or insidiously. Strongly positive tuberculin test favours tuberculous etiology. The fluid is an exudate. The cells are mainly lymphocytes. Tubercle bacilli are difficult to demonstrate in serous effusion by conventional methods. Culture and animal inoculation may be positive. In tuberculous empyema the organisms are more easily demonstrable. Needle biopsy is helpful, but this is not required in the ordinary case.

Management: Standard antituberculosis treatment is started. Pleural aspiration is done electively. Repeated aspiration may be required to make the pleural cavity dry. Respiratory physiotherapy is essential to restore function promptly.

Empyema

Collection of pus in the pleural cavity is called empyema. Pus may be free in the pleural space or loculated.

Pathogenesis: Empyema may result from the extension of infection from the underlying lung, or it may complicate chest injuries, thoracentesis, or generalized pyemia.

Pneumonia, lung abscess, bronchiectasis, tuberculous cavities, hepatopulmonary amebiasis, bronchogenic carcinoma, osteomyelitis of the ribs, fungal infections and actinomycosis are all common causes. Thoracic and upper abdominal surgery may lead to empyema (Fig. 144.3). Common bacterial flora includes *Streptococcus*, *Staphylococcus*, *Pneumococcus*, *Pseudomonas*, *Klebsiella*, *H. influenzae*, anaerobes, *M. tuberculosis*, and Actinomycetes.

CLINICAL FEATURES

All ages may be affected, but children suffer more. Onset is marked by high fever, pleuritic or dull chest pain and dry cough. Physical signs of pleural effusion may be evident. Unlike as in simple pleural effusion the chest wall becomes edematous. Digital clubbing is common. Sometimes the empyema communicates with the bronchus (**bronchopleural fistula**). In this case postural cough is a troublesome symptom and the findings are those of pyopneumothorax. The pus may work its way outside and point on the chest wall. This is called **empyema necessitans**. Left-sided empyema may pulsate due to transmitted pulsation from the heart—'**pulsating empyema**'.

Radiologically the findings closely resemble those of pleural effusion (Fig. 144.1). Demonstration of pus in the pleural cavity by aspiration confirms the diagnosis. The causative organism can be identified by examination of the pus.

Clinically a large lung abscess may resemble an empyema or encysted pyopneumothorax and these two conditions have to be differentiated. Fever, toxemia and digital clubbing occur in both. Shift of the mediastinum to the opposite side and stony dullness on percussion are in favour of empyema. Special radiological techniques may be necessary to differentiate them. In a loculated pyopneumothorax the airfluid interphase may transgress anatomical boundaries of lobes, whereas a lung abscess is limited by the interlobar fissures (Fig. 144.2).



Fig. 144.2: X-ray chest multiple encysted empyema right. Note: Multiple well defined rounded shadows

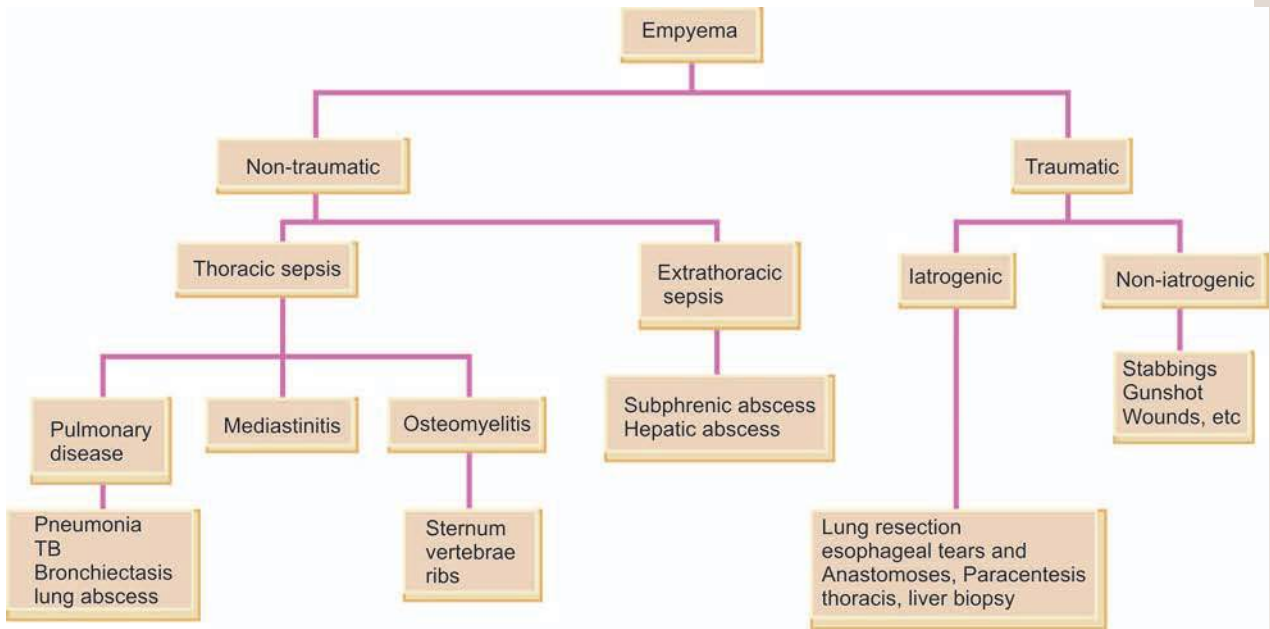


Fig. 144.3: Common causes of empyema

Complications of empyema include severe toxemia, cachexia, anemia, pulmonary fibrosis, pleural fibrosis, metastatic brain abscesses and in longstanding cases, secondary amyloidosis. The overall mortality is 10-11%.

Treatment: After determining the infecting organism, antimicrobial treatment is instituted. The fluid has to be removed by aspiration and this measure is essential to allay fever and toxemia. When the pus is too thick to be aspirated, or if it reaccumulates rapidly, underwater tube drainage has to be established. Clearance of the pleural space and full re-expansion of the lung may take several weeks to complete. Thick pus which is difficult to be aspirated can be liquefied by the instillation of proteolytic enzymes like streptokinase and streptodornase. In most cases chemotherapy and surgical drainage are adequate to clear the empyema. Rarely an intractable empyema may have to be excised surgically.

Tumours of the Pleura

Primary tumour (mesothelioma) is rare, whereas secondary tumours are common. Mesothelioma may be benign or more commonly malignant. Pleural malignancy is more common in persons chronically exposed to asbestos. Secondary tumours arise from carcinomas of the bronchus, stomach, liver, and other structures. Malignant lesions in the pleura give rise to hemorrhagic pleural effusion.

Pneumothorax

Presence of air in the pleural cavity is known as pneumothorax. Pneumothorax may be spontaneous, traumatic, and iatrogenic (*artificial*). Another classification is to divide

them into *open*, *closed*, and *valvular pneumothorax* (*tension pneumothorax*). In open pneumothorax there is a free rent on the surface of the lung through which air gets in and out of the pleural cavity during inspiration and expiration. In closed pneumothorax the pleura does not communicate with the exterior. In tension pneumothorax there is a valvular slit on the surface of the lung through which air enters the pleural cavity, but does not escape. As a result tension pneumothorax develops leading to respiratory and cardiac embarrassment.

Spontaneous pneumothorax: This results from rupture of pulmonary lesion leading to escape of air into the pleura. Pneumothorax may be primary where there is no obvious underlying lesion or secondary to pulmonary lesions such as cavitation, emphysema, bullae and others.

Subpleural blebs or bullae, pulmonary tuberculosis, congenital cystic disease of the lungs, chronic bronchitis with emphysema, bronchial asthma, pneumoconiosis and staphylococcal pneumonia are the common medical causes. Fracture of a rib, thoracotomy, puncture of the lung at needle biopsy, and rupture of a bronchus are the common surgical causes. Sometimes pneumothorax is produced artificially for diagnostic radiology of the lungs or as a therapy to arrest massive hemoptysis. The lung collapses towards the hilum, when air enters the pleura and abolishes the negative pressure.

CLINICAL FEATURES

Onset is with unilateral pleuritic pain and dyspnea. A feeling of something having given way is complained of by many. Shortness of breath and unproductive cough develop soon. In tension pneumothorax respiratory embarrassment and cyanosis may be evident.



Fig. 144.4: X-ray chest—Pneumothorax-left. Note: (1) The airfilled thoracic cavity. (2) collapsed lung-arrow

The affected side is prominent and it does not move with respiration. Midline structures are shifted to the opposite side. Percussion note is hyper-resonant. Breath sounds are absent in many cases. If air enters the pleural cavity as in tension pneumothorax and open pneumothorax, *amphoric breath sounds* may be heard. A special percussion phenomenon is the '*coin sound*'. A coin kept firmly over the front of the chest wall is struck with another coin. Auscultation at the back of the chest reveals a metallic note. Adventitious sounds like clicking sounds synchronous with the heart beat may be heard in a left sided pneumothorax.

Differential diagnosis of pneumothorax includes other painful conditions associated with dyspnea such as myocardial infarction and pulmonary infarction. Severe emphysema, large bullae and diaphragmatic hernia may cause problems in diagnosis.

Radiological features: The radiological features are diagnostic in a well developed case. The affected side is hypertranslucent due to the collection of free air in the pleural cavity and absence of normal lung markings. The outer margin of the collapsed lung is seen as a sharp margin against the background of air. There is shift of the trachea and mediastinum to the opposite side (Fig. 144.4). Skiagram should be taken in the erect posture so that even small collections of air will not be missed.

Complications: Though in the majority of cases spontaneous pneumothorax is uncomplicated, serious complications may develop in some cases. These are: (1) Severe cardiorespiratory embarrassment due to compression of the normal lung by the displaced mediastinum in cases of tension pneumothorax; (2) air embolism; (3) surgical emphysema; (4) infection of the



Fig. 144.5: X-ray chest pneumothorax left. Note: (1) hyper-translucency left hemithorax (2) collapsed lung adjacent to the left cardiac border (3) shift of mediastinum to the right (4) horizontal level of fluid in the left pleural cavity (the pneumothorax is complicated by the development of effusion)

pleural cavity resulting in the formation of hydro- or pyopneumothorax; (5) pneumothorax on the opposite side from pre-existing disease of the lung; and (6) failure of expansion of the collapsed lung.

Hydropneumothorax

When both air and fluid are present in the pleural cavity, it is known as hydropneumothorax. This is usually the result of rupture of a pulmonary lesion letting in air and exudates into the pleural cavity. In many cases it is caused by tuberculosis. Other causes include lung abscess, bronchiectasis, bronchogenic carcinoma, and trauma to the chest. Some cases of pneumothorax get converted into hydropneumothorax when effusion develops as a result of infection (Fig. 144.5).

In hydropneumothorax a horizontal upper level of dullness caused by the fluid can be demonstrated which shifts when the patient is made to adopt different positions (*shifting dullness*). On shaking the patient gently while auscultating on the air-fluid interphase, a *succussion splash* is heard. Chest radiograph reveals a horizontal upper level of fluid with the findings of pneumothorax above it (Fig. 144.6).

Management of pneumothorax: Small closed pneumothorax which is not severely symptomatic can be left alone with bed rest and analgesics, since the air will be absorbed within a few days. Simple aspiration may hasten recovery.

Tension pneumothorax may present as a life-threatening emergency. Unless the tension is relieved by letting out the air, the patient may die of cardiorespiratory failure.



Fig. 144.6: Hydropneumothorax with collapsed lung. Note: On the right side (1) air above and fluid below with horizontal level of fluid (2) shift of mediastinum to the left and (3) collapsed lung on the right hilum

Emergency management: The air is let out by inserting a wide bore hypodermic needle into the second intercostal

space 2-3 cm outside the lateral border of the sternum. The needle is connected to a rubber tube which is led under water, to prevent re-entry of air (underwater seal). This procedure may have to be instituted even outside the hospital at times. Though this procedure may save life in an emergency, sooner or later the needle gets blocked and air reaccumulates with recurrence of symptoms. So it is ideal to hospitalize the patient for further management.

In the hospital the ideal procedure is to establish drainage of the pleura by a rubber tubing—connected to an underwater seal. The tube may have to be kept in place for a few days or weeks. Antibiotics are given to prevent secondary infection of the pleura. Any obvious underlying condition is treated with specific drugs. Recovery of pulmonary function is facilitated by starting physiotherapy at an early stage.

If the lungs fail to expand spontaneously suction of the pleural cavity may help. Surgical repair of the pleural surface may be required in intractable cases.

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Diseases of the Chest Wall

K.E. Rajan

Chapter Summary

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Pectus Excavatum 962
Pectus Carinatum 963
Injuries to the Thoracic Cage 963
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The integrity of the chest wall and muscular action of the intercostals muscles and diaphragm are necessary to ensure proper ventilation. Though minor deformities may not be functionally significant, gross bony deformities and

muscular paralysis impair ventilation and give rise to respiratory embarrassment.

Kyphoscoliosis

Kyphosis is the abnormal curvature of the thoracic spine with convexity directed posteriorly. Scoliosis denotes gradual lateral curvature of the thoracic spine, with rotation of the vertebrae in their longitudinal axis. In kyphoscoliosis, there is progressive deformity of spine consisting of lateral and posterior curvatures. Spine is curved in both coronal and sagittal planes.

Kyphoscoliosis may be congenital or acquired. In majority of patients, it is **idiopathic** in origin. Congenital kyphoscoliosis results from developmental anomalies.

Acquired kyphoscoliosis results from poliomyelitis, myopathies, muscular dystrophies, and diseases of the vertebrae such as osteoporosis. Primary respiratory diseases like pulmonary fibrosis or atelectasis may be associated with this deformity. Causes of acquired kyphosis include ankylosing spondylitis, infections like tuberculosis, connective tissue disorders, disc degeneration, Paget's disease and tumours.

Clinical Picture: The deformity may remain asymptomatic for variable periods of time. It may result in shortening of height. A relative may observe the deformity and bring the patient to medical attention. Mobility of chest wall is impaired. The lung on the narrowed side is compressed. The opposite lung shows compensatory emphysema. Position and relationship of mediastinal structures are altered. Physical examination may demonstrate displaced apical impulse, pulsations at unusual locations, altered tactile/vocal fremitus and variations in intensity of breath sounds.

Chest X-ray shows distortion of spine. Spirometry shows reduction of vital capacity and total lung capacity with preservation of FEV₁. Breathing is shallow and rapid with low tidal volumes. The ventilation-perfusion ratio is grossly reduced and this results in hypoxemia. These subjects are prone to develop repeated respiratory infections. In severe cases, respiratory failure may develop. Cardio-respiratory embarrassment develops in severe kyphosis where the angle of curvature exceeds 20° and in severe scoliosis with the angle less than 100°. Advanced kyphoscoliosis may lead to chronic cor pulmonale.

Management: Milwaukee brace controls moderate deformities. Surgical correction is attempted in selected cases to fix the spine and arrest progression of the deformity. Respiratory physiotherapy improves ventilation. Domiciliary oxygen on a long-term basis may be necessary in patients with significant hypoxemia. Special attention must be paid to prevent respiratory infection.

Ankylosing Spondylitis

In this condition there is marked flexion and rigidity of the thoracic spine. Ventilation is carried out mainly by diaphragmatic movement. Though the vital capacity is reduced, signs of frank respiratory embarrassment are few.

Straight Back Syndrome

Straight back syndrome is a benign abnormality of the spine in which the upper dorsal kyphosis is abolished, giving rise to diminution of anteroposterior diameter of the chest. The heart is shifted to the left and forwards giving rise to prominent parasternal impulses on the second to fourth intercostal spaces and Grade 1-3



Fig. 145.1: Pectus excavatum. Note: The abnormal hollow in the midline below the sternal angle

pulmonary ejection systolic murmur. Pulmonary second sound may be split so as to mimic atrial septal defect. Diagnosis can be made from X-ray of the chest. There is greater incidence of straight back syndrome in association with mitral valve prolapse. It is important to recognize this condition so as to avoid unnecessary invasive investigations.

Pectus Deformities

These deformities usually result from a genetic disorder, which causes an abnormal growth of 4 or more pairs of costal cartilages.

In pectus excavatum (Funnel chest), the sternum is pushed inward. The thoracic cage may be flattened antero-posteriorly. A furrow develops in front of the chest, which is deepest just above the xiphoid process. In many cases, it is familial. Though present at birth, the deformity may aggravate during adolescence. Their severity usually remains the same after age 18 years (Fig. 145.1).

Symptoms include cosmetic problems, shortness of breath, discomfort/pain in the lower anterior chest and decreased exercise endurance. The heart is rotated and displaced to the left to varying degrees. This may give rise to systolic murmurs along the left sternal border. Compression of the heart will reduce the stroke volume and cardiac output in moderate to severe deformities leading to early fatigue. There is compensatory tachycardia during exercise. The sternal depression decreases the intrathoracic volume. Respiratory movements are shallow and rapid.

In Pectus Carinatum (Pigeon Chest)

The sternum gets pushed forwards with the ribs sloping steeply on either side. This deformity used to be a sequel

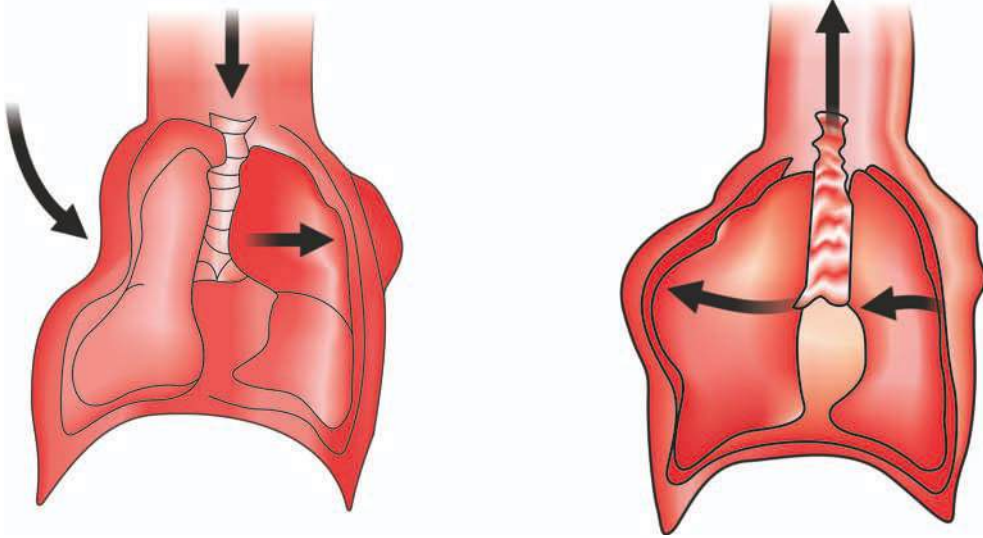


Fig. 145.2: Flail chest. Note: The paradoxical movements of lung

to childhood rickets. There is increased incidence of respiratory infections. Pectus carinatum prevents complete expiration of air from the lungs and significant air trapping. These patients often experience wheezing and occasionally mild to moderate asthma. On exercise, carinatum patients develop tachypnea.

Management: Surgical correction is needed in symptomatic patients. It consists of removal of a small segment of the deformed cartilages medially and laterally on each side of the sternum and bringing the sternum to the desired position with a metal bar support.

Injuries to the Thoracic Cage

The thoracic cage is often injured in accidents. Fractures of individual ribs, contusion of the chest wall/lungs, open wounds (which lead to pneumothorax or hemothorax) and surgical emphysema may be seen. In comatose subjects, injury to the chest wall or viscera may be missed, resulting in fatalities. The need for careful examination to exclude thoracic and abdominal injuries in cases of accidental injuries cannot be overemphasized since at the first examination they may be missed.

Flail Chest

Flail chest results when ribs are fractured in two places. The fractured segment of the thoracic wall floats

independently of the rest of the chest wall and moves paradoxically. The negative intrathoracic pressure during inspiration causes the fractured ribs to be sucked in, thereby preventing expansion of the lung. During expiration this segment moves outwards. When the injury is unilateral air from the lung of the affected side passes into the opposite healthy lung during inspiration and air is sucked into it from the normal lung, during expiration. This type of paradoxical respiration is called “*pendulum breathing*” (Fig. 145.2). This results in serious respiratory insufficiency and respiratory failure.

Management: As first aid, the chest wall should be stabilized to avoid suffocation. Immediate requirement is to prevent the flail segment from moving out paradoxically during expiration. A firm chest wrap is used to support the flail segment. Making the patient lie down with the flail segment against the cot or trolley surface may help. Applying towel clips to the area of paradoxical movement and exerting traction during inspiration is another method. Oxygen supplementation is advisable in all symptomatic patients.

The patient is transported to hospital at the earliest. Stabilization of the flail segment has to be maintained by weight traction. Definitive treatment of flail chest depends upon the degree of respiratory distress. Local anesthetic block is useful to relieve pain. In severe cases where the flail segment is impairing gas exchange or contributing to hypoxemia, internal fixation is done surgically.

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Diseases of the Diaphragm

K.E. Rajan

Chapter Summary

- Diaphragmatic Paralysis 964
- Eventration of Diaphragm 964
- Diaphragmatic Hernia 965
- Hiccough 965
- Diaphragmatic Flutter 966

Diaphragmatic Paralysis

The diaphragm is supplied by the phrenic nerve, which has a long intrathoracic course. Involvement of this nerve anywhere in its course is a common cause of paralysis of the diaphragm. The paralyzed dome is pushed up by the intra-abdominal pressure. It moves paradoxically with respiration, i.e., during inspiration it is drawn up and vice versa.

Diaphragmatic paralysis may be unilateral or bilateral. Table 146.1 gives causes of diaphragmatic paralysis.

Rarely rheumatic fever, typhoid, pneumonia, mediastinitis, pericarditis, and encephalitis lethargica may lead to diaphragmatic paralysis.

Clinical features: Unilateral diaphragmatic paralysis may reduce ventilatory capacity by 20%. Otherwise healthy subjects may remain asymptomatic and may be detected during physical examination or by radiology. Sometimes left-sided paralysis may produce gaseous dyspepsia. In bilateral diaphragmatic paralysis, dyspnea may occur because of ventilatory insufficiency. During inspiration the lower part of the chest moves horizontally, the subcostal angle widens, and the epigastrium and hypochondria recede. Absence of the normal peeling movements of the diaphragm visible on the thoracic cage is known as “Litten’s sign”. Abdomen is drawn in, during inspiration.

Radiologically the dome of the diaphragm on the paralyzed side is seen to be elevated. Unilateral diaphragmatic paralysis has to be differentiated from other causes of elevated hemidiaphragm. Pulmonary fibrosis, atelectasis, eventration of the diaphragm, pulmonary infarct,

TABLE 146.1

Causes of diaphragmatic paralysis

Unilateral	Birth injuries Viral infections (e.g. <i>H. zoster</i>) Carcinomatous infiltration Trauma
Bilateral	Guillain-Barré syndrome Cervical cord lesions Motor neuron disease Poliomyelitis Myasthenia gravis Muscular dystrophies

subphrenic abscess and large space occupying lesions of the liver may cause elevation of the dome. Screening or ultrasound study may confirm the diagnosis by asking the patient to perform sniffing during the procedure. In diaphragmatic paralysis the movement is paradoxical, whereas in pulmonary fibrosis and atelectasis the movement of the elevated diaphragm is considerably restricted.

Treatment: Respiratory embarrassment caused by acute diaphragmatic paralysis may have to be treated by intensive respiratory care and ventilatory support.

Eventration of Diaphragm

Eventration is the abnormal elevation of the diaphragm at a site of weakness. It is seen more often on the left side. This may be a congenital or acquired condition. Congenital diaphragmatic eventration results from the defective development of septum transversum. Affected areas include the vertebrocostal triangle and the central tendon. Acquired eventration is more common, resulting from atrophy of muscle fibers secondary to phrenic nerve injury. In eventration, the diaphragmatic movement is paradoxical. The absence of any underlying cause and, persistence over several years should suggest the possibility of eventration (Fig.146.1). Infants with extensive muscular defect of the diaphragm may present with acute respiratory distress. Many patients remain asymptomatic till accidentally found out by skiagram in

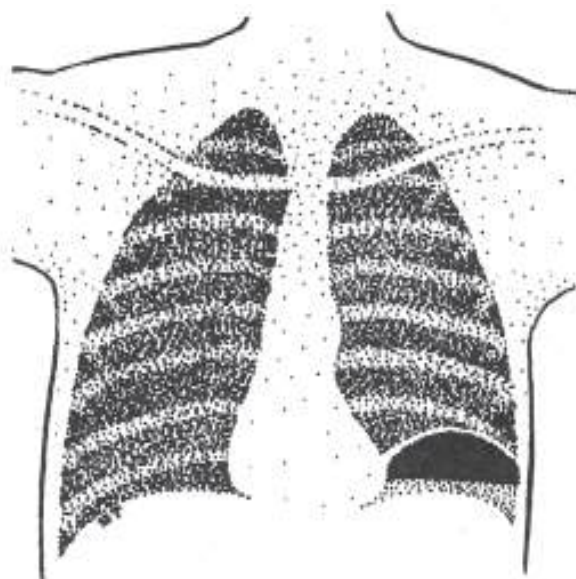


Fig. 146.1: Chest X-ray. Eventration of diaphragm

adult life. Eventration has to be differentiated from a Morgagni's hernia.

Diaphragmatic Hernia

The diaphragm acts as a musculotendinous partition between the thoracic and abdominal cavities. The peritoneum and pleura on either side strengthen it further. Inferior vena cava, esophagus, and aorta pass through the diaphragm. The apertures through which they pass are covered and sealed by the serous membranes. When the apertures become lax or other defects develop, abdominal contents herniate into the thoracic cavity.

Herniation may be spontaneous without any known cause or it may be traumatic. Traumatic hernia is more common on the left side. Though any part may be ruptured, the common site is between the central tendon and ninth rib laterally.

Non-traumatic hernias may occur congenitally or may be acquired. Maldevelopment of the diaphragm or laxity of the apertures occurs in congenital hernias. Four common sites through which herniation occurs are: (1) esophageal hiatus, (2) Foramen of Morgagni (between the sternal and costal slips of origin of the diaphragm) (Figs 146.2 and 146.3), (3) Foramen of Bochdalek (pleuroperitoneal hiatus), and (4) through areas of partial absence of the diaphragm. Among these, in more than 75% cases, herniation occurs through the esophageal hiatus.

Herniation of abdominal viscera into the thorax produces clinical features of decreased intensity of breath sounds on the affected side. Bowel sounds may be heard in the thorax. Congenital hernias may be associated with other anomalies such as dextrocardia. The diagnosis is confirmed by a barium meal follow through examination,

which will show the presence of stomach and/or intestines above the diaphragm.

Hiccough

Syn: Hiccup

This is a common reflex phenomenon resulting from sudden spasmodic involuntary contraction of the diaphragm with the glottis remaining closed. The afferent limb of the reflex arc is the vagus and the sensory fibers of the phrenic nerve. The efferent limb is the motor part of the phrenic nerve. The reflex center is in the upper cervical cord. The increased intrathoracic pressure forces air through the glottis. This produces the characteristic sound of hiccough. In most cases the onset and termination of hiccup may be spontaneous and abrupt. Hasty ingestion of food and fluids may trigger off an attack.

In a gravely ill patient the muscular effort and discomfort caused by hiccup may hasten death. In hiccup due to central causes both sides of the diaphragm contract. In conditions caused by local irritation, the contraction may be unilateral.

Causes of Hiccough

1. Local
 - Irritation of diaphragm
 - a. Gaseous distension of stomach and intestines
 - b. Diaphragmatic pleurisy
 - c. Pneumonia
 - d. Subphrenic abscess
 - e. Peritonitis
 - f. Acute myocardial infarction
 - g. Pregnancy
 - Irritation of phrenic nerve
 - a. Pericarditis
 - b. Mediastinitis
 - c. Compression by tumors
 - d. Surgery of thorax or upper abdomen
2. Metabolic
 - a. Renal failure
 - b. Hepatic failure
 - c. Diabetic ketoacidosis
 - d. Respiratory failure
 - e. Electrolyte disturbances
3. Others
 - a. Cerebrovascular accidents
 - b. Encephalitis
 - c. Brain tumours
 - d. Psychogenic

Persistent hiccough is one which lasts for more than 2 days. It has to be distinguished from diaphragmatic flutter.



Figs 146.2A and B: (A) X-ray chest diaphragmatic hernia right side (B) HRCT scan



Fig. 146.3: X-ray lateral view of diaphragmatic hernia (left) and HRCT scan of the same.
Note: The presence of abdominal viscera above the diaphragm

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Management: Though many cases stop spontaneously, in resistant cases treatment is unsatisfactory. Simple physical measures such as drinking cold water, pressure over the eyeball, Valsalva maneuver, pull on the tongue, stimulation of the phrenic nerve by pressure in the neck or rebreathing into a paper bag may stop the hiccup in many cases. Inhalation of 5 to 10% carbon dioxide is effective. Unilateral hiccup can be arrested by local infiltration of the phrenic nerve with procaine. In cases with abdominal distension, aspiration of gastric contents through a nasogastric tube may provide prompt relief. Some cases are distressing when the attacks cannot be terminated by simple measures. Chlorpromazine given intramuscularly in a dose of 25-50 mg brings about sedation and relief of the hiccough. Other drugs, which may be tried, are metoclopramide in a dose of 10 mg or cisapride in a dose of 10 mg. Some cases recover when sedated for 8-12 hours.

Diaphragmatic Flutter

Sometimes the diaphragm manifests paroxysmal wavelike rhythmic movements at rates going up to 100/min or more. The exact mechanism or cause is not clear. When the condition persists, ventilation may be jeopardized. The term “*diaphragmatic tic*” is given to flutter occurring at a slower rate. Diaphragmatic flutter is seen more frequently in patients recovering from cerebrovascular accidents or encephalitis.

Treatment: The condition responds to anticonvulsant drugs such as dilantin sodium or carbamazepine. In intractable cases temporary phrenic paralysis may have to be induced by crushing the nerve.

147 Diseases of the Mediastinum

C. Sudheendra Ghosh, Dinesa Prabhu V.

Chapter Summary

- Mediastinal Tumours 967
- Cysts 968
- Pneumomediastinum 968

Mediastinal Tumours

An imaginary plane at the lower border of the manubrium sterni divides the mediastinum into superior mediastinum above and anterior, middle, and posterior mediastinum below (Fig. 147.1). Space-occupying lesions in the mediastinum are not uncommon. Due to their location they produce characteristic clinical picture, totally referred to as the mediastinal syndrome. *Diseases of the mediastinum may affect any or all structures with in the chest. It is broadly classified as (a) non-neoplastic disorders, (b) neoplastic disorders, (c) congenital cysts and developmental anomalies.*

Common non-neoplastic diseases of the mediastinum are acute medistinitis, due to mediastinal perforation, post sternotomy mediastinitis, and fibrosing mediastinitis. Pneumomediastinum can be spontaneous or associated with mechanical ventilation.

Tumours: The most common mediastinal tumours are metastases from bronchogenic carcinoma, and lymphomas. Neurofibromas, ganglioneuromas, schwannomas, neuroblastomas, teratomas, dermoids, thymomas and cysts

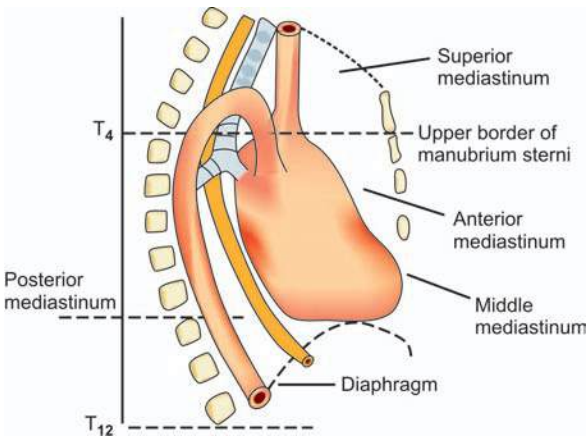


Fig. 147.1: Subdivisions of mediastinum

are seen less commonly. The majority of cases are asymptomatic. Symptoms are caused by obstruction and infiltration. These are lymphatic and superior venacaval obstruction, hoarseness of voice due to recurrent laryngeal nerve paralysis, Horner’s syndrome caused by pressure on the sympathetic chain, dysphagia due to pressure on the esophagus, and cough and dyspnea due to pressure on the trachea. Neural tumours may elaborate hormones, e.g. pheochromocytoma.

Investigations

Both invasive and non invasive procedures are needed for detailed evaluation. Noninvasive are skiagrams in

Superior and Anterior Mediastinum	Middle Mediastinum	Posterior Mediastinum
Thymic tumours	Congenital cysts	Neurogenic tumours
Aberrant Thyroid	Primary cardiac and vascular tumours	Lymphoma
Germ cell tumours	Lymphoma	Mesenchymal tumours
Malignant Lymphomas	Neural crest tumours	
Giant Lymph node hypoplasia		
Teratoma		
Parathyroid tumours		
Mesen chymal and soft tissue tumors		
Lymphovascular tumors		
Primary and secondary carcinoma		



Fig. 147.2: X-ray chest: Mediastinal tumour – widening of the mediastinum



Fig. 147.3: X-ray chest lateral view. Note: The opacity of the superior mediastinum due to retrosternal tumour

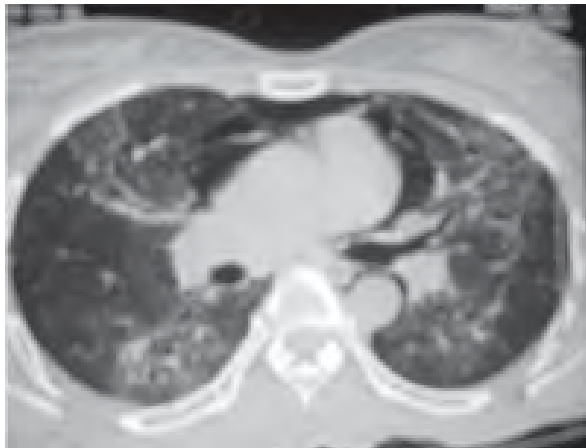


Fig. 147.4: Pneumomediastinum HRCT

Enteric cysts develop in relation to the esophagus. Their lining may resemble the gastric or intestinal mucosa.

Pericardial cysts develop by the side of the pericardium without communicating with its cavity.

Pneumomediastinum

Syn: Mediastinal emphysema

Presence of air within the planes of the mediastinum is called pneumomediastinum. This may occur spontaneously or result from trauma to the chest or perforation of the trachea and esophagus. Surgical emphysema occurring in the fascial planes of the neck or retroperitoneal region may spread to the mediastinum. In emphysema and conditions associated with violent cough, alveolar air may enter the interstitium and reach the mediastinum through the hilum. Other rare causes include Caisson disease and perforation of the esophagus during instrumentation.

Clinical features: The condition may be asymptomatic in many cases. Others complain of retrosternal pain, dyspnea, cough and dysphagia. Crepitus may be felt over the upper part of the chest. Crunching adventitious sounds may be heard on auscultating the heart (Hamman’s sign). In severe cases cardiac failure may develop. Skiagrams reveal the air in tissues (Fig. 147.4).

Treatment

Measures to abolish pain and prevent infection are sufficient in spontaneous cases. In traumatic cases the surgical defects have to be repaired.

different views (Figs 147.2 and 147.3), computed tomography, magnetic resonance imaging, ultrasonography, radionuclide scanning, and biochemical tumor markers. Invasive procedures include bronchoscopy, mediastinoscopy and biopsy of nodes by thoracotomy. Vast majority of the mediastinal lesions can be detected clearly by MRI and CT.

Cysts

The anterior and middle mediastinum may be the seat of benign cysts, the majority of which are asymptomatic.

Bronchogenic cysts are seen by the side of the trachea or the carina most frequently. These cysts do not communicate with the air passages.

Hematology

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Hematology: General Considerations

K.V. Krishna Das

Chapter Summary

Blood Formation 970
 Erythrocyte 970
 Hematological Growth Factors 972
 Leukocytes 974
 Platelets 979
 Clinical Aspects of Hematological Disorders 981
 Laboratory Investigations 982

Blood Formation

As early as the third week of gestation, blood cells are formed in the yolk sac outside the embryo. Hematopoiesis is taken up by the liver and spleen after a few weeks. The bone marrow progressively takes over this function after the 20th week. After birth, hepatic and splenic hematopoiesis ceases and bone marrow is the only site for blood formation. Normally in adults only the marrow in the axial skeleton, skull, and ends of long bones is active, the rest remains in a dormant stage, but it can become active in times of need. In the adult 30% of hemopoiesis takes place in the pelvic bones.

The bone marrow is a highly organized tissue supported by reticular cells and anchored on a spoke-like vascular structure. Functionally there are two components.

1. **The microenvironment** consists of the stromal cells, accessory cells and extracellular matrix formed by them. The stromal cells include fibroblasts, macrophages, endothelial cells and adipocytes. The macrophages elaborate a wide range of cytokines which influence growth of marrow cells—either stimulatory or inhibitory.

Function of stroma is to provide a structural framework for the blood-forming cells and to produce cytokines.

2. **The hematopoietic stem cells in various stages of proliferation and maturation:** A rich network of blood vessels empties blood into sinuses. The hematopoietic cells lie in cords or islands between the

vascular sinuses in a meshwork of reticular cells. Erythrocytes, myeloid cells, and megakaryocytes develop outside the vascular compartment. The marrow contains a rich supply of nerve cells which are sensitive to changes in intramedullary pressure. They are packed into fronds consisting of a network of reticular fibroblastoid cells surrounded by endothelial cells. As the blood cells mature they extricate themselves from this network, pass through the gaps between the endothelial cells and are liberated into the sinusoidal blood. From the sluggish circulation in the sinusoids, ultimately they reach the mainstream of circulation. Each day an adult produces 200 billion erythrocytes, 100 billion leukocytes and 100 billion platelets. These rates can be increased by 10-folds in times of need.

The pluripotent stem cell differentiates first into the myeloid cell progenitor CFU-S (colony forming unit spleen). From this cell the progenitors of erythroid (BFU-E), myeloid and monocytic cells (CFU-GM) and megakaryocytes (CFU-MK) arise. CFU-GM further differentiates into the precursors of macrophages (CFU-M) and granulocytes (CFU-G) (Figs 148.1 and 148.2).

Several growth factors and differentiating factors are produced by different cells which help proliferation of the hematopoietic cell precursors.

Lymphoid cells arise in the bone marrow from the lymphocyte precursor.

Erythrocyte

The most primitive committed erythropoietic precursor cells are called “*erythroid burst-forming cells*” (BFU-E) since they give rise to multiple sub-colonies when they are grown *in vitro*. The burst promoting activity is brought about by the secretions of specific types of T-cells and monocytes occurring in close proximity to each other. As the primitive progenitor cells replicate and mature they become increasingly sensitive to erythropoietin and form erythroid colonies more rapidly (*erythrocyte colony forming units*: CFU-E). These develop into *erythroblasts* and *erythrocytes*. Erythropoietin is the main hormone

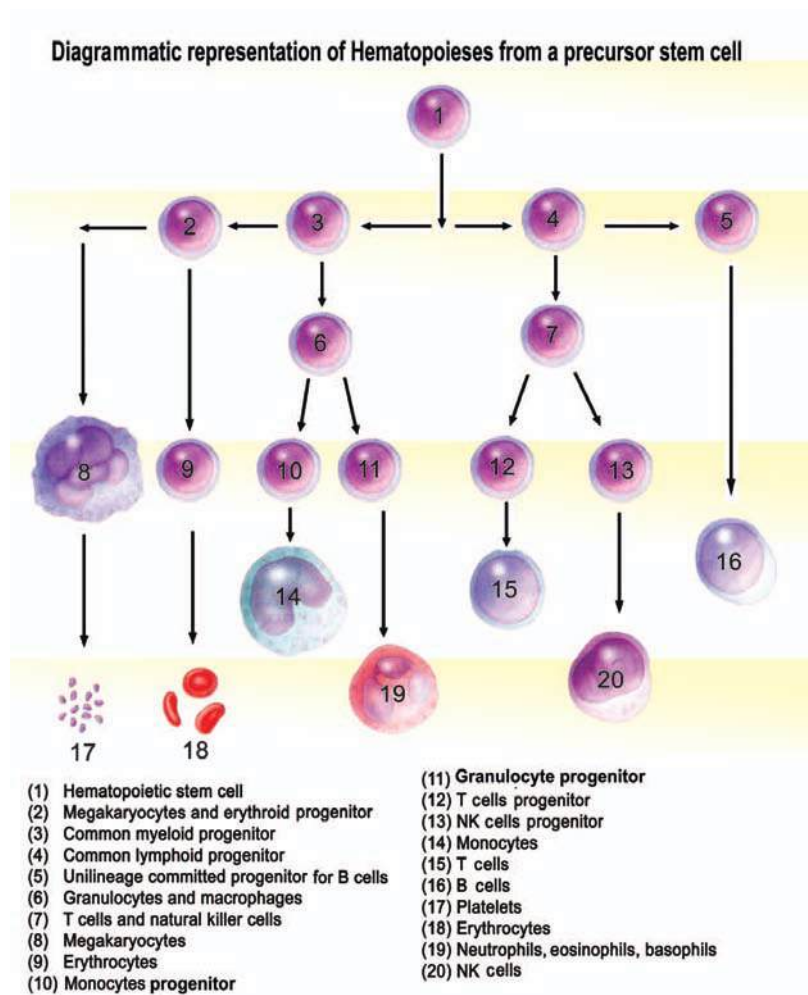


Fig. 148.1: Scheme of hematopoiesis

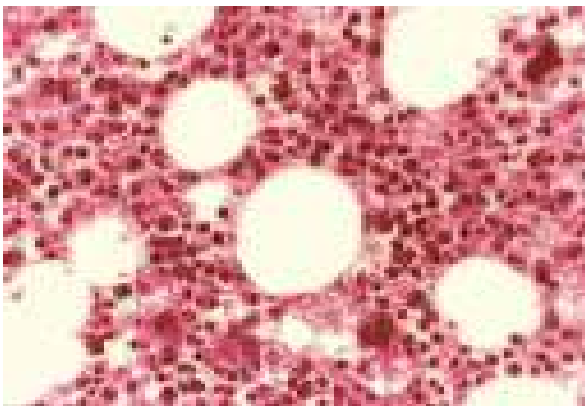


Fig. 148.2: Normal bone marrow $\times 400$

which controls the proliferation and maturation of erythroid precursors.

Stages in the Development of the Erythrocyte

Different stages are recognisable in the process of maturation of the erythrocyte. These are the proerythroblast,

basophilic, polychromatophilic, and eosinophilic normoblasts, reticulocytes, and mature erythrocytes. The nucleus of the normoblast degenerates and it is extruded to give rise to the reticulocyte. In this cell, ribosomes, mitochondria, and Golgi apparatus persist for a short time. These cytoplasmic organelles reveal a granular or strand-like pattern when stained with vital stains like brilliant cresyl blue or aqueous methylene blue. These are called reticulocytes. The remnants of the degenerating nucleus which are in the process of extrusion are demonstrable as *Howell-Jolly bodies* and *Cabot's rings*.

In the normal adult 2×10^{11} erythrocytes die everyday. In replacing this number the marrow synthesises 4×10^{14} molecules of hemoglobin every second. Hemoglobin consists of heme and globin. Heme is synthesised by inserting an atom of iron into an intensely coloured ring of protoporphyrin IX by the developing erythroblast. Simultaneously the developing red cell produces alpha and beta-globin chains which are joined to the heme molecule. This process proceeds in a precisely programmed manner. Heme is formed in the mitochondria from where it has to

move out into the cytoplasm where globin chains are formed. Disruption of these processes leads to disorders such as thalassemias where globin chain synthesis is defective and sideroblastic anemias where incorporation of iron into heme is defective.

The mature erythrocyte is a non-nucleated biconcave disc most suited to perform the function of gaseous exchange. It is a highly specialised, metabolically active cell which obtains energy by utilising glucose by anaerobic pathways. It is provided with enzymes required for metabolism of glucose. Some of the important enzymes which take part in anaerobic glycolysis are hexokinase, glucose-6-phosphate isomerase, phosphofructokinase, and aldolase. Those taking part in oxidative glycolysis are glucose-6-phosphate dehydrogenase (G-6-PD), 6-phospho-gluconate dehydrogenase, transketolase and transaldolase. This pathway is connected with glutathione metabolism through the enzymes glutathione reductase and glutathione peroxidase.

The red cell membrane is unique in that it maintains the biconcave shape of the red cell, it is capable of accommodating increase and decrease of volume of the contents, and it is deformable so as to pass through blood vessels of smaller caliber. The membrane consists of a bilayer of lipids and integral proteins attached to an underlying protein skeleton. The protein skeleton consists of a two dimensional mesh of spectrin tetramers and oligomers, cross linked by protein 4.1 and actin. The protein skeleton is attached to the membrane by the binding of spectrin to ankyrin, and of ankyrin to another protein called band-3 which is an anion exchanger. Other membrane proteins include pallidin. Abnormalities of these membrane proteins lead to early destruction of the erythrocytes.

The protein skeleton helps to maintain the shape of the red cell. The deformability is grossly affected in defects of membrane of the erythrocyte as occurs in spherocytosis and elliptocytosis and also when abnormal hemoglobins such as HbS induce polymerisation under anoxic environment. Normal erythrocyte does not freely adhere to endothelium while in circulation. Under abnormal conditions the adhesive properties of the membrane also changes, rendering them more adherent to endothelium.

The erythrocyte membrane has a major role in ion transport which is mediated by several membrane channels or pumps that can maintain the osmotic gradient within the cell. These functions which require energy can be modified by hormones, cyclic nucleotides, calcium and calmodulin.

Anaerobic metabolism supplies 90% of the energy requirement and only 10% is supplied by the aerobic or pentose phosphate cycle. The mature red cell is incapable of protein synthesis. The full complement of hemoglobin and enzymes present in erythrocytes is handed down by

the erythroblast. Life of the red cells is 120 days. They are destroyed in the reticuloendothelial system subsequently. The red cell number remains nearly constant in the range of 5-6 millions per cmm ($5-6 \times 10^{12}$ /litre) throughout life.

Hemoglobin is a complex molecule consisting of the heme moiety (the red pigment) comprising iron and porphyrin, and the protein moiety, globin. In adult hemoglobin (HbA) the globin consists of two alpha chains, each containing 141 amino acids and two beta chains each with 146 amino acids. The fetal hemoglobin (HbF) consists of two alpha chains and two gamma chains. After birth, within 5-6 months the synthesis of gamma chains stops and beta chains are formed in the required amounts. By the age of six months 98-99% of hemoglobin is made up of HbA. The rate and amount of production of the alpha, beta and gamma chains and their synthesis to form normal and abnormal hemoglobins are controlled by specific genes. In normal persons the production of gamma chains fall rapidly after birth and give place to rapid increase in the production of beta chains. For the continuous production of red cells and synthesis of hemoglobin several nutrients are required. These are mainly iron, proteins, vitamin B₁₂, folic acid, pyridoxine, vitamin C, nicotinic acid, copper and cobalt.

The blood group antigens are attached to the red cell membrane. The molecular basis for the remarkable diversity of the blood group polymorphism includes single base substitutions, deletions and insertions in the genes that encode their protein products.

Mature RBC has no nucleus or mitochondria. Energy is derived through the glycolytic Embden-Meyerhof pathway in which glucose is metabolised with the production of lactate.

Hemoglobin is responsible for transport of oxygen from lungs to tissues and removal of carbon dioxide from tissues and delivery to the lungs. The oxygen dissociation curve of hemoglobin depicts these events. Rise in H⁺ ion concentration and CO₂ levels in the environment reduce the oxygen binding capacity of hemoglobin. This is known as the Bohr effect. Increase in oxygenation of hemoglobin reduces its affinity to CO₂. This is known as the Haldane effect.

Androgens also stimulate the production of erythropoietin and also directly activate the stem cells. Estrogens suppress erythropoietin production and hence depress erythropoiesis. Thyroxine probably stimulates erythropoiesis by producing tissue anoxia. Hypothyroidism leads to a mild degree of anemia, which can be corrected by thyroxine.

HEMATOPOIETIC GROWTH FACTORS

The expansion of the stem cell pool, maturation and expansion of precursor cells and their liberation into circulation are all under control of well defined humoral

influences. These include erythropoietin (EPO), granulocyte colony stimulating factor (G-CSF), macrophage colony stimulating factor, granulocyte-macrophage colony stimulating factor (GM-CSF) and interleukin-3 (also known as multiclonal stimulating factor).

Erythropoietin (EPO): During fetal life it is produced in the liver. In postnatal life, by far the main source is the kidneys (90%), a small amount is also produced in the liver (10%). In the kidneys the erythropoietin producing cells are found in the renal cortex, lying outside the renal tubular basement membrane. These cells are derived either from a subset of interstitial cells or capillary endothelial cells which can sense oxygen levels by a complicated mechanism. Action of erythropoietin on the erythroid precursor cells is receptor mediated.

Erythropoietin is a glycoprotein with a molecular weight of 30,000 daltons. Its principal actions are on the developing erythroid precursor cells after they have become sensitive to erythropoietin. The erythroid precursors are stimulated to proliferate and differentiate and thus accelerate erythropoiesis. Normal apoptotic mechanisms play a role in regulating erythrocyte maturation and disposal.

The viability of the developing erythroid cells is also maintained by this hormone. It is a survival factor for them. Erythropoietin production is tightly controlled to prevent inappropriate rise in red cell mass. Main stimulus for erythropoietin production is anoxia. Rise in red cell mass and viscosity of blood depress erythropoietin production independent of the tissue oxygenation status. Small rise in erythropoietin levels do occur with slight fall in hemoglobin, up to 10 g/dL, but not beyond the normal ranges. The normal range of plasma erythropoietin is 5-25 units/L. In response to anemia or arterial hypoxemia the serum level of EPO may go above 25 u/L.

There is only one form of circulating erythropoietin. Production is controlled at the gene level. There are no stores and the production and clearance are independent of the plasma levels. Erythropoietin gene transcription is inhibited by inflammatory cytokines such as interleukin-1 and tumour necrosis factor.

Actions of EPO

1. EPO leads to proliferation of erythroid precursors which differentiate into normoblasts, which leave the bone marrow after extrusion of the nucleus. Reticulocyte counts start rising within 1-2 weeks of EPO administration.
2. EPO crosses blood brain barrier and it plays a protective role in ischemic neurons. It has also tissue protecting activity in the myocardium and the kidney.

Various conditions such as renal parenchymal diseases, hyperviscosity, cancer, infection, inflammation,

chronic liver diseases, surgery, pregnancy and prematurity suppress erythropoietin production without regard to tissue oxygenation. Erythropoietin is metabolised by erythroid progenitor cells. In hypoplastic anemia, due to defective utilization of erythropoietin, the serum levels are relatively high. Erythropoietins (EPO), their analogues and mimetics are produced by recombinant technology. These include recombinant erythropoietin, darbepoietin alfa which has longer duration of action compared to EPO, continuous erythropoietin receptor activator (CERA), synthetic erythropoietin protein, erythropoietin fusion protein, and erythropoietin-mimetic peptides. All these are under different stages of drug development at present.

Hematopoietic growth factors other than erythropoietin are produced by fibroblasts, endothelial cells, monocytes and lymphocytes which are widely distributed. In experimental studies, stimulation with bacterial endotoxin, monokines and lectins increase the production of these growth promoting factors. They act on progenitor cells to produce precursor cells and simultaneously expand the progenitor pool.

Granulocyte-macrophage colony stimulating factor (GM-CSF) acts on the precursors of granulocytes, monocytes, macrophages, erythrocytes and also megakaryocytes.

GM-CSF is produced by several cell types. It stimulates the proliferation of several myeloid cell lines and megakaryocytes. The result is increased production of neutrophils and other granulocytes and monocytes and improvement in neutrophil survival. GM-CSF stimulates the production of neutrophils, eosinophils, basophils, monocytes and dendritic cells in culture and activates most of these cells into action.

Granulocyte colony stimulating factor G-CSF G-CSF is produced by endothelial cells, fibroblasts and macrophages in virtually all organs. It stimulates growth of neutrophil colonies in vitro and stimulates neutrophils into activity such as phagocytosis and bacterial killing. It leads to release of young neutrophils into the circulation leading to shift to the left of neutrophil distribution. It also causes the presence of toxic granules in the neutrophils in peripheral blood, which is a morphological correlate of their heightened functional state. In inflammation, cytokines such as tumour necrosis factor (TNF α), interleukin-1 and interleukin-6, derived from activated monocytes stimulate G-CSF production. Recombinant G-CSF is available for therapy as injection containing 30 MU (300 μ g)/mL. After injection, peripheral blood neutrophil count rises within 48 hours. Monocytes and eosinophils may show slight rise. The dose is 0.5 MU (5 μ g)/kg bw given SC or as IV infusion.

G-CSF mobilises stem cells from the bone marrow to peripheral blood and therefore increases the yield of stem cells from peripheral blood. G-CSF therapy helps to

prevent chemotherapy-induced neutropenia. G-CSF therapy may increase incidence of treatment related myeloid leukemia especially when co-administered with cyclophosphamide or doxorubicin.

Haemopoietic growth factors are administered for four groups of conditions

1. Correction of cytopenias
2. For harvesting stem cells and progenitor cells
3. Augmentation of hematopoiesis to compensate for accelerated cell destruction
4. Activation of mature hemopoietic cells.

Clinical Applications

Erythropoietin is very successful in correcting anemia and improving the general well-being in chronic renal failure when given in a dose of 75-150 IU/kg body weight thrice a week (total dose required annually for an adult being 2-12 mg). Erythropoietin is also used to stimulate red cell production preparatory to autologous transfusion at a later date.

Erythropoietin is given by SC injection. Indications for erythropoietin include;

1. *Anemia of chronic renal failure (CRF).*
2. *Anemia of cancer.* Patients with Hb< 10g/dL benefit by EPO which also prolongs life.
3. *In patients recovering from myelosuppressive chemotherapy.* Chemotherapy induces apoptosis both in cancer cells and erythroid precursors. EPO blocks the apoptosis of erythroid precursor cells.

Repeated use over long periods may lead to the development of anti-erythropoietin antibody which neutralizes endogenous and exogenous erythropoietin. The patient becomes unresponsive to the use of erythropoietin and may develop pure red-cell aplasia (PRCA). This condition responds to immunosuppressive therapy. Another adverse side effect is the development of hypertension with rise in erythrocyte counts.

A long-acting analogue of erythropoietin which is also used in therapy is *darbepoietin alfa*.

GM-CSF is employed in doses of 10 µg/kg body weight, in order to stimulate neutrophils, monocytes and circulating stem cells, and thereby reducing the duration of dangerous neutropenia following intensive chemotherapy and bone marrow transplantation. For harvesting circulating stem cells preliminary to stem-cell transplantation which is an alternative to bone marrow transplantation, GM-CSF is employed. It is also used in some cases of cyclical neutropenia and agranulocytosis where other therapeutic measures are not fully effective.

G-CSF is also used extensively in leukopenic states and chemotherapy induced neutropenia, both prophylactically and therapeutically.

Leukocytes

White blood cells originate from pluripotent hemopoietic stem cells. Under the influence of various external stimuli including cytokines, matrix proteins and accessory cells, the stem cells differentiate into hemopoietic progenitor cells.

Cytokines involved in the production of different leukocytes	
Cell type	Cytokine involved
Neutrophil	G-CSF, GM-CSF, IL 3, and macrophage colony stimulating factor (M-CSF)
Monocytes	GM-CSF, and M-CSF
Eosinophils	GM-CSF, IL3 and IL 5
T-lymphocytes	A complex process IL 2 and IL 3
B-lymphocytes	IL 7

Broadly they may be divided into phagocytes and lymphocytes. The former includes the neutrophils, eosinophils, basophils (granulocytes), and monocytes (Table 148.1).

The granulocytes are formed from the stem cell through the stages of myeloblasts, promyelocytes, myelocytes and metamyelocytes. As the neutrophil ages, the number of lobes in the nucleus increases and age of the cell can be assessed this way. The cytoplasmic granules are lysosomal in origin and are of two types—the *primary granules* which appear at the promyelocytic stage and the *secondary granules* which appear at the myelocytic stage. Primary granules contain myeloperoxidases, acid phosphatases and other acid hydrolases. Secondary granules contain alkaline phosphatase and lysozyme. The latter predominates in the mature neutrophil. Myeloblasts are the earliest recognizable precursors seen in the bone marrow. The nucleus contains 2-5 nucleoli and the cytoplasm is clear, nongranular and basophilic. In normal

TABLE 148.1

The normal distribution of leukocytes in peripheral blood		
	Range per litre	Percent of total
Total leukocytes (Adults)	5-10 × 10 ⁹	
Neutrophils	3.5-7 × 10 ⁹	60-70%
Eosinophils	0.1-0.6 × 10 ⁹	2-6%
Basophils	0.01-0.1 × 10 ⁹	0-1%
Monocytes	0.2-0.5 × 10 ⁹	2-5%
Lymphocytes	1.5-3 × 10 ⁹	25-35%

Note: 1 × 10⁹/litre = 1000 cells/cmm. Children have slightly higher leukocyte counts.

marrow the myeloblasts do not exceed 4%. Promyelocytes are formed by division of myeloblasts. The nucleoli disappear and the cytoplasm acquires primary granules. The promyelocytes give rise to myelocytes which show specific secondary granules in the cytoplasm. The nucleus is more condensed and nucleoli are absent. Neutrophils, eosinophils, and basophils arise from corresponding myelocytes. Myelocytes divide to form metamyelocytes which do not divide further. Metamyelocytes have indented or horse shoe-shaped nucleus and cytoplasm filled with primary and secondary granules. These cells develop into 'band forms' or *juvenile neutrophils* in which the nucleus starts to show lobulation, but the distinct filamentous constriction between the lobes is absent.

Myeloblasts, promyelocytes, and myelocytes are together known as the proliferative or *mitotic pool*, and the metamyelocytes, band forms, and segmented neutrophils are known as the *postmitotic maturation pool*. The store of granulocytes present in the marrow is 10-15 times the circulating pool. Majority of the marrow granulocytic cells are myelocytes and neutrophils. After release from the bone marrow granulocytes circulate in the peripheral blood for about 10 hours and then enter tissue for phagocytosis. In the peripheral blood, half of the neutrophils circulate freely (*circulating pool* included in the blood count) and the other half forms the *marginating pool* which adheres to vessel wall (not included in the blood count). In the tissues, the granulocytes remain for 4-5 days before they perish during defensive action or due to aging.

The various compartments in the peripheral blood, tissues and bone marrow are regulated by a feedback mechanism. Leukopoietins, analogous to erythropoietin, have been described.

Functions of neutrophils: These include chemotaxis, phagocytosis, intracytoplasmic killing, and destruction of foreign particles and microbes. Neutrophils are phagocytic and this activity is of prime importance in microbial killing. In many inflammatory diseases further processes mediated by the cytokines liberated by neutrophils tend to perpetuate the inflammatory and tissue destructive processes. Functional defects of neutrophils may occur at times. In this condition there will be defects of any or all the functions.

Neutrophils adhere to cells and surfaces by receptor mediated activity and the cell surface glycoproteins are important for this function. Neutrophils activated by phagocytic stimuli or chemo-attractants produce large amounts of microbicidal oxidants. The neutrophils contain cytoplasmic granules of different sizes. The azurophil granules are lysozyme-like, and contain various enzymes and other proteins possessing antibacterial and antifungal properties. The lysosomal granules contain myeloperoxidase. Neutrophil-specific (secondary) granules are rich in

glycoproteins. Deficiency of the contents of granules make the neutrophils functionally defective.

Functional Defects of Neutrophils

This may be acquired or congenital.

Defect in chemotaxis (lazy leukocyte syndrome) occurs in alcoholism, hyperosmolar states, myelogenous leukemia, abnormalities of complement, and rarely as a congenital condition. Drugs like aspirin and corticosteroids impair chemotaxis further.

Defective phagocytosis occurs in hypogammaglobulinemia, hypocomplementemia, post-splenectomy states, and sickle cell anemia.

The killing function is reduced in granulomatous disease, myeloperoxidase deficiency, Chédiak-Higashi syndrome, acute and chronic granulocytic leukemias, preleukemia, and myelodysplastic states.

Alteration in Neutrophil Counts

Neutrophil leukocytosis (count above $7.5 \times 10^9/\text{litre}$): This condition occurs in many bacterial infections, inflammations, tissue necrosis, metabolic disorders such as renal failure, gout, acidosis, toxemias of pregnancy, malignant neoplasms, acute hemorrhage, acute hemolysis, and corticosteroid therapy. Myeloproliferative disorders are characterized by very high granulocyte counts. A rapid increase in the production of neutrophils is generally associated with the appearance of many young forms (*shift to the left*) and the presence of myelocytes in peripheral blood.

Neutropenia (counts below $1 \times 10^9/\text{litre}$) develops as a toxic reaction to several drugs or as a part of pancytopenias. Milder grades of transient neutropenia occur in many viral infections and bacterial infections like typhoid, hypersensitivity, anaphylaxis, auto-immune disorders like disseminated lupus erythematosus, and in hypersplenism. When neutropenia is caused by reduction in the formation of cells, most of the neutrophils in peripheral blood are the older forms. They show four or more lobes in the nucleus (*shift to the right*), the younger forms being particularly absent.

Reduction of neutrophil counts to below 500/cmm is associated with increased risk of several opportunistic infections. Neutropenia associated with fever is a dreaded complication in chemotherapy of malignancy, organ transplantation and others. This calls for special therapeutic intervention.

Cyclical neutropenia is a rare disorder showing periodic reduction in neutrophils at 3-4 week intervals. It is characterized by a regular 21-day cyclic fall and rise in the numbers of circulating neutrophils, monocytes, eosinophils, lymphocytes, platelets and reticulocytes. This is caused by a defect of the stem cells. During the

leukopenic phase the bone marrow shows paucity of myeloid elements. Neutropenia by itself does not cause symptoms, but it predisposes to infection when the neutrophil count falls $<500/\text{cmm}$ and persists so for >10 - 14 days.

During these episodes, infections may develop leading to oral ulceration, gingivitis, pharyngitis, lymphadenopathy and skin infections. Human granulocyte colony stimulating factor given in a dose of $3\mu\text{g}/\text{kg}$ daily subcutaneously has been found to be effective in correcting the neutropenic state. Prolonged use may predispose to the development of acute myeloid leukemia in $>10\%$ of cases.

Sometimes neutrophils migrate from the circulating pool to the marginating pool and the neutrophil count in peripheral blood falls. There is no increased tendency for infections in this condition. This is referred to as *idiopathic benign neutropenia*.

Eosinophils

Eosinophils are generally similar in morphology to neutrophils, with eosinophilic granules in the cytoplasm. The nucleus contains only two or rarely three lobes. Eosinophils develop through the same stages as the neutrophils. Distinguishing features develop at the stage of myelocyte.

Four processes are distinguishable in the development of eosinophils.

1. Differentiation of progenitor cell and proliferation in the BM.
2. Interaction between eosinophils and endothelial cells that includes rolling, migration and adhesion of eosinophils.
3. Chemoalteration which directs eosinophils to specific locations and
4. Activation and destruction.

Three cytokines—interleukin-3, IL-5 and GM-CSF are particularly involved in the development of eosinophils. Among these three, IL-5 is the most important. It is also called eosinophil differentiation factor.

Eosinophils in tissues survive for varying periods, upto 12-24 days.

Several enzymes such as aryl sulphatase, phospholipidase, acid phosphatase, beta-glucuronidase, peroxidase, and cathepsins are present in the cytoplasmic granules. The function of eosinophils has been extensively studied and their importance recognised. They phagocytose a variety of substances such as immune complexes, mast cell granules, mycoplasma, ferritin, and others. But this activity is considerably less than that of neutrophils. Eosinophils suppress allergic inflammatory processes. They play an important role in defence against parasites and in the removal of fibrin formed during inflammation.

Larval forms of parasites like filaria and schistosomes are killed by eosinophils. They kill parasites by releasing

cationic proteins and reactive oxygen metabolites into the extracellular fluid. They also secrete leukotrienes, prostaglandins and various other cytokines. Their life in peripheral blood is longer than that of neutrophils. In many conditions like hypersensitivity reactions, parasitic diseases, drug sensitivity, and polyarteritis nodosa, eosinophil counts are moderately increased (0.4 - $2 \times 10^9/\text{litre}$). Marked increase (over $3 \times 10^9/\text{litre}$) occurs in tropical eosinophilia which is common in India. Asthma, polyarteritis nodosa and helminthiasis are associated with eosinophilia. Primary hypereosinophilic syndrome and eosinophilic leukemia cause high eosinophilia, but these are rare.

Basophils

Basophils form up to 1% of the total leukocytes. They are identified by the presence of coarse basophilic granules which often overlie the nucleus which is bilobed. The granules are rich in histamine, serotonin and leukotrienes. Mast cells are related to, but distinct from basophils. Mast cells are long-lived cells which reside in tissues rather than in peripheral circulation, and they can divide further. Both basophils and mast cells participate in immediate allergic reactions such as urticaria, anaphylaxis, asthma and allergic rhinitis. Increase in basophil leukocytes (counts above $0.1 \times 10^9/\text{litre}$) is uncommon, but this is seen in myeloproliferative disorders such as chronic myeloid leukemia and polycythemia vera. Disorders like myxedema, smallpox, chickenpox, and ulcerative colitis also may be associated with basophil leukocytosis.

Monocytes

Syn: Mononuclear phagocytes: Mononuclear phagocyte system is made up of peripheral blood monocytes, their precursors in the bone marrow and tissue macrophages. Though their nomenclature indicates that they are predominantly phagocytic, they also mediate several other functions including induction of acute phase responses, regulation of hematopoiesis, activation of immune and coagulation systems, killing of microorganisms and tumour cells, and tissue repair.

The precursor of the monocyte is the monoblast which resembles the myeloblast but can be distinguished histochemically. From their sites of origin in the bone marrow the monocytes circulate in the peripheral blood for about three days and enter the tissues where they are known as macrophages. The number of tissue macrophages are several hundred times that of the circulating monocytes and their life-span is around a few months. The macrophages are seen in all tissues, but they are particularly prominent in the spleen, lymph nodes, pulmonary alveoli, liver (*Kupffer's cells*), peritoneum and skin (*Langerhan's cells*). Once the monocyte enters the tissues, it does not return to the circulation.

Mononuclear macrophages secrete several substances (numbering about a hundred) and these take part in several functions ranging from induction of cell growth to cell death. The major functions mediated by monocyte macrophages are listed below.

1. **Inflammation**—The acute phase response which is a systemic inflammatory reaction resulting from infection or injury consists of fever, tachycardia, shock and changes in the concentrations of circulating proteins such as C-reactive protein, fibrinogen interleukin-1, tumour necrosis factor and interleukin-6. These are secreted by the monocytes and they form important mediators of this response.
2. **Regulation of hemopoiesis**—Monocyte products such as granulocyte colony stimulating factor and macrophage colony stimulating factor directly stimulate cell production. Interleukin-1 and tumour necrosis factor activate T lymphocytes to produce granulocyte-macrophage colony stimulating factor and interleukin-3 which also stimulates hemopoiesis.
3. **Hemostasis**—Monocytes and macrophages can activate the blood coagulation process in response to several stimuli including bacterial endotoxin, immune complexes and complement components. Mononuclear phagocytes synthesise tissue thromboplastin which can activate the extrinsic coagulation pathway.
4. **Lymphocyte activation**—Some B- and T-lymphocytes cannot recognize free antigens themselves. Mononuclear phagocytes are capable of taking up such antigens and converting them into immunogenic fragments which are presented to B- and T-lymphocytes which are activated in turn.
5. **Microbial killing**—Mononuclear phagocytes are attracted towards an infective focus by several substances including bacterial components and endotoxins, complement components, immune complexes and collagen fragments. Once they reach the site, they remain there under the influence of a migration inhibitory factor secreted by T lymphocytes and phagocytose the microbes. After ingestion the organisms are killed.
6. **Destruction of tumour cells**—Mononuclear phagocytes infiltrate tumours and lead to lysis of tumour cells. This forms a major defensive mechanism against tumours. Tumour necrosis factor produced by the mononuclear phagocytes has been synthesized by recombinant DNA technology and it is used therapeutically.
7. **Tissue repair and remodelling**—The collagenase and elastase secreted by mononuclear phagocytes help to debride wounds. They also release substances which stimulate the proliferation of fibroblasts and new vessels.

Macrophages in tissues are quiescent under normal conditions, but in times of need they are activated by several stimuli including endotoxin, immune complexes, complement components and products of T-cells. Gamma interferon secreted by lymphocytes is an important activator of macrophages. Macrophage function is essential to life. It is impaired in immunosuppressed states, diabetes mellitus, chronic granulomatous disease and several others.

Bacterial infections such as tuberculosis, brucellosis, bacterial endocarditis and typhoid, and protozoal infections like amoebiasis may lead to moderate monocytosis (over $0.8 \times 10^9/\text{litre}$). Other causes of monocytosis are neutropenia, Hodgkin's disease, and monocytic leukemia.

LYMPHOCYTES

Lymphocytes and plasma cells are together known as **immunocytes**. Their role is to assist the phagocytes in defence mechanism and add specificity to the attack.

Lymphocytes are formed in the bone marrow and thymus during postnatal life. In the fetus, the yolk sac and liver produce lymphocytes. In the lymphopoietic tissues the stem cells undergo spontaneous division without depending on antigenic stimulation. Other lymphoid tissues found in lymph nodes, spleen, organized lymphoid tissues of the alimentary and respiratory tracts and the lymphocytes seen in blood and tissue spaces, constitute secondary lymphoid tissues. In the bone marrow the precursor of the lymphocyte is the lymphoblast. Maturation to the lymphocyte stage occurs without any distinct stages in between.

B-lymphocytes are derived from bone marrow stem cells. When activated by antigens, the B-cells proliferate and mature into plasma cells which secrete specific immunoglobulins, the antibodies.

The primordial T-cells are produced in the bone marrow and the cortex of the thymus, where they are conditioned to recognize the body's antigenic make-up. T-cell precursors migrate from the bone marrow to the corticomedullary regions of the thymus where they begin to differentiate, rearrange their variable region genes and proliferate. This process is completed in the medulla of the thymus from which the mature T-cells exit, 98% of the cells undergo apoptosis during their maturation in the thymus and only 2% emerge as functionally competent T-cells.

They are the main cells responsible for cell-mediated immunity. **Helper T-cells** (CD4+) are specific lymphocytes which instruct B-cells about specific antigens. The T-cell population also contains **suppressor cells** (CD8+) which reduce B-cell responses. The **killer cells** (K cells) cause damage to cells recognized as 'foreign'. Lymphocytes migrate to the lymph nodes and spleen through post-capillary venules. The T-cells are seen in the perifollicular

areas of the cortex of lymph nodes (paracortical areas) and in the periarteriolar sheaths surrounding the central arterioles of the spleen. The majority of lymphocytes in the thoracic duct and peripheral blood are T-cells. B-cells selectively accumulate in the subcapsular periphery of the cortex and medullary cords of lymph nodes, and germinal follicles of lymph nodes and spleen. Majority of B-cells remain for long periods in these sites.

Most of the lymphocytes in peripheral blood are small with scanty nongranular cytoplasm and a central nucleus with coarse chromatin. Larger lymphocytes which may also occur in peripheral blood are probably stimulated by antigenic challenge from viruses or foreign proteins.

T- and B-lymphocytes are not distinguishable morphologically in the smear. The large lymphocytes which form about 10%, characterised by abundant cytoplasm and reddish granules are the natural killer cells. They can destroy virus-infected cells and HLA incompatible target cells.

Cytokines

In addition to specific antibodies produced by specifically stimulated cells the cytokines constitute another type of mediators. They act as messengers both within the immune system and between the immune system and other systems of the body forming an integrated network that is highly involved in the regulation of immune responses.

B-lymphocytes

Bone marrow stem cells migrate to the gut lymphoid tissue associated with the alimentary and respiratory tracts and develop into B lymphocytes. These are concerned mainly with the production of antibodies. B-cells differentiate into plasma cells which produce the antibodies. Antibodies consist of two identical heavy chains and two identical light chains that are held together by disulphide bonds. The amino acid sequence of the constant region of the heavy chain specifically determines the class of immunoglobulins IgG, IgA, IgM, IgD and IgE, and the subclasses of IgG and the IgA. Each type of antibody can be produced as a circulating molecule or a stationary molecule. The latter which is anchored to the B-lymphocyte cell membrane acts as the B-cell receptor. It has been estimated that both B-cells and T-cell can produce about 10^{15} different antibody variable regions and T-cell receptor regions respectively. Unlike antibodies, T-cell receptors are produced only as transmembrane molecules. Peptides held by the MHC molecule are recognized by specific receptors on T-cells.

The extreme diversity of antibody production is achieved by less than 400 genes which are located on three chromosomes 14, 2 and 22. The sequence of receptors on T-cells remains unaltered during cell division whereas the B-cells can undergo further rearrangement in the

genes, their receptors, and their antibody producing capacity, in the germinal centres of the secondary lymphoid organs. This process is referred to as '*receptor editing*'.

When B lymphocytes meet an antigen presented by the MHC class I molecule, they proliferate to produce a few thousands of cells. Each B-cell is capable of producing only the same type of antibody. The term pre-B-cell denotes the immature B-lymphocyte in which immunoglobulins have not appeared on the surface. On exposure to an antigen the clone of specific B-cells proliferates rapidly and produces antibodies promptly. Primary immune response occurs on first encounter with the antigen. During this phase all the three types of cells—cytotoxic and helper T-cells and B-cells (antibody secreting plasma cells) and memory T- and B-cells proliferate.

The memory T- and B-cells enable a quantitatively superior immune response on subsequent exposure to the same antigen. The germinal centres of lymph nodes and spleen are discrete areas where B-cell responses occur. Immunoglobulin class switching of B-cells, production of memory cells and plasma cell precursors occur within the germinal centres. The final stage of differentiation of B-cell into antibody producing plasma cells occurs outside the germinal centres.

When B-cells undergo terminal differentiation into plasma cells they acquire the ability to produce and secrete large amounts of antibodies. The antibody can be directly protective if it can inhibit the binding of the micro-organisms or its toxin to the target tissue. In most instances, in addition to this effect, the antibodies also recruit other arms of the immune system for defence.

Activation of the complement cascade helps to enhance phagocytic activity of neutrophils. Natural killer cells, monocytes, macrophages and neutrophils can all function in IgG-mediated antibody dependent cellular cytotoxicity. Macrophages, eosinophils and platelets are involved in IgE mediated antibody dependent cellular cytotoxicity. If the target cell is too large for phagocytosis, the mechanisms employed include perforins (which perforate the cell wall), granzymes which destroy the cell components and reactive oxygen intermediates.

In normal adults 3-4 g of secretory IgA is produced every day, by plasma cells located under mucosal surfaces. This is transported to mucosal surface. It offers protection against adhesion by microbes on the luminal surface.

In general, plasma cells are short-lived with a half-life of only a few days, but some of them, located within the bone marrow survive for weeks.

T-lymphocytes

Formation of T-cells in the thymus occurs throughout life even when the thymus has involuted. MHC class I molecules are expressed on all nucleated cells in the body.

This allows infected cells to signal their plight to cytotoxic CD8 T-cells and establish intimate intercellular contact by presenting the complex of foreign peptides and MHC molecules to the T-cell receptors.

T-cell Function and Migration

T-cells respond to pathogens when they get contact with pathogen-derived antigens. This is achieved by the T-cell receptors recognizing the peptide or lipid antigen bound to a major histocompatibility complex (MHC) or CD-1 respectively on the surface of another cell. The dendritic cells which are derived from monocytes present in skin, epithelial surfaces and subepithelial tissues are the antigen presenting cells. These cells engulf antigens, break them down to peptides and display them on their surface with the help of MHC complexes, also known as HLA molecules. The site of engagement of the antigen presenting cell and the T-lymphocyte is called the immunological synapse. The MHC molecules help to transport intracellular antigenic material to the surface of the cell.

The T-cells are capable of detecting antigens occurring in any part of the body promptly. The dendritic cells present in various tissues and secondary lymphoid organs trap antigens produced in their territories. Naive (unstimulated) T-cells reach these lymphoid organs preferentially, being attracted by inflammatory cytokines. This is called homing. Maturing dendritic cells also home to the T-cell areas of lymph nodes. They ready their apparatus for antigen presentation and also secrete cytokines which make them attractive to T-cells which have arrived in the lymph nodes. On meeting the antigen the T-cells proliferate to produce 1000 times the number of original activated T-cells. Eventually these activated T-cells 'home' to sites of inflammation. They interact with antigen bearing tissues, parenchymal cells and leukocytes. For allergic reactions eosinophils and basophils are recruited. For inflammatory response the neutrophils and macrophages are involved. Most of the effector cells die after the antigen is cleared, but a few antigen experienced T lymphocytes persists for long-term protection as memory cells.

CD4 T-cells are mainly cytokine producing helper cells. CD8 T-cells are mainly cytotoxic killer cells. CD4 T-cells (helper) can be subdivided into two major types based on their cytokines.

Type 1 (Th₁) helper T-cell secrete interleukin-2 and interferon γ , but not IL 4,5, or 6.

Type 2 (Th₂) helper T-cells secrete IL 4,5,6 and 10, but not IL 2 or interferon γ .

Type 1 helper T-cells (Th₁ cells) facilitates cell mediated immunity including activation of macrophages and T-cell mediated cytotoxicity. On the other hand Th₂ cells help B-cells to produce antibodies.

The null cell which do not possess either T or B markers are also members of the immune system.

Interaction between T- and B-cells

There is close interaction between T and B lymphocytes at several stages of the immune response. Some of the T-cells influence B-cells for humoral responses. Leukocytes engage several sequential adhesion pathways to leave the circulation and enter tissues. Adhesion is effected with the help of selectins and integrins which are adhesion proteins. Chemokines are produced by activated endothelial cells, epithelial cells, leukocytes and several other types of cells. Chemokines direct the migration of leukocytes to the sites of antigens.

Some of the T-cells proceed to eliminate pathogens whereas others find pathogen-specific B-cells which need the help of T-cells for efficient antibody response.

The killer T-cells CD8 (T-cells) kill virus infected cells. The viruses are deprived of the cellular enzymes needed for their replication and they are also deprived of their sanctuary within the host cell. Any virus that is released is destroyed by the antibodies.

In addition to direct killing of infected cells the CD8 T-cells also produce cytokines such as tumour necrosis factor (TNF α), lymphotoxin (also known as TNF β), interferon γ and others. The interferon γ renders neighbouring cells resistant to viral infection. To a minor extent CD4 cells (both Th₁ and Th₂) can become cytotoxic on recognizing peptides presented by MHC class II molecules.

A successful immune response eliminates the inciting antigen, and once rid of the stimulus, the concerned cells go back to their pre-stimulatory state.

Plasma cell series: Plasma cells form about 2-3% of cells in the bone marrow. Though they are not usually seen in the peripheral blood, they may appear occasionally. Plasma cells accumulate in chronically inflamed tissues. Such plasma cells contain eosinophilic (acidophilic) smooth hyaline spherical cytoplasmic bodies called *Russell bodies*. These bodies are composed mainly of gammaglobulin. Plasma cells constitute the main source of antibodies. They are formed from stem cells in the bone marrow though B-lymphocytes and then migrate to other tissues. Plasma cells synthesising IgA migrate to gastrointestinal tissues while cells producing IgG and IgD go to tonsillar tissue.

PLATELETS

Platelets are formed from megakaryocytes. Ten billion platelets/L of blood are produced every day in an adult. This can be increased ten- folds in times of need (Figs 148.3 to 148.8).

Myeloid stem cells give rise to megakaryoblast which resemble myeloblast morphologically.

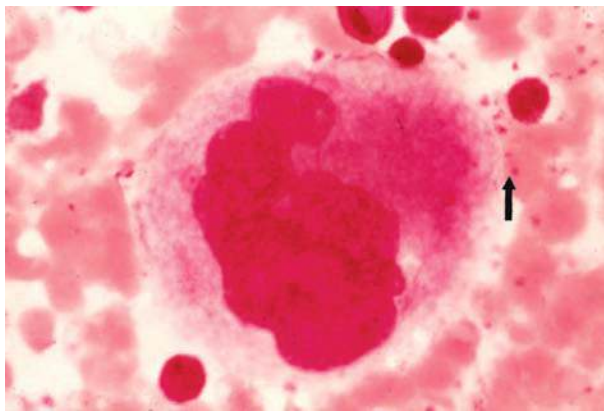


Fig. 148.3: Normal bone marrow × 1000. Note: Platelets escaping from the margins of the megakaryocyte

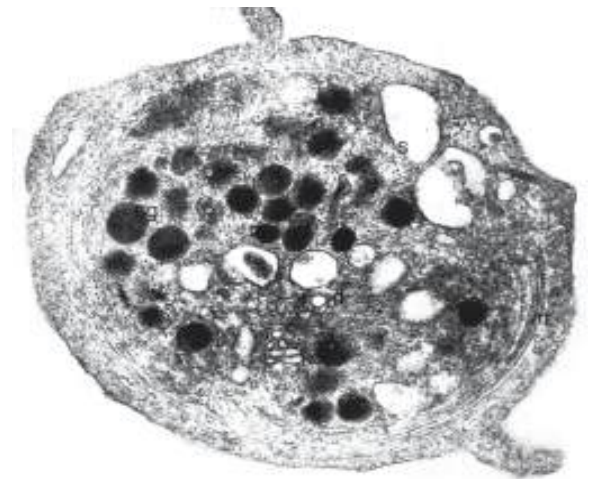


Fig. 148.4: Ultrastructure of the platelet electron microscopy

Promegakaryocytes develop from them by endoreduplication. This is the process in which nucleus divides without cell division. As the megakaryocytes mature, the capacity for endoreduplication increases. This leads to the formation of large cells resembling multinucleated giant cells containing basophilic cytoplasm and a few basophilic granules.

Mature megarkaryocytes are large cells 30-80 µm in diameter and containing 4-16 lobes in the nucleus. The cytoplasm is protruded into the sinusoids of the bone marrow and the platelets are detached and liberated into the circulation. Platelets themselves are nonmotile, but they possess intrinsic contractile activity.

The final product of thrombopoiesis is the platelet which is non-nucleated and is 1-4 µm in diameter. The central part contains red purple granules and the cytoplasm is light blue. Normal platelet count ranges from 150-300,000/cmm of blood.

Thrombopoiesis occurs under the influence of thrombopoietin which controls the proliferation and

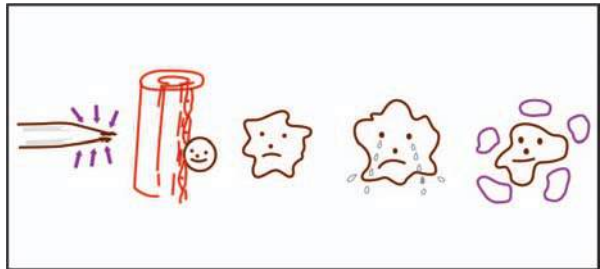


Fig. 148.5: Morphological changes in platelet on vessel injury

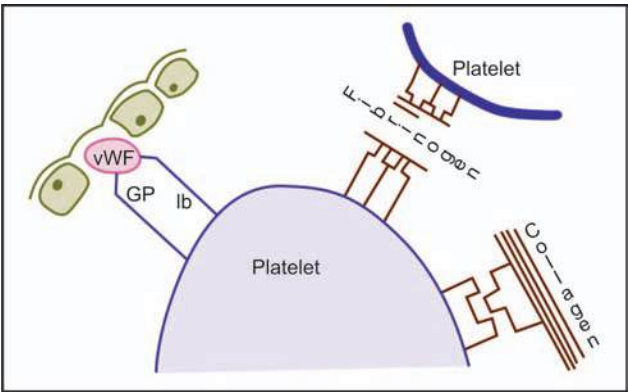


Fig. 148.6: Platelet surface receptors

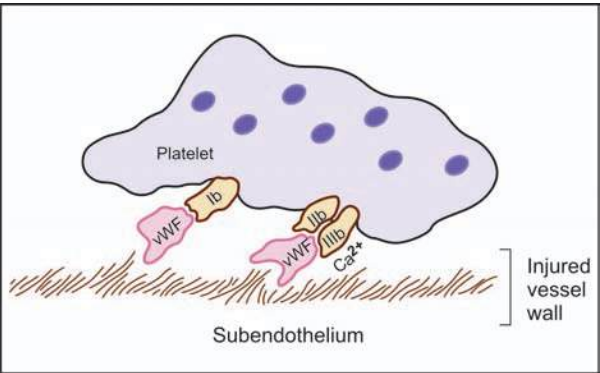


Fig. 148.7: Mechanism of adhesion to vessel wall

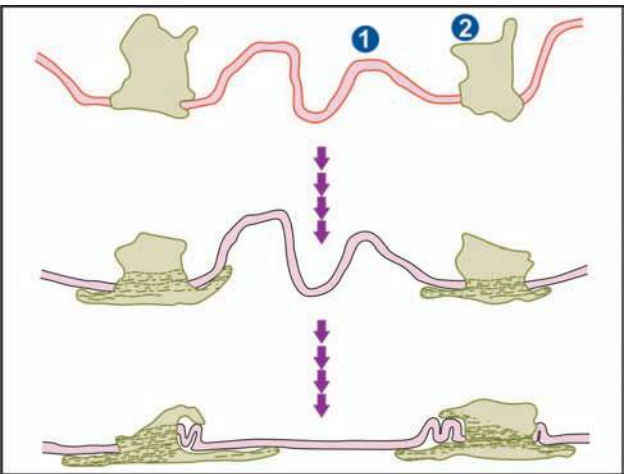


Fig. 148.8: Platelet physiology – action on fibrin to stabilize it (1) Fibrin threads (2) Activated platelets

development of megakaryocytes precursors. Thrombopoietin is a polypeptide growth factor containing 353 amino acids. Plasma levels of thrombopoietin vary inversely with the platelet mass in circulation. It acts as a megakaryocyte colony stimulating factor including the proliferation of the committed precursors. It also promotes platelet production and release.

Freshly formed platelets are non-nucleated, they contain RNA and are able to synthesize small amounts of proteins. Platelet with elevated nucleic acid content can be detected by flow cytometry. These are called 'reticulated platelets,' (RP). The RNA content can be identified by using the fluorescent dye thiazole orange, and platelet surface markers such as CD 41, and CD 61. Estimation of the proportion of reticulated platelets gives an idea of the rate of platelet production. Normal RP is 7.7%. In conditions such as immune thrombocytopenia the RP may go up as high as >20%.

Ref: (Mukherjee et al, Ind J. Haemat and BL Tras XX X1 suppl 2004 1-3).

30% of platelets are in the splenic pool. The rest are in circulation. Under normal conditions, in the absence of overt or occult bleeding, the life-span of platelets is 8-14 days. They are used up in the hemostatic process. Old and effete platelets are destroyed especially in the spleen.

Thrombopoietin (TPO) is produced mainly from the hepatocytes (50%) and sinusoidal endothelial cells of the liver. Small amounts are produced by the kidneys, brain testes and skeletal muscles. It is a polypeptide growth factor containing 353 amino acids. TPO is the primary regulator of platelet production. It supports the survival and proliferation of megakaryocyte (MKC) progenitors. In vitro TPO induces the differentiation of progenitor cells into large MKCs each of which produces thousands of platelets. TPO is a potent stimulator of platelet production and it also enhances the aggregating activity of the platelets. Fall in platelet counts leads to rise in TPO levels by 50% or more within 8 hours and reach a peak by 24 hours. Platelets have receptors for TPO and they take up TPO from the circulation. TPO levels are low in immune thrombocytopenic purpura and they are high in aplastic anaemia. TPO acts synergistically with erythropoietin to stimulate erythrocyte production.

TPO also enhances the survival and expansion of hematopoietic stem cells. It is used to stimulate stem cell production in the bone marrow and peripheral blood.

Hepatic TPO production is enhanced by inflammatory cytokines such as IL-6 and therefore platelet levels increase in infections, inflammations, chronic diseases like rheumatoid arthritis and others.

TPO has a half-life of 30 hours in circulation. Pegylation increases the half-life ten-fold. Platelet counts start rising in 3-5 days after administration of TPO and reach a peak in 10 days. TPO is available commercially

for therapeutic use as recombinant TPO. Prolonged use of TPO leads to production of antibodies which suppress endogenous TPO, thereby leading to thrombocytopenia. This can be reversed by the use of immunosuppressants.

Therapeutically TPO is indicated in thrombocytopenic states, chemotherapy for malignancy, and to improve the yield of platelets and stem cells for therapy.

Thrombopoietin Stimulating Protein

This is a novel protein moiety (AMG 531) developed recently. It is quite different from thrombopoietin. It has been tried to stimulate thrombopoiesis in immune thrombocytopenic purpura. Initial results are encouraging.

Clinical Aspects of Hematological Disorders

Pallor: Pallor of the mucous membranes and skin occurs when the hemoglobin level is below 10 g/dL. Skin colour depends also on other factors such as state of peripheral circulation and pigmentation. Mucous membrane over the soft palate is the most suitable area to assess pallor since this is least likely to be influenced by other factors. Though there is general agreement between pallor and the severity of anemia, these show wide disparity in many cases.

Jaundice: Jaundice is an important finding in hemolytic anemia. The severity of jaundice depends on the level of bilirubin in the blood and this corresponds to the severity of hemolysis. In the majority jaundice is only mild to moderate, but deep jaundice may occur in hemolytic crises. In hemolytic jaundice the serum contains unconjugated bilirubin and the urine is loaded with urobilinogen, but bile pigments are absent. In severe cases methemalbumin may be present in the serum and urine may contain hemoglobin. In fulminant cases renal failure may occur.

Hepatosplenomegaly: Many hematological disorders are associated with hepatosplenomegaly. Mild or moderate hepatosplenomegaly occurs in 10-20% of cases of nutritional anemias, 60-80% of acute leukemias, 90% of hemolytic anemias, 80% of infectious mononucleosis and practically never in idiopathic thrombocytopenic purpura. Gross splenomegaly exceeding 15 cm is seen in thalassemias, hemoglobinopathies, chronic granulocytic leukemia, lymphomas, and myelofibrosis. The liver also shows variable degrees of enlargement in these cases.

Moderate enlargement of lymph nodes occurs in acute leukemias and infectious mononucleosis. Lymphomas, chronic lymphatic leukemia, and blastic transformation of chronic granulocytic leukemia are characterized by gross lymphadenopathy.

Fever: Fever is a common nonspecific accompaniment of many hematological disorders. In anemia, when the

hemoglobin level goes below 7 g/dL, fever is common. The temperature reverts to normal on correcting the anemia. Hectic rise of temperature may accompany hemolytic crises. In all forms of leukemia fever may occur. Often this is due to infection, less commonly it may be due to the malignant process itself. Presence of fever in lymphomas is of diagnostic and prognostic importance.

Bleeding tendency: Hemorrhagic manifestations may be the primary symptom in disorders like immune thrombocytopenic purpura and hemophilia. In acute leukemia and aplastic anemia, secondary thrombocytopenia may occur resulting in bleeding. Purpuric hemorrhage into the skin, mucous membranes or tissues is commonly seen if the abnormality affects the platelets or blood vessels. In disorders of coagulation, spontaneous bleeding occurs into deep tissues and joints. Bleeding from cuts and wounds tends to be prolonged markedly.

Laboratory Investigations

- 1. **Hemoglobin estimation:** It is now accepted that this procedure should be done with internationally accepted standards by the cyanmethemoglobin method using a photoelectric colorimeter. Other visual methods are only approximate at best.
- 2. **Cell counts:** Automated instruments which give several parameters are available commercially. Their advantage is reliability of the result and reproducibility, provided the operator is skilled and the machine is kept in good condition and the laboratory is under quality control organizations. As far as possible, manual testing should be avoided.
- 3. **Reticulocyte count:** It is done directly in the wet preparation after staining with brilliant cresyl blue which is a vital stain.

Corrected reticulocyte count

This is also known as absolute reticulocytes percentage. This is a formula which is used to correct the variations of reticulocyte count in relation to total erythrocyte count or packed cell volume.

$$\text{Corrected reticulocyte count} = \frac{\text{Observed reticulocyte count} \times \text{Patient's PCV}}{\text{normal PCV for that age and sex}}$$

Reticulocyte proliferation index (RPI) is a measure of erythrocyte regeneration.

$$\text{RPI} = \frac{\text{Corrected reticulocyte count}}{\text{'Shift factor'}}$$

where the shift factor is a constant depending upon the PCV.

- 4. **Estimation of packed cell volume (PCV)**—venous hematocrit.
- 5. **The red cell indices:** These are calculated from packed cell volume (PCV), hemoglobin (Hb) and red cell count. They are MCHC, MCH and MCV.

- a. **MCHC: Mean corpuscular hemoglobin concentration.** This represents concentration of hemoglobin in the red cell. It is calculated as follows:

$$\text{MCHC} = \frac{\text{Hb in g/dL} \times 100}{(\text{g/dL}) \text{ PCV}}$$

Normal range is 32 to 36 g/dL.

- b. **MCH: Mean corpuscular hemoglobin.** It represents the average weight of hemoglobin in each cell and is calculated as follows:

$$\text{MCH} = \frac{\text{Hb in g/dL} \times 100}{(\text{pg}) \text{ RBC count in million/cmm}}$$

Normal range is from 27 to 32 pg (picogram).

- c. **MCV: Mean corpuscular volume.** It gives the average volume of red cells and is calculated as follows:

$$\text{MCV} = \frac{\text{PCV} \times 10}{(\text{fl}) \text{ RBC count in million/cmm}}$$

Normal value varies from 76-94 fl (femtolitres).

- 6. **Osmotic fragility of erythrocytes:** It is determined by estimating the hemolysis when a standard volume of erythrocytes is added to increasing dilutions of sodium chloride. Osmotic fragility is increased in spherocytosis and decreased in thalassemia.
- 7. **Peripheral blood smear:** This is the most useful single investigation which will help in diagnosis. All the cellular elements are examined systematically. Erythrocytes may be small (*microcytes*), large (*macrocytes*) or normal in size (*normocytes*). Variation of size is called *anisocytosis*. *Poikilocytosis* refers to difference in shape. The cells may be pear-shaped, elliptical, or sickle-shaped. *Schistocytes* are fragmented red cells. *Acanthocytes* (spur cells) show numerous spiny projections. Both are seen in hemolytic anemias. Burr cells show short projections on their surface. These are seen in renal failure (Fig. 148.9).
- 8. **Bone marrow examination:** It is an important and integral part of hematological examination. Bone marrow examination is absolutely necessary to establish the diagnosis of leukemias, myeloma, myelofibrosis, hypersplenism, lymphomas, aplastic anemia, megaloblastic anemia and other dyshemopoietic states. It is helpful in the diagnosis of kala-azar, histiocytosis, amyloidosis, secondary carcinomatosis, and several other conditions. Commonly used site for bone marrow aspiration and biopsy is the posterior superior iliac spine or other regions on the iliac crest. With proper techniques, in almost all cases successful aspiration can be done from this region.

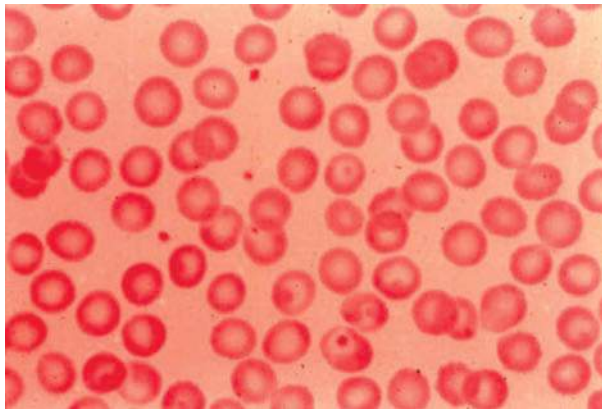


Fig. 148.9: Normal blood film

The posterior superior iliac spine overlies actively cellular marrow tissue. The needle used for aspiration is the Cox needle. For trephine biopsy the Jamshidi needle or Islam’s needle is used. Suitable sizes for adult and children are available. It is better that trephine biopsy is done for the proper morphological diagnosis of the marrow which is confirmatory in lymphomas, granulomas, metastases, tumours, myelofibrosis and hypoplastic anemia. A core of marrow tissue 1½ cm long is taken and processed as tissue for histopathological studies. Imprints, touch smears and smears from blood obtained from the biopsy needle are helpful in the diagnosis of general hematological disorders such as leukemia, anemia and myeloma. Conditions such as myelofibrosis, myelodysplastic syndromes, hairy cell leukemia, lymphomas, secondaries and marrow necrosis can be diagnosed only with marrow biopsy. The biopsy material can be used for electron microscopy and immunophenotyping studies. In non-hematological conditions such as typhoid fever and miliary tuberculosis the success rate of culturing the organisms is higher with bone marrow than blood.

In extreme obesity the iliac crest may not be easily accessible. Other sites for aspiration are the manubrium sterni and body of the sternum, ribs, vertebral spines, and tibial shaft in children. These alternate sites are seldom used now due to higher risks involved and more chances for procedural failure. Failure to get marrow tissue by aspiration is called ‘dry tap’. This may be due to:

- 1. Faulty techniques
- 2. Aplasia of marrow or solid marrow as occurs in fibrosis, osteopetrosis or
- 3. Extreme cellular hyperplasia where the marrow assumes the consistency of solid tissue.

Contraindications to bone marrow aspiration include defects of coagulation, and sepsis at the site of aspiration.

APPENDIX
Normal hematological values

1. Hemoglobin	
Infants	16-18 g/dL
Men	13-16 g/dL
Women	11-14.5 g/dL
2. Red cells	
Infants	5-6 × 10 ¹² /L
Men	4-6.6 × 10 ¹² /L
Women	3.5-4.5 × 10 ¹² /L
3. PCV	
Men	40-54%
Women	35-47%
4. MCV	76-94 fl
5. MCH	27-32 picogram (pg)
6. MCHC	32-36 g/dL
7. Reticulocytes	0.2-2.5%
8. ESR	
Males	0-10 mm 1st hour (Westergren)
Females	0-20 mm 1st hour (Westergren)
9. White cells	
Infants	15-16 × 10 ⁹ /L
Adults	5-10 × 10 ⁹ /L
10. Differential leukocyte count	
Adults:	
Neutrophils	40-75%
Lymphocytes	20-45%
Monocytes	2-9%
Eosinophils	1-5%
Basophils	0.0-1%
11. Platelets	150,000-400,000 per mm ³ (1.5-4 × 10 ¹¹ /L)
12. Bleeding time	(Ivy’s method) upto 10 min
13. Coagulation time	(Lee and White method at 37°C) 5-11 min
14. Prothrombin time	12-14 sec
15. Plasma fibrinogen	150-400 mg/dL
16. Serum iron	60-160 µg/dL
17. Total iron binding capacity (TIBC) (Transferrin)	280-400 µg/dL
18. Serum ferritin	
Males	40-340 µg/dL
Females	14-148 µg/dL
19. Serum folate	6-20 ng/mL
20. RBC folate	160-640 ng/mL
21. Serum vitamin B ₁₂	100-1000 pg/mL

Complications of bone marrow puncture include prolonged bleeding, formation of hematoma and periostitis. Sternal puncture may be complicated by injury to mediastinal structures and mediastinitis. Aortic aneurysm is a contraindication for sternal puncture.

149

Anemias:
General Considerations

K.V. Krishna Das

Chapter Summary

- Clinical Aspects 984
- Investigations 985
- Management of Anemia 989

Anemia is defined as a reduction of hemoglobin levels below the normal values for the different age and sex groups. The normal values of hemoglobin for different age groups accepted by WHO are as follows:

Children	6 months to 6 years	11 g/dL and above
	6 years to 14 years	12 g/dL and above
Adult males		13 g/dL and above
Adult female (nonpregnant)		12 g/dL and above
Adult female (pregnant)		11 g/dL and above

In full health there is no racial variation in hemoglobin. In India any hemoglobin level below 12 g/dL in adult males and 11.5 g/dL in adult females should be diagnosed as anemia and investigated. In general, reduction of hemoglobin is associated with a fall in erythrocyte count and packed cell volume (PCV). In anemic subjects, hemoconcentration, as occurring in dehydration, tends to mask the severity of anemia, so also when there is increase in plasma volume as in pregnancy there is an apparent fall in hemoglobin level even though the total hemoglobin mass remains normal.

Classification: Based on erythrocyte morphology as seen in the stained blood film, anemias may be classified into microcytic hypochromic, normocytic normochromic, macrocytic normochromic, and macrocytic hypochromic (Table 149.1).

Clinical Aspects

General features: Irrespective of the etiology or type, anemic subjects develop a group of symptoms on account of reduction in hemoglobin. The severity of symptoms depends on the rapidity of fall of hemoglobin. When anemias develop slowly, the subject adapts to the lower levels of hemoglobin by reducing his physical activity and the symptoms are less pronounced. With falling levels of hemoglobin, the oxygen carrying capacity of blood diminishes. This is partly compensated by increasing the blood flow to organs by vasodilatation. The cardiac output is increased. Most of the general symptoms are attributable to the diminished oxygen carrying capacity of blood and hyperdynamic circulation. These symptoms include fatigue, disinclination to work, mental apathy, pallor, exertional dyspnea, effort angina, and cardiac failure in severe cases. Symptoms are referable to all systems. Alimentary symptoms include loss of appetite, constipation and abdominal distension. The liver is enlarged and tender due to fatty change. Cardiovascular changes include tachycardia, cardiomegaly, high volume pulse, prominent third heart sound, ejection systolic murmurs heard over the pulmonary and aortic areas and in advanced cases, signs of cardiac failure. Cardiac murmurs are produced as a result of decreased viscosity of blood and increased cardiac output. Pallor is most marked over the mucous membranes, skin, and nails. There may be greying of the hair and premature baldness. Neurological manifestations include apathy, loss of mental alertness, paresthesia over the extremities and brisk tendon reflexes. When severe anemia develops rapidly, signs resembling raised intracranial tension may be rarely encountered. These

TABLE 149.1

Classification of anemia based on erythrocyte morphology

Microcytic hypochromic anemia	Iron deficiency, thalassemias, hemoglobinopathies, and hemolytic anemia
Normocytic normochromic anemia	Aplastic anemia
Macrocytic normochromic anemia	Folate deficiency, vitamin B ₁₂ deficiency, hypothyroidism
Macrocytic hypochromic anemia (dimorphic)	This picture is due to combined deficiency of iron and folate or B ₁₂

TABLE 149.2

Classification of anemia based on etiopathogenesis

1. Dyshemopoietic (disorders of erythrocyte formation)	1. Nutritional anemias—Anemias due to deficiency of essential nutrients such as folate, vitamin B ₁₂ , proteins, vitamin C
2. Hemorrhagic	2. Hypothyroidism
	3. Sideroblastic anemia due to metabolic blocks in the synthesis of hemoglobin
	1. Acute hemorrhage, e.g., antepartum and postpartum hemorrhage, bleeding oesophageal varices, bleeding peptic ulcer, hematemesis and melena, traumatic or surgical bleeding.
	2. Chronic blood loss, e.g., due to intestinal parasites such as hookworms, whipworms and E. histolytica hemorrhoids, excessive menstrual blood loss and repeated pregnancies, chronic peptic ulcer, erosions (drug induced), cancers in the GI tract.
3. Hemolytic	Anemias developing because of increased destruction of erythrocytes—Various causes
4. Hypoplastic	Anemias developing because of decreased formation of erythrocytes—Various causes
5. Myelophthitic	Anemias developing as a result of replacement of normal erythropoietic tissue by abnormal tissue e.g. acute leukemias, lymphomas, multiple myeloma, malignant secondaries in bone marrow, myelofibrosis and storage diseases

include headache, papilledema and retinal hemorrhages. All these regress with improvement in the hemoglobin levels.

Several other criteria have also been employed for classification. Etiological classification is given in Table 149.2.

Splenomegaly occurs in many cases, and the frequency and extent depends on the type of anemia. Whereas in iron deficiency anemia 10% may show mild splenomegaly, in hemolytic anemias it is over 90%.

Diagnosis: Any patient with anemia should be approached with the aim of determining the type, severity, and cause of the disorder. Anemia may be the only apparent general feature of several underlying disorders, and attempts should be made to detect the etiology. Symptomatic treatment of anemia without identifying the cause should be avoided since in many instances a serious underlying disorder like gastrointestinal malignancy or renal failure may be missed at the early stage when effective treatment is possible.

Detailed history should include the onset, course, and duration of anemia. Periodic fluctuation in intensity is common in nutritional and hemolytic anemias. In general they are of longer duration than aplastic and myelophthitic anemias. Nutritional anemias affect several members of the same family or household. Hemolytic anemias such as spherocytosis, hemoglobinopathies, and red cell enzymopathies reveal characteristic genetic patterns.

Common bleeding foci such as hemorrhoids, menorrhagia, peptic ulcer and oesophageal varices should be excluded by interrogation and full physical examination. Rectal and pelvic examinations should be undertaken in all cases.

Investigations

Preliminary investigations: The following investigations are carried out to detect the severity and type of anemia.

Hemoglobinometry and blood counts: The standard procedure is the cyanmethemoglobin method using a reliable standard for comparison. When the hemoglobin level is below 12 g/dL full investigations should be undertaken. Absolute counts of erythrocytes, leukocytes, and platelets, and calculation of the erythrocyte indices should be done by automatic machines which are accurate.

Packed cell volume (PCV-hematocrit) is a reliable parameter which should be done in all cases. The mean corpuscular hemoglobin concentration.

$$(MCHC) = \frac{[(Hb \text{ in g/dL} \times 100)]}{PCV}$$

helps to determine the type of anemia in a borderline case and also in the follow-up of the case. Values below 27 g/dL suggest microcytic hypochromic types.

Examination of blood smear: This is the easiest and reliable method to determine the morphology of erythrocytes. Microcytic hypochromic erythrocytes are smaller than normal [normal mean corpuscular diameter (MCD) is 7.5 ± 0.3 µm] and the centre is empty with only a ring of hemoglobin taking up the stain. Considerable anisocytosis and poikilocytosis are seen. Macrocytic erythrocytes are larger with the centre also showing uniform staining. Normocytic normochromic erythrocytes are normal in size and staining. Reticulocytes appear as polychromatophilic macrocytes in Romanovsky's stained films, but when stained in the fresh state with brilliant cresyl blue the cytoplasmic reticulum is visualized.

Normal value for reticulocytes in Indian subjects is 0.5 to 2.5%. Anisocytosis, poikilocytosis, polychromasia, and reticulocytosis indicate active regeneration of erythrocytes. When erythropoiesis is very much accelerated normoblasts may appear in peripheral blood. In myelophthitic anemias normoblast may be released from the bone marrow even without active regeneration of erythrocytes. The leucocyte picture is often helpful. Neutropenia and relative lymphocytosis may suggest aplastic anemia. Presence of eosinophilia suggests helminthic infestation.

Examination of the platelets will give additional clues regarding the type of anemia and its cause. Normally-functioning platelets occur in small or medium sized clumps. Absence or considerable reduction in the platelets shows up as scanty platelets in the smear and absence of clumps.

In microcytic hypochromic anemia presence of excess platelets generally suggests blood loss. Thrombocytopenia indicates the possibility of hypoplastic anemia. In the tropics special attention should be given to detect malarial parasites in all cases, especially *P. falciparum* (Figs 149.1 to 149.14).

Red Blood Cell Distribution Width (RDW)

With the availability of automated counting machines and recording instruments in hematology, red blood cell distribution curves are provided along with the counts. A routine measurement obtained from these curves is the RDW. Depending upon the technology employed in the machine RDW can be expressed as RDW-SD or RDW-CV. The different technologies employed to count and size the red blood cells determine the shape of the RDW distribution curves (RDW-C). These denote the homogeneity or heterogeneity of erythrocyte size (i.e.) anisocytosis. Manual determination of anisocytosis by light microscopy is at best only approximate.

The values obtained by RDW-SD and RDW-CV differ slightly. The RDW is a reliable parameter to distinguish between iron deficiency anemia and other microcytic anemias. Values of RDW CV >17 are suggestive of iron deficiency. In thalassemias and anemia of chronic disease, the RDW CV is below 17. Increase in RDW is one of the early finding in iron deficiency anemia. In aplastic anemia, leukemia, and megaloblastic anemia the leukocytes also show morphological changes, which are diagnostic.

Examination of the bone marrow: Examination of bone marrow will reveal the type of erythropoiesis and the underlying cause in secondary anemias. Normoblastic hyperplasia suggests iron deficiency. Megaloblastic hyperplasia should suggest primary or secondary deficiency of folate or vitamin B₁₂. Normoblastic, but hypoplastic erythropoiesis occurs in aplastic anemia, anemia of chronic disease and others. Leukaemia, myeloma, disseminated lymphomas, parasitic infections

such as visceral leishmaniasis and several other conditions can be diagnosed by marrow examination (Figs 149.15 to 149.19).

Investigations to Detect the Etiology

1. Microscopic examination of feces for parasites and chemical examination for occult blood to identify gastrointestinal blood loss, rectal examination, proctoscopy. Repeated examination of feces may have to be undertaken to detect occult blood since bleeding from the alimentary tract may be intermittent at times. Negative results may exclude bleeding foci in most of the cases, though not in all.
2. Skiagram of the chest to detect tuberculosis.
3. Investigations for gastric lesions—barium meal, and endoscopy.
4. Studies for detecting malabsorption states.
5. Investigation of the large intestine—barium enema and endoscopy.
6. Blood chemistry—blood urea, serum proteins, serum creatinine, levels of nutrients in blood.
7. **Skeletal survey**—multiple myeloma, secondary deposits, thalassemias, and myelosclerosis produce characteristic skeletal changes. Skiagram of the skull, vertebrae, long bones, and hands are taken for this purpose.
8. **Isotope studies**
 - a. *Schilling's test* for determining the absorption of vitamin B₁₂.
 - b. Determination of life-span of red cells using ⁵¹Cr labelled erythrocytes.
 - c. Determination of ferrokinetics (absorption, utilisation, and disposal of iron) using ⁵⁹Fe.
 - d. Whole body scanning for bone marrow activity and presence of secondaries or tumours.
9. **Other imaging procedures:** Ultrasonography, CT scanning and MRI may be needed in cases where organomegaly, lymph node enlargement, collection of fluid in natural cavities or neoplasms are suspected.

Course and prognosis: This largely depends upon the type of anemia. Nutritional anemias are generally very insidious in onset and course. Periodic exacerbation results from intercurrent infection or physiological stresses like puberty, growth, or pregnancy. The disease progresses over several years and death is due to intercurrent illnesses or rarely severe anemia *per se*.

Hemolytic anemias exhibit wide variability in their course, ranging from fulminant hemolysis ending fatally within weeks to very slow chronic course with periodic exacerbations, extending over several years. Aplastic anemias have an intermediate course. The onset is within months and the course extends over months to a few years, with either recovery in a few or death within a few months in the majority of cases if left untreated. In myelophthitic

Peripheral Blood (PB) Slides (Figs 149.1 to 149.14)

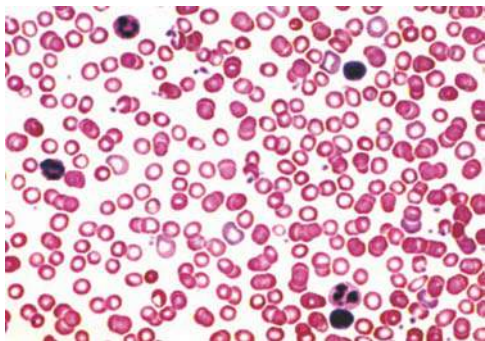


Fig. 149.1: PB iron deficiency anemia

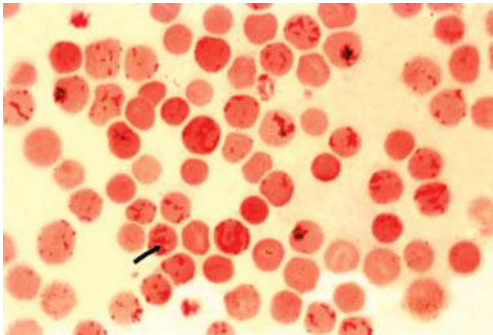


Fig. 149.5: PB reticulocytes in hemolytic anemia—arrow

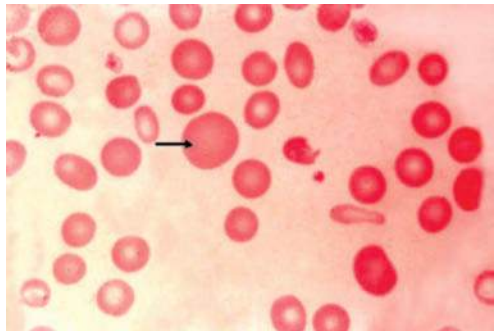


Fig. 149.2: PB megaloblastic anemia.
Note: Macrocyte—arrow

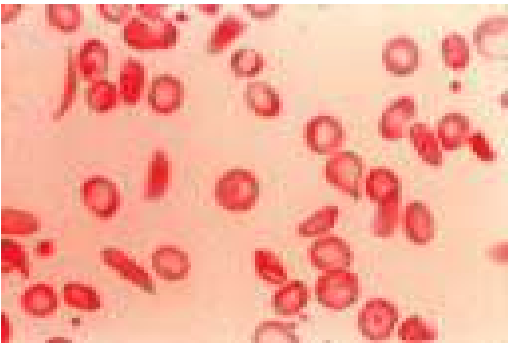


Fig. 149.6: PB sickle cell anemia.
Note: The sickle showed erythrocytes

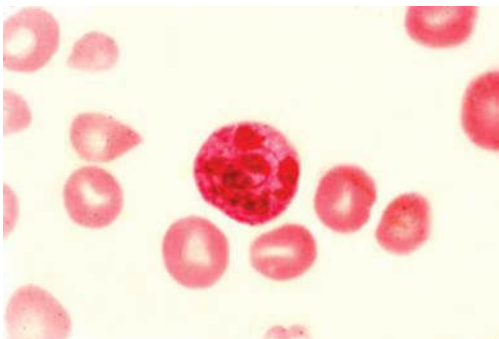


Fig. 149.3: PB megaloblastic anemia with
hypersegmented neutrophil

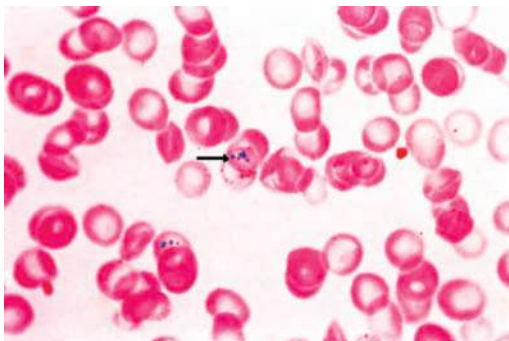


Fig. 149.7: PB sideroblastic anemia.
Note: Sideroblast—arrow

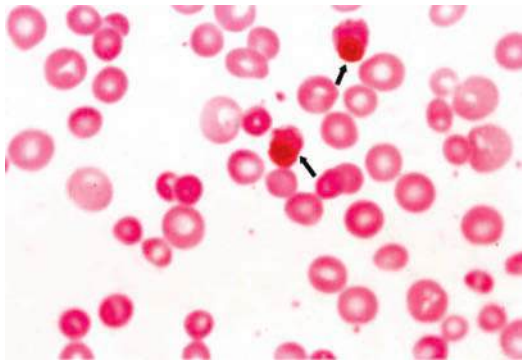


Fig. 149.4: PB hemolytic anaemia with hemolytic crisis.
Note: Normoblasts—arrows

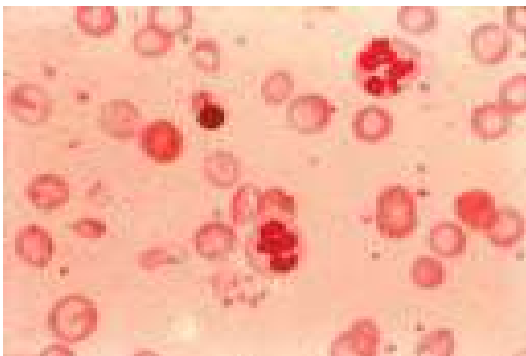


Fig. 149.8: PB thalassemia major. Note: Microcytosis-
anisopoikilocytosis, target cells

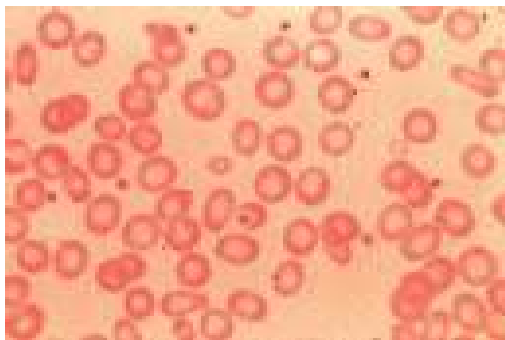


Fig. 149.9: PB thalassemia minor. Note: Mild hypochromia

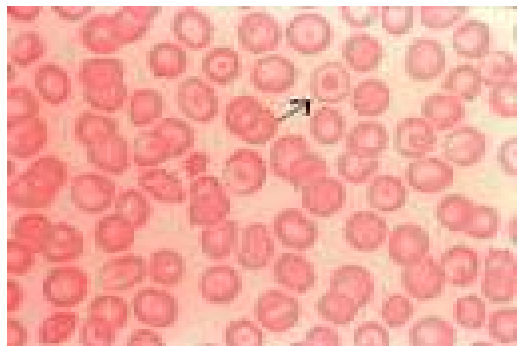


Fig. 149.13: PB post-splenectomy states target cell—arrow

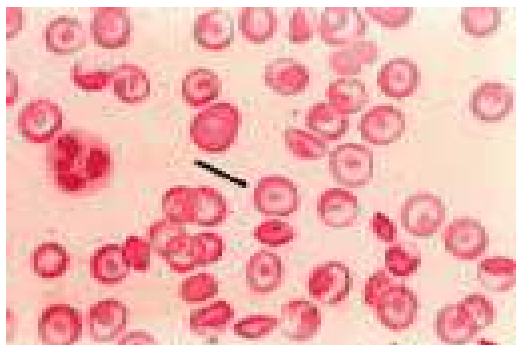


Fig. 149.10: PB target cells in thalassemia—arrow

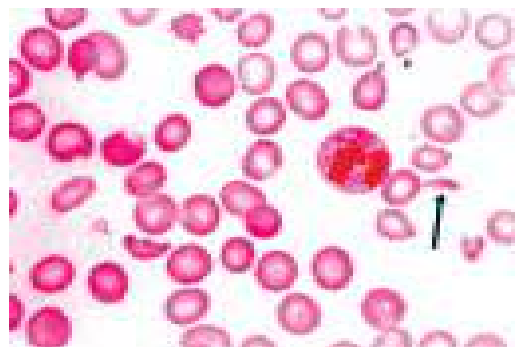


Fig. 149.14: PB microangiopathic hemolytic anemia. Note: The fragmented red cell—schistocyte—arrow

Bone Marrow (BM) Slides (Figs 149.15 to 149.19)

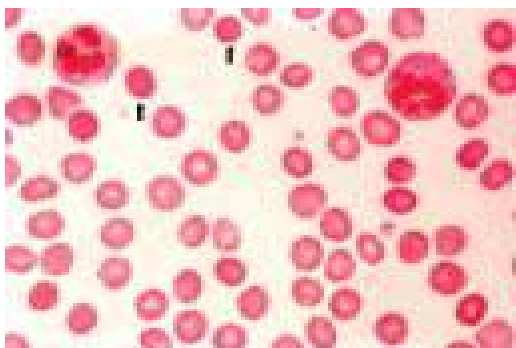


Fig. 149.11: PB spherocytes in hereditary spherocytosis—spherocyte is a smaller dark erythrocyte biconvex—arrows

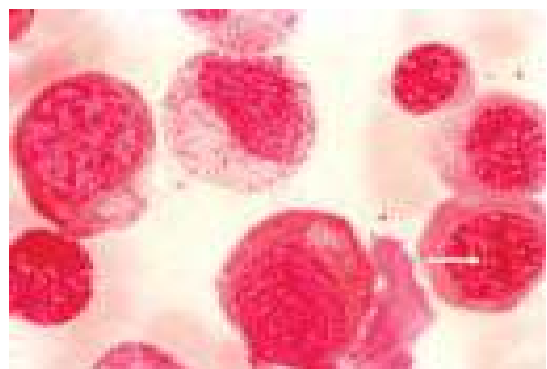


Fig. 149.15: Megaloblastic bone marrow—megaloblast—arrow



Fig. 149.12: PB ovalocytes. Note: The elongated oval erythrocytes—arrow

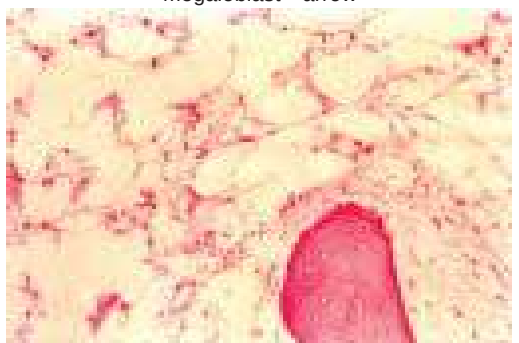


Fig. 149.16: Aplastic anemia bone marrow. Note reduction in cellularity of the marrow

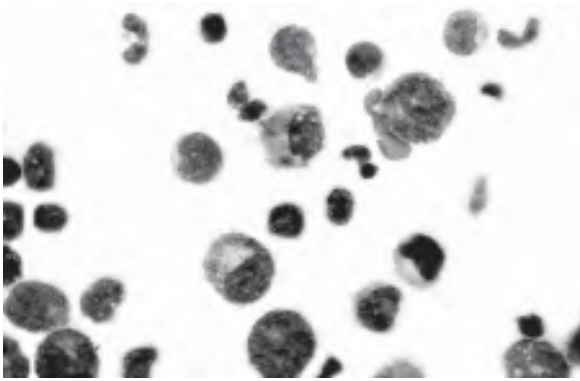


Fig. 149.17: Pure red cell aplasia bone marrow. Note: Absence of erythroid precursors

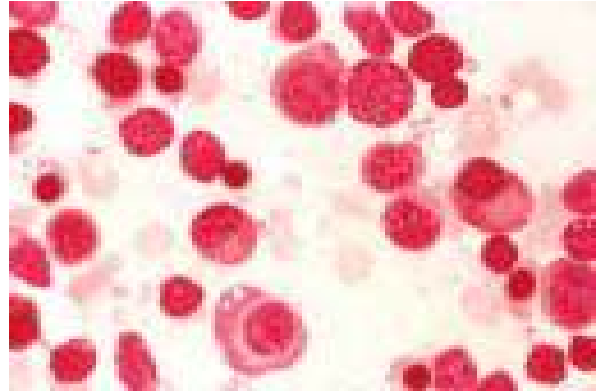


Fig. 149.19: Agranulocytosis bone marrow. Note: The reduction in granulocyte precursor

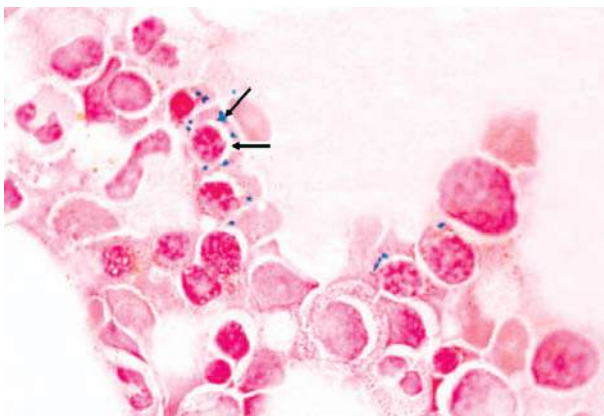


Fig. 149.18: Sideroblastic anemia bone marrow. Note: Ringed sideroblast stained by Prussian blue method arrows

anemia the course and outcome depend entirely on the primary disorders.

Management of Anemia

The specific management depends on the etiology.

General principles: Hospitalization is advisable when the hemoglobin drops below 7 g/dL. With hemoglobin levels below 3 g/dL, severe disability occurs and cardiac failure at this stage may be fatal. In such a case emergency transfusion with packed erythrocytes to raise the hemoglobin above 5 g/dL is life-saving. When cardiac failure is present, intramuscular administration of frusemide 40 mg prior to the transfusion serves to prevent fluid overloading.

Chapter Summary

- Iron Deficiency Anemia 989
- Macrocytic Anemias 993
- Nutritional Megaloblastic Anemia (NMA) 994
- Addisonian Pernicious Anemia 995
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Iron Deficiency Anemia

Microcytic hypochromic anemia occurring in India is mostly due to iron deficiency. Less commonly

thalassemias and other hemoglobinopathies also produce similar morphology. In India and other developing countries, iron deficiency anemia far out numbers all the other types of anemias put together, as it constitutes 90-95% of the total. Iron deficiency anemia is one of the most widespread diseases all over the world.

Epidemiology: In India 5-6% of general population suffer from this disease. It is prevalent in 3% among men and 10-14% among women. About 10% of attendance in the general hospitals is accounted for by anemias. In specific groups like slum dwellers, plantation labourers, and pregnant women the prevalence rate is 30-50% or even more. Iron deficiency is prevalent in 30-50% of the adolescent and young adult women due to their unsatisfactory food habits and moderate or heavy blood loss during menstruation. Even though iron deficiency is mainly caused by inadequate iron intake in food, IDA is not exclusively a disease of the poor. Food fadism and other diseases which cause blood loss account for the majority of anemia cases occurring in the rich.

Causes

1. **Nutritional inadequacy:** It is present in more than 80% of cases, especially in the poorer groups. Meat, poultry and fish form good dietary sources of iron. Milk is low in its iron content. Among vegetable sources, grapes, dates, prunes, amla (gooseberry), green leafy vegetables, onions, jaggery and betel leaf are moderate sources of iron. Due to the cereal-based dietary habits, the optimum intake of dietary iron recommended by Indian Council of Medical Research (ICMR) is 20 mg for adults. Many diets do not contain the optimum amount of bio-available iron. Cooking in cast iron vessels and iron from water sources supplement iron intake to some extent. Replacement of cast iron kitchen vessels from many households has probably deprived this source of iron, though it may be small.
2. **Blood losses:** Sources of chronic blood loss are ankylostomiasis, hemorrhoids, menstrual losses, repeated pregnancies in women, and ulcerating lesions in the gastrointestinal tract. Normal menstrual blood loss is about 60 mL per period. Periods which are heavy and which occur more frequently than once a month predispose to iron deficiency. About 750 mg of iron is utilised from the mother for each pregnancy and lactation. Successive pregnancies occurring at short intervals without supplementation of iron during pregnancy and lactation are bound to deplete the iron stores of the mother.

Hookworms and other soil transmitted helminths lead to chronic blood loss from the upper intestinal region. Though most of this iron is absorbed, a small part is lost

in feces. Hence heavy infestations are bound to cause anemia. *Ankylostoma duodenale* is more pathogenic than *Necator americanus*. If nutritional status is good, anemia may not occur even with moderate worm loads, but in the majority of cases hookworms act as the most common aggravating factor in the presence of undernutrition. In many states in India hookworm infestation rates have come down considerably due to general improvement in sanitation, provision of sanitary latrines and safe drinking water. In some areas *Trichuris trichura* (whipworm) which has established as a common intestinal nematode, causes blood loss and even malabsorption states. Bleeding caused by whipworms is considerably less than that due to hookworms (see chapter 67).

Loss of iron from surface epithelium increases with *excessive sweating*. This is a significant source of iron loss in the tropics, especially in the working classes.

Iron absorption is controlled at the level of the intestinal mucosal epithelium. Excess of dietary or medicinal iron is not absorbed normally, but in the presence of iron deficiency higher amounts of iron are absorbed till the deficiency is corrected. When loss of iron from the body exceeds absorption, the tissue stores gradually become depleted. This phase is asymptomatic and when anemia develops there is considerable depletion of iron stores. So also when iron is supplied the anemia recovers first but it requires prolonged supplementation to replenish the tissue stores, usually up to one year and often, continuously. Bone marrow shows normoblast hyperplasia (Fig. 150.3).

In iron deficiency anemia (IDA) the transferrin saturation is lowered and is often below 15%. Iron is present in plasma also as ferritin. The serum levels of ferritin reflect the iron stores of the individual more reliably than either serum iron or transferrin saturation.

Normal levels of serum ferritin are:

Adult male	40-340 µg/L
Adult female	14-148 µg/L
Children	7-142 µg/L

In iron deficiency states it is below 12 µg/L. Very high levels are reached in siderosis. Normally there is stainable iron in the marrow. When there is iron deficiency this form of storage iron disappears. Absence of stainable iron in the bone marrow is a reliable evidence of iron deficiency state helps to distinguish iron deficiency anemia from hemolytic and hypoplastic anemias in which there is increase in stainable iron. Gross iron deficiency leads to depletion of the iron containing enzymes in tissues and this probably accounts for the generalized tissue effects. These are promptly restored by iron therapy even before the hemoglobin level improves. As the hemoglobin levels fall below 3 g/dL, compensatory mechanisms fail and death is usually due to cardiac failure or infection of the respiratory or gastrointestinal tract.

CLINICAL FEATURES

In addition to the general features of anemia described earlier, special features particular to iron deficiency anemia are described below.

Onset is gradual over months or years. Special features include loss of appetite; **pica**, especially for eating sand, raw cereal, or lime (CaCO_3), glossitis, sideropenic dysphagia, and koilonychia. About 10% of cases may show mild splenomegaly. Extreme pica may itself lead to further nutritional deficiency (Fig. 150.1).

The tongue is pale and small. Dysphagia takes the form of a feeling of obstruction and food sticking at the upper end of the oesophagus especially on swallowing liquids. It is called Plummer-Vinson syndrome or Kelly-Patterson syndrome. Probably dysphagia is produced by loss of afferent impulses for the swallowing reflex due to degeneration of the lining epithelial cells. Sometimes constriction, spasm, or even bands may be detected, but in general, local examination is unrewarding. In one-third cases barium swallow may reveal the narrowed area. Clinical features and the radiological abnormalities clear up easily within months of iron therapy, but in a few neurotic individuals vague symptoms may persist. There is increased incidence of post-cricoid and oropharyngeal carcinoma in these subjects, especially in women.

Nail changes are characteristic of iron deficiency anemia of long standing and in many cases these are diagnostic. The initial changes are thinning, cracking, and brittleness of the toe and finger nails, later becoming typically spoon-shaped (*koilonychia*). With correction of iron deficiency, normal nail grows and replaces the affected nail.

Alimentary system: Gastric acid is reduced, but histamine fast achlorhydria is rare. Motility of the alimentary tract is reduced and this results in constipation. Gastric secretion and gastrointestinal motility recover with treatment.

DIAGNOSIS

Clinical diagnosis of iron deficiency anemia is simple. In areas where thalassemia and other hemoglobinopathies



Fig. 150.1: Male iron deficiency anemia.
Note: Pallor: small pale tongue

occur, these have to be differentiated. Though iron deficiency is by far the most important etiological factor, latent deficiency of folate (20-40%) and/or vitamin B₁₂ (5-10%) may occur simultaneously. These become manifest as megaloblastosis, when the iron deficiency is corrected by treatment. In such cases iron therapy produces initial rise in hemoglobin, but full correction can be achieved only with supplementation of folate and/or vitamin B₁₂.

Laboratory diagnosis: The erythrocytes are microcytic hypochromic. Presence of eosinophilia usually points to a helminthic etiology and thrombocytosis to chronic or acute blood loss. Reticulocytes are mildly increased (2-3%) even before specific treatment is started, but when therapy is started their count rises to 15-30% within days and remains elevated at lower levels till anemia is corrected. The MCHC is below 27 g/dL. Red cell distribution width (RDW) is above 17. Bone marrow shows normoblastic hyperplasia with absence of stainable iron. It is not feasible, nor is it necessary to do bone marrow examination in all cases of iron deficiency anemia. The serum iron is usually below 80 µg/dL (normal 60-160 µg/dL). Transferrin levels are normal (280-400 µg/dL) or increased. Transferrin saturation is about 14-15% or less. Total iron binding capacity (TIBC) in both males and females is 340 mg/dL with the range of 250-450 mg/dL.

Estimation of serum ferritin is helpful to assess the iron stores in the body, and therefore, wherever facilities permit, this should be done. Values below 15 µg/L suggest depletion of stores. Based on the several metabolic steps undergone by dietary and transport iron, specific sophisticated tests are available. These help to distinguish anemia due to iron deficiency from anemia of chronic disease, thalassemias and others.

Free erythrocyte protoporphyrin (FEP) Elevation of FEP, mainly the erythrocyte zinc protoporphyrin (EZP) is a very sensitive index of iron deficiency. In uncomplicated iron deficiency anemia EZP levels reach 100-1000 µg/dL.

Soluble transferrin receptor (STIR) Serum levels of STIR are elevated in iron deficiency. The assay is done by ELISA-Normal serum levels of STIR range from 2.8-8.5 mg/L.

For all practical purposes the beneficial response of oral iron in correcting microcytic hypochromic anemia may be taken as a suggestive evidence of iron deficiency, retrospectively. Search for the cause of iron deficiency should be continued and this should be corrected to prevent relapse.

Complications

1. **Infections** are more common in IDA, especially those of the respiratory, gastrointestinal or urinary tracts. These are associated with higher mortality.

Tuberculosis is more common in them. Cell mediated immunity is reduced in these subjects.

2. **Chronic anemia reduces the efficiency in work** and study, and therefore, widespread nature of this disease in the community impairs efficiency for work and production. Deficiency of tissue iron and presence of anemia have been shown to lead to impairment of cognitive function of the brain and retardation of learning ability and motor skills in children. This may persist for long periods even after correction of the anemia. Reversible diminution of functional reserve of heart, muscles and other organs, has been demonstrated.

Symptomatic Iron-deficiency Anemia

Even though IDA is caused by nutritional inadequacy and gastrointestinal blood loss due to intestinal parasitism in the vast majority of patients, in a small proportion it may be the warning symptom of carcinomas, especially of the gastrointestinal tract—stomach, colon and other sites. Slowly proceeding blood loss as occurring in hemorrhagic telangiectasia, angiodysplasia of the gastrointestinal tract, hemoptysis due to bleeding into the respiratory tract as in Goodpasture’s syndrome and chronic purpura should be looked for, if an obvious nutritional cause is not forthcoming.

TREATMENT OF IRON DEFICIENCY ANEMIA

This can be considered under two heads: (1) *Correction of anemic state* and *replenishment of iron stores*, and (2) *elimination of the cause*.

Correction of anemia: Overall correction of nutrition with articles rich in iron is most important. For the poorer sections of society proper dietary advice, including indigenously available sources of food, is most important. Meat, liver, green vegetables, onions, grapes, and jaggery are good sources of iron.

Iron deficiency is corrected by the administration of **medicinal iron**. Ferrous sulphate given as 300 mg tablets thrice daily after food is ideal and least expensive. The response is evident within a week as improved well-being and activity, return of appetite, and increase in reticulo-cytes and hemoglobin. On an average the hemoglobin rises at the rate of 1% everyday. Ferrous sulphate is well tolerated in most cases but 10% of cases may show side effects such as nausea, vomiting, abdominal pain, metallic taste in the mouth, staining of the tongue (Fig. 150.2) diarrhea, and constipation. Side effects are reduced if the drug is administered after food, but absorption is better if given on empty stomach. Rarely oral iron may not be tolerated.

Other preparations are available for administration to those who show intolerance to ferrous sulphate.



Fig. 150.2: Female staining of tongue by oral iron therapy

The gastric delivery system technology (GDS) consists of the controlled release of the drug which is incorporated into a matrix with inert materials which form the outer capsule. In contact with gastric juice the outer capsule becomes semipermeable. It releases the drug slowly. The capsule floats over the gastric contents and remains for several hours in the stomach. GDS ensures good absorption of the drug with less side effects.

Iron preparations	Weight per tablet (mg)	Elemental Iron
Ferrous sulphate	300	80
Ferrous gluconate	300	40
Ferrous fumarate	200	60
Ferrous succinate	150	35

Chelated iron is available as iron choline citrate. None of the iron preparations is totally free of side effects. Iron salts have to be continued for at least six months after the hemoglobin level reaches normal with a view to replenish the iron stores. In multiple deficiency, the other nutrients also have to be supplemented.

Parenteral iron is indicated when oral medication becomes impossible because of side effects or when the anemia has to be corrected within a shorter period. Parenteral iron raises the hemoglobin by 2% everyday. The preparations are iron dextran complex, iron sorbitol complex, ferric gluconate and iron-sucrose complex. All preparations are effective, but iron dextran complex is more popular. The total dose required for correcting the iron deficiency is calculated using a specific formula and this total dose is given intravenously slowly or given by repeated intramuscular injections over a few weeks.

Formula for Calculating Total Iron Requirement

Total dose of iron required in mg
= (weight of patient in kg) × (deficiency in Hb%) × (0.66).

Intramuscular injection: Iron dextran complex is given in doses of 100 mg of elemental iron given in areas usually covered by clothing, once in 3 days till the total dose is reached. Thereafter only nutritional therapy is continued along with oral supplementation. Hemoglobin reaches normal levels in course of time when the administered iron is used up.

When a large dose is decided to be administered within a shorter period, to save the pressure on hospital beds and avoid frequent injections, intravenous route is adopted. The **total dose infusion (TDI)** is given as a slow drip in which 500-1000 mg of iron dextran complex is diluted in 5% glucose after testing for hypersensitivity with the pilot ampoule supplied by the manufacturers. The whole requirement can be administered in 2 or 3 sessions. In general only mild side effects occur, but rarely, they may be catastrophic.

Side effects of parenteral iron include fatal anaphylactic reactions, iron encephalopathy, local thrombophlebitis, tissue necrosis, pyrexia, arthralgia, arthritis, serum sickness like reactions, and pigmentation over injection sites. Anaphylaxis is more frequent with total dose infusions and the more so if oral iron is concurrently administered. It is advisable, therefore, to stop oral iron therapy for a week before parenteral iron is administered. Administration of excessive doses of parenteral iron leads to hemosiderosis.

Iron sorbitol citrate (Jectofer)

Each mL contains 50 mg of elemental iron. 30% of the injected drug is excreted in urine within 24 hours. This loss has also to be taken into consideration while calculating the total dose. The total dose of Jectofer is given as 10-20 deep I M injections.

Ferric gluconate (Globac, Efficient)

It is safer than iron dextran complex and iron sorbitol complex. Two strengths are available 62.5 mg/mL and 125 mg/mL. It is given in split doses as I V infusions, the total dose being determined before hand.

Iron sucrose (Encifer) – This is a complex of polynuclear iron (111) hydroxide in sucrose. It is available as 5 mL vials each mL containing 20 mg of elemental iron.

It can be given as slow IV injection over 5 minutes or as an infusion mixed with 100 mL N. saline and given over 15 minutes. Total dose infusion should not be undertaken. Compared to iron dextran complex injections, the newer preparations are safer and the utilization time may also be shorter.

Rarely a case of anemia with hemoglobin level below 3 g/dL may require packed cell transfusion and management for cardiac failure.

Prophylaxis

Iron has to be given prophylactically to vulnerable groups which are likely to develop iron deficiency. These include: (1) premature infants, and infants fed solely on unfortified milk formulas; (2) pregnant and lactating women; and (3) patients who had surgical operations on the stomach.

Measures to eradicate iron deficiency anemia in the community: Several attempts have been made in India to eradicate iron deficiency anemia from large sections of the population. Improvement in nutrition, elimination of helminthic parasites, provision of protected water and sanitary latrines, and prompt treatment of respiratory and gastrointestinal infections should all be taken up as a comprehensive programme to eliminate anemia at the community level. Several studies have shown that isolated programmes of deworming or nutritional supplementation are of only marginal and temporary benefit. Attempts have been made to fortify cooking salt with iron.

The problem is to incorporate a stable, at the same time absorbable form of iron in the salt without altering its cooking properties. Iron pyrophosphate has been identified as a suitable salt for this purpose. Field trials are being undertaken by the Indian Council of Medical Research and the findings are encouraging.

In many centres in India tablets containing iron and folic acid are distributed among vulnerable groups and this measure has also proved successful.

Macrocytic Anemias

These constitute about 5% of nutritional anemias seen in India. In these the red cells are larger in size. The mean corpuscular volume reaches above 110 fl or more. These cells are usually fully hemoglobinised and MCHC is normal. Mean corpuscular hemoglobin is increased. In some cases the macrocytes may also be hypochromic due to concomitant deficiency of iron (dimorphic). Common cause of macrocytosis in India is deficiency of folic acid and/or vitamin B₁₂. In the absence of these vitamins DNA synthesis is abnormal. Megaloblastosis results when DNA synthesis is impaired in the presence of normal RNA and protein synthesis. Synthesis of protein, RNA, and hemoglobin continues in the cytoplasm. When DNA synthesis is impaired, cell division is retarded but the cell grows more in between mitotic cycles and hence the megaloblasts are larger in size. As the deficiency becomes more pronounced, many early forms of erythroblasts are destroyed in the marrow, and ultimately erythropoiesis becomes almost totally ineffective.

Macrocytic anemias may be associated with megaloblastic erythropoiesis or normoblastic erythropoiesis. Macrocytic anemia with normoblastic marrow is seen when there are numerous reticulocytes in peripheral blood.

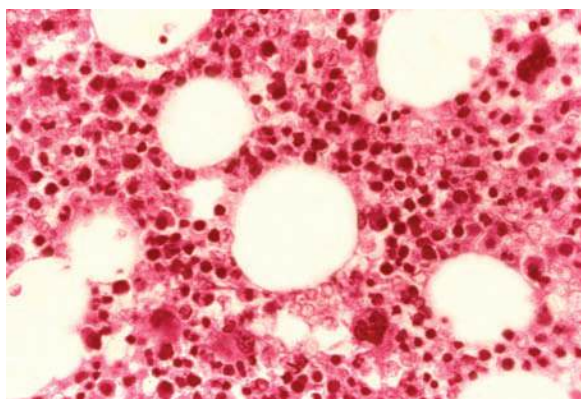


Fig. 150.3: Normoblastic bone marrow.
Note: All elements are present

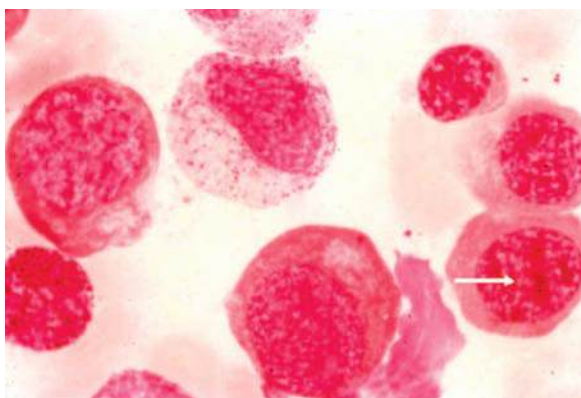


Fig. 150.4: Megaloblastic bone marrow. Note: megaloblast: nuclear chromatin is loose—arrow

Other less common causes include hypothyroidism, liver disease, renal failure, and chronic infections.

Megaloblasts: The defect of DNA synthesis is most pronounced in marrow cells, but it is also present in varying degrees in all rapidly proliferating cells. The nucleus of the megaloblast has a finer reticular pattern which distinguishes it from normoblast. Megaloblastic anemia is common in nutritional deficiency of folate or vitamin B₁₂ or when the metabolic pathways of these nutrients are blocked (Figs 150.3 and 150.4).

15

Causes of Megaloblastic Anemia

I. Those caused by inadequate supply of folic acid, vitamin B₁₂ or both.

- a. nutritional deficiency
- b. increased demand such as pregnancy, infancy, infection
- c. protein-calorie malnutrition
- d. malabsorption states
- e. drugs with antifolate action e.g. phenytoin, methotrexate
- f. total gastrectomy or extensive lesions involving the stomach
- g. infestation with the tapeworm *Diphyllobothrium latum*

II. Acquired vitamin B₁₂ malabsorption in Addisonian pernicious anemia which is due to deficiency of the gastric intrinsic factor. Other rare causes include intense suppression of gastric acid using proton pump inhibitors or H₂ receptor antagonists.

Nutritional Megaloblastic Anemia (NMA)

In India this is the most common form of megaloblastic anemia and is caused by the deficiency of folic acid, vitamin B₁₂ or both. Folate deficiency is more frequent than vitamin B₁₂ deficiency in all parts of the country. In many cases there is also iron deficiency and so the blood picture is dimorphic.

Folic acid is obtained from dietary articles such as green vegetables, sprouted cereals or pulses, liver, meat, yeast and others. The daily requirement of folic acid is 0.1 mg. Excessive demand occurs during growth spurts, pregnancy and convalescence from illnesses. Folic acid is absorbed from the small intestine. Malabsorption states such as celiac disease, sprue and others lead to folate deficiency. In communities in which nutritional status is marginal, diarrheal diseases precipitate folate malnutrition. Several drugs such as phenytoin sodium, methotrexate and sulphonamides exert their therapeutic effects by interfering with the metabolic pathways in the utilisation of folate. Such drugs are liable to lead to folate deficiency on prolonged administration.

Since folate is rapidly used up by the system and body stores are relatively less compared to vitamin B₁₂, folate deficiency manifests within weeks to months of onset of dietary deficiency.

Requirement of vitamin B₁₂ (cyanocobalamin) is 1 µg/day. It is obtained mainly from animal foods such as liver and meat. Smaller amounts are obtained from milk and fermented milk products such as buttermilk and yoghurt or curds, which form an important component of Indian diets. Dietary deficiency occurs in those who are vegans i.e., those who consume only diets of plant origin excluding even dairy products. In general the serum vitamin B₁₂ levels of vegetarians are lower than those of persons consuming adequate amounts of meat products. Vitamin B₁₂ is absorbed in the distal part of the ileum in combination with intrinsic factor. Malabsorption states affecting the ileum and diseases of the stomach which is the source of intrinsic factor lead to secondary deficiency of this vitamin. In blind loop syndromes vitamin B₁₂ is avidly taken up by the bacterial flora colonising the blind loop. In fish tapeworm infection the parasite takes up vitamin B₁₂, and deficiency develops.

In normal subjects there is adequate store of vitamin B₁₂ which may last for several years and therefore dietary deficiency of the vitamin manifests clinically only after several months or even years.

Folate and cyanocobalamin are required for normal metabolic activities of almost all growing cells in the body, and therefore, widespread dysfunction of several organs systems occurs in deficiency states. Maximal effects are seen in bone marrow, epithelial cells and others. Cyanocobalamin is required for the normal metabolism of myelin and other components of the nervous system. Therefore, deficiency of this factor leads to lesions in the nervous system as well.

CLINICAL FEATURES

The onset is insidious. Pregnant women and children are more affected. In addition to the general features of anemia certain distinguishing features seen are: (1) large beefy tongue; (2) dark pigmentation over the palms, soles, face, and tongue; (3) hepatosplenomegaly and (4) mental changes and neurological involvement in vitamin B₁₂ deficiency. Neurological abnormalities include peripheral neuropathy and degeneration of the posterior columns and pyramidal tracts—subacute combined degeneration. Psychiatric disturbances and optic neuritis may occur in a few. The neurological manifestations can develop in nutritional deficiency of vitamin B₁₂ also, if the condition persists for long periods, but compared to pernicious anaemia this complication is less frequent and milder. Nutritional deficiencies of folate and /or vitamin B₁₂ may lead to hyperhomocysteinemia which, in turn, induces thrombophilia and pathological thrombosis in arteries and veins. Stroke occurring in young persons in developing countries is caused by hyperhomocysteinemia in a small proportion of cases. This risk is abolished by nutritional supplementation.

Investigations: Hemoglobin level may vary from 5 to 8 g/dL or less, MCHC is within the normal range (28-32%) while MCV is increased and may be as high as 120 fl. Macrocytosis and anisopoikilocytosis are easily recognizable. Some red cells may show punctate basophilia due to the presence of remnants of ribonucleic acid. Nuclear material may be present in erythrocytes. These are seen as *Howell-Jolly bodies* and *Cabot's rings*. Leukocytes may be normal or decreased in number. Granulocytes are larger than normal, showing increased lobulation with the average lobe count higher than 5 (*macropolycytes*). This change in leukocytes is very helpful in diagnosis when the morphology of erythrocytes is equivocal. Platelet count may be decreased at times. Platelet function may also become defective.

Bone marrow is hyperplastic due to erythroid hyperplasia. All stages of megaloblasts are present. Normoblastic erythropoiesis may also be present simultaneously. In the absence of iron deficiency, hemosiderin content of marrow is increased. Life-span of red cells is moderately decreased.

Levels of serum folate and red cell folate are diminished. The normal level of folate in serum is 6-20 ng/mL

and that in red cells is 160-640 ng/mL. Serum levels below 3 ng/mL and red cell levels below 100 ng/mL indicate deficiency of folate. Serum vitamin B₁₂ values below 100 pg/mL are indicative of deficiency.

Treatment: Overall dietary correction should be undertaken. Oral administration of 1 mg or more of folic acid daily is adequate to correct folate deficiency. Supplementation of folic acid will improve the anemia due to deficiency of vitamin B₁₂ also, but not the neurological complications. In the later stages of therapy, deficiency of iron may develop and iron may have to be given.

Vitamin B₁₂ deficiency can be rapidly corrected by intramuscular injection of 1000 µg of hydroxocobalamin. Oral doses of 1-2 µg are curative in most cases if continued over a few months.

Prevention of NMA: Oral supplementation of folates to 0.1 mg/day to growing children, and subjects receiving anti-epileptic drugs, helps to prevent folate deficiency. In pregnancy a daily dose of 0.5 mg of folic acid should be given prophylactically from the first trimester. Where megaloblastic anemia has developed 5 mg should be given orally daily throughout the pregnancy and puerperium. Infants require 1 mg of folic acid orally daily as supplement. Therapeutic administration of folates (400 µg/day) to pregnant women irrespective of their nutritional status reduces the risk of development of neural tube defects in the baby. If absorption is defective, the folic acid has to be given by IM injection in a dose of 5 mg daily for a few days.

Prophylactic oral supplementation of vitamin B₁₂ is given as 10 µg either singly or along with the other deficient factors during pregnancy and in those with marginal nutritional states. When absorption is defective, IM injection of 1000 µg is given once a week for 3 to 4 weeks.

ADDISONIAN PERNICIOUS ANEMIA

Syn: Pernicious anemia, Biermer's anemia

Etiology: Pernicious anemia (PA) is more common among the Caucasian population, but is rare in Indian subjects. It is found more often in the older age groups and only rarely before 30 years of age. It may be familial and affects both sexes. Antibodies directed against the gastric parietal cells are present in the serum in 85-90% of cases and antibodies against intrinsic factor are demonstrable in the serum as well as in the gastric juice in a smaller proportion of cases. This is an autoimmune disease. Other disorders like myxedema, Addison's disease, thyrotoxicosis, Hashimoto's disease and vitiligo which all have an autoimmune basis may occur along with pernicious anemia. The gastric mucosa undergoes atrophy resulting in the absence of intrinsic factor and gastric acid—achylia gastrica. Dietary vitamin B₁₂ is not absorbed. This leads to megaloblastic erythropoiesis. Several other tissues are also affected, particularly the nervous system. Demyele-

nation of the pyramidal tracts and posterior columns develop (see also Chapter 187). Carcinoma of the stomach develops in 4% of cases on follow-up.

CLINICAL FEATURES

The onset is insidious. In addition to symptoms of anemia, special features include soreness of the tongue, paresthesia of hands and feet, diarrhea, and yellowish tinge of skin and mucous membranes. The tongue is atrophic. Spleen is palpable in 25% of cases. Spinal cord involvement results in sub acute combined degeneration manifesting as varying combination of dysfunctions of the pyramidal tracts and posterior columns.

Psychiatric symptoms are common. These include melancholia, depression and behaviour disorders.

If left untreated, the disease follows a prolonged course, ending fatally due to severe anemia or its complications. The megaloblastic change and anemia are rapidly correctable by the parenteral administration of vitamin B₁₂ or oral administration of folate. The neurological changes tend to remain permanent once they have developed. Only vitamin B₁₂ is capable of preventing their occurrence and arresting their further progress, once they have set in. Folate does not prevent this neuropathy, in some it may even aggravate the lesion.

Laboratory findings: Erythrocytes are macrocytic with marked anisopoikilocytosis. The bone marrow is megaloblastic. In a florid case, the hemoglobin is usually below 7 g/dL. Leukopenia and thrombocytopenia are common. Gastric juice analysis shows histamine fast achlorhydria and absence of intrinsic factor (*achylia gastrica*). Serum vitamin B₁₂ is below 80 pg/mL. Serum and red cell folate are normal. Serum iron levels are elevated.

Defect of absorption of vitamin B₁₂, and its correction by addition of intrinsic factor present in normal gastric juice can be demonstrated by *Schilling's test* using radioactive vitamin B₁₂. Parietal cell antibodies which are detectable in the serum are helpful in diagnosis. Gastroscopy and biopsy confirm the diagnosis.

Therapy: In severe cases where the hemoglobin is below 5 g/dL, transfusion of packed erythrocytes may be required. Specific therapy is to give hydroxocobalamin 1000 µg intramuscularly every week till Hb level becomes normal. Reticulocyte response is noticed within 2 to 3 days of the first injection. Folic acid is contraindicated since it is known to precipitate the neurological complications, if administered alone.

Maintenance: Subjects with pernicious anemia should receive life-long supplementation of parenteral vitamin B₁₂, 1000 µg every month.

Congenital Megaloblastic Anemias

Though in the vast majority of cases of pernicious anemia the defect in intrinsic factor is an acquired one, it can be congenital in some rare cases.

Congenital intrinsic factor deficiency: In this condition the gastric histology and secretions are normal except for the absence of intrinsic factor.

Congenital deficiency of transcobalamin II (TC II) also causes megaloblastic anemia. In this condition the serum level of vitamin B₁₂ is normal, but since it is bound to transcobalamin I, it is not available for hematopoiesis.

Rarer Causes of Nutritional Anemia

Vitamin C deficiency: Normocytic normochromic anemia may occur in early cases of vitamin C deficiency. When bleeding complicates the picture, iron deficiency anemia results.

Protein deficiency: It can lead to anemia due to diminished production of erythrocytes and possibly reduced life-span of these cells. The anemia is mild, and hemoglobin levels range from 8 to 10 g/dL.

Copper deficiency: This leads to hypochromic microcytic anemia in experimental animals. Copper deficiency may occur in infants fed solely on milk or due to severe malnutrition. In adults this is not a significant clinical problem.

Anemia in Systemic Diseases

Thyroxine deficiency: This produces a mild to moderate type of anemia in 20-60% of cases. Thyroxine deficiency *per se* causes a normocytic normochromic anemia or slightly macrocytic anemia. There is mild hypoplasia of erythroid precursors.

Anemia in rheumatoid arthritis: There is mild to moderate anemia with hemoglobin levels ranging from 9 to 10 g/dL. Blood picture is usually normocytic hypochromic. Anemia may be partly due to gastrointestinal bleeding resulting from excessive ingestion of antirheumatic drugs. In addition to concomitant nutritional deficiencies, rheumatoid arthritis *per se* produces a resistant type of normocytic hypochromic anemia, which is relatively resistant to oral iron. Parenteral iron therapy results in significant improvement.

In acute renal failure: Normocytic normochromic anemia develops with reticulocytopenia and depression of erythroblasts in bone marrow. Erythropoietin levels are low.

In chronic renal failure: Severity of anemia correlates well with the glomerular filtration rate and to a lesser degree with blood urea nitrogen (BUN). Anemia is mainly due to reduction in erythropoietin levels and diminution in erythropoiesis. Blood loss and nutritional deficiency contribute in varying proportions. Hemodialysis aggravates the blood loss. When the blood urea exceeds 280 mg/dL hemolysis may develop. The anemia is

generally resistant to treatment, but erythropoietin produces marked improvement in hemoglobin level and several other parameters as well (see Chapter 179).

In chronic liver disease: There is mild anemia which may be multifactorial in origin. The factors are gastrointestinal bleeding, ineffective erythropoiesis and hemolysis. The anemia may be hypochromic or macrocytic normochromic. Usual hematinics are not very effective. Improvement may take place with improvement of liver function.

Malignant neoplasms: These cause anemia at some stage or the other during their course. Different types of anemia are encountered since multiple factors operate. These are:

1. *Iron deficiency anemia* due to gastrointestinal hemorrhage or malabsorption.
2. *Folic acid deficiency anemia* due to increased requirement of the vitamin caused by extensive tumours growths or due to chemotherapy or radiation therapy. Folinic acid therapy together with vitamin B₁₂ are helpful.
3. *Hemolytic anemia* may occur in lymphomas or ovarian neoplasms due to development of antibodies.
4. *Hypoplastic anemia* may result from bone marrow suppression caused by immune mechanisms, e.g., thymoma, lymphoma.
5. Myelophthisic anemia caused by invasion of the marrow by tumour tissue, e.g., malignant secondaries, lymphoma, myelofibrosis.

Anemia of Chronic Diseases (ACD)

Syn: Anemia of inflammation

Anemia may complicate several chronic, and at times, acute inflammatory disorders. These are not uncommon. These may masquerade as other types of anemia. Activation of the immune system by chronic and acute inflammatory disorders lead to ACD.

Causes

Chronic and acute infections- bacterial, parasitic, fungal and viral including HIV and AIDS.

1. Neoplasms: hematological malignancies and tumours of solid organs.
2. Autoimmune diseases, especially rheumatoid disease, systemic lupus erythematosus, vasculitis, sarcoidosis, inflammatory bowel disease, transplant rejection after solid organ transplantation.
3. Chronic renal diseases.
4. Other forms of chronic inflammation.

Mechanism: Immune mediated cytokines and immunocytes are activated which adversely affect iron metabolism, erythroid progenitor development, production of erythropoietin, and RBC life-span. All these factors contribute to the development of anemia. Bleeding, conditioned deficiencies of hemopoietic factors and autoimmune haemolysis aggravate the anemia. The proliferation and differentiation of the proerythroblast, erythroid BFU and CFU are impaired. Interferon-γ is one of the potent inhibitors. Stimulation by erythropoietin is inadequate to compensate for the inhibition. The response of the erythroid progenitor cells to erythropoietin is inhibited in proportion to the severity of the underlying chronic disease and inhibitor cytokines. Erythrophagocytosis (phagocytosis of RBC by macrophages) develops and this worsens the anemia by reducing RBC life-span in some cases of ACD.

Laboratory findings: The anemia is mild (Hb 6-9.5g), normocytic, normochromic or microcytic. Where iron absorption is impaired the anemia resembles IDA. In IDA serum ferritin levels are generally < 30 ng/mL. Ferritin levels are higher in ACD due to the increase in storage iron in RE cells and also the acute inflammatory reaction raising ferritin levels (Table 150.1).

A specific distinguishing test to differentiate between IDA and ACD is the level of *soluble transmembrane receptor* (STR) in serum. STR is a truncated fragment of the membrane receptor that is increased in iron deficiency when the availability of iron for erythropoiesis is diminished. In ACD the STR levels are normal. Another measurement is the determination of the ratio of the STR to the log of ferritin. Ratios above 2 suggest IDA whereas

TABLE 150.1

Shows the clinical parameters to distinguish between IDA and ACD

Parameter	ACD	IDA	Combined ACD+IDA
Iron	Reduced	Reduced	Reduced
Transferrin	Reduced	Increased	Reduced
Transferrin saturation	Reduced	Reduced	Reduced
Ferritin	Normal	Reduced	Reduced or normal
STR	Normal	Increased	Normal or increased
STR/log ferritin	<1	>2 High	> 2
Cytokine levels	Increased	Normal	Increased

ratios <1 suggest ACD. STR can be estimated easily using commercially available test kits.

Hemoglobin levels $< 8\text{ g/dL}$ double the chances of death in chronic renal failure

Treatment: Aims of treatment are

1. To raise hemoglobin up to 12 g/dL and
2. Attention to the underlying disorder

Management consists of supplementation of iron in those with iron deficiency. Iron should not be administered to those without evidence of iron deficiency, since this

may lead to the production of highly active toxic hydroxyl radicals which can worsen tissue damage. Erythropoietin is indicated in those in whom attention to the primary disease is not fully successful. The dose of erythropoietin should be adjusted to keep hemoglobin levels around 12g/dL .

Anemia of infections: Infections suppress erythropoietin production nonspecifically. Inflammatory cytokines also depresses the production of erythropoietin.

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Hemolytic Anemias

K.V. Krishna Das

Chapter Summary

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GENERAL CONSIDERATIONS

Normal life-span of red cells is 120 days. Old erythrocytes are removed from the circulation. Mildly deformed cells are phagocytosed in the spleen, severely injured cells are removed by the liver macrophages, and grossly damaged cells are destroyed in the circulation itself. When destruction of erythrocytes exceeds the normal rate, their life-span diminishes and compensatory hyperplasia of erythroid precursors develops. For considerable periods

this compensates and the hemoglobin level is kept up. Since the marrow can compensate by enhanced erythropoiesis upto seven times the normal rate, anemia need not follow in all cases. When hemolysis is severe and the life-span of the erythrocyte falls below 18 days, anemia is bound to develop. Rarely marrow erythropoietic activity may fail, aggravating the anemia. The term hemolytic anemia is reserved for those disorders where the anemia is caused predominantly by excessive destruction of erythrocytes.

Hemolysis occurs due to several pathogenetic mechanisms (Table 151.1).

1. A decrease in the surface area/volume ratio, e.g. hereditary spherocytosis, autoimmune hemolytic anemia, and drug induced hemolysis.
2. Defect in structure of the erythrocyte membrane, e.g. paroxysmal nocturnal hemoglobinuria (PNH) and drug induced hemolytic disorders.
3. Increased internal viscosity inside the red cell, e.g. sickle cell anemia and Heinz-body hemolytic anemia.
4. Hypersplenism.

Hemolytic anemia contributes 4% of the total anemias seen in south India. Hemolysis may occur intra-or extravascularly. Intravascular hemolysis takes place in many cases of acquired hemolytic anemias whereas in the inherited form, hemolysis is generally extravascular.

TABLE 151.1

Classification of hemolytic disorders

- 1. **Inherited hemolytic disorders**
 - a. Red cell membrane defects, e.g. hereditary spherocytosis, hereditary elliptocytosis, hereditary acanthocytosis, hereditary stomatocytosis
 - b. Red cell enzyme deficiencies, e.g. deficiencies of pyruvate kinase, hexokinase, glucose-6-phosphate dehydrogenase, and glutathione reductase.
 - c. Defects in amino acid configuration of globin chains, e.g. sickle cell anemia, and other hemoglobinopathies including unstable hemoglobins
 - d. Failure to switch over of beta or alpha globin chains in post natal life, e.g. thalassemias
- 2. **Acquired hemolytic anemia**
 - a. Immunologically mediated hemolytic anemia, e.g. incompatible blood transfusion, hemolytic disease of the newborn, autoimmune hemolytic anemia (warm antibody and cold antibody types).
 - b. Microangiopathic hemolytic anemia, e.g. disseminated intravascular coagulation, hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, mechanical causes like implantation of cardiac prosthesis and march hemoglobinuria
 - c. Caused by infections, e.g. malaria, *Clostridium welchii* infections, and bartonellosis
 - d. Caused by drugs, chemicals, and toxins, e.g. nitrofurantoin, sulphonamides, viper venom, and formic acid poisoning.
 - e. Paroxysmal nocturnal hemoglobinuria.

In intravascular hemolysis it is usually a complement mediated antigen antibody reaction. It is seen in conditions such as black water fever in *P. falciparum* malaria, and favism induced hemolysis. This may lead to the presence of hemoglobin in the plasma, methemalbuminemia and hemoglobinuria in addition to hyperbilirubinemia.

Extravascular hemolysis is generally caused by destruction of the erythrocytes in reticuloendothelial organs, particularly in the spleen. In these hyperbilirubinemia and jaundice are more prominent.

Acute massive intravascular hemolysis leads to hemoglobinuria and renal failure. Extravascular hemolysis occurs in the reticuloendothelial system and this produces hyperbilirubinemia without hemoglobinuria.

Clinical Feature

In addition to the general symptomatology of anemia, hemolysis leads to distinctive features which differ from each other in the acute and chronic forms. Chronic hemolysis leads to jaundice, hemolytic facies, chronic leg ulcers, splenomegaly, cholelithiasis, cutaneous pigmentation, and iron overload states. On the other hand, acute hemolytic episodes are characterized by sharp rise in temperature and marked prostration. They may be accompanied by hemoglobinuria, acute renal failure,

disseminated intravascular coagulation, and shock. In many cases the hemolysis is secondary to other underlying conditions such as lymphomas, leukemia, malignancy, or dyscollagenosis.

- 1. **Jaundice:** Hemolytic jaundice is generally mild, but at times this can be very severe, e.g. Rh incompatibility. The degree of jaundice and the extent of hemolysis may not always correlate.
- 2. **The facies:** It is characteristic in chronic hemolytic anemias especially thalassemia. There is enlargement of the skull with frontal and parietal bossing. The malar bones are prominent with flattening of the bridge of the nose, widely set eyes, and malocclusion of the teeth. The appearance may be mongoloid. All these changes are caused by enlargement of the marrow tissue.
- 3. **Chronic leg ulcers:** Chronic non-healing ulcers develop over the malleoli in severe hemolytic states such as sickle cell anemia and hereditary spherocytosis. These heal when the anemia improves.
- 4. **Splenomegaly:** Splenomegaly is invariably seen in all cases of hemolytic anemia though the size of the spleen may be variable. Massive splenomegaly occurs in thalassemia and this may lead to hypersplenism.
- 5. **Cholelithiasis:** Pigment stones in the biliary tree are occasional complications seen in chronic hemolysis, caused by the excessive presence of bilirubin in bile.
- 6. **Hemolytic crisis:** The course of chronic hemolytic anemias may be punctuated by acute episodes called crisis (Fig. 151.1). These are *aplastic, megaloblastic, hemolytic, sickling, and sequestration crisis*. *Aplastic crisis* is due to sudden marrow failure precipitated generally by viral infection especially parvo viruses. *Megaloblastic crisis* is produced by folate deficiency resulting from the excessive demand brought about by accelerated erythropoiesis. *Hemolytic crisis* is rare, which may develop spontaneously or may be an adverse reaction to drugs or viral infections. *Sickling*

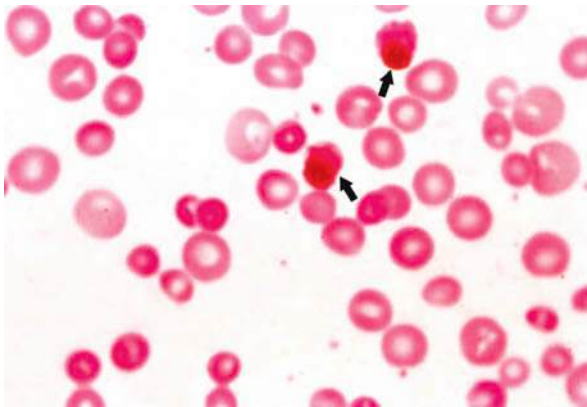


Fig. 151.1: Hemolytic crisis: PB: Note: Anisopoikilocytosis, and presence of normoblasts-arrows

crisis occurs in sickle cell anemia when exposed to hypoxic environment. This leads to vascular occlusion of many organs such as lungs, spleen, kidney, and brain. In *sequestration crisis* sudden splenomegaly develops because of pooling of blood within the organ and severe anemia ensues rapidly.

7. **Darkening of skin and other iron overload syndromes:** Chronic hemolytic anemias lead to iron overload due to liberation of excessive iron which is taken up by the macrophages or deposited in the parenchymal cells of several organs. The absorption of iron from the GI tract is also increased in thalassemias. Repeated blood transfusion adds to iron overload. These result in hemosiderosis characterized by greyish complexion of the skin, cirrhosis of liver, diabetes mellitus, and cardiomyopathy.

Investigations: Proper laboratory investigations are necessary to establish the diagnosis of hemolytic anemia.

1. **Tests to detect the presence of hemolysis:** The direct method is to measure the red cell life-span, but this may not be available in many laboratories in India. The presence of hemolysis can be inferred by demonstrating: (a) reticulocytosis, (b) rise in serum bilirubin, (c) reduction of serum haptoglobin, and (d) increase in serum lactic dehydrogenase.
 - a. **Reticulocytosis:** Reticulocytes are demonstrated by staining with vital stains like brilliant cresyl blue or fresh methylene blue. Increase in reticulocyte count above 1.5% suggests increased erythropoiesis (Fig. 151.2). Hemolytic anemia must be suspected wherever the reticulocyte count is above 5% and this is not accountable by other causes like recent blood loss or hematinic therapy. Rarely reticulocytosis may be absent even in hemolytic states when there are antibodies against red cell precursors or bone marrow aplasia.
 - b. **Bilirubin:** Presence of unconjugated hyperbilirubinemia (above 1 mg/dL) in the absence of

primary hepatic disease strongly suggests hemolysis. The metabolic products of bilirubin like urobilinogen in the urine and stercobilinogen in feces are also increased. Presence of excess pigment in feces makes it darker—polycholia.

- c. **Serum haptoglobins:** These are alpha-2 glycoproteins which are normally present in serum at a concentration of 50-150 mg/dL. They combine with hemoglobin liberated from red cells to form complexes which are rapidly destroyed. Consequently, haptoglobin level in serum is lowered in active hemolysis.
 - d. **Serum lactic dehydrogenase level:** This is invariably elevated above the normal range (70-240 IU/mL) in hemolytic anemia. This is more marked in intravascular hemolysis.
 - e. **Bone marrow:** The bone marrow shows erythroid hyperplasia in the vast majority of cases. Megaloblastosis occurs when there is associated folate deficiency. Chronic overactivity of erythroid tissue leads to expansion of marrow volume and deformity of several bones such as the skull, facial bones, metacarpals, phalanges and others.
 - f. **Isotopic methods:** Red cell survival and the sites of hemolysis can be studied isotopically using ⁵¹Cr. The severity of hemolysis can also be established by this method.
2. **Tests to detect the cause:** History and physical examination help to reveal the cause in most of the cases. Examination of the peripheral blood film, tests for intravascular hemolysis and the demonstration of antibodies serve to identify the underlying factors.

Examination of a properly made blood film gives the most valuable clues to the etiology in most of the cases. Large number of spherocytes is suggestive of hereditary spherocytosis or immune hemolytic anemias. Gross alteration of red cell morphology and the presence of basophilic stippling, hypochromia and target cells favour the diagnosis of thalassemia and hemoglobinopathies. Schistocytes, which are fragmented erythrocytes, are seen characteristically in micro-angiopathy and mechanical causes for hemolysis. Stomatocytosis is seen in hereditary stomatocytosis and hepatic disorders. Acanthocytes are seen in abetalipoproteinemia and in chronic liver diseases. In elliptocytosis the erythrocytes are oval—hence called ovalocytes. In India no examination of blood film is complete without careful search for malarial parasites which may be the cause of hemolysis in many cases in endemic areas.

Anisopoikilocytosis, polychromasia, punctate basophilia, and Cabot's rings are suggestive of active erythropoiesis and also dyserythropoiesis which may indirectly indicate hemolysis. In hemolysis due to drug toxicity Heinz bodies can be demonstrated by suitable techniques.

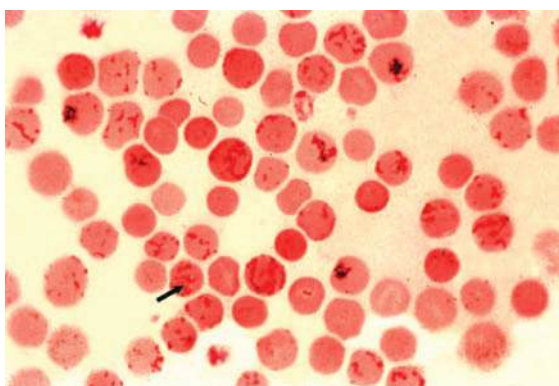


Fig. 151.2: Hemolytic anemia peripheral blood x 1000 reticulocytes increased—note reticulum within erythrocytes—arrow

Intravascular hemolysis: In this condition free hemoglobin in the serum rises to 100-200 mg/dL or even more whereas the normal level is only 2-5 mg/dL.

Demonstration of antibodies by Coombs' test: The direct Coombs' test is a screening test for the detection of antibodies present on the erythrocytes. It is usually positive in immunohemolytic anemias. The indirect Coombs' test detects antibodies present in the serum.

3. **Other special tests:** Various other special tests are employed for the diagnosis of hemolytic anemias: (1) *Osmotic fragility* is increased and autohemolysis is present in spherocytosis. (2) *Sucrose-hemolysis test* and *Ham's acid serum test* are positive in paroxysmal nocturnal hemoglobinuria. (3) Detection of abnormal hemoglobins, assays for erythrocyte enzymes, demonstration of Heinz bodies, and immunological studies are all employed in specific cases.

Course and Prognosis

Prognosis in hemolytic anemias is very variable. Mild cases may extend over several years with aggravation of hemolysis during periods of stress. On the other hand acute fulminant hemolysis can be fatal. Death is due to severe anemia and shock or acute renal failure. The course of secondary hemolytic anemias depends on the primary cause.

Management

General measures: When the drop in hemoglobin is severe, it has to be restored by transfusion of packed erythrocytes. In acute intravascular hemolysis emergency transfusion is needed to avoid cardiorespiratory failure. Packed cell transfusion obviates the risk of volume overloading and also the risk of sensitisation by plasma proteins. When the hemolysis is aggravated by complement, as in paroxysmal nocturnal hemoglobinuria, washed erythrocytes should be given.

In severe hemolysis compensatory erythropoiesis leads to excess demand for hematinic factors, especially folic acid, which has to be supplemented. In general since the iron is not lost from the body iron deficiency does not occur. On the other hand many types of hemolytic anemias such as thalassemias may lead to iron overload. Hence administration of iron should not be routinely undertaken. In cases with prolonged hemoglobinuria and hemosiderinuria iron deficiency may develop and these require iron therapy.

The specific treatment of immune hemolytic anemias involves the administration of corticosteroids and immunosuppressants. Splenectomy is the treatment of choice in hereditary spherocytosis, immune hemolytic anemia refractory to medical treatment, and in the presence of hypersplenism. In enzyme deficiencies and

Causes of autoimmune hemolytic anemias	
Warm antibody type	Cold antibody type
1. Idiopathic (primary)	1. Idiopathic
2. Drugs, e.g. penicillin and methyl dopa	2. Infections by viruses e.g. EB virus and mycoplasma infection
3. Systemic lupus erythematosus and other collagen disorders	3. Drugs, e.g. stibophen
4. Lymphomas and chronic lymphatic leukemia	4. Chronic lymphatic leukemia
5. Immune deficiency states	5. Paroxysmal cold hemoglobinuria

hemoglobinopathies, splenectomy is not generally indicated.

Intravenous immunoglobulin given in a dose of 0.4 g/kg b.w daily for 3-4 days is effective in acute hemolytic episodes. This should be reserved for intractable cases since its cost is high.

Acquired Hemolytic Anemias

Autoimmune Hemolytic Anemia (AIHA)

Autoantibodies develop against the erythrocytes. The antibody may agglutinate the red cells at 37°C (*warm antibody*) or at lower temperatures (*cold antibody*). Warm antibodies generally belong to IgG class whereas cold antibodies are IgM. In the warm antibody type hemolysis takes place extravascularly in the spleen, while in the cold antibody type hemolysis occurs intravascularly or in the liver. Warm antibody type may vary in its course from mild chronic anemia to explosive and life-threatening hemolytic crisis.

Etiology: Table 151.2 lists the causes of autoimmune hemolytic anemias.

CLINICAL FEATURE

The majority of cases present symptoms like anemia, jaundice and splenomegaly. In secondary AIHA, features of the underlying disorder may be evident.

Acute massive hemolysis with shock and renal failure may develop in some cases.

Hemolytic anemia of the cold antibody type may give rise to two clinical syndromes an exposure to cold environment: (1) **Cold agglutinin syndrome**, and (2) **Paroxysmal cold hemoglobinuria**. Cold agglutinin syndrome occurs in older patients and presents with acrocyanosis, Raynaud's phenomenon, gangrene of fingertips, and a mild chronic hemolytic anemia. In paroxysmal cold hemoglobinuria, sudden hemolysis develops leading to hemoglobinuria. Paroxysmal cold hemoglobinuria is the first identified autoimmune disease

described by Karl Landsteiner, pathologist from Vienna. The antibody reacts with erythrocytes in the cold.

The *peripheral blood film* shows marked anisopoikilocytosis, polychromasia, spherocytosis, and increase in reticulocytes. *Neutrophil leukocytosis* is common. Rarely platelets may be reduced due to the development of antibodies against them (*Evan's syndrome*). The antibodies present on erythrocytes can be demonstrated by the *direct Coombs' test* and free antibodies in the serum can be identified by the *indirect Coombs' test*. The thermal characteristics are demonstrable by suitable tests.

Treatment: In secondary hemolytic anemia, treatment is directed towards the underlying cause. If blood transfusion is necessary, properly cross-matched erythrocytes should be given.

Majority of cases of primary AIHA responds to prednisolone in a daily dose of 1-2 mg/kg body weight. Once the acute episodes are controlled, the dose should be tapered off but the maintenance dose may have to be continued for prolonged periods. Methyl prednisolone in doses of 1-2 g/day given IV as infusion may prove to be superior to other steroids in some cases. In cases where steroids fail, or the maintenance dose is high, splenectomy has to be considered. If erythrocyte destruction can be demonstrated in the spleen by isotopic methods, such cases benefit promptly by splenectomy. In the others, although the response is unpredictable, 33-50% still derive benefit.

Immunosuppressive drugs like azathioprine (2-3 mg/kg body weight) cyclophosphamide (1-2 mg/kg body weight) or cyclosporine may be required, if steroids given alone are not fully effective.

In cold antibody type, if the hemolysis is mild, only general measures such as avoidance of cold may be necessary. If transfusions are necessary the blood should be warmed to body temperature before infusion. Steroids and splenectomy are less effective in this type, compared to warm antibody type of AIHA.

Secondary Hemolytic Anemias

Syn: Symptomatic hemolytic anemia

Hemolysis may develop in the course of infections such as malaria, viral hepatitis, infectious mononucleosis, and mycoplasma infection. Collagen disorders, leukemia, lymphomas, and other malignancies may be associated with immune hemolysis. Several drugs like penicillin and methyl dopa are associated with the production of antibodies and hemolytic anemias. Drugs act in several ways: (1) drugs like penicillin may act as haptens and make the erythrocyte antigenic; (2) drugs like stibophen, quinine, quinidine, INH, PAS, and sulphonamides, lead to the development of immune complexes which get attached to the erythrocytes and lead to complement-

mediated hemolysis (innocent bystander type); and (3) drugs like methyl dopa lead to production of antibodies directed against specific antigen sites in the erythrocyte and lead to hemolysis.

Rarely hemolysis may be due to physical factors. Prosthetic cardiac valves lead to mechanical injury and damage of red cells. Long marches and severe physical exertion lead to hemolysis by the same mechanism—march hemoglobinuria. Severe burns lead to extensive hemolysis.

Hemolytic Disease of Newborn (HDN)

The newborn may suffer from Rh incompatibility or ABO incompatibility if there is Rh or ABO incompatibility between the parents. If the father is Rh positive the fetus may also sometimes be Rh positive and entry of fetal erythrocytes into the Rh negative mother leads to production of anti-negative-Rh antibodies which reach the fetus and destroy its erythrocytes. A similar phenomenon may occur in ABO incompatibility as well.

RH INCOMPATIBILITY

This accounts for the vast majority of isoimmune hemolytic anemias of the newborn and manifests as jaundice on the first day of life. Among the Rh antigens 'D' is most antigenic. Fetuses with this phenotype cause more severe immunisation of the mother and greater degrees of hemolysis in the fetus. In India 8% of population is Rh negative, unlike in the West where the frequency is 15%. About 17% of Rh negative women get immunised during pregnancy if the fetus is Rh positive.

Pathogenesis

The Rh isoimmunisation occurs when an Rh negative individual receives Rh positive blood by transfusion or by other sources. When an Rh negative mother carries an Rh positive fetus there is transplacental exchange of small quantities of fetal blood into the maternal circulation during the last weeks of pregnancy and during labour. Therapeutic obstetric procedures increase this risk. The fetal cells immunise the mother and antibodies of IgG class are produced depending upon the amount of fetomaternal transfer. Usually the first born child escapes unless the mother is previously sensitised due to Rh incompatible blood transfusions during childhood or due to previous abortions. With successive pregnancies and abortion the antibody titre in the mother progressively rises. Spontaneous or induced abortions, ectopic pregnancy, amniocentesis and other similar procedures increase the risk. The maternal antibodies pass back into the fetus and lead to hemolysis of fetal erythrocytes, resulting in hemolytic disease of the newborn. Severity of hemolysis depends upon the amount of maternal antibody and the period of gestation at which the fetus is affected.

Hemolysis leads to the development of marrow hyperplasia and extramedullary hemopoiesis. Hepatosplenomegaly occurs. Hepatic function suffers and therefore hypoalbuminemia, ascites and hydrops fetalis develop. In the severe form there is congestive heart failure, impairment of placental circulation, intrauterine growth retardation and stillbirth. The excess of bilirubin resulting from excessive hemolysis is handled both by the liver and placenta during fetal life, but after birth, this bilirubin load has to be handled by the liver alone. Unconjugated bilirubin crosses the blood brain barrier when the serum levels are high. It gets deposited in neural cells when the serum level exceeds the binding capacity of serum albumin. It interferes with mitochondrial function and leads to cell death and permanent-neurological defects. Neurones in the brainstem, basal ganglia and other regions are affected most. Neurotoxicity of bilirubin may also lead to nerve deafness, seizures, athetoid movements, spasticity and death.

D-phenotypes cause maximum sensitisation and lead to most severe disease. Factors determining the extent and severity of the disease are the timing, number and extent of fetomaternal exchanges of blood. Fetal cells which are both ABO and Rh incompatible are more rapidly destroyed in the maternal circulation than purely Rh-incompatible cells. Hence the latter type is more immunogenic and it leads to clinically more serious type of disease. The unconjugated bilirubin formed by hemolysis is bound to albumin, but when the bilirubin level exceeds 20 mg/dL, the unbound bilirubin passes to the CNS and causes damage, which is most pronounced in the basal ganglia.

Clinical presentation The mild form manifests as moderate hemolytic anemia in the first days of life. Hepatosplenomegaly may be just detectable. The moderately severe form presents as *icterus gravis neonatorum*. This leads to jaundice within 24 hours of birth and this feature distinguishes it from physiological jaundice. Anemia may progress and lead to cardiac failure. Hepatosplenomegaly may be more evident. Neurological abnormalities develop in severe cases. This is known as *kernicterus* which is characterized by a high pitched cry, opisthotonus and convulsions. Sequelae include choreo-athetosis, deafness, cerebral palsy and mental deficiency which become evident as the child grows.

The severe form manifests as *hydrops fetalis*. Usually the affected baby is born dead or it dies soon after birth. Gross edema, hepatosplenomegaly, anemia and effusions into serous cavities are the common stigmata.

Investigation in a suspected case of Rh isoimmunisation: The mother's blood shows the presence of antibodies by the indirect Coombs' test. Titres above 1/64 or rising titres are indicative of risk to the fetus. Further adjuncts to diagnosis are amniocentesis and analysis of bile pigments in amniotic fluid. Unlike normal amniotic fluid which is colourless, in Rh hemolytic disease the

amniotic fluid is bright yellow and this can be quantitated spectroscopically.

Postnatal diagnosis: The baby's blood shows positive direct Coombs' test, elevated serum bilirubin, reticulocytosis, anemia and presence of large number of erythroblasts (over 10% of nucleated cells).

MANAGEMENT

Rh immunisation is a preventable disease by proper Rh typing during the prenatal check up.

Prenatal Management

1. When the mother is not immunised or the Rh antibody titre is low and static the pregnancy is allowed to continue.

The Rh-D antibody titres are estimated at the first month itself in at-risk pregnancy and repeated. If the titre exceeds 1/16 at 20 weeks or the titres double from the original value, amniocentesis is done to estimate the bilirubin level in amniotic fluid. Polymerase chain reaction (PCR) has been employed to determine the fetal genotype using amniotic cells or fetal blood or maternal plasma collected early in the second trimester.

Other investigations to be undertaken include ultrasonography, and two-dimensional Doppler studies to detect fetal ascites and hydrops. If the risk of hydrops fetalis or stillbirth before 34 weeks is high, blood transfusions have to be given to the fetus to ameliorate anemia, reduce ascites and hydrops and suppress erythropoiesis. With modern techniques, direct intravascular transfusion is possible in upto 80% of cases. The alternative is to give intraperitoneal infusion of blood.

2. If the risk of hydrops fetalis or stillbirth is high, induction of labour between 34 and 38 weeks is indicated.

Test for pulmonary maturity is carried out by estimating the lecithin sphingomyelin (L/S) ratio of the amniotic fluid. If the L/S ratio is above 2, the pulmonary surfactant will be normal and so there is no risk of acute respiratory distress syndrome in the newborn.

Postnatal Management

The principles of management include the correction of anemia, acidosis, hypoglycemia and hyperbilirubinemia. When the serum level of unconjugated bilirubin is above 20 mg/dL in term babies or 15 mg/dL in preterm babies, exchange transfusion with Rh negative group O blood is indicated. By this procedure antibody coated erythrocytes and excess bilirubin are removed, and anemia is corrected. Hemoglobin level below 14 g/dL and serum bilirubin above 3 mg/dL in cord blood are also indications for immediate exchange transfusion. Usually 150 mL/kg body weight of compatible blood is used for each exchange.

Other forms of therapy: Mild or even moderate cases can be controlled by *phototherapy* and *phenobarbitone*. Natural sunlight and fluorescent light oxidise bilirubin to biliverdin and then to nontoxic water soluble products. Phototherapy reduces indirect bilirubin level and helps to reduce the need for exchange transfusion. Phenobarbitone induces liver enzymes to conjugate bilirubin and favour its excretion.

Prevention: Rh negative mothers who are at risk are protected from getting immunised by the administration of 300 µg of anti-D gammaglobulin (Rhogam) within 72 hours of delivery or abortion, amniocentesis or rupture of ectopic gestation. Rh immunoglobulin is prepared from plasma obtained from persons with Rh D antibodies. It agglutinates and destroys the circulating fetal cells.

ABO Hemolytic Disease

In 15-20% of pregnancies ABO incompatibility occurs between the mother and fetus. IgG antibodies against fetal red cells are produced in the mother. Group O mothers produce antibodies more readily than A or B group mothers. The ABO hemolytic disease of the newborn is mild compared to Rh hemolytic disease. Further differences are: (1) the first pregnancy may be affected as frequently as subsequent pregnancies, and (2) even if one pregnancy is affected the subsequent one may escape.

The clinical features are milder compared to Rh hemolytic disease and they may subside spontaneously. Phototherapy and exchange transfusion may be required at times.

Non-Rh Hemolytic Anemias

Other alloantibodies are increasingly being recognized as causes of non-Rh hemolytic anemia. These include antibodies of the Kell system (K and K), Duffy (Fy), Kidd (JKa and Jk^b) and MNSs systems (M, N, S and S). Some women get immunised to more than one system of antigens. Next to anti-D, anti-Kell is the most common. 6-8 weeks after the recovery from the hemolytic process with treatment, hyporegenerative anemia may develop in the infant. This may require transfusion.

Inherited Disorders of the Erythrocytes

RED CELL MEMBRANE DISORDERS

Hereditary Spherocytosis

Hereditary spherocytosis is the most common inherited disorder of erythrocyte membrane. It is an autosomal dominant disorder presenting as a chronic hemolytic anemia with the presence of spherocytes in peripheral blood, intermittent jaundice, and splenomegaly. In 80% cases family history indicates hereditary involvement.

Pathogenesis: Though the exact molecular lesion in spherocytosis is yet unknown, several alterations in structure and function of the cell membrane have been noticed. These include: (1) reduction in membrane lipid; (2) increased permeability to sodium; and (3) defective phosphorylation of the membrane protein—*spectrin*. Abnormalities in membrane proteins such as spectrin, ankryn, pallidin (protein 4.2) and band 3 have been identified. The spherocytes are erythrocytes which assume a spherical shape due to inability to maintain the normal biconcave shape. Spleen destroys the defective erythrocytes. Bone marrow shows erythroid hyperplasia. In long-standing cases gall stones are common.

CLINICAL MANIFESTATIONS

In the vast majority the condition presents in the second and third decades with mild hemolytic anemia and recurrent jaundice. Occasionally it may manifest as persistent anemia and failure to thrive in infants. Many cases remain asymptomatic throughout life. Hemolytic and aplastic crises may occur from time-to-time. Extreme cases may present as neonatal hyperbilirubinemia requiring exchange transfusion.

Laboratory findings: Hemoglobin level is usually 8-10 g/dL. Reticulocyte count ranges from 5-20%. Over 30% of erythrocytes in the peripheral blood are spherocytes (Fig. 151.3). They are smaller in diameter, thicker, and appear uniformly stained with loss of the central pallor. Mean corpuscular volume is increased. The osmotic fragility is increased. Autohemolysis occurs in stored blood and this is corrected by the addition of glucose or ATP. Coombs' test is negative.

Diagnosis: Recurrent anemia, jaundice, splenomegaly, and spherocytosis should suggest this diagnosis, though spherocytosis may occur in other types of hemolytic anemias also as an acquired defect. Occurrence of spherocytosis and hemolysis in siblings or parents strengthens the diagnosis. In addition, demonstration of autohemolysis and its correction by glucose or ATP are



Fig. 151.3: Spherocytosis-PB: Note: The small densely stained RBCs-(spherocytes)-arrows

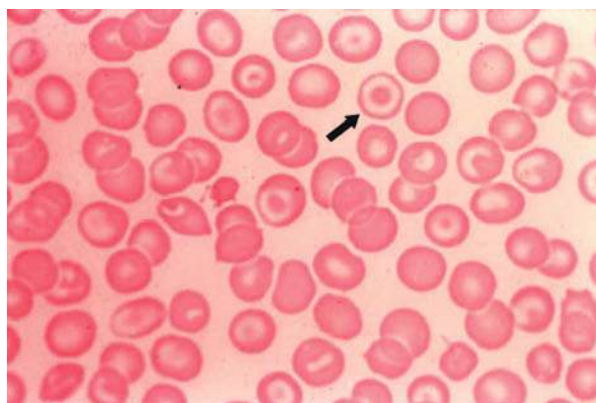


Fig. 151.4: Peripheral blood-post splenectomy
Note:Target cells-arrow

diagnostic, since these tests are specific for hereditary spherocytosis.

Treatment: Hereditary spherocytosis is functionally curable by splenectomy in almost all cases. Poor response to splenectomy or relapse suggests a wrong diagnosis or the development of accessory splenic tissue. Children have a higher tendency to develop pneumococcal and other types of septicemia after splenectomy and, therefore, splenectomy should be avoided in children below 10 years of age. In some intractable cases splenectomy may have to be done but this should be preceded by pneumococcal vaccination and prophylactic penicillin therapy when infections are likely to occur. Target cells appear in peripheral blood after splenectomy (Fig. 151.4).

OTHER RED CELL MEMBRANE DISORDERS

Hereditary elliptocytosis (HE): This is a specific autosomal dominant disorder where mild or moderately severe hemolysis occurs, but may remain unnoticed in about 90% cases. Almost all the red cells are elliptical in shape (elliptocytes) (Fig. 151.5). Diminished spectrin interactions, deficiencies or dysfunction of protein 4.1, and glycophorin deficiency have been identified.

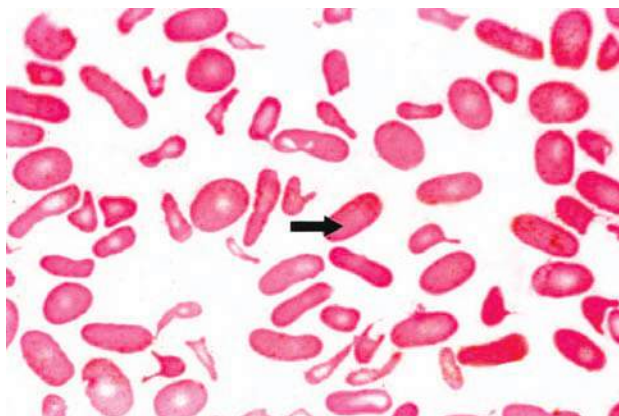


Fig. 151.5: Ovalocytosis peripheral blood x 1000-
(elliptocytosis). Note: The oval erythrocytes

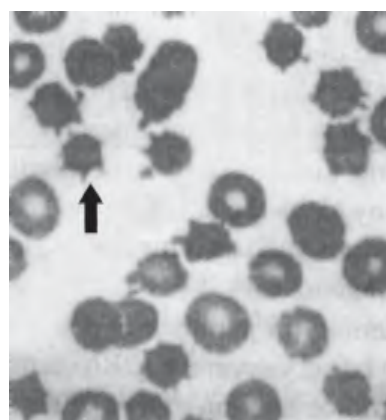


Fig. 151.6: Acanthocytes (arrow)

Treatment is symptomatic. Results of splenectomy are unpredictable.

Acanthocytosis: Acanthocytes are abnormal erythrocytes showing projections of variable width and length on their surface. They are seen in abeta-lipoproteinemia and severe liver disorders (Fig. 151.6).

Red Cell Enzymopathies

General considerations: A mature red cell cannot synthesize proteins since it has neither the nucleus nor ribosomes. It has lost its mitochondria, and therefore, it cannot generate ATP via the tricarboxylic acid cycle. It has also no ability to synthesize nucleic acids or lipids. Still it completes its full life-span of 120 days through other metabolic pathways for which it is endowed with a full supply of several enzymes. Important among them are hexokinase, glucose-P-isomerase, phosphofructokinase aldolase, triose-P-isomerase, glutathione peroxidase, glutathione reductase, glutathione synthetase, glucose-6-phosphate dehydrogenase and many others. Most enzymopathies are inherited in an autosomal recessive manner but some are sex linked or autosomal dominant. Hemolytic anemias caused by enzymopathies are also known as hereditary non-spherocytic hemolytic anemias.

GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY (G-6-PD)

Prevalence: The G-6-PD deficiency is prevalent in different parts of the world, commonly in the Mediterranean population. In India, the incidence varies from 1 to 20% in different ethnic groups, the highest incidence being in Naga tribals, Parsees and others. Three common variants of G-6-PD have been identified. These are G-6-PD Kerala, G-6-PD West Bengal and G-6-PD Jammu. At present over 400 isoenzymes of G-6-PD have been recognised. G-6-PD deficiency gives partial protection against falciparum malaria in female heterozygotes. G-6-PD deficiency is sex

linked recessive phenomenon which is transmitted from mother to son. The gene for G-6-PD is located on the long arm of the X chromosome. Fifty percent of the sons are affected while the heterozygous females may show only slightly lower enzyme values. The G-6-PD deficiency finds full expression in hemizygous males and homozygous females. Clinical features depend on the severity of enzyme deficiency and the racial patterns. Normal G-6-PD level is 12-18 units/mL.

Clinical Severity of G-6-PD Disorders	
Class I:	Enzyme activity is below 10% and this results in chronic hemolysis.
Class II:	Enzyme activity is below 10% but there is no chronic hemolysis, e.g. G-6-PD-B.
Class III:	Functional activity 10 to 60%. Here hemolysis occurs only after exposure to drugs or infections, e.g. G-6-PD-A.
Class IV:	Normal functional activity.
Class V:	Increased activity.
Classes IV and V are of no clinical significance.	

The Indian variant usually produces hemolysis on exposure to several drugs and infections. Drug-induced hemolysis may present as a life-threatening disorder in such subjects. Rarely neonatal jaundice may occur—icterus neonatorum.

Common Drugs Causing Hemolysis in G-6-PD Deficiency

1. Antimalarials:	Quinine, primaquine, chloroquine, mepacrine.
2. Sulfa group:	Sulfanilamide, sulfapyridine, acetylsulfanilamide, sulfacetamide, sulfafurazole, thiazosulfone, salazosulfapyridine, aldesulfone sodium, sulfamethoxypyridazine, cotrimoxazole.
3. Analgesics:	Acetanilide, acetylsalicylic acid, phenacetin, phenazone, aminophenazone.
4. Other drugs:	Furozolidone, nitrofurantoin, chloramphenicol, para-aminosalicylic acid, naphthalene, vitamin K, probenecid, quinidine, trinitrotoluene, methylene blue, dimercaprol, phenylhydrazine.

In addition several articles of food may precipitate hemolysis, e.g. Fava beans.

Clinical features: The subjects carrying the enzyme defect do not show any evidence of disease but exposure to oxidant drugs and/or infection may lead to hemolysis. Drug induced hemolysis starts 24 to 72 hours after administration of the drug. Urine is dark and jaundice may be present. Hemolysis stops when the drug is withdrawn and the hemoglobin level improves. Sometimes spontaneous arrest of hemolysis occurs even when the drug is continued. Babies with G-6-PD deficiency may develop severe icterus neonatorum.

Laboratory findings: Severe anemia may result. Red cells may show *Heinz bodies* before the onset of hemolysis. These are refractile inclusions which are seen in the erythrocyte in the wet unstained preparation. They are indistinguishable by the Romanowsky stains, since they stain uniformly with the surrounding hemoglobin. Hemoglobinuria may develop and this may result in renal failure. Reticulocytes are increased. Red cell morphology is generally normal. Estimation of the enzyme helps to establish the diagnosis. Since reticulocytes are generally rich in G-6-PD, the enzyme activity may be normal in the presence of active reticulocytosis. In such cases the enzyme assay should be repeated after the reticulocytosis has subsided.

Course: In the majority of G-6-PD deficiency patients it is a self-limiting phenomenon and it tends to subside when G-6-PD levels increase with the onset of reticulocytosis.

Therapy: Mild cases are self-limiting and demand only withdrawal of the offending drugs. In severe cases, blood transfusion may be required. Renal failure should be managed on its own merits. Subjects who are G-6-PD deficient should be informed of the condition to prevent further recurrence.

Other important inherited enzymopathies include the following:

Pyruvate kinase deficiency: This is an autosomal recessive disorder with several different mutations of the gene. It also manifests as hemolytic anemia. Splenectomy may benefit some cases.

Triose-phosphate deficiency: This leads to hemolytic anemia as well as neurological defects, cardiomyopathy and susceptibility in infection. Many cases die in childhood.

Red cell enzymopathies should be suspected in children with hemolytic anemia which is not associated with abnormalities of hemoglobin and morphological abnormalities of erythrocytes and absence of antibodies against erythrocytes.

Hemoglobinopathies, Thalassemias, and Thalassemia Syndromes

GENERAL CONSIDERATIONS

Hemoglobinopathies are among the most widespread genetic disorders seen in humans. The hemoglobin in normal individuals is made up of three components. These are HbA₁ (94-97%) HbA₂ (1-3.5%) and HbF (0-2%). During fetal life HbF is the main hemoglobin and it is replaced by HbA within the first six months of life. This transformation is under genetic control. Failure of formation of adult hemoglobin to replace the fetal hemoglobin results in thalassemias.

The hemoglobin molecule is made up of heme and globin. Chemical changes in the heme lead to the production of methemoglobin, sulphhemoglobin, and carboxyhemoglobin. The globin contains four polypeptide chains. The polypeptide chains are alpha, beta, gamma and delta. HbA₁ has 2 alpha and 2 beta, HbF has 2 alpha and 2 gamma and HbA₂ has 2 alpha and 2 delta chains. The genes for beta, gamma and delta chains are located in a closely linked cluster on the short arm of chromosome 11. Alpha and beta chains are produced on separate ribosomes in nearly equal amounts. Each polypeptide chain has a specific amino acid constitution. When the sequential order of amino acids is altered or the chain is altered by deletion or addition, abnormal hemoglobins are formed. For example, substitution of valine for glutamic acid at sixth residue of beta chain results in the formation of HbS and lysine for glutamic acid results in formation of HbC. Such alterations result in the change of electrical charge of the molecule and consequently, the electrophoretic mobility alters. This property enables these abnormal hemoglobins to be separated by electrophoresis. Abnormal hemoglobins and thalassemias are inherited as autosomal dominant trait, but their expressivity and penetrance vary considerably. This factor accounts for the very heterogenous mode of transmission. Many authors consider that inheritance of abnormal hemoglobins may clinically resemble that of autosomal recessives. Variants of Hb A have been identified.

Hemoglobinopathy in India: Several hemoglobin variants are encountered in India. These are hemoglobins D, E, F, H, I, J, K, L, M, S, Q, Norfolk, and Lepore. Of these, prevalence of hemoglobins S, E, D, J, K, and Q have been studied in detail in population groups. Hemoglobin S is found mostly in the tribals. HbE is seen in Bengal and Assam; Hb D, J, and K are seen in Punjabis and Gujaratis and HbQ is seen in Sindhis. Among these only HbS and HbE are widely prevalent. The sickle cell gene is widespread in India. In some tribal populations

the frequency is up to 45%. Hemoglobin C is not reported from India.

The cumulative gene frequency for HbS, E and D in India is 5.45. For HbS it is 4.5, for HbD it is 0.86, and for Hb E in the northern states it is 10.9 (Balgir RS JI Ass Phys India 1996:44, 1, 25-28). In Wynad district of Kerala, Kurumas, Paniyas, Adiyas and Wynad Chettys have HbS disease. The disease is mild in 52.2% of cases. Crisis occurs in 43% of cases. Splenomegaly and leg ulcers occur with a frequency of 4.3% in these tribes.

Sickle cell β^+ thalassemia has HbA levels of 20-30% whereas sickle cell β^0 thalassemia has only much lower levels of HbA and therefore the former is less severe. Sickle cell β^+ thalassemia and sickle cell HbC disease tend to be milder than sickle cell anemia.

Inheritance Pattern

If both parents carry one each HbS gene 25% of children develop SS disease and the others will be heterozygous for S. All pregnancies carry the same risk. If one parent is SS and the other is heterozygous (AS), the risk of having SS for the offspring is doubled. The study of the structure of DNA flanking the beta-globin locus has helped to classify population groups who possess the HbS gene. The genetic constitution of HbS patients in India belongs to the Asian haplotype. This is the same seen in eastern Saudi Arabia too.

Hemoglobinopathies lead to physical and chemical alterations in the function of the hemoglobin molecule depending on the site and nature of the amino acid substitution. Many lead to hemolytic anemia, e.g. HbS. Substitution of certain nonpolar amino acids within the hemoglobin molecule makes it unstable so that even in the heterozygous state it leads to hemolytic anemia. Certain substitutions lead to congenital methemoglobinemia.

Some substitutions lead to increased affinity of the hemoglobin to oxygen and this prevents the release of oxygen to the tissues. Tissue anoxia leads to polycythemia. Abnormal hemoglobins can be separated by electrophoresis in suitable buffers. In comparison with the mobility of hemoglobin A, they can be classified as slow moving, fast moving, and very fast moving types as given below.

Electrophoretic mobility at pH 8.6		
Very fast	H group	H, I, Barts
Fast	J group	J, K, No, Norfolk
Normal	A group	A, M, F
	G group	G, L, P, Q
Slow	S group	S, D, Stanville-2, Lepore
	C group	C, E, A ₂ O, F, Alexandra

Hemoglobinopathies

SICKLE CELL DISEASE

Sickle shaped red cells were first described by Harrick in 1902. Sickle cell disease is the most widespread hemoglobinopathy in India. Though nation wide epidemiological data is not available for India, it is known to be widely prevalent in many areas, particular communities being affected. Many tribal populations of Tamilnadu, Assam, Andhra Pradesh, Orissa, Madhya Pradesh, Kerala (particularly Paniyas), Maharashtra and all other states do suffer from the disease. Occurrence among high caste population in Kerala has also been reported. HbS may constitute more than 50% of the contents of the red cell.

Sickle Cell Anemia

Homozygous sickle cell disease: It leads to sickle cell anemia. In sickle cell trait the condition is heterozygous and the levels of HbS are much lower. Hemoglobin S offers partial protection against falciparum malaria (*balanced polymorphism*) accounting for the persistence and relative increase in HbS hemoglobinopathy in regions having high prevalence of falciparum malaria.

The genetic variants are:

Sickle cell anemia	homozygous S-S
Sickle cell trait	heterozygous A-S
HbS-thalassemia	heterozygosity between HbS and thalassemia
	The thalassemias may be B ⁰ or B ⁺
	HbS + B ⁰ has severe manifestations whereas
	HbS + B ⁺ give rise to milder manifestations
HbS-C disease	heterozygosity between S and C
HbS-D disease	heterozygosity between S and D
HbS with hereditary	The clinical manifestations are milder persistence of fetal hemoglobin

PATHOLOGY

Hemoglobin S is formed by the substitution of valine in place of glutamic acid in the sixth residue of the beta chain of adult hemoglobin and it is a slow-moving hemoglobin. Oxygenated HbS is normally soluble and the erythrocyte carrying it behaves normally. On deoxygenation the abnormal hydrophobic valine becomes exposed. On encountering another deoxygenated HbS molecule, polymerisation occurs at an explosive rate. Higher concentration of HbS and low pH favour

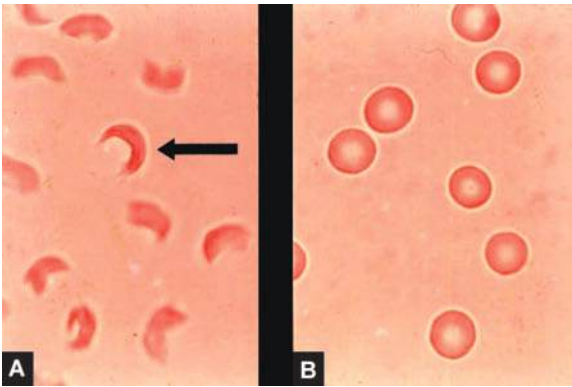


Fig. 151.7: Sickle cell anemia (HbS)
Note: (A) sickling-arrow (B) oxygenated blood

polymerisation. This leads to change of shape of the erythrocyte- *sickling*. The erythrocyte loses its deformability due to stiffening.

On reoxygenation the polymerised HbS promptly fall apart instantaneously.

The polymerisation of hemoglobin S is central to the pathogenesis of the disease. Polymerisation which occurs in anoxic environment stiffens the sickled erythrocytes, changing it from a flexible and deformable biconcave disc to an unyielding obstacle that blocks the circulation leading to the anoxic and nutritional damage to distal tissues. The polymerised HbS forms liquid crystals (tactoids) which distort the erythrocytes and make them assume the sickle shape (Fig. 151.7).

Only deoxygenated HbS polymerises. On reoxygenation the processes are promptly reversed. Organs with relatively sluggish circulation, high level of oxygen extraction and low pH such as the spleen and bone marrow are the most vulnerable to polymerisation and anoxic damage. Vaso-occlusion and tissue ischemia are caused by other factors as well, which are triggered by sickling and adhesion of erythrocytes. These include interaction between erythrocytes, endothelium, platelets, leucocytes and plasma factors. Endothelial dysfunction also plays a major role in the final outcome of vaso-occlusion. High molecular weight von Willebrand's factor favours adhesion of red cells and platelets to endothelium. Reticulocytes release free oxygen radicals which lead to endothelial damage and further changes. These pathological changes are most marked in SS disease. They are milder in HbS-β⁺ thalassemias and HbS+ persistence of HbF.

The painful episodes in the spleen and bones are caused by anoxic infarction. As a result of repeated infarcts the spleen may shrink and become functionless (autosplenectomy). In the bone marrow periodic infarction leads to fat necrosis and fat embolism and embolisation in the lungs is one of the precipitating factors for acute chest syndrome.

Normally the lung is the de-polymerising organ which protects the arterial side of the circulation from blockage by sickled erythrocytes.

Vaso-occlusion by sickle cells is a two step process that begins with adhesion of red cells to endothelium, probably in the post-capillary venules. This is followed by a propagation phase caused by accumulation of poorly deformable red cells behind the site of adhesion.

In addition to the abnormalities in sickled red cells several other factors also favour their adhesion to the endothelium. These include endothelial injury caused by release of cytokines liberated by granulocytes, thrombospondin released by activated platelets leading to adhesion, and the influence of young reticulocytes called “stress reticulocytes”. These cells express adhesive ligands that facilitate interaction between sickle cells and endothelial cells. Expression of adhesion receptors on endothelial cells is accelerated by hypoxia, thrombin, tissue necrosis factor, platelet activating factor and interleukin-1. Among the various hemolytic anemias, the vaso-occlusive component in sickle cell anemia is unique.

Life-span of the erythrocyte is reduced to 10-12% of normal. A new equilibrium with hemoglobin around 6-9 g/dL and reticulocytes forming 10-15% gets established.

Sickled cells are easily destroyed and this leads to hemolytic anemia. Factors which precipitate sickling are hypoxia, acidosis, dehydration, fever, and infections. Occlusion of the microcirculation resulting from sickling aggravates acidosis further, thereby establishing a vicious circle. Maximal lesions are seen in the heart, lungs, spleen, bone marrow, brain, and placenta. Pulmonary hypertension, demonstrable by Doppler studies is common in adults with sickle cell disease. Hemolysis seems to be the causative factor, stimulating procoagulant activity leading on to microvasculopathy and thrombosis. Primary pulmonary hypertension is also not uncommon. Presence of pulmonary hypertension confers higher mortality.

Obstruction of the microcirculation of the bone marrow leads to ischemic necrosis, marrow embolism and fibrosis. Priapism occurs due to occlusion of the corpora of the penis. This may be persistent, painful and troublesome. Retinitis proliferans may develop in children.

In HbS-thalassemia the presence of large amounts of HbF protects against sickling.

CLINICAL FEATURES

Most of the clinical features can be explained on the basis of anemia, hemolysis, obstruction to microcirculation, and siderosis of parenchymal organs. Sickle cell disease may present in different ways, with a wide spectrum ranging from subclinical cases to mild, moderate and severe manifestations. The child may appear normal at birth. The disease becomes evident after six months of age, by which time; normally adult hemoglobin takes over completely

from HbF. The defects in the synthesis of the chains are manifest by this period. Severe cases of HbS disease have higher neonatal and perinatal mortality due to pneumococcal infections. Untreated, severe cases die within 10 years. When the disease is severe, growth is retarded with delay in skeletal maturation giving rise to the characteristic picture of stunted growth, long limbs, narrow hips, and exaggerated lordosis. Anemia, mild or moderate splenomegaly, swelling of fingers and a characteristic appearance develop.

Sickling crises supervene frequently involving several organs, and untreated cases are fatal before the third decade. This extreme form is more common in negros and many tribals. In mild cases there may be only mild anemia, growth and development being normal. This variety is more common in the Middle East. In India the cases show an intermediate severity.

The splenic sequestration syndrome is characterised by sudden painful splenomegaly associated with rapid fall in hemoglobin and hypotension. This is seen more frequently in children. The condition may be fatal if left untreated. As a result of repeated infarction, the spleen may shrink and be converted into a fibrous streak. This is referred to as *autosplenectomy*. The infarcts may become calcified. The spleen becomes impalpable in sickle cell anemia by the age of 10-12 years. In other sickle cell syndromes such as S-thalassemia, S-C and S-D, the spleen remains palpable throughout life.

Acute Chest Syndrome

This is a painful pneumonia like presentation occurring in sickle cell disease. This may be due to vaso-occlusion, infection or both. Precipitating causes include infection by any organism, bone marrow embolism and atelectasis. Physical signs of consolidation or collapse may occur. X-ray may show local infiltration. If severe, respiratory failure may develop.

Renal involvement manifests as hematuria, hyposthenuria, acute nephritis, or occasionally nephrotic syndrome. **Priapism** may occur due to obstruction to corpora cavernosa. **Skeletal symptoms** are common. These include bone pain, arthralgia, backache, dactylitis, salmonella osteomyelitis, and multiple bone infarcts. **Dactylitis** is seen in young children. The femoral and humeral heads may undergo avascular necrosis. Neurovascular accidents develop due to occlusion of intracranial vessels. **Stroke** is a very disabling complication occurring in 10% of patients annually. This occurs around the age of 10-20 years and this confines them to a life of morbidity up to the age of 30. **Blindness** may develop due to repeated vitreous hemorrhages, and retinal tears and detachment. **Aplastic crisis** occur rarely and it is characterised by the rapid development of severe anemia due to marrow

hypoplasia and accelerated hemolysis usually the result of parvovirus B-19 infection. It is self limiting if the crisis is tided over.

Complications include anemia with hemoglobin levels below 6g/dL, cholelithiasis, aplastic crisis, sickling crisis, acute chest syndrome, stroke, infections by *Str. pneumoniae*, *E. coli* and gram-positive cocci, *salmonella osteomyelitis* and adverse effects of repeated blood transfusion.

Diagnosis: In endemic areas the clinical diagnosis can be easily confirmed by demonstrating the sickling phenomenon. One drop of blood is mixed with an equal volume of 2% sodium metabisulphite solution. A cover slip is applied and the edges are sealed with vaseline. After incubation at 37° for 30 minutes sickle cells are demonstrable. Sickling may occur with other hemoglobins also in some cases, e.g. HbC group and Hb Barts. Electrophoresis of Hb at pH 8.6 shows HbS as a slow-moving band.

Course and prognosis: Majority of severe cases die in childhood before reaching five years of age. Only one-fourth live up to 30 years or more. Acute splenic sequestration, chest syndrome, septicemia, meningitis, stroke and gastroenteritis account for most of the morbidity and deaths. Pregnancy carries increased risk to mother and fetus. By proper transfusions and chelation therapy the risk of stroke can be reduced to 1% annually. Proper transfusion therapy even helps to reduce the narrowing of the cerebral blood vessels. Those with lower levels of HbS develop painful crises and chest syndrome and they may live up to 40-45 years.

Cases with thalassemia with higher levels of HbF live up to 40 years or more and may have only minor episodes of crisis. Their transfusion requirements are also low.

MANAGEMENT

Aim of treatment is to prevent deterioration and avoid crisis. The hemoglobin level should be maintained around 8 g/dL with the hematocrit around 25%. Since folic acid deficiency may develop in a few cases, supplementation of 1 mg folic acid daily is beneficial. Intercurrent infections should be treated promptly. Crises have to be managed as emergencies with rest, sedation, maintenance of fluid and electrolyte balance and blood transfusions.

Blood Transfusion

Indications for blood transfusion
i. Symptomatic episodes of acute anemia and acute sequestration syndromes
ii. Prevention of recurrent strokes in children
iii. Surgery, eye complications

The aim of transfusion is to raise the general level of hemoglobin and also reduce the relative proportion of HbS to below 30%. Partial exchange transfusion may be needed during hemolytic or sickling crises if other methods fail.

In severe cases exchange transfusions and simple transfusions in milder cases are life-saving. In the case of stroke, the exchange transfusion should be adequate to lower HbS level below 30%. Follow up transfusions to prevent rise of HbS above 30% are required. Packed cell transfusions are preferable. The transfused packed cells should be sickle cell negative and preferably leukocyte depleted.

Priapism can be managed by packed cell transfusion and alpha adrenergic agonists like terbutaline. Surgery may be required in resistant cases. Iron overload occurs and this has to be treated with iron chelating agents. This is detailed on pp 1013.

Hydroxyurea (hydroxycarbamide) given in a dose of 500 mg bd orally improves the production of HbF and this helps to reduce the frequency and severity of sickling crisis. Reduction in level of neutrophils and platelets reduces the adhesion of sickled cells to vascular endothelium. The drug also reduces the frequency and severity of painful episodes, hospitalisation, chest syndrome and need for transfusions. Increasing the level of HbF is the most widely studied method to prevent sickling. In addition to hydroxyurea, 5-azacytidine, decitabine, erythropoietin, short chain fatty acid like valproic acid and others are also active in this respect.

Sickling is precipitated by cellular dehydration caused by injury to cell membrane. Substances which modulate the ion transport systems of RBC membrane have been tried. Such drugs include *clotrimazole*, and *magnesium pidolate*. Nitric oxide (NO) has shown anti-sickling activity. A drug which improves blood flow in the microcirculation is *polaxamer*, which a non-ionic surfactant co-polymer.

Bone marrow transplantation is curative in over 70% of cases and this is the only modality which is curative. Bone marrow transplantation is ideal if suitable donors are available. Transplantation of cord blood stem cells is an alternative. **Gene therapy** has been tried with success; but the progress has been slow.

Prophylactic measures: These include: (1) screening of babies born to carriers of HbS, with a view to make an early diagnosis and prevent crises, (2) detection of an affected fetus by amniocentesis, and termination of the pregnancy, and (3) genetic counselling to avoid marriage between heterozygotes.

Since pneumococcal infection leads to septicemia, meningitis and pneumonia in children with sickle cell

disease, long-term penicillin prophylaxis has been tried. Oral penicillin (penicillin V potassium) given in a dose of 125 mg bid introduced before four months of age prevents infection and reduces morbidity and mortality. *Pneumococcal infection* is common to produce crisis in sickle cell anemia and therefore antipneumococcal vaccination should be given.

Thalassemias

In normal intrauterine life fetal hemoglobin made up of alpha and gamma polypeptide chains constitutes more than 95% of the total. After birth there is a switch over to beta globin chains which are produced in progressively increasing amounts, substituting gamma chains, thereby giving rise to the transition from HbF to HbA by the age of six months. Fetal hemoglobin is not as efficient as adult hemoglobin for oxygen transport in postnatal life, though it is ideally suited for the intrauterine environment.

Thalassemias are genetic disorders in which the synthesis of normal polypeptide chains forming adult hemoglobin is suppressed. Though the adult hemoglobin level does not come up, the production of gamma chains subsides, and therefore, the absolute level of HbF falls even though its level may be proportionately higher.

Selective deficiency of one or more polypeptide chains has two consequences.

- 1. Reduction in hemoglobin leading to anemia and exaggerated erythropoiesis.
- 2. Imbalance between alpha and non-alpha chains, which is even more dangerous. In the absence of the complementary globin chains, the normally produced chains form aggregates, precipitate within the cytoplasm, damage cell membranes and leads to premature destruction of cells. In beta thalassemias where beta chains are not formed normally, alpha chains are in excess, and they precipitate in the erythroid precursors to form structures similar to Heinz bodies. True Heinz bodies contain denaturated hemoglobin (alpha 2-beta 2) whereas the precipitates in beta thalassemia contain only alpha chains with some amount of attached heme. In the ordinary case of beta thalassemia only 15-30% of cells escape destruction in the marrow. The condition manifests with varying degrees of severity. In decreasing order of severity they may be classified as *thalassemia major*, *thalassemia intermedia*, *thalassemia minor*, and *thalassemia minima*.

Thalassemia major	In this there are major clinical abnormalities with profound anemia.
Thalassemia intermedia	Anemia is not so severe as to necessitate regular blood transfusion.
Thalassemia minor	This is seen in parents of children with thalassemia major who have genetic

abnormalities and morphological abnormalities in erythrocytes but no anemia.

Thalassemia minima	This is the condition in which the person who is an obligate carrier of the abnormal gene manifests neither anemia nor abnormal erythrocyte morphology.

Another scheme of nomenclature takes into account the polypeptide chain involved. The condition is designated alpha or beta thalassemia if the synthesis of alpha chain or beta chain is depressed respectively. In some cases of beta thalassemia, the adjacent delta chain gene is also affected and this gives rise to delta-beta thalassemia.

Several genetic mechanisms have been shown to be responsible for thalassemia. These are gene deletion, gene loss due to unequal crossover, defective transcription of mRNA, unstable mRNA, and nucleotide mutation leading to premature termination of polypeptide chain synthesis. More than 100 different mutations have been identified giving rise to thalassemia, and therefore, genetically and clinically the disease has a highly varied presentation. The single nucleotide mutation produces defects in transcription, RNA splicing and modification and abnormalities of translation, in beta thalassemia either no beta chains are produced (β^0) or β chain production is only impaired (β^-). In alpha thalassemia there are two main abnormal forms. In alpha+ thalassemia there is deletion of only one alpha chain gene, and therefore, some amount of alpha chains are produced. In α^0 thalassemia both alpha chain genes are deleted and therefore there is no alpha chain formation. In the homozygous state only gamma chains are produced. The gamma chains combine with each other to form Hb Barts (γ^4). In the heterozygous form some alpha chains are produced. Excessive production of beta chains without corresponding production of alpha chains leads to formation of tetramers of beta chains Hb-H (β^4). Interaction of the genes for abnormal hemoglobins and thalassemia gives rise to heterozygous states showing the characteristics of both. Homozygous thalassemia presents as a severe hemolytic anemia, whereas in the heterozygous state beta-thalassemia is asymptomatic or only mildly symptomatic. It is beta thalassemia which is most commonly seen in India.

BETA THALASSEMIA MAJOR
Syn: Cooley's anemia

Also known as homozygous beta thalassemia, this is the most severe form of thalassemia, and is reported from all parts of India. In homozygous β^0 thalassemia, there is no synthesis of beta chains, while in homozygous β^+ thalassemia, beta chains are present, but only in small

amounts. In most cases the formation of gamma chains is also reduced.

Pathogenesis: Due to the absence of beta chain synthesis, the alpha chains which are in excess are precipitated to form inclusions within the erythroid precursors. These alpha globin inclusions lead to impairment of erythroid cell replication, membrane function, migration from bone marrow, and red cell survival. Such cells are selectively destroyed in the bone marrow. Erythropoiesis becomes ineffective and this, in turn, stimulates further erythropoiesis.

The relative excess of alpha chains determines the clinical severity. In those cases in which production of gamma chains continues, some of the alpha chains combine with them to form fetal hemoglobin and such cases are clinically less severe.

Hyperplasia of erythroid marrow leads to skeletal changes, thalassemic facies, increased cardiac output, hyperdynamic heart failure, arthralgia and recurrent fractures. Because of diversion of a major part of the cardiac output to the marrow and consequent hypoperfusion of other parts, muscular development is poor.

There is considerable increase in absorption of iron from the intestines and together with iron introduced by blood transfusion, iron-overload results. On an average 19-21 mg of iron accumulate every day from both sources. The body stores of iron may reach 40-60 g or above. This leads to deposition of iron in several organs such as liver, pancreas, spleen, gonads, heart muscles and others. These organs develop hemosiderosis and dysfunction. Secondary diabetes, hypogonadism and skin pigmentation may develop. Cardiac dysfunction and intractable cardiac failure set in later and this is a major cause of death in those cases which live up to adolescence or more. Serum ferritin is raised to very high levels and this indicates the tissue iron load.

By transfusion of 250 mL erythrocytes 250 mg of elemental iron is introduced into the recipient. The end organ manifestations of iron overload include hepatic cirrhosis, cardiac failure, diabetes mellitus, hypopituitarism and hepatocellular carcinoma. These shorten life expectancy in the same manner as hereditary hemochromatosis. Cirrhosis occurs in β thalassemia when the hepatic iron concentration rises above 15 mg/g (0.268 μ mol/g) dry weight.

CLINICAL FEATURES

The child is quite normal at birth and for the first few weeks or months of life, but anemia appears and gradually increases from the 6th to 24th week. Gross hepatosplenomegaly causes protuberance of the abdomen (Fig. 151.8). The limbs are thin. Overgrowth of malar bones, depression of the nasal bridge, protrusion of the upper row of teeth, and bossing of the frontoparietal regions

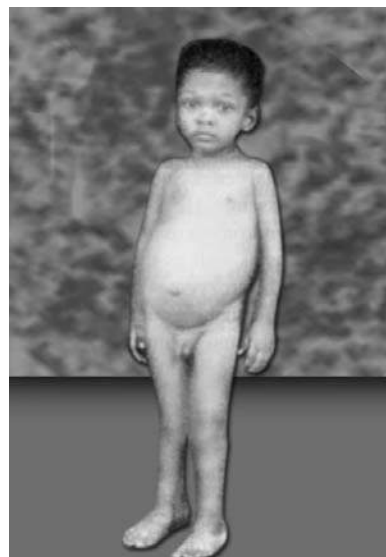


Fig. 151.8: Boy aged 4 years. Thalassemia major
Note the gross splenomegaly

contribute to the *classic thalassemia (chipmunk) facies*. There is increased susceptibility to infection. Intercurrent infection may be the presenting complaint, anemia being detected incidentally. Anemia and hepatosplenomegaly increase with time. The hemoglobin level is generally 3-4 g/dL on presentation. Erythrocytes are hypochromic and microcytic with the presence of anisopoikilocytosis, schistocytes, *target cells*, basophilic stippling, and normoblasts (see Fig. 149.10). Presence of target cells in large numbers is suggestive of the diagnosis. Other features indicating hemolysis are the presence of Howell-Jolly bodies, Cabot's rings, and reticulocytosis. Leucocyte count is generally normal but in some cases leukemoid blood picture may occur. Osmotic fragility of red cells is decreased. Marrow is hypercellular with marked erythroid hyperplasia. "Hair-on-end" appearance on skull X-ray and thinning and widening of metacarpal shafts indicate enlargement of marrow tissue. Primary pulmonary arterial hypertension develops in the majority of cases. Main endocrine disturbances include retardation of growth, hypogonadism, osteopenia and osteoporosis. These lead to bone pains and fractures.

Diagnosis: Thalassemia should be looked for in all children showing persistent or progressive anemia, hepatosplenomegaly, and the characteristic facies. Positive family history strengthens the diagnosis. Microcytic hypochromic anemia unresponsive to iron therapy and the presence of numerous target cells and other evidences of hemolysis are strongly suggestive of thalassemia.

The diagnosis is established by estimating the fetal hemoglobin level which forms even up to 80% of the total.

Fetal hemoglobin is easily estimated by alkali denaturation test. Hemoglobin A is considerably diminished. Hemoglobin A₂ may be increased in most of the cases though it can be normal at times. Normal level of hemoglobin A₂ in adults ranges from 1.8-3.2%. The abnormal hemoglobins are identified by electrophoresis in paper, cellulose acetate or starch block, using appropriate buffer solutions. Further identification is done by studying the polypeptide chains. Genetic characterisation is facilitated by gene mapping and DNA splicing techniques or chain synthesis studies using reticulocytes. In iron deficiency anemia which is the commonest cause for hypochromic microcytic anemia in India HbA₂ levels are subnormal. The red cell distribution width (RDW) is small unlike as in iron deficiency anemia in which the RDW is above 17.

Course and prognosis: Children do not survive without adequate blood transfusions. With passage of time hemosiderosis eventually develops. Damage to several organ systems manifests as delayed puberty and maturation, diabetes, cirrhosis of liver, and heart failure. Cardiac failure is the result of accumulation of iron in the myocardium and the increased demands caused by anemia. The majority of patients succumb before the age of 20 years. Ferritin levels below 2000 ng/mL indicate better prognosis. Rise in levels of tissue iron in the liver and the heart is associated with poorer prognosis. *Magnetic susceptibility* is a non-invasive method to measure the iron content of the liver. This investigation is not available in India at present.

In addition to the damage done by tissue iron, non-transferrin bound serum iron is highly toxic since it catalyses the formation of reactive oxygen and leads to tissue damage.

MANAGEMENT

Blood transfusion is the mainstay of therapy. If Hb level is maintained above 10.0 g/dL all the time by regular transfusions, erythroid hyperplasia is suppressed. If the treatment is started early, skeletal deformities are prevented and growth and development continue normally. **Hypertransfusion** is the use of packed red cell transfusion in doses adequate to keep the Hb above 10 g/dL. This method helps to ensure near-normal growth, physical and mental development and sexual maturity. Splenomegaly, cardiac failure, infective episodes, bone marrow hyperplasia and hypogonadism can be prevented. The average requirement of packed cells is 200 mL/kg/year. If hypertransfusion is started around 3 years of age, bony deformities can be prevented and near-normal growth ensured. If the programme is started after 4 years, the catch-up growth may not be complete. Even in ideally transfused subjects the growth lags behind the ideal due to the ill-effects of iron overload.

Supertransfusion programmes aim at keeping the hemoglobin level above 14 g/dL. This allows the bone marrow volume to shrink further. Growth pattern also becomes normal. When the hemoglobin rises, intestinal absorption of iron is reduced.

Refinements in transfusion techniques include the following:

- Proper compatibility testing of ABO and RhD, and matching for other components of Rh system and Kell system
- Use of packed cells within 7 days of collection-This ensures longer survival
- Phenotypically matched donor
- Use of leucocyte depleted packed red cells – this reduces the incidence of non-hemolytic transfusion reactions
- Use of washed packed red cells-this reduces allergic reactions caused by plasma proteins and
- Transfusion of neocytes, which are young red cells selectively harvested and transfused. They have longer in-vivo survival and therefore the number of transfusions and total annual quantity of packed cells are reduced

Iron chelation therapy should be started when the serum ferritin levels reach >2000 ng/mL.

Iron Chelating Agents

These are employed to mobilise tissue iron from iron stores and eliminate it in urine. The original drug **desferrioxamine** is in use for over five decades. It has to be given parenterally preferably as continuous subcutaneous infusion lasting for 8-12 hours at night over the abdominal wall or other regions. Infusion pumps are available. The dose is 1.5-2 g (up to 12g) daily.

Infusions are given 5-6 times a week. Prior administration of 100 mg vitamin C increases the mobilisation of iron and its excretion. The drug is available as Desferal in vials and the daily injection costs Rs. 200-500.

Though generally safe, the adverse effects include local pain and visual and auditory impairment. Posterior capsular cataract may develop in some and it is essential to monitor vision to avoid toxic damage.

Patients with β thalassemia have fewer cardiac related complications, iron overload, and better survival when the serum ferritin is kept below 2500 μ g/L or hepatic iron concentration is kept below 15 mg/g dry weight.

Oral iron chelating agent: l-2-dimethyl-3-hydroxypyrid-4-one (**Deferiprone**) is a good chelator of iron. It is available as 0.5 g tablets and it is given an hour before food. The total dose is up to 100 mg/kg body weight, the average being 2-3 g/day. In short-term studies the drug is safe. Concurrent administration of vitamin C enhances iron excretion. This drug chelates iron selectively without leading to the loss of calcium, zinc and magnesium. Toxic

side effects include agranulocytosis, arthralgia, arthritis and drug induced lupus erythematosus. Daily elimination of iron in urine may reach up to 36 ± 19 mg, if the drug is given daily in a dose of 100 mg/kg body weight. The commercial preparation is Deferiprone. The drug is available as Kelfer, 250 and 500 mg tablets.

Long-term observations on this drug show that even though it eliminates iron, accumulation of hepatic iron is not prevented to the same extent as desferrioxamine. Deferiprone removes myocardial iron effectively. When regular therapy with desferrioxamine is not possible due to economic reasons and lack of facilities, deferiprone is the next best alternative. This drug is also expensive, a day's treatment costing more than Rs. 60.

A newer iron chelating agent is a *tridentate orally active iron chelator (1cL 670)* which is still under trial. When given in a dose of 20 mg/kg body weight it is effective and well tolerated.

Splenectomy is indicated if transfusion requirements exceed 250 mL/kg of packed cells annually.

Bone marrow transplantation (BMT): Allogenic BMT done early in the disease before iron accumulation develops, is effective in curing the disease in over 80% of cases when followed up for 3 years or more. If the procedure is done after siderosis of the liver has started, the cure rates are lower. Facilities for BMT are available on a limited scale in India. The cost is around Rs. 6-10 lacs or more.

Attempts have been made to increase the production of gamma chains, with a view to increase the content of fetal hemoglobin. Drugs such as 5-azacytidine, cytarabine and hydroxyurea have been shown to increase the production. At present these methods have not gained universal acceptance, though individual cases they may show benefit.

Thalassemia Syndromes

In a population where genes for abnormal hemoglobins and thalassemia are present, random mating gives rise to offspring carrying both the abnormal genes. Such double

heterozygosity may lead to HbE thalassemia, HbS thalassemia, and so on. The term thalassemia syndrome is used to include these double heterozygote conditions as well as the classic homozygous thalassemia. The double heterozygote states present with milder manifestations compared to thalassemia major. In such subjects the presence of abnormal hemoglobin as well as the elevation of fetal hemoglobin can be demonstrated by suitable tests.

Lepore Hemoglobins

Lepore hemoglobins are formed when normal alpha chains combine with chains consisting of the N-terminal residues of delta chain and G terminal residues of beta chains. Three variants of Hb Lepore have been identified. In the homozygous state, clinical picture is that of Cooley's anemia, the hemoglobin consisting of 75% HbF and 25% Hb Lepore.

Hereditary Persistence of Fetal Hemoglobin (HPFH)

In this condition the gene for HbF persists beyond the neonatal period, resulting in the production of large amounts of HbF throughout life. The hematological picture varies. In homozygous subjects, HbF constitutes 100% and in heterozygotes it forms about 25%. Except for slight morphological abnormalities of erythrocytes, the clinical picture is almost normal. It is important to distinguish them from thalassemia syndromes which have different courses and prognosis.

Prevention: Considerable progress has been achieved in the treatment and prevention of thalassemia. Chorionic biopsy and amniocentesis done during pregnancy help to make accurate prenatal diagnosis in the fetus at risk. Such pregnancies can be terminated. This is done on a wide scale in many countries where thalassemias are rampant.

Other hemoglobinopathies: Several other hemoglobinopathies have been described from time to time in India. Except HbE these are less common and hence not described in this book. The student should refer to larger monographs for further details.

152

Anemias Characterized by Defective Erythrocyte Production

K.V. Krishna Das

Chapter Summary

Sideroblastic Anemias 1015
 Paroxysmal Nocturnal Hemoglobinuria (PNH) 1016
 Aplastic Anemia 1017
 Special Forms of Aplastic Anemia 1019

Sideroblastic Anemias

Anemias may result from impaired red cell production due to disorder in the synthesis of heme. The term sideroblast denotes an erythroblast containing one or two stainable iron granules in the cytoplasm. When such stainable iron granules are present in the erythrocyte, it is called *siderocyte*. Even under normal conditions a few of these iron granules may be seen lying free in the cytoplasm without relation to any particular organelle within the cell. But under pathological conditions, iron granules accumulate in the mitochondria and they appear in the form of a perinuclear ring in the late erythroblasts and such cells are called *ringed sideroblasts*. Sometimes pathological non-ringed sideroblasts occur, with excess of free iron granules in the cytoplasm.

Sideroblastic anemias form a heterogeneous group of inherited or acquired disorders characterised by anemia of variable severity, microcytic erythrocytes in peripheral blood and ringed sideroblasts in the bone marrow (Fig. 152.1). Ringed sideroblasts are erythroblasts with large perinuclear Prussian blue positive granules made up of amorphous iron deposits in the mitochondria. The inherited form (hereditary sideroblastic anemia) may occur as an isolated congenital disorder arising from a new mutation, or an autosomal defect, but in most cases it follows an X-linked pattern of inheritance. In many cases the first enzyme required for heme biosynthesis i.e., 5-aminolevulinate synthase which is controlled by a gene located in the X-chromosome is defective.

The acquired form occurs in later life as a clonal disorder in most cases without any obvious etiological factor but some may be drug induced or disease related.

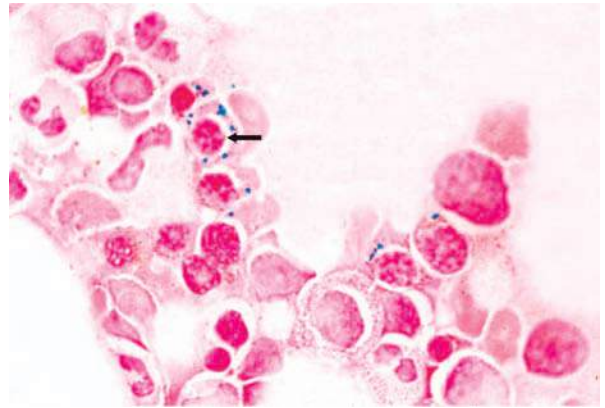


Fig. 152.1: Sideroblastic anemia: Bone marrow × 1000 note ringed sideroblasts (arrow)

In all sideroblastic anemias the synthesis of heme is defective even though the delivery of iron to the mitochondria is normal.

The inherited variety responds to pharmacological doses of pyridoxine.

Etiology: Sideroblastic anemia may be hereditary or acquired. The hereditary form shows a sex-linked inheritance manifesting in males and being transmitted by females. It manifests as a microcytic hypochromic anemia resistant to iron therapy. It follows a benign course.

The acquired form is seen in elderly subjects. In the majority of cases there is no detectable cause but known causes include rheumatoid disease, malignancy, myelosclerosis, chronic myeloid and lymphatic leukemias, acute leukemia, myeloma, polycythemia vera, myxedema, pyridoxine deficiency (nutritional and that induced by antituberculous drugs like INH), alcoholism, lead poisoning, ingestion of drugs like chloramphenicol, cycloserine and rifampicin, and erythrocytic porphyria.

Diagnosis should be suspected when a patient with microcytic hypochromic anemia fails to respond to adequate iron therapy. Diagnosis is established by the demonstration of ringed sideroblasts in the bone marrow stained for iron by Prussian blue reaction. Siderocytes may be seen in peripheral blood (Fig. 152.2).

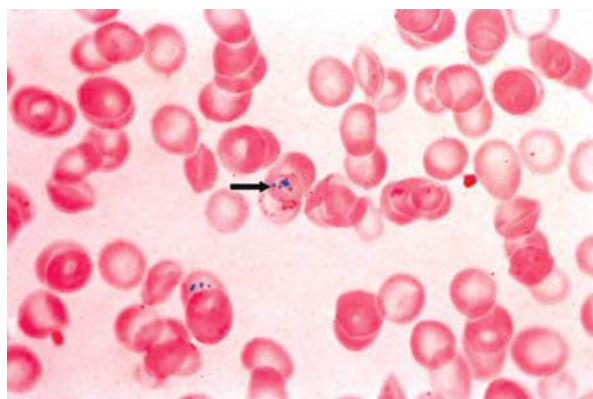


Fig. 152.2: Sideroblastic anemia peripheral blood $\times 1000$. Note: Siderocytes (RBC containing iron pigment)-arrow Prussian blue stain

Course and prognosis: In secondary causes, prompt clinical improvement occurs on removal of the primary cause. The idiopathic form may be resistant to all forms of therapy. Some cases of idiopathic sideroblastic anemia progress to acute myeloid leukemia and, therefore, this may be considered as one of the preleukemic conditions.

Treatment: The primary cause, if identified, should be rectified. In the presence of overt pyridoxine deficiency small doses of pyridoxine (5-10 mg) are effective. Rarely even in the idiopathic variety large doses of pyridoxine given orally (100-500 mg/daily) are beneficial and, therefore, this should be given a trial. Concomitant folate deficiency should be corrected by oral folic acid 5 mg/day. In resistant cases symptomatic relief can be achieved with regular transfusion of packed erythrocytes.

Paroxysmal Nocturnal Hemoglobinuria (PNH)

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal stem cell disorder which leads to complement mediated haemolysis, deficiency and defect in hematopoiesis, and with a tendency to develop aplastic anemia later. Both sexes are affected. Though more common in middle age, all age groups may be affected. The name is derived from the fact that intravascular hemolysis being at night and hemoglobinuria occur more frequently in the morning intermittently. In addition to hemoglobin, hemosiderin is also present in urine. In PNH a clone of abnormal erythrocytes proliferates and co-exists with other normal erythrocytes. The erythrocyte membrane is abnormal, and several proteins are missing. The genetic defect is somatic mutation of the X-linked gene for phosphatidylinositolglycan protein A (GP1A). This protein is required for the production of glycerylphosphatidylinositol (GPI), which acts as an anchor which tethers several proteins to RBC surface, which protects the red-cell membrane from complement mediated damage. Biosynthesis of GPI is disrupted and this results in the

PNH phenotype. The biosynthetic defect always affects the transfer of glucosamine from UDP-N acetyl glucosamine on to phosphatidyl inositol. PNH is a unique disorder in which an abnormal clone or small number of abnormal clones expand to replace the whole hematopoietic stem cell pool, but they have no malignant potential as evidenced by normal processes and absence of invasion and metastasis.

Other proteins implicated in the pathogenesis of PNH include decay-accelerating factor (CD55) and CD59, absence of which will result in complement mediated red cell lysis.

Absence of complement regulatory protein leads to abnormal sensitivity to complement and results in complement mediated hemolysis. The surface abnormalities can be demonstrated by flow cytometry. The granulocytes also show complement mediated lysis whereas lymphocytes do not. Platelets show increased prothrombinase activity and this results in thrombotic tendencies. The erythrocytes undergo autohemolysis through the complement-mediated pathway with consequent reduction in complement levels.

Clinical Features

The condition presents as chronic anemia with or without jaundice, and splenomegaly.

Abdominal pain, dysphagia due to esophageal spasm, erectile failure and lethargy are attributable to intravascular hemolysis and the presence of haemoglobin in the plasma. Hemolytic episodes may be acute paroxysms or may be chronic. Hemolytic episodes may be precipitated by infections, drugs or transfusion of whole blood. Hemolysis leads to fall in serum levels of nitric oxide and this may be a direct reason for many of the symptoms. Haptoglobin efficiently combines with, and removes free haemoglobin from plasma. In PNH when intense haemolysis occurs the capacity of haptoglobin is exceeded and free hemoglobin circulates. Free hemoglobin is a scavenger of nitric oxide (NO). This avidly combines with nitric oxide NO and the fall in NO levels results in smooth muscle dysfunction and leads to symptoms in an acute paroxysm.

Venous thrombosis occurs in about 50% of cases. The intra-abdominal veins including the hepatic vein, and cerebral veins show predilection.

Other complications may develop during the course of the illness. These include aplastic crises and iron deficiency anemia due to loss of hemosiderin in urine. Presence of hemosiderin in urinary deposit can be demonstrated by Prussian blue staining.

Diagnosis of PNH is confirmed by **Ham's test** and **sucrose lysis test**. In the Ham's test the serum is acidified. PNH erythrocytes undergo accelerated hemolysis compared to normal, since acidification activates complement. PNH cells also show lysis in solution of sucrose. The gold standard diagnostic test is the analysis of GPI- linked molecules on the surface of hemopoietic cells by flow

cytometry. Absence of the CD55, CD59 and other antigens on these cells is diagnostic. Based on the number of missing antigens and their decrease, PNH can be graded as PNH I, PNH II, and PNH III in increasing order of severity.

Prognosis: Survival is 65% at 10 years and 48% at 15 years after diagnosis. Complication rate for pancytopenia, thrombotic events and myelodysplasia is 15%, 25% and 5% respectively when assessed at 8 years after diagnosis. Age above 55 years and occurrence of complications worsen the prognosis. Five percent may progress to develop acute leukemia. 15% may undergo spontaneous remission.

Treatment: In mild cases treatment is supportive with avoidance of offending agents. If hemolysis becomes active and anemia develops, transfusion of washed erythrocytes is given to tide over the crisis. Whole blood transfusion may precipitate a fresh bout of hemolysis due to the introduction of complement in transfused blood. In acute hemolysis corticosteroids may be beneficial. Androgens produce benefit in some. Anticoagulant therapy is indicated if thrombotic complications occur. Life-long anticoagulation may be necessary in a few. Eculizumab, an antibody with high affinity for C5 complement can reduce the hemolytic episodes as shown by clinical trials. Further studies are continuing.

Ref: Peter Hillmen et al The New Eng. J Med. 2006: 355, 1233-43.

Severe form of PNH is an indication for bone marrow transplantation.

Aplastic Anemia

Definition: Anemia resulting from failure to produce the formed elements of blood by the bone marrow is called aplastic anemia (AA). Morphologically in the vast majority of cases, the bone marrow is hypocellular or even totally acellular. Generally all the formed elements are affected though at times the affection may be selective.

Incidence: Aplastic anemia is a rare disorder contributing to 1-2% of the total number of anemias. Males suffer twice as many as females. The disease is primary (idiopathic) in over 75% of cases, in the rest it is secondary to known causes (Table 152.1).

PATHOPHYSIOLOGY

In this disorder the proliferation and differentiation of hemopoietic stem cells are deranged.

- 1. Loss of pluripotent stem cells.
- 2. Dysfunction of progenitor cells.
- 3. Defects in the microenvironment of the marrow.
- 4. Abnormalities of humoral regulators of hematopoiesis.
- 5. Autoimmune inhibition of hematopoiesis

TABLE 152.1 Causes of aplastic anemia	
Primary:	Acquired idiopathic Congenital (Fanconi's)
Secondary:	Chemicals and toxins including drugs
1. Agents which regularly produce bone marrow hypoplasia	
a. Anti-cancer drugs (busulphan, cyclophosphamide, and others)	
b. Ionizing radiations	
c. Benzene and its derivatives	
These damage the stem cell and arrest mitosis. If the damage is not severe, withdrawal of the drug is curative.	
2. Agents that occasionally produce bone marrow hypoplasia: chloramphenicol, sulphonamides, phenylbutazone, gold, thiouracil, anticonvulsants, antidiabetic agents, insecticides, industrial solvents, hair dyes, and several others	
These are not dose related. Many have an immunological basis. Withdrawal of the drug may not improve the marrow aplasia.	
3. Infections: Viral hepatitis (HCV), human parvovirus B19, chickenpox, miliary tuberculosis.	
4. Pregnancy	
5. Thymoma (autoimmune)	
6. Paroxysmal nocturnal hemoglobinuria (PNH)	
7. Systemic disorders such as chronic renal failure, hypothyroidism, and Addison's disease	
8. Autoimmune diseases such as systemic lupus erythematosus	
9. Hemophagocytosis syndrome	

In over 70% of cases, autoimmune processes lead to destruction of hemopoietic stem cells by autoreactive T-cells via Fas ligand in a HLA-DR restricted manner. It is also possible that basic stem cell defects may coexist since AA is more frequent in myelodysplastic syndrome and acute myeloid leukemia. The immune process may be triggered by factors such as viral infection, chemicals or drugs.

The marrow is reduced in volume; often it is yellow due to increase in fat. It is difficult to obtain a specimen and dry taps are common. In an ordinary case all the formed elements are reduced. Megakaryocytes, myeloid elements, and erythroblasts are progressively wiped out resulting in thrombocytopenia, neutropenia, and anemia as the disease evolves. The marrow shows pancytopenia. Unlike as in leukemias there are no abnormal infiltrating cells. There is no increase in reticulin. MRI may reveal the replacement of bone marrow by fat tissue.

In the final stage all cells are uniformly reduced. Due to reduction in granulocytes, the lymphocytes, plasma cells, and other reticuloendothelial cells may appear to be relatively increased.

CLINICAL FEATURES

The disease is insidious in onset. The peak age groups are 10-25 and above 60 years. Symptoms are slow in

onset, taking 1-2 months for manifestation. Sometimes bleeding and infection may set in early. Symptoms are due to the consequences of pancytopenia. Varying grades of anemia develop and often it is severe. Hemorrhagic manifestations occur due to thrombocytopenia. Common presentations are purpura, ecchymosis, epistaxis, bleeding from the gums, gastrointestinal bleeding, and vaginal bleeding. Bacterial infections occur due to neutropenia. These present with fever or other localised infections.

Hematological features: The erythrocytes, granulocytes, and platelets are all reduced, reticulocytes may be absent. In some cases granulocytes may be present in small numbers, but the young forms are considerably reduced. Erythrocytes are normocytic and normochromic with uniform size and shape. The bone marrow shows aplasia or hypoplasia. Stainable iron in the marrow may be increased.

Diagnosis: The picture of peripheral pancytopenia with aplastic bone marrow confirms the diagnosis. Bone marrow biopsy is essential in all cases, since it helps to rule out conditions like acute leukemia, myelodysplastic syndromes, lymphomas, multiple myeloma, and myelofibrosis which may superficially resemble aplastic anemia. Peripheral pancytopenia with normocellular or hypercellular marrow should suggest the possibility of aleukemic leukemia, sideroblastic anemia, dyserythropoietic states, myelodysplastic syndromes and paroxysmal nocturnal hemoglobinuria. Acute myeloid leukemia may be mistaken for aplastic anemia in the initial stages, but presence of splenomegaly is suggestive. Hypoplastic MDS is diagnosed by the presence of cytopenias, hypocellular bone marrow and definite dysgranulopoiesis and dysmegakaryopoiesis in addition to dyserythropoiesis. In AA the marrow is uniformly hypoplastic (Fig. 152.3) whereas it may not be so in MDS. The proportion of CD34+ cells is below 0.3% in AA whereas it is normal (0.5 to 1%) or higher in MDS.

Paroxysmal nocturnal hemoglobinuria (PNH) may lead to clinical AA, this has to be distinguished by appro-

priate tests such as demonstration of hemosiderinuria, Ham's acidified serum test, sucrose lysis test and demonstration of the PNH clone. Some cases of PNH present initially as aplastic anemia, their true nature becomes evident only later during the course.

Differential diagnosis includes thrombocytopenic purpura, agranulocytosis and hemolytic anemia with aplastic crises. In immune thrombocytopenia, the marrow shows increase in the number of megakaryocytes. In agranulocytosis only the granulocyte precursors are diminished. Other elements are normal. In hemolytic anemia with aplastic crises, erythroid precursors are selectively depressed. Pure red cell aplasia has to be distinguished from aplastic anemia. Death is due to severe anemia, bleeding or infection.

Course and prognosis: The course is variable in aplastic anemia and the course may extend for periods ranging from a few months to even years. Severe cases have particularly grave prognosis and the median survival is less than 4 months. Early response to therapy is a favourable sign. About 80% of nonresponding patients die within 3-4 months. Life can be prolonged for several years by proper substitution therapy.

The criteria for assessing severity are given below:

1. Marrow with cellularity below 25% of normal or cellularity below 50% of normal with less than 30% made up of hemopoietic cells.
2. Two of three of the abnormal peripheral blood values:
 - a. granulocytes below $0.5 \times 10^9/L$,
 - b. platelets below $20 \times 10^9/L$, or
 - c. anemia with reticulocytes corrected for hematocrit less than 1%.

MANAGEMENT

This consists of: (1) withdrawal of the offending agents; (2) supportive measures to compensate for the pancytopenia and prevent complications; and (3) positive attempts to restore bone marrow activity. Supportive measures include transfusion of blood or packed red cells, platelets, and granulocytes. The patient should be isolated and care should be taken to prevent cross infection from attendants and endogenous infections by the commensal flora. Infection should be diagnosed early and treated with bactericidal antibiotics.

Effective treatment of primary aplastic anemia consists of two modalities

1. Immunosuppression and
2. Bone marrow transplantation or peripheral blood stem-cell transplantation.

Both are effective in about 70% of cases. Cases which do not respond to immunosuppression may be benefitted by subsequent bone marrow transplantation (BMT).

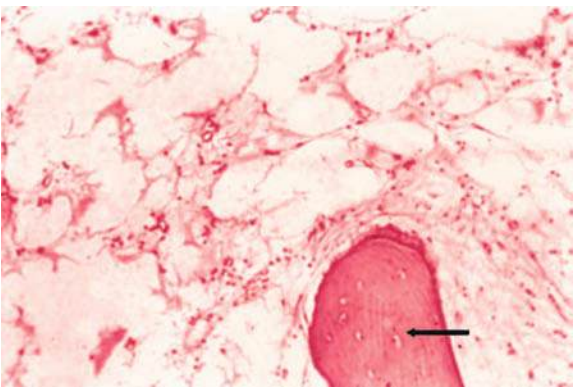


Fig. 152.3: Aplastic anemia – Bone marrow. Note: (1) Reduction in cellularity (2) Increase in fat spaces and (3) arrow points to a spicule of bone

Immunosuppression : This is the first line of treatment. Antithymocyte globulin (ATG) causes effective immunosuppression. This is the treatment of choice – Both horse ATG and rabbit ATG are available, depending on the source of production.

ATG contains polyclonal IgG₁ antibodies specific to interleukin-2 receptor, which is present on activated lymphocytes. ATG reacts with T-cells, B-cells, NK cells, monocytes macrophages and dendritic cells. It acts on neutrophils and platelets and reduces their levels in blood. Cell migration, adhesion and apoptosis of immunocytes are modulated by ATG to produce profound immunosuppression. This leads to greatly increased susceptibility to infection. The dose is 40 mg/kg/bw IV infusion slowly for 4-14 days or till the lymphocyte count dropped to 200/cmm. Immediate side effects include rigor, rash and dyspnea. Serum sickness like reaction may develop. This is controlled by corticosteroids. Lymphopenia, neutropenia and thrombocytopenia develop later. Infections are common, occurring in about 80%. These have to be anticipated and managed.

Patient has to be nursed with strict aseptic precautions. Adjuvants to ATG include hydrocortisone or methyl prednisolone initially given IV, later replaced by oral corticosteroids. Cyclosporine, given in a dose of 3-4 mg/kg bw orally acts synergistically.

When ATG is not available immunosuppressants like cyclosporine or high dose cyclophosphamide can be given, but success rate is slightly less. Complete response is defined as normalisation of hemoglobin, neutrophil count above 1500/cmm and platelets above 150,000/cmm.

The cost of a course of ATG is around Rs. 150-200000. The Indian experience on the treatment of aplastic anemia using ATG is given in Table 152.2.

ATG manufactured in India is much less expensive than other brands.

Bone marrow transplantation (BMT)- Transplantation of HLA compatible donor marrow is effective in 50-60% of cases of severe AA, especially if the recipient is below 40 years of age. Long-term survival is achieved in those who get successful graft.

Peripheral blood stem cell transplant can be done with success and it is being increasingly used. Whereas severe cases respond only to immunosuppression therapy or BMT, milder cases can be kept reasonably active and asymptomatic by supportive therapy and immunosuppression with high dose cyclophosphamide 0.5-1g/m² body surface once a month. Previously, nonvirilising semisynthetic androgens such as oxymethalone in doses of 2-3 mg/kg bw orally for three months were used. This did produce clinical and hematological benefit in 50-60% of cases, though complete response was not achieved in all patients. Corticosteroids have been used, but at present these modalities are not employed if immunomodulation therapy and/or stem cell restitution is available.

Vast majority of mild and moderate cases respond partially, to reach symptom-free state, and they are able to lead almost normal lives. Some of them get cured on long-term follow up. Therefore the prognosis in such cases has to be guarded.

Secondary aplastic anemia may respond to the treatment of the primary condition and appropriate use of hematopoietic cytokines.

Points to remember

1. AA is not uncommon in India
2. Precise diagnosis of the type and possible mechanism is essential for proper management
3. Severe AA is as fatal as acute leukemia, if untreated. Immunosuppressive therapy, appropriate replacement of blood cell components and marrow transplantation are highly successful.

Special Forms of Aplastic Anemia

The term constitutional aplastic anemia is used to denote congenital, genetic, or familial aplastic anemias.

Fanconi's Anemia

Syn: Congenital pancytopenia

In this syndrome congenital abnormalities like hyperpigmentation, absence or hypoplasia of the thumbs and radii, strabismus, mental retardation, deafness and dwarfism are seen. Pancytopenia and bone marrow hypoplasia develop by the age of 5-10 years. Untreated, the mortality is high (Fig. 152.4).

Fanconi's anemia (FA) is an autosomal recessive disorder characterised by developmental abnormalities, bone marrow failure and cancer predisposition; especially squamous cell carcinoma and acute myeloid leukemia.

It is usually lethal by the age of 20 years. The underlying defect in Fanconi's anemia is not fully known. Cultured fibroblasts from these patients show increased generation time and increased cell death. More than 8 groups of FA have been distinguished genetically (termed FA-A to H), each carrying a distinct genetic lesion. Germ

TABLE 152.2

Showing Indian experience in the treatment of aplastic anemia

Therapy	Response in ordinary cases	Response in severe AA
ATG alone	40.2%	30.6%
ATG + cyclosporine	68.5%	58.7%
Cyclosporine alone	28.3%	16.2%

Ref: Agarwall MB ATG (Thymogam) - The Indian experience; Haemato-oncoscan 2005, published by Bombay Hospital-Mumbai 2005



Fig. 152.4: Fanconi's anemia, boy aged 12
Note hypoplastic thumb left hand

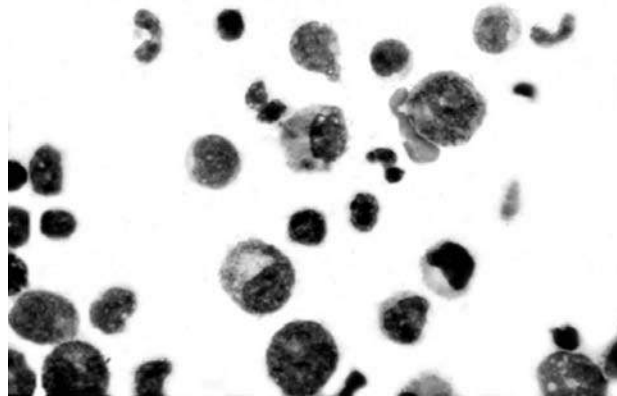


Fig. 152.5: Bone marrow pure red cell aplasia
Note the reduction in erythrocyte precursors

line mutations in six different genes have been identified. Cell lines established from FA patients show two unique characteristics

1. Accumulation of broken and mishapen chromosomes that originate from DNA replication.
2. Increased sensitivity to the action of DNA cross linking agents like mitomycin-C which trigger chromosomal abnormalities.

Leukopenia and thrombocytopenia precede pancytopenia. Fetal hemoglobin level is elevated.

The diagnostic laboratory test is the chromosomal breakage analysis using metaphase preparations of phytohemagglutinin stimulated peripheral blood lymphocytes. Spontaneous chromosome breakages are demonstrable in up to 70% of lymphocytes and 25-50% fibroblasts. Such an abnormality is not present in Diamond-Blackfan syndrome. Prenatal diagnosis is possible by chromosome breakage studies done by chorionic villus sampling at 9-12 weeks gestation, amniocentesis at 16 weeks or by fetal blood sampling done later.

Treatment

Anabolic Steroids

Mild cases may benefit by the administration of anabolic agents such as oxymethalone 2-3 mg/kg bw given orally for 2-3 months. Adverse side effects such as virilisation and fluid retention may develop. Blood component therapy may be required for symptom relief. Bone marrow transplantation from HLA matched normal donors is curative. Umbilical cord blood is a good source of stem cells for transplantation.

PURE RED CELL APLASIA

This is a rare form of aplasia selectively affecting the erythroid precursors, reticulocytes and red cells; the other formed elements and their precursors being normal. Usually the onset is insidious. If red cell aplasia supervenes on hemolytic states where the life-span of the

red cell is considerably shortened the onset is much more rapid and the condition is more serious. This is what happens in sickle cell anemia and other acquired or inherited hemolytic anemias when aplastic crises develop as a result of parvovirus B19 infection.

The patient presents with severe anemia without any bleeding tendencies or infective episodes. Reticulocytes are very low, often absent. Bone marrow shows pure aplasia of the erythrocyte progenitors (Fig. 152.5). Most cases are transient and they recover spontaneously or with treatment. Some follow a prolonged course and end fatally.

Etiology: Majority of cases are immune mediated and various autoimmune mechanisms have been postulated. Antibodies against erythroblasts and erythropoietin may develop and selectively suppress and destroy them. T-cells may produce selective cytokines inhibiting erythroid precursors or leading to their lysis. Another mechanism is loss of MHC class 1 expression on the erythroid progenitor cells which become increasingly susceptible to destruction by NK-T lymphocytes. Autoimmune PRCA may be primary (idiopathic) or secondary. Secondary PRCA may be due to:

- a. Infections —parvovirus B19, AIDS
- b. Autoimmune diseases like rheumatoid disease and systemic lupus erythematosus
- c. Neoplasms such as thymoma, lymphoma or carcinoma
- d. PRCA may be a preleukemic or pre myelodysplastic manifestation and
- e. PRCA may be drug induced

Prolonged use of erythropoietin in chronic renal failure may lead to development of neutralising antibody against erythropoietin, by about one year after the start of therapy. These cases present as PRCA. Treatment with corticosteroids, other immunosuppressant and IV immunoglobulins is successful.

Occasionally ABO incompatibility between donor and recipient of bone marrow transplantation or stem cell transplant can lead to antibody mediated PRCA.

PRCA has to be differentiated from aplastic anemia, in which all the blood cell precursors are affected. Early stages of myelodysplastic syndrome may produce diagnostic difficulty. In MDS, dysplasia is evident in all cell lines.

Management: Transient cases are self-limiting in prolonged anemia with evidence of parvovirus infection and immunological processes, steroids, immunosuppressants such as cyclosporine or mycophenolate mofetil are beneficial. In intractable cases intravenous immunoglobulin in a dose of 0.4g/kg bw for 6-8 days is effective. In those with thymoma, thymectomy is curative. In those with other underlying disorders, treatment of the primary disease relieves the PRCA as well.

RED CELL APLASIA IN CHILDREN

Syn: *Diamond-Blackfan anemia, Congenital hypoplastic anemia, Chronic congenital aregenerative anemia, Erythrogenesis imperfecta.*

This is a form of congenital anemia developing in infancy or in early childhood. The children develop normocytic anemia (at times macrocytic) caused by selective aplasia of erythroid precursors beyond the stage

of pro-erythroblasts, and reticulocytopenia. Leucocyte and platelet counts and their precursors are generally normal. 75% of cases are sporadic, 25% show inheritance patterns. Both dominant and recessive inheritance has been identified. Chromosomal abnormalities, mainly involving chromosomes 19 and 13 (translocation or deletions) have been reported. Congenital abnormalities occur in about 30%. These include short stature, atrial or ventricular septal defects, urogenital abnormalities, facial abnormalities and others. Fetal hemoglobin level may be increased.

Management consists of symptomatic measures in mild cases. Severe cases require bone marrow or stem cell transplantation.

Transient Erythroblastopenia of Childhood (TEC)

This is an acquired form of PRCA in previously healthy children. TEC occurs in children older in age than Diamond-Blackfan anemia even though the majority is below one year of age. Possible causes include viral infections, or autoimmune mechanisms as in adults. The condition is generally benign with spontaneous recovery within 4-8 weeks. Management is symptomatic.

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Blood Transfusion

K.V. Krishna Das

Chapter Summary

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General Considerations

Transfusion medicine has become a major speciality encompassing several subspecialties such as immunohematology, blood banking, component preparation, genetic studies and so on. Many of the present day state-of-the-art technologies such as complicated cardiac surgery, other major surgical procedure, traumatology, organ transplantation, cancer chemotherapy, management of haematological and immunological disorders, prenatal and neonatal interventions and several

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others owe their existence and development to sound transfusion medicine practices. The present day problems of transfusion transmitted infections including AIDS have given further impetus to the growth of this speciality.

Blood Group Antigens

The outstanding landmark in the history of blood transfusion is the discovery of human *ABO blood group system* in 1900 by Landsteiner. He differentiated human blood into four distinct groups on the basis of two antigens A and B.

Following the discovery of the ABO system in 1900. Landsteiner and co-workers described further blood group systems. The human MN and P antigens were described, but those systems seemed to have only little clinical importance. In 1937, Landsteiner and Wiener discovered the rhesus factor by a new method.

Subsequent workers have identified several other antigens present on the red cell surface and these form the basis of blood grouping.

On the basis of different antigens about 15 different red cell blood group systems are known with wide distribution in different radical groups. These are ABO, MNSs, P, Rh, Lutheran, Kell, Lewis, Duffy, Kidd, Diego, Yt, Xg, Ii, Dombrack, and Cotton system. Except Xg system which is determined by genes on the X chromosome all the others are determined by genes located on autosomes.

Among all the different blood group antigens ABO system and Rh system are the most important in clinical transfusion practice. The others which are less prevalent assume importance when dealing with hemolytic states developing in multiply transfused individuals and while cross-matching blood for patients who may require life-long transfusion therapy.

Antibodies

Two types of antibodies against red cell antigens occur. These include:

- 1. **Naturally occurring antibodies:** which develop even without external antigenic stimulus, e.g. anti-A and anti B. These antibodies which are present in the serum are directed against antigens which are not present on the red cells of the same individual.
- 2. **Immune or acquired antibodies:** These develop as a result of immunisation by a red cell antigen which is foreign to the same individual. These develop as a result of mismatched transfusion or pregnancy, e.g. Rh antibodies, ABO antibodies. All red blood cell antigens are capable of stimulating antibody production, but some such as Rh antigen are more powerful than others.

In addition to red cell antigens other immunising antigens such as tetanus toxoid, TAB vaccine,

pneumococcal vaccine and others which contain substances closely mimicking A and B antigen do stimulate the production of immune anti-A and anti-B antibodies. These assume clinical importance in persons who have been repeatedly immunised against infections.

Naturally occurring red cell antibodies belong to IgM class and they react best at temperature below 37°C. In contrast immune antibodies are mainly IgG or IgM and their optimal temperature for reaction is 37°C. Immune antibodies produced early during the process of immunisation are IgM class, whereas the antibodies produced long-term are IgG. IgM does not cross the placenta whereas IgG readily crosses it.

Antibodies are detected in the laboratory by four types of tests:

- 1. Saline agglutination
- 2. Agglutination in colloid solutions-albumin
- 3. Tests using enzyme treated cells
- 4. Indirect antiglobulin test (Coombs')

Complete antibodies are detectable by saline agglutination. Incomplete antibodies are detectable by the other three methods. The various immune antibodies behave differently in the various tests. Their detection and cross-matching in their presence involve very delicate and highly developed laboratory techniques.

Blood group systems form the cornerstone of transfusion medicine. The study of blood groups help to:

- 1. Perform blood banking
- 2. For anthropological studies
- 3. Performance of medicolegal investigations in paternity disputes, and
- 4. To correlate with prediction of diseases. Several diseases show associations with particular blood groups (Table 153.1).

TABLE 153.1
Distribution of ABO blood groups in the Caucasian population and Indians

Blood group	Caucasian	Indian
O	47%	40%
A	42%	22%
B	8%	33%
AB	3%	5%

Blood Group Systems

ABO system: This comprises of the four main blood groups A, B, AB and O designated according to the presence or absence of A or B antigens on the red cell surface. In the O group there is neither A nor B antigen. In addition to the presence of the antigen on the red cell surface, in the natural state itself the plasma contains antibodies against the A or B antigen that is not naturally present in the same individual (Table 153.2).

TABLE 153.2

Antigens and antibodies present in each of the four main groups of the ABO system		
Blood group	Antigen in red cell	Antibodies in plasma
O	Nil	Anti-A, anti-B
A	A	anti-B
B	B	anti-A
AB	A and B	Nil

The formation of the A and B antigen is controlled by three allelic genes A, B and D located on the long arm of chromosome 9. The A and B genes are codominant. O gene is an amorph (i.e.) it has no effect on antigenic structure. Another gene, the H gene controls the formation of a precursor H substance which is present in the serum. Action of A and B genes leads to the formation of A and B antigen and in the process the H-substance is consumed. The O genes does not act on the H substance therefore O group individuals have higher levels of H-substance in the serum. Conversely AB group individuals have the lowest levels of H-substance. Very rarely some O group subjects not possessing the H-substance in the serum develop antibodies against H-substance as well. There are several subgroups of A, among which A₁ and A₂ are important. 80% of A group subjects possess A₁ and 20% possess A₂. Correspondingly AB subjects also fall into the subgroups A₁B and A₂B. Compared to A₁, A₂ cells react only weakly with the antiserum. It is therefore necessary to use strong antisera which will agglutinate both A₁ and A₂ cells in order to detect A₂ subtypes. Rarely A₂ subgroups persons may produce anti-A₁ antibody which can destroy transfused A₁ cells.

The Bombay blood group: O group individuals normally possess serum antibodies against A and B antigens only. O group individuals who have antibodies against H-substance are designated as the Bombay blood group, being described first by H.M. Bhatia and his colleagues from the Blood Group Reference Centre, Bombay.

Secretors are individuals who secrete these blood group substances or antigens in the body secretions (80%) whereas non-secretors are those who do not secrete blood group antigens in body secretions (20%). For purposes of testing saliva is examined (Table 153.3).

TABLE 153.3

The specific ABH substances present in the saliva of secretors	
ABO group of red cells	Soluble antigen in saliva
O	H
A	A and H
B	B and H
AB	A, B and H

Rhesus system (Rh system): Next in importance to the ABO system are the Rh antigens. The Rh antigens (C, c, D, d, E and e) are inherited through three closely linked allelic genes C or c, D or d and E or e, located on chromosome 1. One set of three genes is inherited from each parent giving rise to various combinations of genotypes e.g. CDE/CDE or CDe/CDe. The antigens produced by the genes are given similar notations. All the genes except d express their corresponding antigens, while 'd' being an amorph, there is no 'd' antigen.

Among these antigens the presence or absence of D antigen is most important and Rh+ and Rh-ve are decided by the presence or absence of 'D' antigen.

Among caucasians 85% are Rh positive and 15% are Rh-ve. Among Indians 4-10% (average 7) are Rh -ve. A study from Bangalore in 2001 gave the prevalence of Rh +ve as 94.25% and Rh -ve as 5.75%.

Unlike the ABO blood groups antibodies to the missing Rh-antigens do not occur naturally, but Rh-ve persons can be allo-immunised to produce anti-Rh antibodies on challenge with the foreign Rh antigen obtained either through transfusion or during pregnancy, See Rh hemolytic disease pp 1002.

Leukocyte groups: HLA antigens are present on the surface of granulocytes and lymphocytes. ABO antigens may be present on lymphocytes and possibly, granulocytes, in very small quantities.

Platelet groups: ABO, HLA-A, HLA-B, and HLA-C are present on platelet surface in addition to several other platelet specific antigens. Platelet antibodies may be detectable in multitransfused persons and these shorten the life-span of transfused platelets.

Lewis system: These antigens are glycosphingolipids which are produced in the plasma and are absorbed to the red cell surface. There are two subtypes Le-a and Le-b. Though they are independent systems, often they interact with other systems. This system does not lead to hemolytic diseases of the newborn.

Ii blood group system: This system consists of two antigen I and i. At birth the neonatal red cells are rich in i antigen and are low in I. There is a gradual change over from i to I antigen up to the age of 2 years. In some persons this change over may not take place and i antigen predominates. In hemoglobinopathies and dyshemopoietic states also, the red cells may contain more of i antigen.

MNS system: This system is made use of for anthropological and genetic studies and for medicolegal purposes. This group is not generally responsible for hemolytic anemia.

Blood Bank Procedures

These include: (1) Collection of blood, (2) preservation of blood, (3) separation of components, (4) cross-matching, and (5) monitoring the adverse reactions.

At present blood is collected in citrate phosphate dextrose with adenine (CPD A₁) solution. In this medium the blood can be stored for 35 days.

ABO and Rh groupings may be done by slide method, tube method, or tile method using specific known antisera and red cells. Detection of incomplete antibodies in the serum and red cells is done by the indirect Coombs' test and direct Coombs' test respectively.

Indirect Coombs' test: This is used for detecting the presence of incomplete antibodies in the serum, e.g. Rh antibodies or antibodies in autoimmune hemolytic anemia. The test serum is incubated with saline washed O group Rh positive cells for one hour at 37°C, washed, and a 2% suspension of the sensitised washed red cells is made. One drop of washed cell is mixed with one drop of Coombs' serum and examined for agglutination by microscopy. A positive test indicates the presence of antibody in the test serum.

Direct Coombs' test: It is done to find out whether the cells are already sensitised by an incomplete antibody *in vivo*. The washed red cells are suspended in saline and one drop of Coombs' serum is added to one drop of red cell suspension. Agglutination indicates that the cells are already sensitised by the antibodies *in vivo*.

Indications for Transfusion (Table 153.4)

- 1. Replacement of whole blood—Sudden loss of 30% of the blood volume (1.5 L) demands urgent replacement.
- 2. Specific components are indicated under special circumstances when there is selective deficiency of these components.

Examples

Anemia	Packed erythrocytes
Thrombocytopenia	Platelets
Fibrinogenopenia	Fibrinogen
Hypogammaglobulinemia	Gammaglobulin
Hypoalbuminemia	Albumin
Deficiency of clotting factors	Coagulation factor concentrates

Many of the coagulation factors are produced by recombinant DNA technology at present.

Present policy is to separate blood into its components such as erythrocytes, plasma, coagulation factor concentrates, platelets and fibrinogen and give them selectively when indicated. These components are useful for specific indications. Whole blood is given mainly for replacement of extravasated blood. Plasma fractions are coagulation factor concentrates, immunoglobulins, and albumin. In many situations specific component therapy is more effective and safer than whole blood. Component therapy serves to raise the missing coagulation factor rapidly and predictably with a small volume of the concentrated material. In many cases the exact dose to be transfused can be calculated so that the coagulation factor level can be raised to the desired level and maintained for long periods depending on the specific requirement.

Collected whole blood retains all the stable coagulation factors for 7 days. The labile factors disappear rapidly and only 30% of factors V and VIII will be present in stored blood. RBC maintains their oxygen carrying capacity for 7-10 days, after which the oxygen dissociation curve shifts to the left due to reduction in the levels of diphosphoglycerate. Platelets lose their viability rapidly, unless stored under special conditions. Granulocytes undergo degeneration and become non-functional after 24 hours (Table 153.5).

The term '**massive transfusion**' refers to the transfusion equal to the patient's blood volume within 24 hours.

At present donor blood is collected in polythene bags. By using appropriate bags a single unit of blood can be fractionated into packed red cells, platelet concentrates and plasma. From the plasma further preparations such as cryoprecipitate, fibrinogen and coagulation factors are produced. Erythrocyte fraction is also processed further.

Erythrocyte Preparations

- 1. Packed cells with or without the buffy coat
- 2. Partially packed red cells
- 3. Washed red cells
- 4. Frozen red cells
- 5. Leukocyte-poor and platelet-poor red cells

TABLE 153.4

Blood components: Use and abuse		
Component	Indications	Abuse
Red cells	To increase oxygen carrying capacity in anemic patients	a. as a volume expander b. to improve general "well-being"
Platelets	To control or prevent bleeding associated with deficiencies in platelet number or function	a. Routine treatment of immune thrombocytopenic purpura b. Prophylactically in other conditions
Fresh frozen plasma	As a replacement of clotting factors when specific deficiency is demonstrated	As a simple volume expander

TABLE 153.5

The storage requirements and shelf-life of blood products

Blood product	Storage specification	Shelf-life
1. Red cells	2-6°C	35 days
2. Frozen red cells (reconstituted)	2-6°C	24 hours
3. Washed red cells	2-6°C	6 hours
4. Granulocyte concentrates	Room temperature	24 hours
5. Platelet concentrates	Room temperature with agitation	5 days
6. Fresh frozen plasma	-20-40°C	12 months
7. Cryoprecipitate	-20-40°C	12 months

Platelets: These are frequently used to tide over periods of thrombocytopenia occurring during anti-cancer chemotherapy, naturally occurring disease such as thrombocytopenia and thrombocytopathy and to prevent excessive bleeding during and after surgery on thrombocytopenic individuals.

The original method was to concentrate platelets by centrifugation of freshly collected blood. This preparation has the disadvantage of lower yield of platelets and presence of excessive amounts of leukocytes and plasma. Moreover several donors have to be recruited for optimal therapy.

Present method is to separate platelets by apheresis in a cell separator from a single donor. On an average 5×10^{11} platelets are removed in each sitting. Platelets lose their ability to aggregate if stored at refrigerator temperature. They can be stored at room temperature for up to five days with constant shaking in order to facilitate gas exchange. Infused platelets may remain viable in the system for short periods. Presence of antibodies directed against class I HLA antigens on platelet surface, or specific antiplatelet allo-antibodies developing as a result of repeated transfusions result in rapid destruction of transfused platelets.

This can be avoided to some extent by making the platelet concentrate as pure as possible without admixture of leukocytes. Another method is to expose the platelet concentrate to ultraviolet light, which inhibits lymphocyte function while sparing platelet function.

Indications for Platelet Transfusion

- 1. Prophylactic in bleeding thrombocytopenic patients when the platelet count is < 50000/cmm
- 2. In head injury when platelet count is < 100000/cmm
- 3. ITP when other measures do not help to bring up the platelet count and arrest bleeding
- 4. ITP with pregnancy when the maternal and fetal platelet counts are low

- 5. In cancer chemotherapy when iatrogenic thrombocytopenia is likely
- 6. In leukemia patients when platelets count is < 20000/cmm.

Platelets can be administered as platelet concentrates obtained by apheresis using a cell separator from single donor or as platelet rich plasma (PRP). 1 unit of PRP raises the platelet count by 5000-10000/cmm. 1 unit of platelet concentrate obtained by apheresis is equivalent to 6-8 units of PRP.

Fresh frozen plasma (FFP): This is prepared from fresh blood by separating and freezing the plasma within 6 hours. It can be stored at -20°C or below for up to one year. The volume of one unit of FFP is 200-250 mL. It contains mainly factors V and VIII, but other factors as well. It is indicated for bleeding in multiple coagulopathies, liver disease, DIC, and bleeding due to massive blood transfusion as a first time therapy.

Cryoprecipitate: This is prepared from single donor plasma, by controlled precipitation from fresh plasma, at 4°C. It is rich in factors VIII, von Willebrand's factor, factor XIII, fibrinogen and fibronectin. Before transfusion it is thawed at 30°C. 1 mL of cryoprecipitate contains 10 units of factor VIII compared to 1 unit/mL in FFP. The dose of cryoprecipitate is 1 unit for every 10 kg body weight.

Plasmapheresis: In this process only plasma is removed from the donor. Plasmapheresis can be used as a therapeutic measure to treat circulatory overload, hyperviscosity syndromes, or for removal of circulating immunoglobulins and immune complexes. This method is also employed to obtain high titre immune globulins from suitable subjects.

Hazards of Transfusion Therapy

Febrile reactions: These are caused by pyrogenic substances present in the material or in the infusion set. Sometimes these indicate bacterial contamination.

Allergic manifestations: Allergic reactions like urticaria and edema may occur due to antigen antibody reactions.

Bacterial contamination: If the blood is heavily infected, severe reactions set in even with the introduction of a small quantity of blood. Shock may ensue which may be followed by disseminated intravascular coagulation (DIC).

Mechanical complications: Circulatory overloading, air embolism, thrombophlebitis and pulmonary embolism may develop if the infusion is not carefully supervised.

Metabolic complications: These develop due to citrate toxicity, potassium toxicity, toxic substances eluted from synthetic containers, and vasoactive substances, especially after massive transfusion.

Hemolytic reactions: These reactions usually develop due to the presence of incompatible antibody in the recipient's plasma which cause destruction of donor red cells. Less commonly potent antibodies such as anti-A or anti-B present in donor plasma may react with the homologous antigens present in the recipient's red cells and provoke hemolysis.

Hemorrhagic reaction: This complication may be encountered after massive transfusions using stored blood.

Immune reactions: Various types of immunological reactions may develop varying in severity from fatal to mild symptoms. Among this, hemolytic reactions due to transfusion of incompatible blood or hemolysed blood are the most common. This manifests with pain in the back, dyspnea, and circulatory collapse. At times persistent hypotension may be the only finding. In severe cases jaundice, hemoglobinuria, and anuria develop within 24 h. Renal failure may be fatal. Rarely DIC may follow ABO incompatibility.

Non-hemolytic reactions: These may vary from simple allergic reactions to fatal anaphylaxis. Antibodies to drugs such as penicillin may be present in the donor's blood causing allergic reactions in the recipient.

Transmission of disease: Several diseases are transmitted by blood. These are hepatitis viruses (virus B, hepatitis C and others), cytomegalovirus, EB virus, syphilis, brucellosis, malaria, trypanosomiasis, and acquired immunodeficiency syndrome (AIDS). HCV seropositivity among blood donors in Punjab was 0.78% and that of HBs Ag was 1.7%. The infectivity of *T. pallidum* is lost on storing the blood at 4°C for five days or more. Detection of infection in the donor should exclude him from blood donation. Most of the blood banks in India insist on tests for syphilis, viral hepatitis and AIDS. Recent reports from several parts of India show a downward trend in the prevalence of hepatitis B and C, HIV and syphilis.

occasions at 5 days interval when estimated at 14-180 days after the transfusion.

3. Other viruses: Human T-cell lymphotropic virus (HTLV) I and II, cytomegalovirus (CMV).
4. Parasitic infections: Malaria, trypanosomiasis, toxoplasmosis, babesiosis.
5. Bacterial infections: *Yersinia enterocolitica*, *Staph. epidermidis*, *Bacillus cereus*, syphilis and others.
T. pallidum can remain viable in refrigerated blood for up to 5 days.

The risk of infection from needle stick injuries to medical personnel handling infective blood is given below:

HIV	3/1000
HBV	30%
HCV	1.2-10%

The rates are much higher if infected blood is transfused.

Apart from extreme care in selecting donors, proper methods to sterilise the equipment are absolutely essential to avoid microbial contamination of the blood and blood products and infection of the medical and laboratory personnel. Common norms to be followed include:

1. Proper handwashing before and after handling every patient.
2. Use of protective gloves.
3. Use of mask and eye-protectors when blood or body fluids are likely to splash.
4. Handling all infective fluids and tissues with the same precautions as for blood, e.g., semen, vaginal and cervical secretions, amniotic fluid, cerebrospinal fluid, other aspirated fluids, saliva, tissues and organs including the cornea.

Disinfection

Most of the disinfectants available in India are capable of destroying almost all microbes including HIV, if used properly. Since blood and tissue fluids will protect the microbes embedded within them, they have to be properly cleaned before applying the chemical disinfectant. The following disinfectants are amply effective in the recommended dosage.

1. Chlorine releasing compounds.
2. Iodine compounds—povidine iodine 1% strength.
3. Ethyl alcohol 70% (denatured spirit)
4. Cetrime (Savlon) 1/1000 solution.
5. Dichloroxylenol (Dettol) 1.5% solution.

Gamma Irradiation of Blood

Transfusion associated graft-vs-host disease is a rare immunological complication caused by the presence of immunocompetent T-lymphocytes in the donor blood. Gamma irradiation of blood and blood products prevents this complication.

Transfusion Transmitted Diseases

1. **Viral infections**
 - a. Human immunodeficiency virus HIV I and HIV II.
Data from Delhi gave seroprevalence for HIV rate as 0.71 to 0.77% for blood donors. In Trivandrum the seroprevalence of HIV is 0.2%. In Punjab it was 0.26%.
2. **Hepatitis viruses**

All the hepatitis viruses HBV, HCV, delta virus, HAV, HGV and HEV can be transmitted. HBV and HCV are clinically the most important in this group. The approximate risk for transfusion associated hepatitis in India for HBV is 0.07% and for HCV is 0.04%. Transfusion associated hepatitis (TAH) should be diagnosed if there is elevation of SGPT levels in the recipient to 1.5 times the normal value or more, on two

Hemosiderosis: In subjects receiving repeated transfusions iron overload may occur leading to deposition of iron in reticuloendothelial and parenchymal tissue. Usually this complication is seen in persons who have received 100 units or more of blood.

Each unit of 250 mL of erythrocytes introduces 250 mg of elemental iron into the recipient. The end organ manifestations of iron overload include cirrhosis, hepatocellular carcinoma, cardiac failure, diabetes mellitus and hypothyroidism.

Autotransfusion: This is the use of blood collected from the patient for use at a subsequent occasion such as selective surgery. Several units of blood can be collected from the patient at regular intervals preceding the surgical procedure, to be used at the time of need. Stimulation of erythropoiesis by erythropoietin and nutritional supplements helps to increase the yield of blood. Autotransfusion is safe and it is free from several of the drawbacks of external blood.

Any reaction occurring in the patient within 48 h of transfusion should be reported to the blood bank. Whenever there are good grounds for suspecting any untoward reaction the transfusion should be discontinued, and the patient should be monitored. The blood sample should be taken for tests.

CORD BLOOD TRANSFUSION

Use of blood collected from the umbilical cord after delivery as a source of stem cells has become an established procedure within the past 15 years. Cord blood contains large number of granulocyte-macrophage progenitor stem cells, sufficient enough to re-populate marrows of irradiated subjects. This has paved the way for organised cord blood banking. There are several blood banks undertaking storage and delivery of cord blood, all over the developed countries. In India there are a few privately-owned cord blood banks. Cord blood can be cryopreserved in the viable state for many years. The services provided include:

1. Use of cord blood as a source of stem cells and
2. Preservation of the cord blood indefinitely for long periods, for use in the same individual if a need for stem cells arises. The donor is charged for this service.

Uses of Cord Blood

1. Allogenic transplant
2. Autologous transplant
3. As a source of pluripotent stem cells for reconstitution and repair of damaged tissues such as the heart, after myocardial infarction.

The immunological properties of cord blood stem cells differ from those of adult marrow or peripheral blood.

Cord blood contains a higher proportion of T-cells expressing (C D 45 R A +/ C D 45 R A O-) and

CD 62 L+. These cells are immunologically naive and therefore graft versus host disease is less common. The chemokine receptor C C R5 expressed by Th-1 T lymphocytes is less abundant in cord blood T-cells compared to adult T-cells.

Cord Blood Banking

Pregnant women are recruited as donors after obtaining informed consent, and excluding common communicable diseases. Blood is collected from the placental side of the severed umbilical cord either in utero before the delivery of the placenta or ex-utero after its delivery. Long-term storage is done under temperatures below -180°C and released for use on demand after proper cross-matching.

Indications for Cord Blood Transfusions

- a. Stem cell replenishment in hematological malignancies—acute leukemias, chronic myeloid leukemia and myelodysplastic syndrome.
- b. Non-malignant conditions—aplastic anemia, thalassemias, hemoglobinopathies, immunodeficiency states.

Advantages of cord blood are its availability, lower incidence of graft versus host disease (GVHD) and good success rate even if mismatched for two antigens. The waiting period for transplantation is also shorter. Disadvantages are the higher infection rates with cord blood stem cells, compared to preparations from bone marrow or peripheral blood from adult donors.

Future strategies for improving the service include:

1. Pooling of cord blood
2. Cord blood expansion using cytokines which stimulate stem cell proliferation
3. Combining cord blood and haplo-identical bone marrow transplants
4. Non myeloablative or reduced intensity conditioning regimen.

BLOOD SUBSTITUTES

Several attempts have been made from time-to-time to find out substitutes for blood, (i.e.) fluid media which can transport oxygen from the lungs to the tissues and remove carbon dioxide. Perfluorocarbon compounds have the property to transport oxygen and carbon dioxide and these are under study. Hemoglobin solutions have also been studied for this purpose. It may not be long before blood substitutes are available for clinical use on a wider scale.

STEM CELL TRANSPLANTATION

Stem cells are capable of pluripotent differentiation when exposed to the appropriate chemical or biological influences, both in vivo and in vitro. Such cells are present in several tissues in the body such as the bone marrow,

peripheral blood, skin, periodontal ligament of teeth sockets and others. When transplanted, these cells can reconstitute the cell population of several organs such as the hemopoietic tissue of bone marrow, myocardium, neural tissue, immunocytes, periodontal ligament and others. Stem cells have the unique property of self-perpetuation (i.e.) a proportion of the stem cell pool remain in the pluripotent phase without differentiation, and these proliferate and help to perpetuate these primordial capabilities, without decline.

Sources of stem cells include bone marrow, peripheral blood, umbilical cord blood, fetal organs and artificially produced human embryos in vitro. Active research is going on in several countries on the potential use and production of stem cells.

Mainly stem cells are used for haematological disorders such as aplastic anemia, leukemia, myeloma, thalassemias, hemoglobinopathies, congenital immunodeficiency

syndromes, inherited disorders of metabolism and for repopulating the marrow after intensive chemotherapy for malignancies.

Stem cells have been used for the treatment of non-haematological diseases as well. There include:

1. Intra-coronary infusion of stem cells for restoration of function of ischemic myocardium.
2. Restoration of periodontal tissues
3. Reconstitution of immunocytes
4. Generation of neural precursors- using stem cells derived from adult human skin
5. Amyotrophic lateral sclerosis
6. Diabetes mellitus and several others

Creation of human embryos for purposes of organ donation and stem cell production are matters involving ethical issues and therefore this matter is under discussion and debate.

154

Leukemias: General Considerations and Acute Leukemias

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General Considerations

Definition: Leukemias are a group of neoplastic disorders affecting mainly the leukopoietic tissues in the body and characterised by the presence of leukocytosis, immature leukocytes in the peripheral blood and proliferation of these immature cells in the bone marrow resulting in the

suppression of normal tissue. The abnormal cells infiltrate several organs in the body. Considerable information has accrued over the past decade in understanding the molecular basis of and cellular characteristics which lead to leukemic transformation. Genetic abnormalities transform precursor stem cells into potential leukemia cells. The disease process starts in the bone marrow or lymphatic tissue depending on the cell type and the peripheral blood is flooded with abnormal cells at some stage of the disorder. Less commonly erythroid precursors, plasma cells, or megakaryocytes may be involved.

Leukemias may be broadly grouped into two—acute and chronic leukemias. Acute leukemias affect younger age groups more frequently. They run a rapid course and the peripheral blood and bone marrow show the presence of large number of blast cells. If left untreated, these are fatal within weeks or months. Chronic leukemias generally affect the older age groups, they run a more protracted course, and terminate life within 2-3 years of onset.

TABLE 154.1

Frequency of leukemias in adults seen in India	
	Percent
Chronic myeloid leukemia	25-30
Acute myeloid leukemia	20-25
Acute lymphatic leukemia	20-25
Other varieties of leukemia	1-2
Chronic lymphatic leukemia	1-2

Leukemias account for 0.15-0.6% of the total medical admissions in many general hospitals in India.

It is to be noted that chronic lymphatic leukemia is less common in India and the neighbouring countries when compared to West (Table 154.1).

Classification of leukemias: Acute leukemias being heterogenous, several parameters have been employed for classification. These include morphology, histochemistry, cell surface and cytoplasmic immunological markers and cytogenetic and immunogenetic studies.

It is important to classify the disease precisely since the clinical behaviour, course, prognosis and response to treatment differ in the different types (Table 154.2).

In over 80% of cases of ALL and AML non-random chromosomal abnormalities are usually present. Leukemias have been classified by several authors based on different criteria. At present the *French, American British, (FAB) classification* is one of the accepted systems for acute leukemia (Table 154.2). Acute myeloid leukemia is classified on the degree of maturation and differentiation of the abnormal cell. Acute lymphatic leukemia is classified on the basis of cell size, nuclear chromatin pattern, nuclear shape, nucleoli, amount and basophilia of cytoplasm, and extent of cytoplasmic vacuolisation.

Etiology and pathogenesis: Leukemias are multicentric in origin. An abnormal stem cell undergoes mutation and proliferates in a disorderly and unrestrained manner so as to fill the marrow, spill into the peripheral blood, and infiltrate almost all organs in the body. The clone of malignant cells proliferates by division but fails to differentiate and hence immature forms persist in the marrow and peripheral blood. Though the exact stimulus for the mutation is not clear in an individual case, several factors are known to induce leukemia in experimental animals and humans.

1. Genetic factors are important as evidenced by the increased incidence of leukemia in mongolism and Fanconi's anemia.
2. RNA viruses such as the retrovirus and DNA viruses such as Epstein-Barr virus may induce leukemogenic changes in cells.
3. Exposure to ionising radiation (accidental and therapeutic) and long-term use of drugs and chemicals

TABLE 154.2

Classification of neoplasia involving leukocytes	
1. Acute leukemias	
Acute myeloid leukemia (AML) French, American, British (FAB) Classification. Differentiation of the immature cells forms the main criteria.	
Subclass	Type of cell
M ₀	Undifferentiated by light microscopy
M ₁	Poorly differentiated
M ₂	More differentiated
M ₃	Dysplastic promyelocytes
(acute promyelocytic leukemia)	M ₃ h-hyper granular PML M ₃ v-inapparent or fine granules M ₃ a-less hypergranular blasts
M ₄	Both granulocytic and Monocytic
M ₄	Eo-Myelodysplastic eosinophils
M ₅	Monocytic differentiation M ₅ a-predominantly blasts M ₅ b-differentiation into promonocytes and monocytes
M ₆	Myeloblasts with dysplastic erythroid precursors
M ₇	Megakaryoblastic
Acute lymphatic leukemia (FAB):	
When stained with Wright's stain three types—L1, L2 and L3 can be distinguished morphologically	
L1	The blast cells are small and there is no appreciable variation in size and shape. The nuclear chromatin is smooth and the nucleoli are indistinct.
L2	The blast cells vary in size with prominent nucleoli and a variable amount of cytoplasm.
L3	The cells are deeply basophilic with vacuolated cytoplasm. Immunological markers and other cytochemical markers help to identify the cell precisely.
Different hematological cancers can be distinct at the molecular level even though they may appear similar morphologically. This is true for acute and chronic leukemias and lymphomas. Acute lymphatic leukemias can be broadly grouped into three	
1. Precursor B lymphoblastic leukemia 2. Precursor T lymphoblastic leukemia 3. Burkitt lymphoma or leukemia	
In addition there are acute leukemias of ambiguous lineage. These are:	
1. Biphenotypic acute leukemias 2. Undifferentiated acute leukemias	
The availability of immunological probes like monoclonal antibodies, techniques like flow cytometry and DNA microarray analysis have enabled the sub-typing of acute leukemias and lymphomas based on immunological markers such as CD positivity (cluster group of differentiation). This has helped to devise specifically effective therapy with less of side effects.	
2. Chronic leukemias	
Chronic myeloid leukemia (CML)	
Chronic lymphatic leukemia (CLL)	
Hairy cell leukemia (variant of CLL)	
Prolymphocytic leukemia (variant of CLL)	
Plasma cell leukemia	
Chronic myelomonocytic leukemia	
Sézary syndrome: (leukemic phase of mycosis fungoides)	

which depress bone marrow (benzol, chloramphenicol and cytotoxic drugs such as alkylating agents and cyclophosphamide) have been incriminated to be leukemogenic by clinical, experimental and epidemiological observations.

4. Occurrence of cases in close relatives or in successive generations and in clusters in closed communities have strengthened the role of environmental factors in leukemogenesis.
5. Diseases like multiple myeloma and lymphomas transform into acute myelogenous leukemia in some cases. It is likely that the development of leukemia is the total effect of the environmental factors on the genetically predisposed individual. The clone of leukemic cell multiplies in exponential rates. The cell cycle time is generally longer for leukemias than for many other tumours (AML 80-84 h, CML 120 h).

The role of oncogenes in the causation of malignancies has been established (see chapter 6). Several leukemias show chromosomal abnormalities which point to their basic role in leukemogenesis. The formation of proto-oncogenes, their activation to form oncogenes by translocation, and the production of the malignant clone have all been studied. Diagnostic and prognostic information is obtained by chromosomal studies of almost all hematological malignancies especially in chronic myeloid leukemia and myelodysplastic syndromes.

Pathophysiology: The underlying defect in acute leukemia is the unregulated proliferation of primitive cells without undergoing differentiation. The transformation into a leukemic cell may occur at any point in the maturation and differentiation of the pluripotent stem cell. Both ALL and AML are unicellular in origin, and this abnormal cell proliferates to form a clone of malignant cells which populate the marrow and other tissues. AML may develop at any stage of development of the myeloid stem cells (CFU-S). If the malignant transformation takes place at the early stage, both erythroid and granulocytic series are involved (M6). Similar CML originating from a very primitive precursor which has the capability of differentiating into lymphoid or myeloid cell lines, can develop lymphoid blast crisis during transformation. If it occurs at a later stage of development after formation of the committed granulocyte macrophage progenitor (CFU-GM) only the myeloid and monocyte series are involved (M1-M6). In acute lymphatic leukemia the committed myeloid progenitor cells (CFU-C) are normal and the leukemic cells are superimposed on the normal hematopoietic cells. In acute leukemia the bone marrow contains both abnormal and normal cells, the latter being considerably suppressed, so that with eradication of the malignant cells, the remaining normal cells can repopulate the marrow. In contrast, in CML almost all the cells in the bone marrow are abnormal.

General symptomatology: Symptoms differ between acute and chronic leukemias. These are summarised in Table 154.3.

Diagnosis of leukemias: Acute leukemia should be suspected in all cases of rapidly developing anemia, prolonged fevers, hepatosplenomegaly, lymph node enlargement, hemorrhagic tendency, local tumour formation, neurological manifestations, and other bizarre clinical presentations. Acute lymphatic leukemia may be mistaken for rheumatic or rheumatoid arthritis in children. Early diagnosis is possible only if the clinical suspicion is strong.

It is not uncommon for acute myeloid leukemia to present with atypical features initially. Local tumour formation (also known as granulocyte sarcomas) without or with blood and bone marrow abnormalities is a rare presentation. Granulocytic sarcomas may develop in acute myeloid leukemia, and less commonly in chronic myeloid leukemia or other myeloproliferative disorders. They can be typed histologically into mature, immature (intermediate) or blastic types according to the cell composition. They may involve any tissues.

As the disease evolves, characteristic bone marrow and blood picture become evident. Aleukemic leukemia cutis is such a condition in which the skin lesion appears as an induration, nodule or tumour caused by leukemic cell infiltration, blood and bone marrow remaining normal.

Acute lymphatic leukemia is more common to produce local lesions in the bone.

Serum uric acid is elevated during the active phase of leukemias. Uric acid levels are elevated further during treatment with cytotoxic drugs due to rapid cell destruction.

Since early institution of treatment is more effective in curing the disease, specific investigations should not be delayed. Rarely leukemias may be brought out by routine investigations in asymptomatic individuals. This is more so for chronic myeloid leukemia.

Clinical diagnosis has to be followed up with hematological confirmation.

Peripheral blood film examination: The diagnosis of acute leukemia is suggested by the presence of blast cells, which are the precursors of leukocytes. Blast cells are characterised by deep blue non-granular cytoplasm and a rounded or oval nucleus showing pale stained inclusions—the nucleoli—which vary in number from 2 to 5. Though some idea about the nature of the blast can be obtained by morphology, further identification is done by cytochemical and immunological methods (Figs 154.1, 154.2, 154.9 and 154.10).

Peroxidase and *Sudan black* are stains which detect the presence of lysosomes containing the primary granules of the neutrophilic and monocytic series. *Terminal*

TABLE 154.3

Differences between acute and chronic leukemias		
	Acute leukemia	Chronic leukemia
Age group	More in the first and second decades but can occur in all age groups	Mostly in the 4th, 5th and 6th decades but even young children may be affected rarely
Sex ratio	M:F is 2:1	M:F is 1:1
Duration of symptoms	Weeks to months	Several months to one year
Presenting complaints	Anemia, fever, infections, hemorrhagic tendencies or complications, especially neurological	Vague symptoms, loss of weight, mass in the abdomen, or lymph nodular masses
Organomegaly	Liver, spleen and lymph nodes are moderately enlarged in 70-80% of cases	Moderate to gross splenomegaly is the rule in CML. Moderate to gross lymphadenopathy occurs in CLL.
Blood picture	Total leukocyte count is moderately elevated ($15-30 \times 10^9/\text{litre} = 15-30,000/\text{cmm}$), Blast cells form 10-90% of the total. Platelets are often reduced	Total leukocyte count is grossly elevated, $15-25 \times 10^{10}/\text{L}$ (150-250,000/cmm)
Bone marrow	Shows depression of erythroid cells, myeloid cells and megakaryocytes, and infiltration by the abnormal cells. Blast cells form more than 30% and may be even up to 90%	CML shows increase in myeloid cells, especially myelocytes, metamyelocytes, and neutrophils, infiltration by small lymphocytes is seen in CLL. Erythroid and megakaryocytic precursors show variable cellularity.
Chromosomal studies	Different patterns in different subtypes	Ph chromosome is demonstrable in over 95% cases of CML.
Course and prognosis	Untreated, fatal within weeks to six months due to infections, hemorrhage, anemia or other complications	Untreated, CML has a median survival of 18-24 months, CLL has a generally more prolonged course
Response to treatment	Spontaneous remissions have rarely been reported. With modern treatment, over proportion of 90% of cases go into remission and 60-70% get complete cure. Acute lymphatic leukemia in children gives the best results	With modern chemotherapy a small CML is cured With bone marrow transplantation at the ideal-time cure rates exceed 50%. CLL follows a variable course with chemotherapy

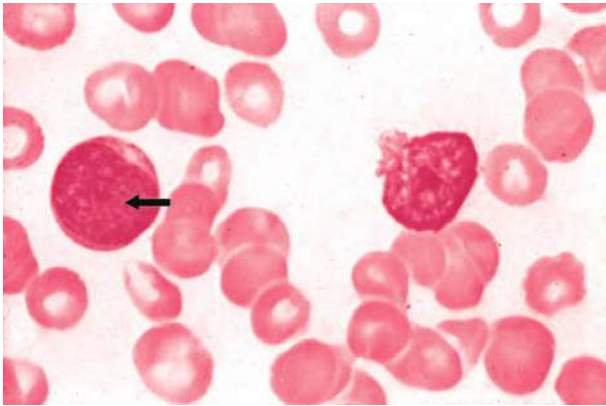


Fig. 154.1: ALL peripheral blood $\times 1000$.
Note: The blast cell (arrow)

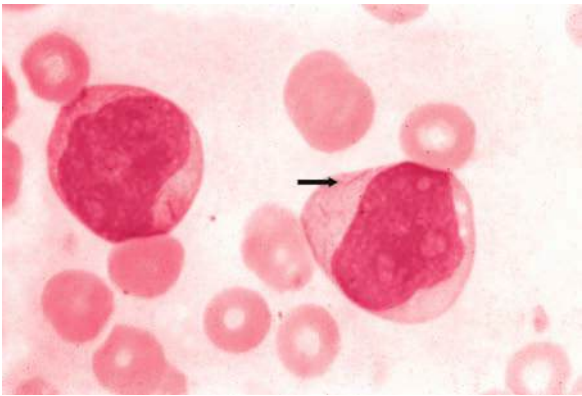


Fig. 154.2: AML peripheral blood $\times 1000$ myeloblast with Auer's rods (arrow)

deoxynucleotidyl transferase (TdT) is seen most commonly in ALL, occasionally in the blastic phase of CML and rarely in AML (Table 154.4).

Cytological differentiation and immunophenotyping are important since the treatment, complications, and

prognosis are different. Even with a battery of tests 5-10% of acute leukemias may defy final identification initially. Follow-up helps to reveal their true type.

Bone marrow examination is mandatory in all cases. Presence of blasts in excess of 30% of the total cells in

TABLE 154.4

Differences between lymphoblasts and myeloblasts		
	Lymphoblasts	Myeloblasts
Number of nucleoli	1-2	2-5
Accompanying cells	Lymphocytes and non-granular cells	Promyelocytes, myelocytes and neutrophils
Peroxidase staining	Negative	Promyelocytes, myelocytes and neutrophils are positive; early blasts are negative
Sudan black staining	Negative	Positive
PAS staining (periodic acid Schiff)	Coarsely positive	Finely positive
TdT (terminal-deoxytransferase)	Generally positive	Generally negative

Note: Many more histochemical and immunological markers are available for precise diagnosis. Figures 154.1 to 154.3 and 154.9 to 154.11

the marrow confirms the diagnosis of acute leukemia. Elevation above 5% should be noted with suspicion.

In the case of chronic leukemias, diagnosis is easy by examining the blood film, since the cells show typical differentiating features. In chronic myeloid leukemia, neutrophils, and myelocytes predominate in the peripheral blood. In chronic lymphatic leukemia mature lymphocytes predominate.

Though the vast majority of leukemias show leukocytosis, in 10-20% the count may be normal or low even though immature cells are present. These are termed as **subleukemic leukemias**. When there are no abnormal cells in the peripheral blood, the term **aleukemic leukemia** is used. Bone marrow is hypercellular in most cases and shows infiltration by abnormal cells irrespective of the leukocyte count in peripheral blood.

Leukemias have to be differentiated from leukemoid reactions which are less common.

Leukemoid Reaction

Leukemoid reaction is a non-neoplastic reactive leukocytosis characterised by the presence of immature cells of all stages in peripheral blood. This may involve the myeloid, lymphatic, or other cell types. Children are affected more frequently than adults.

Causes

1. Acute infections like pneumonia, septicemia, whooping cough, chickenpox, infectious mononucleosis, diphtheria, and meningitis.
2. Chronic infections like tuberculosis, and amebic liver abscess.
3. Hemolytic crisis and massive hemorrhages.
4. Metastatic carcinoma involving the bone marrow especially from neuroblastoma, lungs, thyroid, prostate and others.
5. Other hematological malignancies, e.g. multiple myeloma, myelofibrosis, and Hodgkin's disease.
6. Toxic states like eclampsia, burns, and mercury poisoning.

The blood picture is myeloid in pneumonia, meningitis, diphtheria, tuberculosis, amebic liver abscess, metastatic malignancies, multiple myeloma, post hemorrhagic states and hemolysis. Lymphoid picture occurs in whooping cough, chickenpox, infectious mononucleosis, and tuberculosis. Monocytic reaction rarely occurs in disseminated tuberculosis. Eosinophilic picture occurs in amebiasis, melanomatosis, and invasive stages of helminthiasis. The bone marrow is normal with accelerated leukopoiesis in leukemoid reaction unlike as in leukemia. Total leukocyte counts may vary widely and overlap with those of leukemia. Liver and spleen are not usually enlarged. **Leukocyte alkaline phosphatase is increased in leukemoid reaction whereas it is low in chronic myeloid leukemia.**

Treatment of the underlying disorder corrects the blood picture also.

Congenital Leukemia

This is leukemia presenting within the first month of life. Almost always it is acute non-lymphatic leukemia. Chromosomal disorders such as Down's syndrome, Turner's syndrome, trisomy 13, monosomy 7, mosaic trisomy 9, and abnormalities of chromosome 11 have a higher incidence of congenital leukemia.

PRINCIPLES OF TREATMENT OF ACUTE LEUKEMIAS

Management of leukemia requires the coordinated efforts of the physician, oncologist, radiotherapist, clinical psychologist, and blood bank officer. The services of a well-equipped laboratory are absolutely essential for proper work-up of the case and follow up. The prime requirements expected of the general physician is to detect leukemias early and arrange treatment for them under the specialist team. Attempting to treat cases of leukemia single-handed in general hospitals will lead at best only to less satisfactory results. In the following description, only principles of diagnosis and management are given,

omitting precise practical details. Monographs on the subject should be consulted for more practical information.

When the disease is clinically evident the tumour load is heavy and the malignant tissue proliferates rapidly. At this stage it is essential to reduce the tumour load within a short time by the use of intensive chemotherapy. This phase is called **“induction of remission”**. The patient is deemed to have achieved remission when the clinical and hematological abnormalities (both blood and bone marrow) have disappeared. Even at this stage, although tumour cells are not demonstrable by the usual laboratory techniques, 10^5 - 10^6 tumour cells persist in the body which are capable of proliferating and re-populating the bone marrow and blood. This is the common cause for relapse.

Consolidation: After the induction and cranial prophylaxis another course of chemotherapy, meant to decrease the leukemic burden and to avoid the development of resistance is given, employing a different combination of drugs.

Many tissues in the body such as the brain, meninges, CSF cisterns, and testes act as sanctuaries for the leukemic cells since the systemically administered drugs do not freely reach them. The residual leukemic tissue in the brain and CSF is destroyed by drugs like methotrexate or cytosine arabinoside introduced intrathecally or intravenously in high doses. This constitutes **neuroprophylaxis**.

Testicular involvement occurs in 10-15% of ALL cases before the onset of therapy. This usually clears up with chemotherapy. Next to the central nervous system, testis is the most frequent sanctuary site where leukemic cells proliferate. Though overt testicular leukemia is treated by local irradiation, at present there is no consensus regarding testicular prophylaxis.

The present schedules of chemotherapy do not eradicate the leukemic cells completely. Hence **maintenance therapy** is given after the achievement of remission to prevent the surviving cells from proliferating and leading to relapse. Maintenance therapy is generally given for varying periods after which it could be withdrawn. During maintenance, regular short intensive regimen as given for induction are included in many treatment protocols. These pseudoinduction regimens are given to ensure that the leukemic cells do not reach significant numbers. It is possible that if the leukemic cell population is kept low, immunological defences of the host will eliminate them.

Maintenance therapy is more commonly employed for acute lymphatic leukemia. For acute myeloid leukemia, the success depends more on the effectiveness of induction therapy.

A modern approach to the problem of eradicating the residual leukemic cells is the use of monoclonal immunoglobulins which selectively destroy the malignant

TABLE 154.5

Drugs used for the treatment of acute leukemias

1. *Antimetabolites*
Methotrexate
Cytosine arabinoside
6-mercaptopurine
6-thioguanine
2. *Antimitotic drugs*
Vincristine
3. *Antibiotics*
Daunorubicin (Daunomycin)
Doxorubicin (Adriamycin)
Rubidazole
Bleomycin, Mitomycin
4. *Enzymes*
L-asparaginase
5. *Alkylating agent*
Cyclophosphamide
6. *Corticosteroids*
Prednisolone

cells. Monoclonal antibodies have been employed therapeutically and diagnostically in clinical situations rarely. Their greater use is for the removal of leukemic cells from harvested marrow before transplantation.

The total duration of treatment is generally limited to 5 years since the majority of patients attain freedom from the leukemic process by this period. Many of those who remain in the first remission without relapse achieve long-term survival (above 10 years) and cure, though a few may relapse even after this interval. In those in whom relapse occurs, survival is considerably shortened. Relapses are treated on the same lines as initial induction. If relapse occurs the therapeutic modality of choice is marrow transplantation. If this is not available, the next best is chemotherapy. Tables 154.5 and 154.6 give the details of drugs used to treat acute leukemias.

Supportive treatment: Infections are very common in the active phase of acute leukemia, especially during the induction phase, because of impairment of cellular and humoral defence mechanisms. They account for 80% of deaths during induction and remission. The common infective agents include the pyogenic cocci, gram-negative bacilli, *Pseudomonas aeruginosa*, anaerobes, *candida spp.*, *aspergillus* and the herpes viruses. Relatively avirulent organisms such as *Mycoplasma pneumoniae*, *Pneumocystis carinii* and *Cryptococcus neoformans* become invasive and account for many deaths. The risk of tuberculosis flaring up during treatment with corticosteroids is also high. Fulminant infections are seen most frequently during the stage of induction. Bacterial infections are common when the neutrophil count is below 1000/cmm. Reduction of absolute neutrophil counts below 500/cmm is dangerous, unless prompt antimicrobial therapy is instituted. Infection may be nosocomial or endogenous from the flora inhabiting the alimentary tract.

TABLE 154.6

Mechanism of action and toxic side effects of anti-leukemic drugs

Drugs	Mechanism of action	Adverse side effect
1. Vincristine (Oncovin)	Mitotic inhibitor	Alopecia, leukopenia, peripheral neuropathy, and myelopathy
2. Daunorubicin Doxorubicin (Adriamycin) Rubidazole Hydroxydoxorubicin	Binds DNA and inhibits mitosis	Alopecia, leukopenia, cardiomyopathy as a sequel. Doxorubicin cardiomyopathy is dose dependent and is more frequent when the total dose exceeds 550 mg/m ² . It leads to oxidative stress and cellular injury which can be demonstrated by myocardial biopsy studies. Often it occurs after long latent periods, even up to 20-40 years. Echocardiographic studies show reduction in ejection fraction. Slow administration of the drug as IV infusion over a period of 48-96 hours reduces cardiotoxicity. Antioxidants such as probucol are being tried as protective drugs.
3. L-asparaginase 4. 6-Mercaptopurine 6-Thioguanine Cytosine arabinoside Methotrexate	Deprives the cells of asparagine Inhibit purine or pyrimidine synthesis or inhibit incorporation into DNA	Hypersensitivity, hepatic dysfunction, pancreatitis Ulceration of mouth and GI tract, leukopenia
5. Cyclophosphamide	Alkylating agent, cross-links DNA and impairs RNA formation	Alopecia, leukopenia, marrow aplasia, pigmentation, hemorrhagic cystitis, pulmonary fibrosis. Second neoplasms on follow-up.
6. Corticosteroids 7. All transretinoic acid	Mechanism of action not clear Induces differentiation in acute promyelocytic leukemia	Several toxic effect, see Chapter 5.
8. Interferons	Immunomodulation	Several adverse effects.

NB: All the cytotoxic drugs, irrespective of their type, are capable of producing marrow aplasia and this effect is cumulative. This is probably the most serious toxic effect which limits the total dose. Till the advent of stem cell transfusion therapy intended to repopulate the marrow with normal cells, intense cytotoxic chemotherapy could not be given in eradicated doses due to toxicity on the host. With the support of stem cell transfusion and judicious use of cytokine growth factors it is possible to give more intensive chemotherapy and achieve higher cure rates at present. Specific monoclonal antibodies are also being introduced in selected cases.

Note: Drugs are usually given in combination cyclically or as continuous dosage. The selection, dose, and sequence of administration of these drugs depend on the type of leukemia. The dosage is usually calculated in terms of body surface area (which can be read off from nomograms using the height and weight), and this is more reliable than determining the dose on the basis of body weight. Combination of different drugs and intermittent administration has served to reduce the dosage and toxicity of each drug, and improve the effectiveness by optimal action at the appropriate phases of the cell cycle. Over the past four decades several collaborative studies have been conducted and evidence based protocols have been formulated for different subtypes of leukemia. It is important to follow the protocols strictly. Breaking the protocol, or use of individual drugs at random results in sub-optimal outcome. Studies on the management of leukemias are continuing.

Several methods have been employed to prevent such infections.

These include

1. the provision of an isolated sterilized environment,
2. reverse barrier nursing to avoid infection from the attendants,
3. provision of sterilized articles for food and drink,
4. special care of intravenous lines and injection sites, and
5. prophylactic use of antimicrobial drugs like cotrimoxazole and nystatin with a view to sterilise the gut flora.

Prophylactic antimicrobial drugs are started prior to the induction of remission and are continued during

the phase of leukopenia. Systemic infection should be anticipated when there are early symptoms like fever and rigor or any local lesions such as furuncles, cellulitis, or ulcers. A combination of powerful bactericidal antibiotics should be instituted early, after taking blood and bacteriological specimens from the nose, throat, mouth, anus, and genitalia for culture and sensitivity studies. Superficial candidiasis is treated by administering nystatin 500,000 units every 6 h orally and more serious fungal infections by amphotericin B in a dose of 1 mg/kg body weight intravenously or fluconazole. Antiviral drugs such as vidarabin 5 mg/kg/day or acyclovir 5 mg/kg/day intravenously every 8 h may be given for treating

herpes and other viral infections. *Pneumocystis carinii* infection responds to cotrimoxazole in a daily dose of 9-12 g given in divided doses.

Delay in starting antimicrobial therapy results in heavy mortality and hence it is necessary to start treatment on clinical grounds, even before bacteriological evidence is obtained. The advent of newer antimicrobial agents has been a great help in treating these patients. Blood component therapy.

Chemotherapy induced thrombocytopenia and anemia are promptly reversed by transfusion of platelets and packed red cells. Coagulant factors may be needed as and when bleeding tendencies develop.

Use of colony stimulating factors such as G-CSF and GM-CSF help to reconstitute the neutrophil and macrophage population early, shorten the period of dangerous neutropenia and risk of severe infections. Adverse side effects of colony stimulating factors include worsening of autoimmune disorders, inflammation of ocular structures and allergy.

Other supportive measures include red cell transfusions for anemia, platelet transfusions for hemorrhage, and whole blood to correct blood loss.

Hyperuricemia may lead to secondary gout and renal failure during treatment. Prompt use of allopurinol 100 mg thrice daily orally during the initial phases of treatment helps to keep the uric acid levels normal. Adequate hydration and maintenance of urine output of at least two litres daily help to minimise the risk of nephropathy.

Prognosis: Leukemia is invariably fatal if untreated. Modern treatment has helped to prolong useful life in the vast majority of cases of acute leukemias and in about 50-60% of cases to bring about cure. Best results are obtained in acute lymphatic leukemia in children. Those who are not curable by chemotherapy are subjected to bone marrow transplantation (BMT) which is curative in more than 2/3 of the cases. Stem cell transplantation is a more readily available alternative to repopulate the marrow.

At present management of acute and chronic leukemias is a highly evolved procedure, requiring the services of specialised equipment and trained teams who have experience of treating these patients. If treatment is done in such units, the results are excellent. No physician should undertake to treat them if these facilities are not available. Moreover, administration of corticosteroids or individual drugs instead of well-defined treatment protocols serve to alter the clinical and hematological picture, produce problems in diagnosis and worsens the prognosis. In India treatment of leukemias is undertaken in several centres.

During the past decade several protocols for treating acute leukemias have been developed by international teams. At present more and more aggressive chemo-

therapeutic combinations are being employed, each major centre using its own protocol depending on the availability of the drugs, cost, facility for supportive services and availability of marrow or stem-cell replacement. In general, over 95% of acute leukemias must go into remission and at least 70% should get long-term cure.

The Favourable Prognostic Factors

1. Initial leukocyte count below 20,000/cmm,
2. Platelet count above 100,000/cmm,
3. Absence of organomegaly, i.e. lymph nodes, spleen, and liver are impalpable,
4. Null cell (common ALL) leukemia, promyelocytic leukemia
5. Absence of complications,
6. Absence of mediastinal lymphadenopathy in acute lymphatic leukemia,
7. Younger age groups,
8. Institution of proper therapy from the beginning, and
9. Availability of trained teams for management and BMT.

The Unfavourable Prognostic Factors

1. Older age groups,
2. Initial leukocyte count above 20,000/cmm,
3. Thrombocyte count below 100,000/cmm,
4. Organomegaly,
5. Presence of complications,
6. T-cell acute lymphatic leukemia, and
7. Presence of mediastinal lymph nodes in lymphatic leukemia.

Cases which fall in the poor-prognosis group are given more intensive induction regimen using a larger number of drugs and early bone marrow transplant.

Bone Marrow Transplantation (BMT)

BMT has been employed as a therapeutic modality in several diseases for over four decades, to reconstitute stem cells in conditions where there is deficiency, (e.g. aplastic anemia and immunodeficiency states) or abnormality of the patient's own stem cells (e.g. leukemias and thalassemia). The success of this procedure and availability of BMT in several centres in many parts of the world have established its place in treatment. The pioneer in initiating BMT was ED Thomas who reported success of this procedure in 1959. Later he was awarded the Nobel Prize for his work. Stem cells are obtained from several sources—bone marrow, peripheral blood and cord blood. They have the potential to repopulate the marrow and differentiate into appropriate mature cells.

The indications and ideal time to perform BMT have also been defined. Unlike as in other solid organ transplants, there is no need for a major surgical procedure

since the stem cells collected from the donor reach their location in the bone marrow when injected intravenously. Within a few weeks of marrow donation, the donor's marrow fully regenerates so that there is no organ-loss for the donor. The marrow to be transfused may be homologous or allogenic (derived from another person with non-identical genetic status), isologous or syngenic (derived from identical twins with the same genetic status) or autologous (marrow recovered from the patient on an earlier occasion and transplanted later). Selection of the donor depends upon the compatibility of the HLA complex. Theoretically a single stem cell can repopulate the entire marrow. The genes for the HLA complex are closely linked on chromosome 6 and they are inherited as haplotypes. Thus two siblings have a one-in-four chance of being HLA identical. Transplantation between HLA identical persons does not evoke a graft versus host disease (GVHD). In selecting donors siblings are the most suited, next only to identical twins.

PRINCIPLES IN BMT

Conditioning Regimen

Ablation of the recipient's marrow cells: This is done by the administration of cyclophosphamide 50 mg/kg bw daily for 4 days along with total body irradiation of 800-1500 rads. This regimen destroys all the hemopoietic cell lines in the patient, including most of the leukemic cells. Several other regimens are used by different centers for ablating the patient's marrow. The present trend is to use less aggressive regimen to ablate the recipient's marrow since such regimen are associated with better success rates and survival.

Infusion of donor marrow: About 750 mL of marrow withdrawn from the HLA matched donor by multiple punctures under anesthesia is prepared for infusion and administered IV at a dose of $2-6 \times 10^6$ donor marrow cells per kg bw.

In the vast majority, the recipient's marrow increases in cellularity within two to four weeks. Thereafter all the hematopoietic cells, plasma cells, tissue macrophages and immunological cells are derived from the transplanted marrow.

Though in principle BMT appears to be simple, elaborate equipment, facilities to control infection of the recipient during the pre-transplant preparation and during the leukopenic phase before the donor marrow proliferates, need for powerful antibiotics, and hyperalimentation during the critical period, make BMT a highly specialised and very expensive procedure which can be undertaken only in advanced institutions where trained teams are available. Several institutions undertake BMT in India. The approximate cost is Rs. 10 to 12 lacs (\$ 22000).

An immunological complication that develops in all successful transplants is graft versus-host disease

(GVHD), if the donor happens to be other than an identical twin. The immunocompetent T lymphocytes in the donor marrow derived from the stem cells proliferate and attack recipient's tissues and give rise to the clinical picture of GVHD. GVHD may be acute or chronic. Acute GVHD occurs within 1-2 months of BMT. The incidence ranges from 10-80% depending upon the initial disease and technique of preparation of bone marrow. Main targets of attack of GVHD are the immune system, skin, GI tract, liver and brain. Profound immunosuppression occurs as a result of GVHD, leading to fatal infections. Selective epithelial damage occurs in the target tissues.

Chronic GVHD occurs after about 3 months or persists for more than 100 days. Two stages may be recognised in the pathogenesis. First step is activation of donor T lymphocytes by recipient tissues. Second step is the production of cytokines by the activated T-cells, recruitment of more cells and mounting the immune response in the host's tissues.

Administration of immunosuppressants, particularly methotrexate, and cyclosporine helps to suppress GVHD by inhibiting donor T-cell activation. Corticosteroids and cyclosporin inhibit the synthesis of interleukin. Methotrexate blocks cell proliferation. After varying periods these drugs can be discontinued. Newer immunosuppressants such as tacrolimus and mycophenolate mofetil are also useful.

The occurrence of GVHD is associated with more complete eradication of the leukemia clone and therefore, better long-term results. Cases that survive successful management of GVHD have longer leukemia-free survival.

Other fatal complications include graft rejection, severe infections, pulmonary complications including acute respiratory distress syndrome and interstitial pneumonia, and iatrogenic problems. Availability of growth promoting factors such as GM-CSF has enabled earlier reconstitution of recipient's neutrophils and macrophages, thus reducing infections and mortality. The mortality in the post-transplant period is 30-40% and the main causes are infection, marrow failure or GVHD. Refinements in techniques have given better results and lower failure rates.

A major offshoot of this procedure is the employment of autologous marrow transplant. This is the procedure in which bone marrow of the patient is harvested prior to administration of aggressive chemotherapeutic regimen and infused back after chemotherapy is administered. This helps to repopulate the marrow after ablating cancer tissue. The harvested marrow is treated with monoclonal antitumor antibodies which help to remove the intrinsic malignant cells contained in it. This procedure is called purging the marrow. Use of autologous marrow obviates the problem of donors and GVHD.

Peripheral Stem Cell Transplantation

Another modality that is more popular is stem cell transplantation. Peripheral blood normally contains stem cells which can be used to repopulate marrow after chemotherapy. The stem cell pool is allowed to proliferate under stimulation by appropriate colony stimulating factors (GM-CSF or G-CSF) and the harvested stem cells are infused into the patient instead of bone marrow.

Cord blood is a rich source of pluripotent stem cells. They are less likely to mount immunological reactions. Cord blood stem cell infusion is becoming more popular.

Prophylactic use of fluconazole and ganciclovir ensure prophylaxis against fungal and cytomegalovirus infections respectively.

Indications for BMT

- 1. Acute and chronic leukemias, myelodysplastic syndrome.
- 2. Multiple myeloma.
- 3. Lymphomas which have relapsed after initial chemotherapy.
- 4. Aplastic anemia, radiation injury, paroxysmal nocturnal hemoglobinuria.
- 5. Hemoglobinopathies, thalassemias.
- 6. Immunodeficiency states—severe combined immunodeficiency, Wiskott-Aldrich syndrome, Chédiak-Higashi syndrome, chronic granulomatous disease.
- 7. Other genetic disorders such as malignant osteopetrosis, Gaucher’s disease, infantile metachromatic leucodystrophy and X-linked adrenoleucodystrophy.

Results of BMT in Different Diseases

See Table 154.7.

Acute Lymphatic Leukemia
Syn: Lymphoblastic leukemia—ALL

This type of leukemia which is more common in children, arises from lymphoid tissue. About 75% cases are null cell type, 20-25% T-cell type and a few are B-cell type. Maximum incidence is in the first two decades. There is also a peak in the fourth and fifth decades. Male to female ratio is 2:1.

CLINICAL FEATURES

The presenting features are fever, pallor, lymphadenopathy, and bleeding tendencies. Some cases present with neurological involvement. These take the form of meningitis, cranial nerve palsies, focal neurological deficits, convulsions, or coma. About 20% present with arthralgias and arthritis resembling rheumatic or rheumatoid arthritis. Moderate lymphadenopathy,

TABLE 154.7 Gives the present indications for BMT and survival rates		
Indication	Timing	Approximate long-term survival
ALL	Second relapse	70%
AML	First relapse	70%
CML	Within 1 year of diagnosis, while in CML phase	70%
CLL	Variable	50%
Multiple myeloma	Stage I	66%
	Stage II	33%
Poor prognosis lymphomas	Failure of initial or second course of treatment	Over 50%
Hemoglobinopathy, Thalassemia	As early as possible	Over 80%
Severe aplastic anemia	As early as possible	Over 60%
Note: There are several other conditions in which BMT is an accepted treatment modality at present. A complete list is not attempted in this table. Autologous stem cell transplantation is done for almost all indications given in Table 154.8. Supportive stem cell transplantation given along with intensive cancer chemotherapy has improved the curability of several malignant diseases.		

TABLE 154.8 Gives the present status of autologous stem cell replacement	
Curative potential	Diseases
Certain	Acute leukemias, Aggressive NHL, Relapsed Hodgkin's disease
Possible	Germ cell tumours
	Breast cancer
	Low-grade NHL
	Chronic leukemias
	Multiple myeloma
More than 30000 autologous and more than 15000 allogenic stem cell transplants are done annually, world-wide. Ref: Copelan EA. hematopoietic stem cell transplantation N Engl J Med 2006. 354:17, 1813-1826.	

especially the posterior cervical and mediastinal groups, mild hepatosplenomegaly (spleen 2-5 cm), and pallor are detectable on physical examination. Bone involvement is more common.

Ophthalmoscopic examination reveals pallor of the optic disc, venous engorgement, hemorrhages, and exudates. Vitreous hemorrhage and subconjunctival hemorrhage may occur in severe cases.

T-cell leukemia is more serious since it is less responsive to therapy. It is characterised by higher total leukocyte count and enlargement of mediastinal lymph nodes. There are reports that the frequency of T-cell lymphatic leukemia is higher in India. A subgroup of ALL, especially in adults shows Ph¹ chromosome positivity on karyotyping. Probably these arise from a very early totipotent stem cell which has the capacity to develop towards the myeloid cell line as in chronic myeloid leukemia. Ph¹ positive ALL has a poorer prognosis compared to Ph¹ negative ALL.

Laboratory findings: Normocytic normochromic anemia may be seen. Total leukocyte count is moderately elevated (20-30,000/cmm) (Fig. 154.3) but sometimes it may go up to 100-200,000/cmm. Lymphoblasts may form 5 to 95% of the total. Platelets are reduced. Bone marrow shows infiltration by lymphoblasts.

TREATMENT

Remission is induced by a combination of vincristine, prednisolone and L-asparaginase. Several other drugs such as doxorubicin (adriamycin), etoposide and cytosine arabinoside are also used for induction in high-risk cases (Tables 154.6 and 154.9). Newer modalities and treatment protocols are still being developed.

About 95% of children and 90% of adults respond to this regimen and achieve complete remission. Poor prognostic factors include the following:

- 1. Age < 1 and > 10 years
- 2. Male sex
- 3. Presence of mediastinal mass in X-ray
- 4. Presence of organomegaly involving the spleen, liver, lymph nodes and other organs
- 5. Laboratory features
 - a. Total leukocyte count exceeds 50,000/cmm
 - b. Blasts are of T-cell phenotype, which do not express CD 34 or CD 10 with a hypodiploid, diploid or near diploid karyotype.
 - c. Presence of Ph¹ chromosome.

Remission is consolidated by giving 1 or 2 doses of the drugs used in the induction regimen.

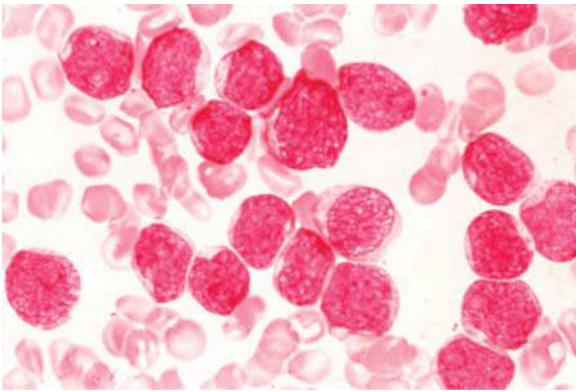


Fig. 154.3: ALL bone marrow × 400. Note: Replacement by lymphoblasts

Maintenance: Methotrexate in a dose of 15 mg/m² as a single weekly dose and 6-mercaptopurine in a total dose of 600 mg/m²/week divided into daily doses are given orally. Vincristine 1.5 mg/m² is given intravenously every month. Maintenance therapy has to be continued for 2 years.

Neuroleukemia

Neuroleukemia occurs in 50% of ALL and 10-12% of AML cases, if neuroprophylaxis is not given along with initial therapy.

Pathological lesions include infiltration by leukemic cells, hemorrhage, and demyelination. In addition, drug toxicity, and occlusion of cerebral microcirculation due to leukostasis add to the total neurological picture. When the leptomeninges are infiltrated, CSF shows the presence of a large number of blast cells, rise in protein and increased pressure, and this may be mistaken for meningitis. Neuroleukemia may manifest during remission, or this may even be the presenting symptom in some.

Clinical features may be those of meningitis, raised intracranial tension with papilledema, stupor, coma, focal neurological symptoms like convulsions or paralysis, cranial nerve palsies, spinal cord or spinal root compression, or intracranial hemorrhage. Sometimes hyperviscosity syndrome develops because of very high

TABLE 154.9

TABLE 154.9

Treatment of ALL				
	Dose	Route	Interval	Total number of courses
Vincristine	1-1.5 mg/m ²	Intravenous	7 day intervals	4-8
Prednisolone	40 mg/m ²	Oral	Daily	
L-asparaginase	10000 units/m ²	Intravenous	Daily × 5 days	
Flow chart for the management of ALL				
	Consolidation			
Induction of remission	Neuroprophylaxis		Maintenance	
	Intrathecal drugs		Consideration of BMT	



Fig. 154.4: Bilateral facial palsy in ALL

leukocyte counts above $200 \times 10^9/L$ (200,000/cmm). Symptoms of cellular hyperviscosity include auditory and visual disturbances, ataxia, headache, profound lethargy, and coma. Leucapheresis relieves these symptoms dramatically (Fig. 154.4).

Neuroprophylaxis: It is started along with induction regimen and is a must in acute lymphatic leukemia. Intrathecal methotrexate in a dose of $10\text{--}12 \text{ mg/m}^2$ should be given twice a week for a total of 6 doses. A single dose should not exceed 15 mg. An alternative is cytosine arabinoside 50 mg intrathecally given twice a week for 6 doses.

CNS involvement should be diagnosed when the CSF cell count exceeds 5/cmm with or without the presence of blast cells. Cytospin studies and flow cytometry help to identify abnormal cells more accurately.

Treatment of established neuroleukemia is less effective. Cranial or craniospinal irradiation combined with intrathecal methotrexate or cytosine arabinoside is the method of choice. Intrathecal drugs may cause chemical meningitis or neuromyolytic accidents. Cranial irradiation may give rise to cerebral irritation, rise in intracranial pressure, somnolence or convulsions. Children who have received more than 2000 cGy to the cranium may develop impairment of intellectual performance on long-term follow-up. Therefore, it is the present consensus to limit the dose to 1800 cGy or even lower. Many centres have abandoned cranial irradiation. Drugs such as methotrexate when given intravenously in high doses reach the CSF in therapeutic concentrations.

At present, results in the management of the primary disease are very good. But neuroleukemia once it occurs, worsens the prognosis for long-term survival. Therefore, prevention of this complication has an important place in overall management.



Fig. 154.5: Testicular leukemia. Boy aged 2 years with acute lymphatic leukemia. Note: The enlarged testes

Testicular Leukemia

The testes may be enlarged, firm and tender, or the involvement may be clinically inapparent. Affection of the testes may occur before, during, or after the induction therapy. Testicular involvement leads on to relapse. Treatment of testicular lesion is by irradiation with 1000–2000 rads over a period of 2–10 days. Prophylactic irradiation of the testes has been tried in some centres, but the high incidence of sterility limits its routine application (Fig. 154.5).

Treatment of Relapse

Reinduction can be achieved by the same regimen as for the initial presentation. After achieving remission a second time the possibility of bone marrow transplantation should be explored since the chances of long-term survival with medical therapy are less in such cases. With the improvement in the results of bone marrow and stem cell transplantation, these modalities are considered even earlier.

Acute Myeloid Leukemia

Syn: Acute non-lymphocytic leukemia—ANLL

Acute myeloid leukemia arises from a common precursor stem cell and it is subdivided into seven types—M1 to M7. Ref: (Table 154.2). Risk factors include exposure to

ionizing radiations, benzene and cytotoxic chemotherapy, especially alkylating agents. Cigarette smoke is a common cause of benzene exposure. AML blast cells develop from normal blasts which have undergone genetic damage. Marrow blasts are protected by the marrow stroma from apoptosis induced by chemotherapy.

AML shows various cytogenetic abnormalities. WHO has proposed the **WHO classification of AML**, based on genetic abnormalities. This helps to select the best therapeutic approach and to assess the prognosis. Cytogenetic markers help to categorise the therapeutic response in AML as *favourable*, *intermediate* or *adverse*. The myeloid blast cells have surface markers CD33 or CD13.

All age groups are affected, though the second and third decades show a higher incidence. Both sexes are equally affected.

CLINICAL FEATURES

The disease presents with progressive anemia, fever and focal or general infections or hemorrhages (Fig. 154.6). Usual sites of infection are the gums, mouth, throat, skin, perianal regions, genitalia, and the respiratory tract. In many cases lymphadenopathy and hepatosplenomegaly may be absent. Atypically the disease may present with affection of unusual sites. Sites of extramedullary involvement include:

- 1. Bilateral or unilateral retro-orbital masses producing exophthalmos (Fig. 154.7).
- 2. Breasts—uniform or localised enlargement occurs in one or both sides (Fig. 154.8).
- 3. Skin—nodular or diffuse lesions. *Chloromas* are cutaneous manifestations of myeloid leukemia. They appear as reddish blue thickening of the skin. On pressing out the blood from the area a greenish hue is noticeable for a few seconds due to the presence of myeloperoxidase.
- 4. Bones—diffuse osteoporosis or localised tumours affecting the long bones.



Fig. 154.7: AML female retro-orbital tumours

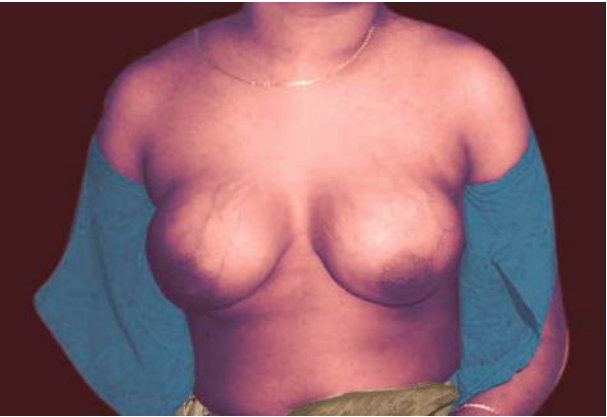


Fig. 154.8: AML female tumour breasts

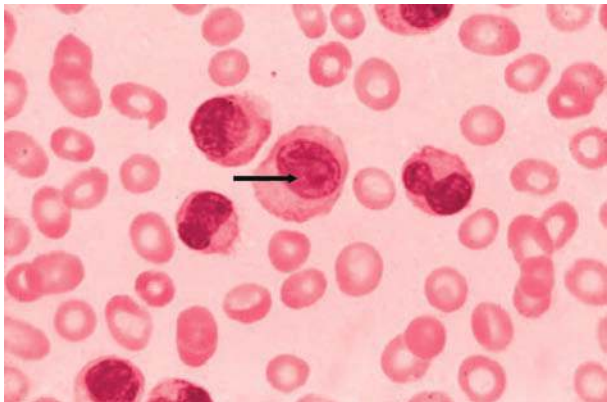


Fig. 154.9: AML P B × 500. Note myeloblast arrow



Fig. 154.6: AML female sub-conjunctival hemorrhage

Acute Promyelocytic Leukemia (APML) (M3)

About 15-20% of AML fall under this group. The predominant cells are promyelocytes with coarse granules in the cytoplasm. In addition to the general features of acute leukemia, APML is characterised in most cases by major bleeding tendency, caused by disseminated intravascular coagulation.

In APML there is translocation between chromosomes 15 and 17 (L 15:17). The genes for retinoic acid receptor (RAR) alpha on chromosome 15 fuses with the promye-

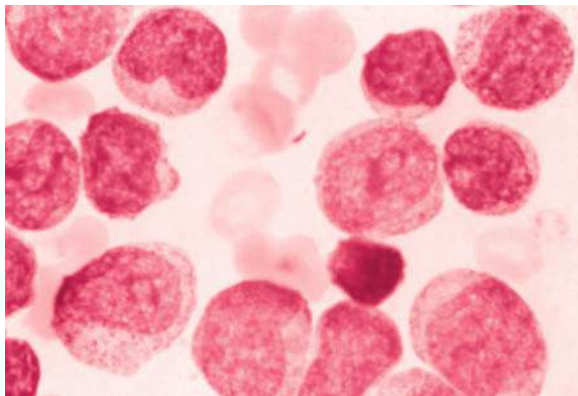


Fig. 154.10: AML: Bone marrow is replaced by myeloblasts

locytic leukemia gene (PML) on chromosome 17, resulting in the formation of PML-RAR fusion product. All trans retinoic acid acts at this fusion product and normalises it.

APML responds very satisfactorily to initial treatment with all-trans retinoic acid (isotretinine-ATRA) which is the treatment of choice at present. The dose is 45 mg/m² body surface per day for 15 days, once in three months as maintenance therapy. The remission induced by this therapy tends to be short lived, and therefore, it has to be followed up by chemotherapy.

Acute Myelomonocytic Leukemia (M4)

It shows a high proportion of monoblasts and monocytes. Hypertrophy and infection of gums are prominent features. Neuroleukemia is more common in this group (Fig. 154.11).

Erythroleukemia (Deguglielmo's Syndrome) (M6)

In this variety abnormal erythroid precursors proliferate. Erythroleukemia forms 5-7% of all acute nonlymphatic leukemias. It presents as progressive anemia, hepato-splenomegaly, and the presence of numerous erythroblasts in peripheral blood. Marrow shows gross hyperplasia of erythroblasts, many of which have a superficial resemblance to megaloblasts (hence termed megaloblastoid). As the condition progresses, numerous myeloblasts also appear in peripheral blood.

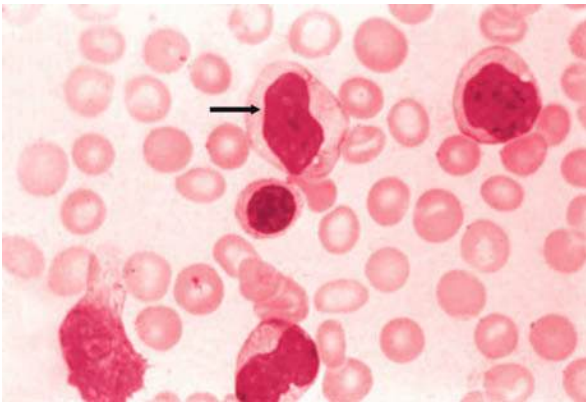


Fig. 154.11: Acute monoblastic leukemia peripheral blood. Note monoblasts (arrow)

Acute Megakaryoblastic Leukemia (M7 Type) (M7)

This may occur rarely. The cells may be indistinguishable from the other types of AML. Histochemical staining for platelet peroxidase and electron microscopy helps to identify the abnormal cells as megakaryoblasts. The histological appearance of the marrow is similar to that of myelofibrosis with presence of increased amounts of bone marrow reticulin.

Bone marrow or stem cell transplantation should be considered on achieving first remission.

TREATMENT OF AML

Except for APML the induction regimen consists of daunorubicin, and cystosine arabinoside (Table 154.10).

Induction therapy: The most popular regimen is the 3+7 combination of daunorubicin 45 mg/m² or 60 mg/m² / I V for 3 days and standard dose cytarabin 100 mg/m² by continuous infusion for 7 days. This combination produces severe neutropenia and when the neutrophil count falls below 0.5 × 10⁹ cells/L fatal infections may occur. Therefore, in order to achieve good results proper germ-free environment and prophylactic antimicrobial therapy are essential. Judicious use of colony stimulating factors such as GM-CSF and G-CSF helps to reduce the duration and severity of drug induced leukopenia. Availability of these cytokines has helped to plan more aggressive and curative chemotherapeutic regimens. Other induction regimens employ idarubicin or mitoxantrone

TABLE 154.10			
Treatment schedule for acute myeloid leukemia (3 + 7 regimen)			
	Dose	Route	Frequency
Daunorubicin	45-60 mg/m ²	Intravenous	Daily for 3 days
Cytosine arabinoside	100 mg/m ²	continous IV infusion or push doses 8-hourly	for 7 days
6-Thioguanine	100 mg/m ²	Oral	Given 8-hourly
or			
6-Mercaptopurine	100 mg/m ²	Oral	Daily

instead of daunorubicin. Therapy related AML is more resistant to treatment.

The induction of remission and its maintenance depends mainly on the effectiveness of initial inducing regimen. The value of maintenance regimen is not as clearcut as in the case of acute lymphatic leukemia. Therefore, many centres do not follow a continuous maintenance regimen.

Neuroprophylaxis may be indicated for acute myelomonocytic leukemia even though the incidence of neuroleukemia is much less compared to acute lymphatic leukemia. BMT has to be considered earlier than in the case of acute lymphatic leukemia.

Transient Myeloid Disorder of Infancy

Transient myeloproliferative disorder or transient leukemia of infancy may occur in the first few weeks of life. It is always associated with Down’s syndrome or trisomy 21. Infants with these disorders have leukocytosis, often with blast cells in peripheral blood, exceeding that in the bone marrow. Most often the blast cells are of megakaryocytic or erythroid lineage and are clonal. Hepatosplenomegaly, pericardial and pleural effusion and liver involvement are common. Majority show spontaneous remission. In 30% myelodysplastic syndrome or acute myeloid leukemia may develop.

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Chronic Leukemias

P.K. Sasidharan, K.V. Krishna Das

Chapter Summary

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Chronic Myeloid Leukemia (CML) and Its Variants

Chronic myeloid leukemia also known as chronic *granulocytic leukemia*, is the most common type of Chronic leukemia affecting adults in India. It forms 30% of the total leukemias. It is clinically characterised by gross overproduction of granulocytes. The disease is rare (less than 5% of total) below the age of 5 years. Maximum

incidence is in the age group 40-60 years, men are affected more often than women (3:2). Neutrophilic leukemia forms more than 95% of the total, though rarely eosinophils and basophils may be the affected cells.

Etiology: Chronic myeloid leukemia is a neoplastic disorder arising from the malignant transformation of a single hematopoietic stem cell. Over 95% of CML shows a constant chromosomal abnormality in the myeloid, erythroid and megakaryocytic cells. This abnormal chromosome known as the *Philadelphia chromosome* (Ph¹) is formed by the reciprocal translocation of the long arms of chromosome 22 and chromosome 9. CML arises from a single pluripotent hematopoietic stem cell which acquires Ph¹ chromosome carrying the BCR-ABL fusion gene which confers a proliferative advantage over normal cells and thus allow the Ph¹ carrying cells to proliferate at the expense of other hematopoietic cells. CML cells also live longer since they resist apoptosis.

Ph¹ chromosome: This chromosomal abnormality was identified in 1960 but only in 1973 that it was attributed to 9:22 translocation which involves a reciprocal translocation of genetic material (containing proto-oncogene C-abl, from chromosome 9 to chromosome 22, at the break point of the bcr locus) resulting in the fusion gene bcr-abl which encodes for an abnormal tyrosine

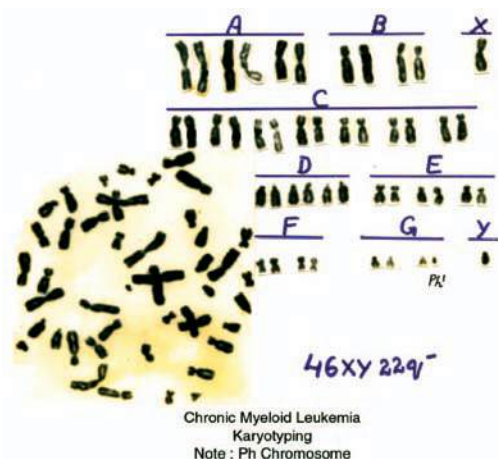


Fig. 155.1: CML karyotype showing Ph¹ chromosome

kinase with abnormally increased activity. There is clonal expansion of the stem cells with bcr-abl probably due to reduced adhesion of progenitor cells to stromal elements, as a result of which the stem cells escape the physiological inhibition. Even though the specific cellular disturbances involved are not fully known it is certain that bcr-abl is directly involved in the pathogenesis as evidenced from animal experiments. Philadelphia chromosomes are demonstrable in the dividing cells from the marrow as well as in the circulating cells. Myeloid, erythroid, and megakaryocytic, cell lines show Ph¹ chromosome (Fig. 155.1).

What causes the mutation in human beings with CML is not known, viruses, radiation, and toxic chemicals are all implicated.

Molecular Pathogenesis of CML

Molecular consequence of t (9;22) (q 34; q 11) translocation is the creation of the fusion gene bcr-abl which encodes for an abnormal tyrosine kinase that mediates an unregulated signal transduction. Depending on the site of breakpoint in the bcr gene the fusion proteins may vary in size from 185 kd to 230 kd. Nearly all patients with CML express 210 kd bcr-abl fusion protein. Fusion proteins of different sizes can be related to different outcomes. 190 kd-bcr-Abl protein has greater tyrosine kinase activity and is a more potent oncogene, than 210 kd protein.

As a consequence of increased tyrosine kinase activity the bcr-abl protein can phosphorylate several substances, thereby activating multiple signal transduction cascades affecting growth and differentiation of cells. Since the bcr-abl signal is constitutive, these cells escape the normal constraints of growth, and become leukemic. On the basis of this findings remission in CML can be defined as hematologic, cytogenetic (disappearance or reduction of Ph¹ chromosome) and molecular (disappearance of bcr-abl gene). Modern PCR assays enable quantitative monitoring of bcr-abl messenger RNA transcripts

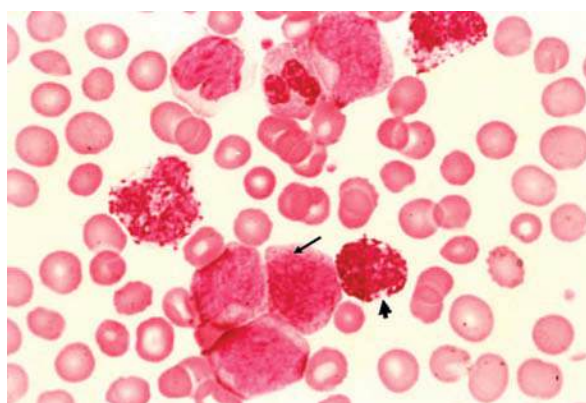


Fig. 155.2: CML: PB × 1000. Note neutrophil myelocyte (arrow) Basophil (arrow head)

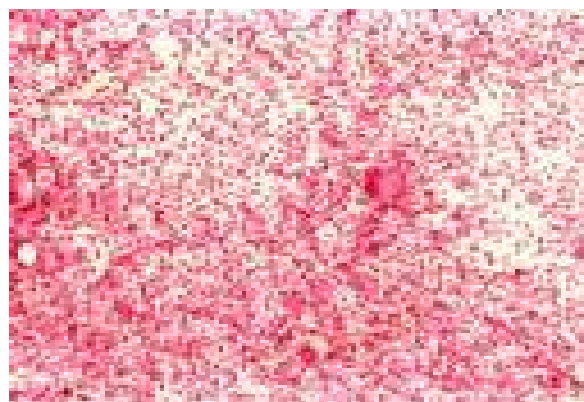


Fig. 155.3: CML: Bone marrow × 400. Note myeloid hyperplasia. All the elements are present

periodically. This is used for assessing prognosis and predicting cure.

Pathology: There is gross increase in granulocytes and their precursors in the blood and marrow. The bone marrow is filled with granulocytes, myelocytes, metamyelocytes and promyelocytes (Figs 155.2 and 155.3). Blasts are less than 5% in the chronic phase but can increase in the accelerated and blast phase. Erythroblasts are usually decreased. Megakaryocytes are normal in number or may be increased. The spleen is grossly enlarged and the liver is moderately enlarged. All organs show infiltration by myelocytes and a smaller number of promyelocytes. When blastic transformation occurs the percentage of blast cells increases in the marrow and peripheral blood. The diagnostic finding in the peripheral blood is the gross leukocytosis with the total leukocyte count often exceeding 50,000 to 100,000/cmm or more and the differential count showing 40-50% neutrophils, 20-30% myelocytes, 10-30% metamyelocytes, 5-10% promyelocytes, an occasional blast and the rest constituted by basophils, lymphocytes and monocytes. Basophil count is increased in CML during the chronic phase and remains elevated even when the patient responds to treatment. Platelet count is increased or

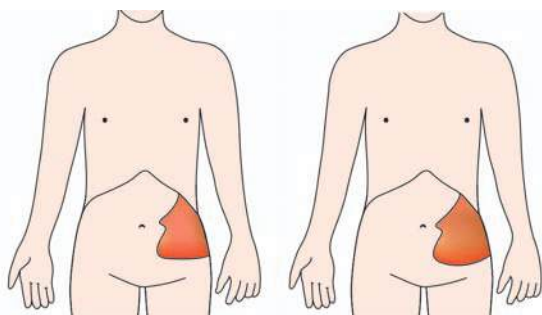


Fig. 155.4: CML: Gross splenomegaly in males aged 34 and 46 without gross impairment of general health

normal. Mild anemia may occur. In an occasional case the peripheral smear may show only leukocytosis with mature neutrophils. This is called *chronic neutrophilic leukemia* or *Emil-Weil's CML*.

Serum proteins are elevated with increase in gamma globulin. Leukocyte counts exceeding 300,000 cmm may give rise to cellular hyperviscosity syndrome. The serum uric acid is high due to more rapid cell turnover. Basal metabolic rate is increased. **Leukocyte alkaline phosphatase score (LAP score)** is low or absent in more than 90% in the chronic phase. Serum vitamin B₁₂ and B₁₂ binding capacity are elevated due to increase in transcobalamin I and II.

CLINICAL FEATURES

The disease is insidious in onset and it is almost impossible to assess the duration of illness when the patient comes up for examination. Some asymptomatic cases are picked up by routine blood tests. Majority of patients present with the feeling of a mass and dull ache in the abdomen caused by splenomegaly. The spleen is grossly enlarged in over 95% of cases (Fig. 154.4). Splenic size correlates reasonably well with the total leukocyte count. Gross splenomegaly is associated with episodes of splenic infarction which present as painful episodes. Some cases reveal bone tenderness. Pallor, exertional dyspnea, and tachycardia may occur due to moderate or severe anemia. Hypermetabolism leads to loss of weight, lassitude and night sweats. With progress of the disease the abdomen becomes distended due to huge splenomegaly and moderate hepatomegaly. Nutritional deficiencies, cachexia and intercurrent infections complicate the picture. When the leukocyte count is high, the ocular fundus shows hyperemia of the disc, venous engorgement and occasionally hemorrhages.

Complications

Several complications may occur from time-to-time. These are infections, malnutrition, anemia, trauma, infarction of the spleen and secondary gout. Thrombotic tendencies due to high leukocyte counts, consequent leukostasis and

associated thrombocytosis, develop resulting in venous thrombosis and priapism. Hemorrhagic complications may also occur because of the defective platelet function despite a normal or high platelet count.

Most of the CML patients present in the chronic phase with very few blasts in the peripheral blood and marrow and after a variable period of months to years enter the more serious and inescapable complication of **blastic transformation** (blast crisis). A range of additional non-random chromosomal changes occur including duplication of Ph chromosome and trisomy 8. Multiplication or deletion of tumour suppressor genes such as p16 and p53 occur with variable frequency. Probably these contribute to the blastic transformation. Blastic transformation is heralded by unresponsiveness to conventional treatment and the development of severe anemia, fever, infections, lymphadenopathy, bleeding tendencies and rapid deterioration of general health. In 75% of cases, the blast transformation is into myeloid (AML) and in 25% lymphatic (ALL). Extramedullary tumours consisting of myeloblasts may develop especially in the bones, lymph node and skin. These are called **granulocytic sarcomas**. The peripheral blood count and the proportion of blast cells increase, the blasts cells forming more than 20 to 30%. Thrombocytopenia develops as well. In the blastic stage the prognosis is that of AML, but response to therapy is less satisfactory than primary AML. The lymphatic blast crisis responds better to treatment than the myeloid type. Successful chemotherapy in blast phase converts the clinical and blood picture to that of CML. A few patients may develop secondary myelofibrosis even during the chronic phase.

Diagnosis

CML should be considered in the diagnosis when there is moderate to massive splenomegaly in the presence of reasonably good general health. A very high total leukocyte count and the blood smear examination confirms the diagnosis. Presence of thrombocytosis and basophilia are supporting evidences. Low or absent leukocyte alkaline phosphatase score almost confirms the diagnosis. When the diagnosis is in doubt, demonstration of the Ph¹ chromosome by karyotyping or FISH (fluorescent *in situ* hybridization) is diagnostic of CML. In addition, highly sensitive and specific molecular probes are now available to detect the presence of bcr-abl in peripheral blood or bone marrow leukocytes. This helps to diagnose and monitor therapy. PCR testing of peripheral blood RNA is so sensitive as to detect one Ph⁺ cell in 10⁶ cells. For clinical purposes bone marrow examination and genetic studies are not mandatory.

Differential Diagnosis

Other causes of splenomegaly such as myelofibrosis, portal hypertension, chronic malaria, leishmaniasis, and hemolytic anemias should be considered in the differential

diagnosis Leukemoid reactions should be excluded. Leukocyte alkaline phosphatase score is low in CML, whereas in leukemoid reactions it is high. Idiopathic myelofibrosis may pose some difficulty to be distinguished from CML. Myelofibrosis is characterised by gross splenomegaly, only modest elevation of the total leukocyte count (15,000 to 30,000) and is characterised by a leuko-erythroblastic blood picture. Teardrop shaped erythrocytes are characteristic. Bone marrow is scanty and trephine biopsy reveals fibrosis.

Course and Prognosis: Chronic myeloid leukemia runs a relentless course to end fatally in all cases. Unlike as in acute leukemia, medical therapy does not bring about predictable cure. Untreated, the average period of survival used to be 2-3 years in the early 1990s. Treatment given early in the disease brings about clinical relief and clears the blood picture, but the disease is not eradicated, and therefore, relapse is the rule. About 20% patients survive up to 10 years. Death is due to blastic transformation, infection, hemorrhage or rarely drug toxicity. Presence of Ph¹ chromosome confers a better prognosis. Ph¹ positive cases do better and live longer with an average period of survival of 4 years whereas Ph¹ negative cases invariably run a downhill course and die within one year. Ph¹ chromosome negative cases have been termed as *atypical CML*, and most of these occur in children.

Bone marrow transplantation brings about cure in the vast majority who survive the procedure. With the introduction of the specific tyrosine kinase inhibitor, Imatinib the disease undergoes clinical, hematological and even molecular remission. Symptoms are completely abolished and quality of life improves.

Treatment: Since conventional medical therapy does not eradicate the disease, the aim is to relieve symptoms and bring about clinical and hematological normalcy. The high leukocyte count and organomegaly subside completely with treatment and the patient becomes asymptomatic though a few abnormal cells and the Ph¹ chromosomes persist.

Drugs

Imatinib (Gleevec)

The *inhibition of tyrosine kinase* activity is the most effective therapy for CML if bone marrow transplantation is not available. The signal transduction inhibitor (STI 571), imatinib selectively inhibits the fusion protein tyrosine kinase of the bcr-abl gene. It has been approved for use in CML patients as first line therapy. It is given in doses of 400 mg orally as single dose for adults continuously for an indefinite period. At times, upto 800 mg can be given daily. It is still not clear how long the treatment has to be continued. Within weeks of starting therapy the leukocyte counts, the abnormal cells and splenomegaly come down and full clinical normalcy is

restored. The median survival has also improved. Complete cytogenetic response at 12 months was 69% and at 60 months was 87%. Blast crisis develops in 7% even while on treatment. Overall median survival at 60 months in those who were put on imatinib from the start was 89%.

Cessation of therapy promptly brings back the leukocytosis and abnormal blood picture. 60-80% show full clinical response with 68% showing cytogenetic clearance in the chronic phase. Real time PCR measures the ratio of BCR-ABL transcripts to BCR transcripts. This helps to monitor recovery at the molecular level.

Imatinib may produce response in accelerated and blastic phase as well, even though the results are poorer. In such cases the duration of response is also shorter. Adverse side effects include peripheral and periorbital edema, muscle cramps, joint pains, neutropenia, elevated liver enzymes and rarely, congestive heart failure. Resistance to imatinib has been recorded. Administration of hydroxyurea in doses of 1-2 g orally daily in combination with imatinib restores the clinical effects of the latter. Combination therapy with two tyrosine kinase inhibitors is also under evaluation.

Imatinib mesylate is finding its use in several other neoplasms where the tyrosine kinase receptor is expressed prominently. The present cost of imatinib therapy is Rs. 300 /day.

Dasatinib (Bristol-Myers Squibb) is an ABL kinase inhibitor that differs from imatinib in that it combines to both the active and inactive conformations of the ABL kinase domain. In imatinib resistant cases and in those who are intolerant to imatinib, dasatinib given orally in doses ranging from 15-240 mg/day leads to hematological and cytogenetic response. Major adverse effects include reversible myelosuppression and non-malignant pleural effusion.

Nilotinib (Novartis) – This is a new orally active aminopyrimidine-derivative tyrosine kinase inhibitor which is more potent than imatinib in vitro against CML. In doses starting from 50 mg oral daily and worked up to 1200 mg od or 400-600 mg bd, this drug is effective during the chronic phase, accelerated phase and blastic phase in diminishing effectiveness. Adverse effects include myelosuppression, transient direct hyper-bilirubinemia and rashes.

Hydroxyurea (hydroxycarbamide) This used to be the drug of choice for over 5 decades for the treatment of CML before the advent of interferon alpha and imatinib.

The dose varies from 0.5-2 g daily orally in divided doses. It brings about a steady fall in total leukocyte count with reduction in the immature cells within 1-2 months. The mechanism of action is inactivation of the enzyme ribonucleotide reductase with consequent inhibition of cellular DNA synthesis leading to cell death in the

S-phase. Adverse side effects include gastrointestinal upsets, marrow suppression, skin pigmentation, alopecia and ulceration in the feet. These regress on stopping the drug. The cost of treatment is Rs. 70/day.

Busulphan (myeleran): This is an alkylating agent belonging to the group of sulphur mustards. It is given orally in the dose of 2-8 mg/day. Blood counts are done at weekly intervals. By 2-3 weeks the total leukocyte count starts falling. At this stage, the dose is reduced and continued till the total leukocyte count falls below 10,000/cmm. At this stage the splenomegaly also disappears. In the majority of cases, this is achieved when the total dose reaches 200-220 mg of busulphan. Once the leukocyte count falls below 10,000/cmm busulphan is withdrawn to avoid marrow suppression. Further treatment is indicated when the total leukocyte count goes above 50,000/cmm. Busulphan is effective in over 75% of cases to give symptomatic relief. Relapses also respond to busulphan, but with the passage of time the response becomes less satisfactory and the duration of clinical remission progressively shortens.

Adverse side effects include bone marrow aplasia, allergic manifestations, and pigmentation resembling Addison's disease, (Fig. 155.5) but without the endocrine abnormalities. Rarely busulphan produces extrinsic alveolitis and interstitial pulmonary fibrosis (busulphan lung). This is an absolute contraindication for further busulphan therapy. The use of busulphan has been stopped in preference to hydroxyurea or imatinib. Treatment with busulphan costs Rs. 500/month.

Interferon Alpha (IFN alpha)

IFN was the first line of therapy for all patients with CML before the advent of imatinib. It has to be given by subcutaneous or intramuscular injection daily for a period of two years or more in a dose of 3 to 9 million units IM daily for 4 to 6 weeks initially and later at lower doses for long periods. Adverse effects include 'flu' like

syndrome, anorexia, diarrhea, weight loss, polyneuropathy, psychosis and others. The drug is costly (Rs. 1500/day). The exact duration of therapy is not yet defined.

Sustained disappearance of Ph occurs only in 5-10%. Better results are achieved by combination of IFN with cytarabine. IFN alpha is not used routinely for CML at present.

Management of Hyperviscosity State

Leukapheresis using a cell separator may be temporarily beneficial in hyperviscosity state and may be required when the total leukocyte count exceeds 300-400,000/cmm. The procedure may also bring about temporary hematological remission.

Bone marrow transplantation (BMT): Since this is the only predictable curative modality of treatment at present, it should be considered as early as possible after diagnosis. BMT done in the chronic phase of the disease, and in younger subjects, gives the best results with cure rates well above 70%. The procedure related mortality is a major deterrent in opting for this form of therapy. At present the cost of BMT in India is Rs.10 to 15 lacs. BMT done during the accelerated or blastic phase is less successful and more risky.

Variants of CML

EOSINOPHILIC LEUKEMIA

In this disorder the patients present with marked eosinophilia often above 100,000/cmm with the clinical picture of chronic myeloid leukemia. The blood shows eosinophils, eosinophil myelocytes and occasional neutrophil myelocytes. In a few cases Ph¹ chromosome may be found.

CHRONIC BASOPHILIC LEUKEMIA

This clinically resembles CML, but there is gross increase in basophils. A few neutrophils may be present. Ph¹ chromosome may or may not be present.

CHRONIC MONOCYTIC LEUKEMIA

This term is used to denote the condition in which the monocytes are also considerably increased in addition to the blood picture of CML.

CHRONIC MYELOMONOCYTIC LEUKEMIA

This entity which is considered as one of the myelodysplastic syndromes is seen in patients over the age of 50 years and the clinical picture resembles that of refractory anemia with excess of blasts (RAEB). Blood shows absolute elevation of monocytes (2×10^9 litre or more), many of them being atypical. The spleen enlarges



1046 Fig. 155.5: CML female pigmentation due to myeleran therapy



Fig. 155.6: Juvenile CML in blastic crisis.
Note: The gross lymphadenopathy (arrow)

progressively. The main difference from AML (M2, M4 and M5) is that the count of promyelocyte + blasts in the marrow is less than 30%. Over one-third of the cases develop AML on follow-up.

CHRONIC MYELOID LEUKEMIA IN INFANTS AND CHILDREN

In children only less than 5% of leukemia is formed by CML. There are two types.

1. Ph¹ positive CML, which has the same biological behaviour and response to therapy as adult CML, and;
2. Ph¹ negative CML which is more frequent. These may occur at any age, between 2 months to 9 years, though the peak incidence is between 1 and 2 years. This is termed *juvenile CML*.

Juvenile CML

Juvenile CML is characterised by the proliferation of myelocytes in bone marrow, peripheral blood and tissues. Both sexes are equally affected. They show marked enlargement of spleen and liver. The peripheral blood shows increase in myelocytes and monocytes, but the total leukocyte count may be lower than that in adults. Platelets are often reduced. There is increase in fetal hemoglobin which may form upto 85% of the total. The disease runs a more rapid course and ends fatally within one year of diagnosis (Fig. 155.6).

A diagnostic feature is the finding that, on *in vitro* cultivation of peripheral blood stem cells stimulated by GM-CSF, only colonies of monocytes are produced whereas in Ph¹ positive CML, both myelocytes and monocytes are produced. There is suggestion that juvenile CML may be more akin to acute myelomonocytic leukemia.

Treatment: The response to conventional drugs is less satisfactory. Cytosine arabinoside and 6-mercaptopurine

are found to be partially effective. Isotretinoin given orally in a dose of 100 mg/m² daily is reported to produce durable improvement in clinical and laboratory parameters. The newer drugs and BMT have to be employed when indicated.

Chronic Lymphatic Leukemia (CLL) and Its Variants

This is the most common type of leukemia occurring in adults in the west, but in India, this is much less common. In the Mongoloid and Chinese races also the incidence is very low. Chronic lymphatic leukemia is a neoplasm arising usually from a clone of B lymphocytes, occurring usually above the age of 45 years, characterised by the presence of excessive number of mature looking lymphocytes in the bone marrow and peripheral blood, and organomegaly due to infiltration by lymphocytes. In around 2% of cases the neoplastic cells are of T-cell origin and this is termed T-cell prolymphocytic leukemia (PLL). *The modern trend is to include chronic lymphatic leukemia and its variants such as hairy cell leukemia and prolymphocytic leukemia along with primary lymphatic malignancies. This is so, because there is considerable overlap in the cell characteristics and clinical manifestations.*

CLL is now considered to be two related entities, both originating from antigen stimulated mature B-lymphocytes which either avoid death through the intercession of external signals or die by apoptosis, only to be replaced by proliferating precursor cells. The monoclonal populations of B-cells shows CD19, CD5 and CD23 markers and have reduced levels of IgM, IgD and CD 79b which is, the phenotype of mature B-cells. Pathological features of lymph nodes resemble those of small cell lymphocytic lymphoma. Antigenic stimulation and presence of pro-CLL activating factors have been identified. These cytokines help the CLL cell to proliferate and avoid apoptosis. CLL cells are highly dynamic with brisk proliferation rates and reduced apoptosis (0.1 to 1% of the clone/day). The size of the spleen and lymph nodes bear some relationship to the proliferation rate.

At present early treatment is advised, newer modalities of therapy are being tried.

Pathology: Most of the cases are B-lymphocyte type, though rarely T-lymphocytes may be involved. These cells proliferate. The lymph nodes are enlarged and histologically resemble diffuse well-differentiated lymphoma. Liver, spleen and bone marrow show varying degrees of lymphocytic infiltration. Progressive replacement of the normal bone marrow leads to compensatory hyperplasia of the yellow marrow, but finally the bone marrow fails. Lymphocytes may infiltrate other organs and the skin. At times monoclonal paraproteins of the kappa or lambda type are produced by the tumour cells even without antigenic stimulation.

Normal immune mechanisms of the host are impaired since the abnormal immunocytes are functionally incompetent. Other autoimmune disorders like hemolytic anemia, autoimmune thrombocytopenia, rheumatoid disease and Guillain-Barre syndrome may occur in association with chronic lymphatic leukemia.

CLINICAL FEATURES

Males are affected twice as frequently as females. Most of the patients are above 50 years. The disease is rare in younger individuals. The onset is insidious with fatigue, tiredness and vague ill health, and on many occasions, the disease is revealed by routine physical examination and/or blood examination in asymptomatic subjects. Clinically, two forms of the disease can be identified – benign and aggressive forms. In about 80% of cases, the disease presents with painless lymphadenopathy. The nodes are moderate to large in size, rubbery in consistency, discrete, and are most prominent in the neck and axillae. Tonsils may be enlarged considerably. Enlargement of the lacrimal and salivary glands is known as *Mikulicz's syndrome*, but this presentation is more common with *lymphoma*. Anemia develops due to marrow infiltration by lymphocytes replacing the erythroid series, auto-immune hemolysis, hypersplenism, vitamin B₁₂ or folic acid deficiency or even iron deficiency and blood loss.

Spleen is moderately enlarged (5-10 cm) in 75% of cases and in 10% splenomegaly may be the only sign in the absence of lymphadenopathy. Splenic enlargement can lead onto hypersplenism and associated clinical problems. Cutaneous involvement presents as nodules, or diffuse infiltration producing a picture of erythroderma (*homme rouge*). Some have an exaggerated cutaneous response to mosquito bites. Immunodeficiency due to poor T-cell function and hypogammaglobulinemia contribute to recurrent infections of the respiratory and urinary tracts. Intractable pruritus is a distressing feature.

Diagnosis

The disease should be suspected from the clinical findings. Diagnostic finding in peripheral blood is the marked leukocytosis ($50-200 \times 10^9/L$ or 50,000-200,000/cmm) consisting almost totally of small mature lymphocytes. The cells are uniform in type and blasts are usually not seen except in the later stages (Fig. 155.7). The total leukocyte count does not bear a direct relationship to the tumour load. Many lymphocytes are ruptured and these are termed *smudge cells* or *basket cells*. The bone marrow is replaced by lymphocytes which form 90-95% of the total cells. Pseudohyperkalemia can occur due to severe leukocytosis (Fig. 155.8).

Differential diagnosis includes other causes of lymphocytosis like viral infections – the lymphocytosis in such infections is not persistent, the patients are

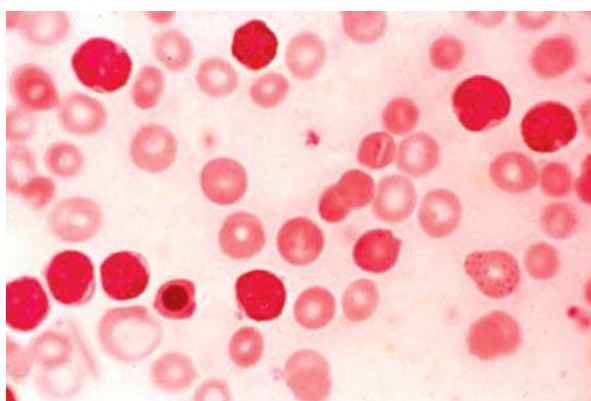


Fig. 155.7: Peripheral blood film chronic lymphatic leukemia. Note: Mature looking lymphocytes

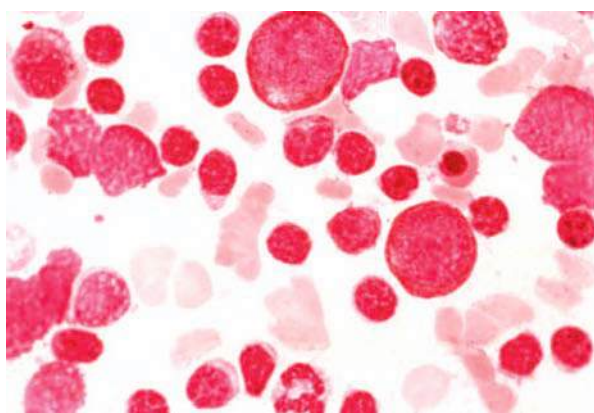


Fig. 155.8: Bone marrow chronic lymphatic leukemia. Note: Infiltration by lymphocytes

younger, the clinical setting is different and the cells are not monoclonal. Low grade small lymphocytic B-cell lymphoma comes in the differential diagnosis, since the lymph node histology is similar; the distinction is basically made by clinical evaluation. CLL is associated with blood lymphocytosis and marrow lymphocytosis with or without lymphadenopathy. Whereas lymphoma is primarily associated with lymphadenopathy but marrow and blood lymphocytosis are uncommon except in late stages when these organs are involved. Prolymphocytic lymphoma closely mimics CLL but the cells here are larger. Hairy cell leukemia can be differentiated by the larger size of the lymphocytes and the electron microscopic hairy projections on the cells (Fig. 155.9). Waldenström's macroglobulinemia is another condition to be differentiated from CLL.

A system of *clinical staging* has been accepted since it correlates with the response to treatment and survival.

Course and Prognosis

In the Caucasian races, the disease follows a slow and progressive course, remaining asymptomatic for several years, and ultimately ending fatally because of infection, bone marrow failure, cachexia, or iatrogenic complica-

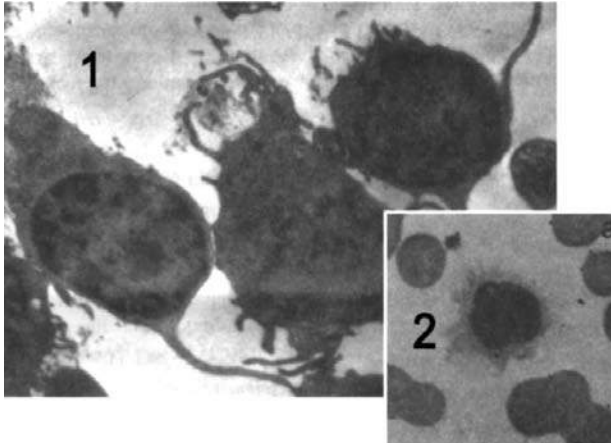


Fig. 155.9: Hairy cell leukemia (1) electron microscopy (2) blood film

tions. In general, patients with stages I, II and III disease survive for 150, 101 and 71 months respectively. Stage III and IV do not show any significant difference in survival. Though acute lymphoblastic or even acute myeloid leukemia may occur terminally in a few cases, unlike chronic myeloid leukemia terminal blast crisis is much less common. CLL can transform to an aggressive large B-cell high grade lymphoma at any point in the course of the disease and this is called **Richter's syndrome**.

Staging of Chronic Lymphatic Leukemia (Rai 1975)

Stage 0	Lymphocytes 15×10^9 /litre or more in peripheral blood and 40% or more in the bone marrow. No enlargement of lymph nodes, spleen or liver. Hemoglobin is above 11 g/dL and platelet count is over 100×10^9 /L
Stage I	Features as in Stage 0, but with enlarged lymph nodes
Stage II	As in stage 0, but with enlarged spleen, liver or both. Lymph nodes may or may not be enlarged
Stage III	As in stage II, but with hemoglobin less than 11g/dL
Stage IV	As in stage III, but with platelet count below 100×10^9 /L

In 1981 Binet suggested an alternate three stage classification considering total lymphoid mass. Stage A having less than three areas of lymphoid enlargement, Stage B having three or more areas of lymphoid enlargement. The advanced form of stage C includes all patients having anemia and thrombocytopenia.

The aggressive form is more common in Indians. This type follows a more rapidly progressive course, punctuated by episodes of infection. Death occurs within 2-3 years in the advanced stages, in the majority of cases. Since the total leukocyte count does not bear a direct relation to the tumour load, this is not useful in prognosis. High leukocyte count by itself is not an indication for starting

therapy. In general the following are the indications for starting treatment:

1. Anemia
2. Thrombocytopenia
3. Disease related symptoms
4. Markedly enlarged spleen
5. Disfiguring or symptomatic lymph node enlargement
6. Blood lymphocyte doubling time less than 6 months
7. Prolymphocyte transformation and
8. Richter transformation. Treatment helps to allay symptoms and relieve suffering and hence treatment is indicated in all symptomatic cases though it is not clear whether it prolongs life.

A subgroup of CLL is present in which the leukemic cells show deletion of chromosome 13q14 and also contain mutated immunoglobulin heavy chain variable (VH) region genes. This subgroup has a better prognosis. It is seen in 50% of cases of CLL. Other conditions where the gene situated at 13q14 is deleted include non-Hodgkin's lymphoma and multiple myeloma. Trisomy 12 confers a poor prognosis to CLL.

TREATMENT

Although it is customary in the west to withhold treatment till the disease reaches stages III or IV, in Indian subjects treatment may have to be started earlier, depending on the progress and extent of the disease. Specific treatment is with **chlorambucil** (*Leukeran BW*) started usually with 2 to 4 mg per day continuously till the total leukocyte count becomes normal and the morphological lesions disappear. An alternate dosage schedule is 0.4 mg/kg/body weight of total dose divided into 4 equal doses and given on days 1 through 4. This cycle can be repeated every two to 4 weeks. Cyclophosphamide 50-100 mg/day can be used instead of chlorambucil. Corticosteroids, given in cycles, enhance the effect of alkylating agents. Optimal improvement occurs in 1-2 years, though the neoplasm is not eradicated. Combination chemotherapy has been beneficial in resistant cases. The usual combination is cyclophosphamide, doxorubicin, vincristine and prednisolone.

Fludarabine which is a nucleoside analogue given in a dose of 25 mg/m² body surface area IV daily for 5 days every 28 days is effective in bringing about higher response rates and longer remissions especially in chlorambucil resistant cases. The drug is expensive. Another nucleoside analogue, **Cladribine** also is equally effective. Pentostatin which is a purine analogue and Alemtuzumab which is a monoclonal antibody are occasionally used in patients refractory to common drugs.

Infective episodes demand prompt treatment with antibiotics. Immunoglobulin can be given prophylactically in doses of 50-100 mg/kg/bw periodically to reduce the frequency and severity of bacterial infections.

Leukapheresis has been found to be beneficial in removing the leukemic cells and thereby reducing the

tumour load in intractable cases and also to reduce leukostasis.

The role of bone marrow or stem cell transplantation has not been definitely established. Results and evidence based guidelines have not yet become clear.

Monoclonal antibodies especially campath-1H has been tried in relapsed and refractory CLL. The response rate is around 40%.

Combination Therapy

- A. Fludarabine 25 mg/m²/day plus cyclophosphamide 250 mg/m²/day given IV for 3 days.
- B. Fludarabine 24 mg/m²/day plus cyclophosphamide 150 mg/m² given orally for 5 days repeated at 4 week intervals for six course has given better mission rates and quality of life, compared to others drug schedules.

Ref: D. Catovsky, et al. Assessment of fludarabine plus cyclophosphamide for patients with chronic lymphocytic leukemia (The CRF CLL 4 trial) a randomised controlled trail. The Lancet 2007;370:230-39.

Hairy Cell Leukemia

Syn: Leukemic reticuloendotheliosis

This is a variant of chronic lymphatic leukemia and is rare. It is seen in the age group 40-80 years and males are affected four times more common than females. Presents with massive splenomegaly, anemia, relative lymphocytosis, more often with a low total leukocyte count, often pancytopenia is present. The B-lymphocytes are larger than that in CLL and show the characteristic fine hairy projections which can be detected in peripheral smear and bone marrow, but best brought out by electron microscopy.

The cytoplasm shows a number of villi which give the hairy appearance. The diagnostic histochemical test for hairy cells is *acid phosphatase staining reaction resistant to the action of tartarate*. Bone marrow is infiltrated heavily and it is difficult to aspirate and often a dry tap is obtained. Marrow biopsy and imprint smears show the hairy cells.

Treatment: In the early stages corticosteroids are useful. The disease responds best to splenectomy. Other drugs include pentostatin (Deoxycoformycin, Nipent-Parke Davis), a purine analogue and Cladribine (2-Chloro-deoxyadenosine-Leustatin-Ortho Biotech) which produce lasting remissions.

Dose: Pentostatin - 4 mg/m²/week for three weeks, then once in 2 weeks for 6 weeks followed by once a month for 6 months, given intravenously.

Cladribine is given in doses of 0.1 mg/kg/bw by continuous IV infusion for 5 days every month. Alpha interferon given in doses of two million units/m² thrice a week used to be the treatment of choice. It is most probably only palliative.

Prolymphocytic Leukemia

This is a rare variant of CLL, seen in males above the age of 60 years and showing gross splenomegaly and a very high white cell count, often above 400 × 10⁹/L. Lymphadenopathy is rare. The characteristic cell is the large lymphocyte showing a prominent nucleolus. The course is rapidly downhill and prognosis is poor.

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Myelodysplastic Syndrome

K.V. Krishna Das

Chapter Summary

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- Clinical Features 1051
- Management 1052
- Pre-leukemia 1053
- Leukoerythroblastic Blood Picture 1053

General Considerations

Myelodysplastic syndromes (MDS) comprise a group of heterogenous hematopoietic disorders affecting predominantly the elderly age groups. The overall general disease incidence is 4 per 100,000 people, but in the age group above 60 it may go upto 30 or more per 100000.

In India the disease affects relatively younger persons, median age group being 45 years, children also may be affected rarely.

The term MDS covers a range of neoplastic disorders of hemopoietic tissues in which the progeny of transformed stem cell gradually expands and replaces normal marrow cells. The hallmark of MDS is ineffective hematopoiesis evidenced by peripheral cytopenias despite a normo- or hypercellular bone marrow. Clinically and hematologically five distinct conditions can be included under this term. These are given below (FAB) classification.

1. Refractory anemia (RA)—which do not respond to nutritional supplements.
2. Refractory anemia with ring sideroblasts—presence of excess of ring sideroblasts in bone marrow (RARS) (see Fig. 149.18).
3. Refractory anemia with excess of blasts—1-4% in peripheral blood and 5-20% in bone marrow (RAEB).
4. Refractory anemia with excess blasts in transformation—5% blasts in peripheral blood and 20-30% in bone marrow (RAEB-E).
5. Chronic myelomonocytic leukemia (CMMOL).

PATHOGENESIS

MDS results from the expansion of an abnormal clone of stem cells, with concomitant suppression of normal hemopoiesis. The main pathological processes include:

- a. Augmented apoptosis leading to ineffective hematopoiesis and peripheral cytopenias and
- b. Transformation to acute myeloid leukemia (AML)

MDS originates in the pluripotent stem cells and involves all myeloid cell lines and in some cases, possibly lymphoid cells as well.

The cells produced by the abnormal clone do not mature normally, and are also functionally abnormal. They survive poorly in the blood and bone marrow. The final outcome is the development of pancytopenia. The precise abnormality varies from patient-to-patient. The clonal evolution is characterised by increasing chromosomal abnormalities, progressively increasing malignant characteristics in the bone marrow and the final evolution into AML with the appearance of large number of blast cells. It is difficult to define where MDS ends and AML begins though several attempts have been made to define the condition as far as possible. Several newer criteria have been added to modify the FAB classification.

One popular scheme is the WHO classification which identifies 8 classes. Scoring systems which quantify the risk of development of AML and prognostic factors which modify treatment schedules have been made. The International Prognostic Scoring System (IPSS) which is well accepted, takes into account three parameters (see Table 156.2).

(1) Percentage of blasts in the bone marrow (2) karyotype and (3) number of cytopenias. The total score 0-2.5 is taken to help in predicting the risk of progression and survival MDS is characterised by regular chromosomal

abnormalities. Interstitial deletions involving the long arm of chromosome 5 are among the most common cytogenetic finding. The clinical and hematological features, response to treatment and prognosis depend to a great deal on the cytogenetic abnormalities.

The common chromosomal abnormalities include trisomy 8, monosomy 5 or 7, loss of y and interstitial deletion of the long arm (q) of 5,7,11 and 20. Deletion of bands q13 to q5 of chromosome 5 is the most frequent abnormality. Patients with this type of deletion show particular features and hence this is even known as 5-q syndrome. This is seen more in elderly females. Oncogene mutations are reported in MDS—ras mutation in upto 40% of cases and p53 mutations in 5-10%. Activation of ras oncogene plays a part in the pathogenesis, even though its clinical significance is not yet clear. Cases with N-ras mutation have higher mortality.

MDS has a great predisposition to develop into acute myeloid leukemia. This transition may be insidious or rapid. In some cases there may be clinical similarity but they can be distinguished by clinical features and investigations.

The hematological findings include macrocytic anemia, normal or raised platelet counts, erythroid hypoplasia and mononuclear megakaryocytes in the marrow. The features of MDS vary depending on the genetic defect.

CLINICAL FEATURES

MDS affects the older age groups more, though children may also be affected at times. The disease presents insidiously as cytopenias affecting the erythroid, myeloid and megakaryocyte cell lines, resulting in anemia, leukopenia and thrombocytopenia. The presenting features are those of refractory anemia, recurrent infections, and hemorrhage. Organomegaly (liver, spleen and lymph nodes) is rare, or if at all present, mild compared to AML. The bone marrow is cellular and shows evidence of defective maturation (i.e.) dysplastic changes in all cell lines. The morphological abnormalities include arrest of maturation, nuclear division without cytoplasmic division and other changes. In over 90% of cases chromosomal changes are demonstrable. The erythrocytes may be macrocytic. Neutrophils may show Alder-Reilly and Pelger Huët anomalies (Figs 156.1 and 156.2). In Pelger-Huët anomaly the granulocytes in peripheral blood show rod, dumbbell, peanut or spectacle like nuclei, with coarse chromatin. This abnormality may be inherited or acquired. There is no gross disturbance of function.

Though it is difficult to distinguish MDS from AML in borderline cases, in the majority this distinction can be made by clinical and laboratory parameters (Table 156.1). RA and RARS generally show only less than 1% of blast cells in peripheral blood. Their median survival is over 50 months.

RAEB and RAEB-E show about 5% blast cells in peripheral blood. Their median survival is 5-12 months.

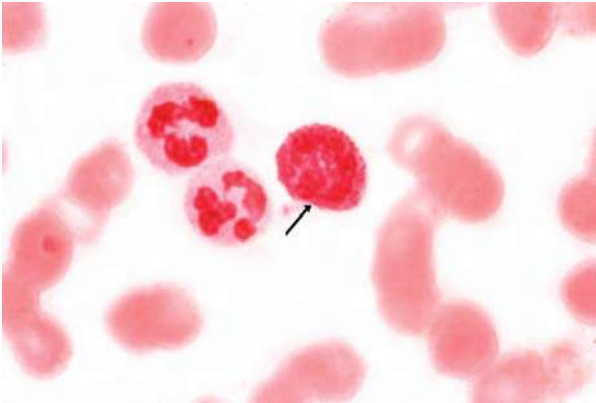


Fig. 156.1: Alder-Reilly anomaly neutrophils: heavy azurophilic granules in some neutrophils—(arrow), monocytes and lymphocytes—Functional significance not clear

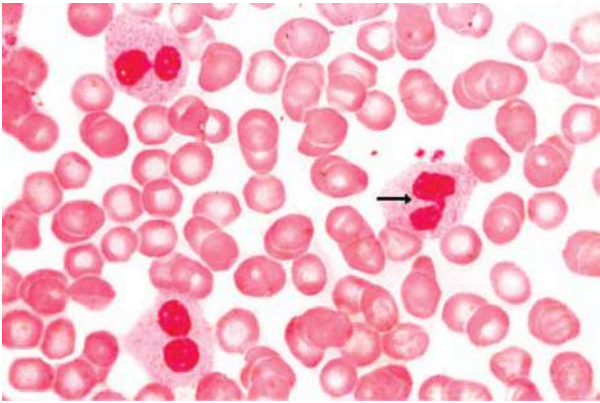


Fig. 156.2: Peripheral blood smear Pelger-Huët abnormality neutrophils: Note: The absence of segmentation of neutrophils—arrow points to bilobed nucleus—Functional significance is not clear

Prognosis depends on the type of MDS 50% of cases die within one year of diagnosis due to marrow failure. About 30% develop AML. Groups 3, 4 and 5 show a greater tendency to evolve into AML. Prognosis also depends on the type of chromosomal abnormalities. Prognostic scoring systems based on bone marrow blasts, karyotype and severity of cytopenias are available. Primary MDS has to be distinguished from treatment related MDS (t-MDS), also known as secondary MDS, which may follow radiotherapy or chemotherapy for malignancies such as lymphomas, myeloma and carcinomas.

MANAGEMENT

Management of MDS can be divided into two broad categories (Tables 156.3 and 156.4)
A. For those with low and intermediate- 1 risk
B. For those with intermediate- 2 and high risk
Since the pathogenesis of these two groups is different, treatment goals are also different.

Main aims are:
1. To improve hematopoiesis and correct the cytopenias
2. To improve survival and
3. To delay the transition to AML.
For FAB classes 1 and 2 monitoring and occasional blood transfusion may be the only treatment required over prolonged periods.
Several treatment strategies have been evolved at present. These include single agent chemotherapy with cytosine arabinoside, 5-azacytidine, topotecan, oral idarubicin and hydroxyurea. Combination chemotherapy with or without hemopoietic growth factors is used in some cases. Anti-cytokine therapy using the following combination is found to benefit some (Table 156.4).
Pentoxifylline 800 mg tds
Ciprofloxacin 500 mg bid
Dexamethasone 4 mg qid
A small proportion go into cytogenetic remission. Antithymocyte globulin (ATG) given to selected cases brings about remission in 40% of cases. Supportive

TABLE 156.1 Showing the differences between MDS and AML		
	Myelodysplastic syndrome (MDS)	Acute myeloid leukemia (AML)
1. Age group	More in the older age groups	All age groups
2. Course	More protracted	More acute
3. Hepatosplenomegaly	Rare	More common
4. Peripheral blood studies	Cytopenias and morphological abnormalities. Blasts rare—usually below 5%.	Presence of blasts more frequent, demonstrable invariably
5. Nonspecific hematological phenomena	Red cell enzymopathies, low levels of neutrophil alkaline phosphatase, raised fetal hemoglobin levels, altered blood group antigens, positive Ham's tests	Rare
6. Bone marrow	Blasts less than 30% in many cases much liver dysplasia present	30% or more
7. Chromosomal studies	Abnormality in 90%	Variable
8. Prognosis	Depends on the type	Uniformly bad
Note: Though in the majority of cases these features help to distinguish MDS from AML, in a borderline case this distinction can be made only by prolonged observation.		

TABLE 156.2

IPSS scoring system					
Allotment of scores	0	0.5	1.0	1.5	2
Bone marrow blasts%	<5	5-10		11-20	21-30
Karyotype	Good	Intermediate		Poor	
Number of cytopenias	0/1		2/3		

TABLE 156.3

Risk stratification	
IPSS score	IPSS risk group
0-0.5	Low
0.5-1.0	Intermediate – 1
1.5-2.0	Intermediate – 2
>2.5	High

TABLE 156.4

Relation between IPSS risk groups and disease progression			
Risk group	Probability for AML%	Median time for AML to develop years	Median survival years
Low	19	9.4	5.7
Intermediate-1	30	3.3	3.5
Intermediate-2	33	1.1	1.2
High	45	0.2	0.4

measures include packed cell transfusions, use of growth factors G—CSF and G—MCSF and erythropoietin and control of infections.

Thalidomide and linalidomide have been employed with good response. Thalidomide, in a dose of 400 mg/day has given good response in low risk patients.

Bone marrow transplantation or stem cell transplantation may be necessary in many cases, to effect cure.

Further reading- Hematology today 2005 edited by M B Agarwal – XIth National CME in hematology and hemato-oncology, Mumbai. Myelodysplastic syndromes by Hussain I. Saba pp 175-192.

PRE-LEUKEMIA

Four undermentioned groups of conditions fall under this category since they may develop into acute myeloid leukemia on follow-up.

1. Well-defined hematological disorders such as polycythemia vera, idiopathic myelofibrosis, paroxysmal nocturnal hemoglobinuria, Fanconi’s anemia, idiopathic sideroblastic anemia, multiple myeloma, and lymphomas. CML invariably transforms into AML or ALL if the patient lives long enough.
2. Genetic disorders like Down’s syndrome.
3. Primary malignancies such as those of the breast or ovaries when treated with cytotoxic drugs or immuno-suppressants.
4. The myelodysplastic syndromes.

Long-term exposure to several drugs used in cancer chemotherapy, especially the alkylating agents, is associated with the development of second cancers, among which AML is frequent.

It is not clear whether prophylactic therapy will prevent the emergence of acute leukemia and thereby change the natural history and therefore the treatment is symptomatic.

Leukoerythroblastic Blood Picture

This is the simultaneous presence of the precursors of both myeloid and erythroid series of cells in peripheral blood (Fig. 156.3).

It is also characterised by abnormal RBC, WBC and platelet morphology. RBCs appear pear-shaped or distorted. Nucleated red cell precursors occur. WBC count is elevated, with immature cells like myelocytes, promyelocytes and even myeloblasts suggesting a leukemoid reaction. Platelets are generally normal, but they may be reduced or increased or may be larger size. All these are the result of hematopoiesis occurring outside the marrow (extramedullary hematopoiesis) in foci such as the spleen, liver and even lymph nodes, consequent to marrow fibrosis, or infiltration by inflammatory or neoplastic tissue. The condition should not be mistaken for leukemia.

The developing cells proliferating in the extra medullary sites enter the blood stream prematurely without passing through the normal tissues which prevent immature precursors and defective cells from entering the circulation. Normally the spleen destroys and removes deformed erythrocytes from circulation. In the absence of normal

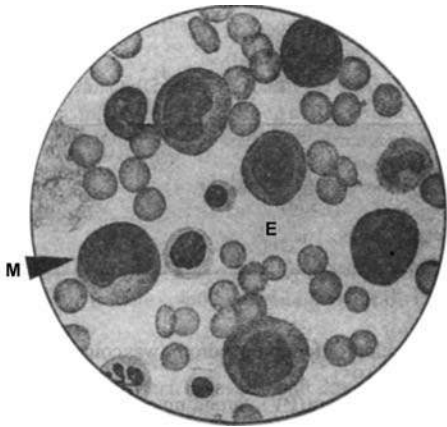


Fig. 156.3: Leukoerythroblastic picture
M—Myeloid cell, E—Erythroblast

splenic function leukoerythroblastic blood picture may result.

The causes of leukoerythroblastic blood picture include:

1. Primary idiopathic myelofibrosis
2. Secondary myelofibrosis
3. Infections like tuberculosis, HIV, fungal infections
4. Radiation
5. Associated with polycythemia, chronic myeloid leukemia, lymphoma, myeloma, hairy cell leukemia
6. Marrow infiltration
 - a. Carcinoma breast
 - b. Carcinoma lung
 - c. Carcinoma prostate

- d. Neuroblastoma
- e. Sarcoidosis

All the conditions other than primary idiopathic myelofibrosis can be called myelophthisic. In all these conditions there are three processes occurring in varying grades (1) proliferation of fibroblasts in the marrow space, (2) extramedullary hematopoiesis (myeloid metaplasia) and (3) ineffective erythropoiesis. Similar blood picture can some times occur when a normally functioning marrow is under stress due to acute hemorrhage, hemolysis or DIC. When megaloblastic anemia is treated with large doses of vitamin B₁₂ and folate there is severe erythroid hyperplasia the immature cells pass out of the normal marrow in large numbers.

157

Agranulocytosis (Severe Neutropenia)

P.K. Sasidharan, K.V. Krishna Das

Chapter Summary

General Considerations 1054
Clinical Features 1055
Diagnosis of Neutropenia 1055
Treatment 1055

GENERAL CONSIDERATIONS

Agranulocytosis (severe granulocytopenia) refers to decrease in absolute neutrophil count below 500/cmm. Though the term indicates absence of granulocytes (especially neutrophils), for practical purposes neutrophil counts below 500/cmm should be taken as agranulocytosis and remedial measures have to be instituted. Severe neutropenia of this level will predispose to life threatening infections. It can occur due to various causes such as chemotherapy with anticancer drugs, hypersensitivity to other drugs in common use, infections, bone marrow failure, irradiation by ionizing radiations and at times, without an obvious underlying cause.

It should be remembered that almost all drugs can cause severe neutropenia, and hence this risk should be anticipated when introducing any new drug. Some drugs have a predilection to cause agranulocytosis.

Drug induced agranulocytosis: Pathogenesis: In the majority of cases it is caused by immunological

mechanisms, where the antibody coated granulocytes are preferentially removed by the reticuloendothelial system. It may also be due to direct effect on bone marrow as in the case of anticancer drugs. Two clinical patterns are usually seen. Sometimes it can occur even with first dose administration or on intermittent administration, but the agranulocytosis occurs abruptly. In the second pattern as exemplified by drugs like phenothiazines, prolonged administration leads to a gradual reduction of neutrophils. Often this neutropenia recovers when the drug is withdrawn or sometimes the neutrophil count can get stabilised at a lower level even when the drug is continued. It is to be noted that no drug is completely free from this

Major Causes of Neutropenia

- a. Drug induced
- b. Infections; viral hepatitis, enteric fever, tuberculosis, HIV
- c. Septicemias
- d. Acute leukemias
- e. Myelodysplasias
- f. Aplastic anemia
- g. Bone marrow infiltration/metastasis
- h. Autoimmune destruction
- i. B₁₂ or Folate deficiency
- j. Hypersplenism
- k. Radiation

Note: Though several conditions lead to neutropenia, many of them do not lead to agranulocytosis.

Drugs causing Neutropenia

1. Cytotoxic and anticancer drugs
2. Immunosuppressants
3. Antithyroid drugs- propylthiouracil, methimazole, carbimazole
4. Anticonvulsants- Phenytoin, carbamazepine
5. Antihypertensives-methyldopa, captopril
6. NSAIDs: indomethacin, ibuprofen, gold salts
7. Antibiotics-chloramphenicol,sulfonamides, rifampicin
8. Diuretics, acetazolamide, hydrochlorothiazide
9. Others: dapsone, quinine, interferons, allopurinol,

form of toxic reaction. All antineoplastic drugs are capable of producing severe neutropenia if administered in sufficient dosage and this is due to direct impairment of cell production. History of drug ingestion may not be forthcoming in 20% of cases.

CLINICAL FEATURES

Irrespective of the cause, the risk of infections is maximum when the absolute neutrophil counts fall below $500/\text{mm}^3$. The neutropenia may be asymptomatic when the counts are above $1000/\text{mm}^3$ and also when it is acute in onset or of brief duration. When neutropenia is chronic, monocytosis may occur and might compensate for the risk of infections. The sources of infection in such patients are usually gums, throat, tonsils, lips, tongue, genitalia, perianal regions, genitourinary tract, gut, skin and lungs and the organisms are the usually suspected ones from these respective sites from which infection spreads. In the hospital settings they can have infection by unusual organisms and even by drug resistant ones. Usual signs and symptoms which suggest an infection may be absent in neutropenic patients owing to the absence of inflammatory mediators and hence a careful search for infections at these sites is mandatory.

Serious pneumonia can present with only minimal or even absence of chest signs, no sputum or only non purulent sputum and minimal or no infiltrates on X-ray chest. Signs of inflammation may be absent at sites of skin infections and if ulcers are present they may be covered with grayish black offensive exudates. The surrounding skin may be red and necrotic without any tendency to localise the lesion and since these infections are not contained locally, they get disseminated very fast and hence empirical broad spectrum antibiotic treatment is warranted without delay. Clinical features are basically those of the primary disorder causing neutropenia, and those due to neutropenia which can predispose to severe bacterial and some fungal infections. The patient may present with high fever, chills and rigor, sore throat or only extreme prostration without fever.

Diagnosis of Neutropenia

Total neutrophil counts below $1000/\text{cmm}$ should alert the physician. Counts below $500/\text{cmm}$ indicate serious neutropenia. Whenever any unusual symptom develops in a patient who can potentially have neutropenia, or when

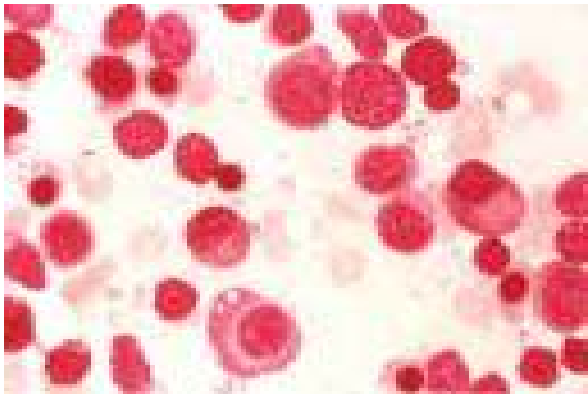


Fig. 157.1: Agranulocytosis bone marrow: Note: The absence of myelocytes promyelocytes and neutrophils

very low neutrophil counts are documented bacteriological samples are collected from the appropriate sites for culture and sensitivity and broad spectrum antibiotics are started without waiting for the culture reports. Culture report might help to modify the regime in a given patient or at least help to plan empirical treatment in future.

Agranulocytosis has to be differentiated from acute aleukemic leukemia, aplastic anemia, infectious mononucleosis, Vincent's angina and thrush. Bone marrow study is mandatory when the cause is not obvious, especially when it is a bicytopenia or pancytopenia.

Examination of peripheral blood reveals leukopenia with absence of neutrophils or presence of only a few old neutrophils with multilobed nuclei. Young forms with less than three lobes in the nuclei are rare or absent. This should suggest depression of leukopoiesis. Bone marrow examination shows suppression of neutrophil precursors (Fig. 157.1).

Treatment

At the earliest clinical suspicion all potentially offending drugs should be withdrawn. Otherwise treatment depends on the cause of neutropenia; and treatment of infection by powerful bactericidal antibiotic combinations. Empirical broad spectrum antibiotic therapy should be started without delay whenever infection is suspected. A useful combination is gentamicin, ciprofloxacin and metronidazole all given intravenously. Other drugs that may be considered for use are cefotaxime, ceftazidime, ceftriaxone, imipenem, and amikacin. Severe neutropenia in selected situations are benefited by recombinant granulocyte colony stimulating factor (GCSF) or granulocyte macrophage colony stimulating factor (GM-CSF) but the routine use of these drugs especially to prevent infections is not recommended, except in the setting of potentially toxic anticancer chemotherapy. Prognosis depends on the cause, prompt diagnosis and intervention. Drug induced agranulocytosis is a preventable disease if it is remembered that all drugs, including even apparently safe drugs are capable of producing this complication.

Plasma Cell Dyscrasias

K.V. Krishna Das, Mathew Thomas

Chapter Summary

Multiple Myeloma 1056

Variant Forms of Myeloma 1060

Smouldering Multiple Myeloma 1060

Plasma Cell Leukemia 1060

Nonsecretory Myeloma 1060

Osteosclerotic Myeloma
(POEMS Syndrome) 1060

Amyloidosis 1060

These include a group of disorders mainly characterized by: (1) uncontrolled proliferation of antibody producing cells, and (2) secretion of a structurally homogenous gammaglobulin or its polypeptide chains—the ‘M’ component.

Traditionally, multiple myeloma, Waldenström’s macroglobulinemia, heavy chain diseases, benign monoclonal hypergammaglobulinemia, and amyloidosis are included in this group, though Waldenström’s macroglobulinemia and heavy chain diseases are actually lymphoid dyscrasias.

Characteristic protein abnormalities form the hallmark of these disorders.

myeloma proteins may be biclonal. Any of the immunoglobulins—IgG and its subclasses, IgA, IgM, IgE, and IgD, or their light chains-kappa or lambda—may be produced in large amounts. The abnormal immunoglobulins are produced without antigenic stimulation and the normal immunoglobulins are reduced. Hence infections are common. Rarely abnormal immunoglobulins may not be secreted—*non-secretory myeloma*.

Evolution of Myeloma

First step is the emergence of a limited number of clonal plasma cells. This is the stage of monoclonal gamopathy of undetermined significance (MGUS). This is not detected clinically. Annually 1% of these develop multiple myeloma or other related malignant diseases. With the progression of MGUS into myeloma, complex genetic events occur in the abnormal plasma cells and bone marrow micro environment. These include angiogenesis, suppression of cell mediated immunity, and development of paracrine signalling loops involving cytokines such as IL-6, and vascular endothelial growth factor. The resultant interactions of myeloma cells, bone marrow stromal cells and micro vessels contribute to the persistence of the tumour and its resistance to drugs. Asymptomatic cases may become symptomatic in two to three years.

Pathology: There is gross hyperplasia of the plasma cells and these almost fill the bone marrow, eroding into bone and leading to pathological fractures. Myelomatous bone disease represents an imbalance between bone resorption and formation as a result of increased osteoclastic activity and reduction of osteoblastic activity. The plasma cells produce osteoclast activating factors which are cytokines including IL-1 β , TNF β and possibly IL-6. Osteolysis occurs in the proximity of the abnormal plasma cells. A vicious cycle of myeloma cells activating osteoclasts and the osteoclasts in turn stimulating plasma cells through the cytokine IL-6 which is a potent myeloma growth factor, is established. Proliferation of the plasma cells may take a diffuse pattern (*myelomatosis*) or may be localized and nodular (*myeloma*).

Multiple Myeloma

Syn: Myelomatosis

This is the most common disorder among the group of plasma cell dyscrasias. Myeloma is a malignant tumour arising from the plasma cells. The tumour may arise unicentrically or multicentrically from the bone marrow or as localized tumours in other sites.

Genetics of myeloma Many cases show a 14q 32 translocation (1gH translocation). The immunophenotype in myeloma is characterized by CD₃₈⁺⁺, CD₁₃₈⁺, CD₅₆⁺, CD₂₀[–] and FMC7.

Myeloma is a clonal disorder arising from one abnormal clone of plasma cells, secreting only the same type of immunoglobulin-monoclonal myeloma. Rarely

The plasma cells show abundance of cytoplasm, with foamy vacuoles and many of them may be multinucleated (*myeloma cells*). Signs of nuclear immaturity may be evident. Due to increased cell turnover serum uric acid level is elevated. Primary type of amyloidosis occurs in 10% cases. In over 60% of cases the light chains appear in urine in demonstrable amounts. These are called *Bence Jones proteins*. The Bence Jones proteinuria, amyloidosis, and hyperuricemia lead to renal damage resulting in renal failure. The light chains are toxic to renal tubules. Mobilization of calcium from bones causes hypercalcemia, hypercalciuria, and nephrocalcinosis.

Hyperviscosity syndrome may develop due to the presence of abnormal immunoglobulins. The signs of hyperviscosity include weakness, anorexia, impairment of cerebral circulation leading to neurological deficits, and retinal abnormalities. This is more pronounced in IgA myeloma.

Invasion of the bone marrow by plasma cells may cause myelophthisic anemia, leukopenia, and thrombocytopenia. In the majority of cases, plasma cells occur in small numbers in peripheral blood and can be demonstrated in the buffy coat. In a few, large number of plasma cells and plasmablasts (showing nucleoli) appear in the peripheral blood when the condition may be termed *plasma cell leukemia*. At autopsy several organs show infiltration by myeloma cells, but clinical abnormality may not be detectable in many. Chromosomal changes have been detected in myeloma though they are not quite specific or universal as in CML.

CLINICAL FEATURES

This disease is more frequent in the middle and older age groups majority of cases being between 50 and 70 years. It is more common in males. The onset is insidious with symptoms of vague ill-health, back pain, aches and pains, arthralgia and progressive anemia. In the majority of cases diagnosis is made on routine investigation for anemia, raised ESR, bone pains or pathological fractures, localized tumours, or recurrent bacterial and viral infections. In the more advanced cases all evidences of myelophthisic anemia may be present. 20% of cases are asymptomatic and detected by routine laboratory work-up during health checks.

Bone changes: Vertebrae, sternum, ribs, skull, and clavicles show characteristic osteolytic changes (Fig. 158.1). Localised bony or soft tissue swellings may be detectable over these sites. In some, the disease presents abruptly with the onset of pathological fractures in an otherwise healthy subject. In about 3% of cases the osseous lesion is confined to a single bone, without evidence of generalised marrow involvement. Vertebral compression may result in reduction in height of the individual and compressive myelopathy.

Other neurological manifestations develop due to demyelination, amyloid peripheral neuropathy, paraproteinemia neuropathy, carpal tunnel syndrome, and rarely cranial nerve palsies.

Splenomegaly occurs in 20%, hepatomegaly in 40%, lymphadenopathy and involvement of organs like thyroid, adrenal, ovaries, testes, lung, pleura, pericardium, skin, and others in a smaller proportion of cases. Infections like pneumonia and herpes zoster are more common due to immunodeficiency state.

Renal failure may present as insidious onset of azotemia, which is made out on investigation, or it may occur acutely with renal shut down due to tubular obstruction. Contrast radiography (IVP) may precipitate renal failure due to dehydration. Aggressive chemotherapy is also associated with the development of uric acid nephropathy.

Hematology: Normocytic normochromic anemia may be present and neutropenia and thrombocytopenia may develop later. In addition to thrombocytopenia, qualitative platelet defects occur. These include abnormalities of adhesion, aggregation and platelet factor 3 release. Inhibitors of coagulation factors may develop. Hyperviscosity develops as a result of increase in paraproteins. This manifests as bruising and bleeding tendency. In 5% of cases cryoglobulins occur as part of the paraproteins. Such patients may manifest Raynaud's phenomenon. The peripheral blood smear shows marked rouleaux formation which reflects the high ESR. Plasma cells may be seen in small numbers. Presence of numerous plasma cells suggests *plasma cell leukemia*. In some cases plasma cell precursors (plasmablasts) are seen in peripheral blood and bone marrow.

DIAGNOSIS

Myeloma should be suspected in any elderly person presenting with vague rheumatic symptoms, pains, and deformity over the spine. Neurological symptoms, pathological fractures, unexplained anemia, and recurrent infections should alert the physician to the possibility of myeloma. Investigations are absolutely essential to diagnose the condition and assess the extent of the disease. Presence of a very high ESR (often above 100 mm in 1 h) should suggest the possibility of myeloma, if other more common causes can be excluded.

Urine examination: Over 50% of cases show *Bence Jones proteinuria*. Bence Jones proteins are made up of light chains which cross the glomerular filter. On heating acidified urine above 80°C, the protein precipitates and on continuing heating it redissolves above 90°C. Another method for detection is to add an equal volume of 5% sulphosalicylic acid which precipitates the proteins.

Immunoelectrophoresis of urine reveals the type of protein. Though Bence Jones proteins are very suggestive of myeloma, other conditions such as combined light



Fig. 158.1: X-ray skull showing punched out areas

chain nephropathy, lymphomas, leukemias and congenital renal tubular defects may also be associated with this abnormality.

Radiology: X-rays of the skull, long bones, pelvis, ribs, and vertebrae reveal characteristic punched out lesions. One or several vertebrae may be affected. The bone lesions are usually localized. Despite the bone lesions plasma alkaline phosphatase is normal (Fig. 158.1).

Bone marrow examination is diagnostic: Material aspirated from any site is usually diagnostic, but in case of doubt aspiration must be done from an area of radiological abnormality. Normally the proportion of plasma cells ranges from 2 to 10%. Rarely it may rise even up to 20%. In myeloma the number of plasma cells is considerably increased (> 10%) and the plasma cells show morphological abnormality (Fig. 158.2).

Some plasma cells show multinucleation and cytoplasmic vacuoles. These are called myeloma cells. Plasmablasts possess nucleoli. Increase in plasma cells due to myeloma has to be distinguished from reactive plasmacytosis in which plasma cells are increased. Several conditions give rise to reactive plasmacytosis. These include chronic infections like tuberculosis, amyloidosis and secondary neoplasms. In this condition the plasma cells do not generally exceed 10% of the total. Morphological abnormalities are not produced. The secondary plasmacytosis resolves on removing the cause.

Diagnostic Criteria for Myeloma

- 1. Plasma cells in the marrow more than 10%
- 2. Presence of monoclonal proteins in the serum or urine
- 3. Evidence of end organ damage. This may include
 - a) hypercalcemia
 - b) renal insufficiency
 - c) anemia and
 - d) bone lesions (CRAB)

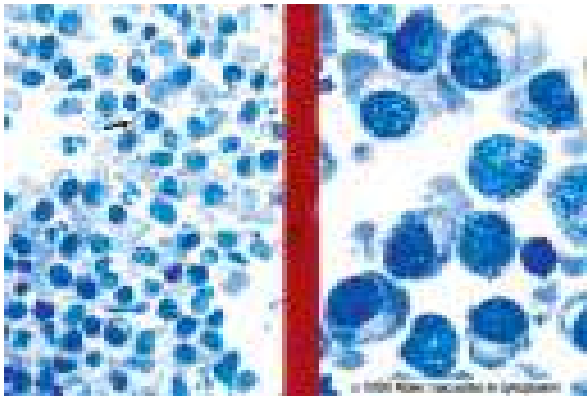


Fig. 158.2: Plasma cells in bone marrow

Electrophoretic studies: Demonstration of paraprotein by electrophoresis and determination of the immunoglobulin type by immunoelectrophoresis or diffusion techniques help to confirm the diagnosis and type the myeloma.

Serial measurement of the paraprotein level helps to assess progress since its level reflects the tumour load. 75% show IgG, 25% IgA and 1% IgD. In younger patients the proportion of IgD myeloma is slightly more. IgD myeloma is more often associated with hypercalcemia and renal failure. Bence Jones myeloma is also more common in the younger age group. Assessment of renal function by blood urea, creatinine, uric acid and glomerular filtration rate are essential to indicate the prognosis and plan therapy. Table 158.1 gives the clinical staging for assessing the prognosis and which is of help to plan therapy.

Differential diagnosis of multiple myeloma includes multiple bony secondaries from carcinoma of the prostate, adrenals, breast, thyroid, and other organs. In this condition, the protein abnormalities are absent or only minimal. Biopsy from these sites may be required to confirm the diagnosis. Eosinophilic granuloma of bone or other lipidoses like Hand-Schüller-Christian disease and Niemann-Pick disease may produce multiple lytic lesions in the skull.

Genetic analysis helps to differentiate Waldenström’s macroglobulinemia from multiple myeloma.

TABLE 158.1

Staging of myeloma		
Criteria	Stage 1	Stage III
Hemoglobin	above 10 g/dL	below 8.5 g/dL
Serum calcium	below 12 mg/dL	above 12 mg/dL
X-ray of bones	normal or sparse lesions	advanced lytic lesions
M-components		
IgG	below 5 g/dL	above 7 g/dL
IgA	below 3 g/dL	above 5 g/dL
Urinary		
M-component	below 4 g/24 h	above 12 g/24h

Benign monoclonal gammopathy is a rare disorder in which paraproteins are increased to high levels, but often lower than that in myeloma. Normal immune mechanisms are not suppressed. The stage of the disease can be assessed by the laboratory values.

Stage II is intermediate between stage I and III. Subclass A indicates normal and B indicates impaired renal function based on serum creatinine levels. In A it is < 2 mg/dL and in B it is > 2 mg/dL.

Course and prognosis: The disease runs a chronic course extending over a few years, but relentlessly progresses to death. Blood urea level above 80 mg/dL (13 mmol/L), hemoglobin below 7 g/dL, and hypoalbuminemia are bad prognostic factors. Cases with blood urea above 80 mg/dL rarely survive a few months. Complications include painful pathological fractures, anemia, hypercalcemia, recurrent bacterial infections and renal failure.

Prognosis varies with the different types of myeloma and treatment administered. At present chemotherapy and radiotherapy are only palliative. Bone marrow transplantation is curative in a smaller proportion when compared to leukemias. Younger patients do better. Median duration of remission with palliative treatment is 2 years. Less than 10% of cases may survive 10 years. Even this small group ultimately succumbs to the disease.

TREATMENT

Melphalan

The drug freely available at low cost is melphalan which is an alkylating agent (phenylalanine mustard). This is the most time honoured specific drug. Several dosage schedules have been used. One of the standard regimens is to give melphalan 8 mg/m² and prednisolone 60 mg/m² orally after breakfast for 4 consecutive days repeated once in 4 weeks. If the response is not satisfactory the dosage of both the drugs should be increased by 20%.

40% of cases get remission with reduction of myeloma protein by 75%, Bence Jones proteinuria by 95% and reduction of bone marrow plasma cells below 5%. Maintenance therapy has to be given by repeating the course. High dose melphalan therapy may even give cure in a small proportion of cases. Various dosage schedules and combinations using melphalan are in vogue at present.

Bone Resorption Inhibiting Agents

The bisphosphonates-pyrophosphate analogues—suppress osteoclastic activity and indirectly myeloma cells as well. The different members of this group of drugs vary in their therapeutic potential and possibly mode of action as well. Etidronate is the least effective, but the later analogues are definitely beneficial by reducing vertebral and other fractures, bone pains, plasma levels of paraproteins and

also serum calcium. Several preparations are available. These include etidronate, clodronate, pamidronate, ibandronate, zolendronate and alendronate in the ascending order of therapeutic potency. They have to be given under supervision. Alendronate is highly effective. The drug is expensive.

It is now clear that patients who have bone lesions, with or without hypercalcemia benefit by the addition of bisphosphonate. Bisphosphonates may lead to osteonecrosis of the jaw. Treatment consists of withdrawal of bisphosphonates and antibiotics to treat infection.

Thalidomide (α -N phthalimido glutarimide) which is a derivative of glutamic acid has produced very good results in myeloma. When given orally it is readily absorbed. Its main actions are anti-TNF α activity, anti-angiogenesis activity and immunomodulation. It inhibits IL6, IL12 and IFN α . It reduces expression of intracellular adhesion molecules. Different doses have been tried. The drug has been used singly, and in combination with dexamethasone in a dose schedule of thalidomide 200 mg oral on days 1-28 and dexamethasone 40 mg/m² oral on days 1-4, 9-12 and 17-20. This produces favourable response in 65-70% of newly diagnosed cases and 50% in relapsed cases. Adverse effects include teratogenicity, somnolence, peripheral neuropathy, constipation and others. Thalidomide is also effective in advanced myeloma. A newer analogue of thalidomide, lenalidomide is an amino substitute variant which is more potent with less side effects.

Other drugs which can be combined with thalidomide include cyclophosphamide and melphalan. Studies are going on to identify the best regimen.

Resistant Cases

If the response to standard drugs is unsatisfactory, a combination of vincristine, doxorubicin and dexamethasone may be successful.

Dose: Vincristine 0.4 mg/day, and doxorubicin 9 mg/day, are given as continuous IV infusion through a central venous catheter for 4 days, along with oral administration of 40 mg dexamethasone on days 1, 9 and 17 of each 28-day cycle. About 30-40% of resistant cases do respond. High dose dexamethasone and methyl prednisolone (2 g given IV once a week) are very potent drugs which suppress myeloma, in combination with other drugs.

Newer drugs include **bortezomib** (velcade) which is a proteasome inhibitor which inhibits nuclear factors and also induce apoptosis. It is given in a dose 1.3 mg/m² I V over 3-5 minutes on days 1, 4, 8 and 11. Cyclically every 21 days. The results are encouraging in relapsed and resistant cases. This drug is very expensive.

Bone marrow transplantation (BMT): Allogenic or autologous BMT is an accepted and very useful therapeutic modality employed, when the myeloma is not amenable to chemotherapy. With the present state of technical

advancement, persons up to 65-70 years can be considered for successful engraftment. At present less aggressive bone marrow ablative regimen to the recipient is being tried in several centres (mini transplant). The post-BMT complications are less severe. With the use of modern immunosuppressive drugs results are quite encouraging.

Stem Cell Transplantation

Autologous stem cell transplantation preceded by high dose chemotherapy is beneficial.

Tandem transplantation in myeloma. In this procedure a second autologous stem cell transplant is given after the patient has recovered from the first. The rates of cure are better than single transplants.

Supportive Measures

Infections have to be treated promptly with antibiotic combinations. **Hyperuricemia** has to be prevented by the oral administration of allopurinol 100 mg tid.

Renal complications of hyperuricemia can be avoided by hydrating the patient, alkalinising the urine by the administration of sodium bicarbonate, and ensuring a daily urine output of at least 2 litres by the use of frusemide in small doses. Hemodialysis may be required to tide over acute renal failure. Dangerous **hypercalcemia** may occur. Management of hypercalcemia is given in section 11. Chapter: 99.

Hyperviscosity syndrome is treated by plasmapheresis using a blood cell separator. Administration of thiols inhibits the synthesis of myeloma proteins. Bleeding and fractures demand symptomatic treatment in addition. Spinal cord compression demands immediate laminectomy and irradiation to the spine.

Treatment of localized myeloma: Local irradiation in a dose up to 4000 cGy gives rapid pain relief and helps to clear the lesions. This has to be accompanied by chemotherapy.

Extramedullary plasmacytomas may occur, most commonly in the upper respiratory tract, gastrointestinal tract and other regions.

Localized plasmacytomas in soft tissues have to be removed surgically, and the patients have to be followed up for several years to watch for the development of multiple myeloma.

Variant Forms of Myeloma

SMOULDERING MULTIPLE MYELOMA

This condition presents with the following features.

- 1. Abnormal monoclonal protein in excess of 3 g/dL in serum.
- 2. Presence of abnormal plasma cells in excess of 10% in bone marrow.

Bence Jones proteins may be present in urine. Levels of normal immunoglobulins may be decreased. Many of them follow a prolonged benign course which may resemble benign “monoclonal gammopathy”. Risk of developing florid myeloma is 51%, 66% and 73% at 5, 10 and 15 years respectively. Management consist of close follow-up every 4-6 months.

PLASMA CELL LEUKEMIA

In this condition the peripheral blood plasma cells form more than 20% of nucleated cells or absolute count of plasma cells exceed 2000 cmm. If the presentation of the plasma-cell disorder is with the leukemic phase it is called primary plasma cell leukemia, and if this phase develops during the course of multiple myeloma it is termed secondary.

NONSECRETORY MYELOMA

One percent of multiple myelomas fall under this category. In this condition the plasma cells may produce the abnormal protein, but do not secrete it into the plasma. The presence of monoclonal protein within the plasma cells can be confirmed by immuno-peroxidase staining or immunofluorescence studies.

OSTEOSCLEROTIC MYELOMA (POEMS SYNDROME)

This produces osteosclerotic shadows in skiagrams and accounts for 3-5% of all the myelomas. The lesion may be single or multiple. This is a rare condition in which the number of plasma cells in bone marrow is below 5% but bone biopsy may show localized plasmacytomas. The components of this syndrome include:

Polyneuropathy, mostly demyelination, motor disability

- Organomegaly—liver, spleen, lymph nodes
- Endocrinopathy—gynecomastia, atrophic testes
- Monoclonal protein abnormality, and
- Skin changes—pigmentation, hypertrichosis.

The major disability is due to a chronic inflammatory polyneuropathy. Bone marrow shows only less than 5% of plasma cells. Diagnostic finding is the presence of plasmacytoma on histology of the bone lesion. Treatment consists of local irradiation over the affected bone.

Amyloidosis

Virchow coined the term amyloid in the mid 19th century. Amyloidosis consist of a large group of diseases in which misfolding of the extracellular proteins has a major role. This dynamic process which occurs in parallel with, or as an alternative to physiological folding, generates insoluble toxic protein aggregates that are deposited in tissues as bundles of β short fibrillar protein. These consist

TABLE 158.2

Characteristics of systemic amyloidosis			
Type	Fibril composition	Precursor protein	Clinical spectrum
Primary AL	Monoclonal immunoglobulin light chains	Lambda or kappa light chain	Cardiomyopathy, hepatomegaly, proteinuria, macroglossia, autonomic dysfunction, orthostasis, ecchymosis, shoulder pad sign, carpal tunnel syndrome (CNS not affected, peripheral and autonomic nervous system are affected)
Familial ATTR	Transthyretin	Abnormal transthyretin	Mid-life onset of peripheral and autonomic neuropathy, myopathy, vitreous opacities.
Secondary AA	Amyloid A protein	Amyloid A protein	Underlying inflammatory disease, hepatosplenomegaly renal failure

of strands of polypeptides arranged in zig-zag manner. The unique feature of amyloidosis is the capacity of these proteins to acquire more than one conformation. Amyloidosis is characterized by the extracellular deposition of amyloid which appears as a homogenous eosinophilic material in several tissues. Amyloidosis may be primary or secondary. The amyloid fibrils in primary amyloidosis are fragments of immunoglobulin light chains. Lambda light chains predominate over kappa light chain in the ratio of 2:1. Different proteins make up the amyloid fibrils in reactive (secondary) and familial amyloidosis.

Clinical Classification (Table 158.2)

- 1. *Primary*: without any detectable underlying cause or associated with myeloma
- 2. *Secondary*
 - a. Chronic infections- tuberculosis, bronchiectasis
 - b. Rheumatoid disease
 - c. Lymphoma and other neoplasms
- 3. *Heredo-familial mediterranean fever*
- 4. *Local amyloidosis*—skin, joints, tendons, nerves, and other structures
- 5. *Senile amyloidosis*

Modern biochemical classification is based on the nature of precursor plasma proteins that form the fibril deposits:

AL amyloidosis: immunoglobulin light chain related (AL)

Familial amyloidosis: transthyretin-associated (ATTR)

Secondary amyloidosis: Amyloid A protein (AA)

Primary amyloidosis is a plasma cell dyscrasia related to multiple myeloma. Clonal plasma cells in the BM produce immunoglobulins that are amyloidogenic.

Familial Amyloidosis

This consists of a group of autosomal dominant diseases in which a mutant protein forms amyloid fibrils beginning in mid-life. The most common form is caused by mutant

transthyretin (ATTR). Other genetic and environmental factors may play a role in the phenotypic expression of this disease.

Secondary Amyloidosis

These are due to amyloid formed from serum amyloid A (SAA) which is an acute phase protein produced in response to inflammation. There are several SAA proteins, out of which at least four different molecular forms take part in the formation of amyloid.

Clinical Features

Systemic amyloidosis: Clinical features depend on the tissues involved. Since the kidneys are affected most frequently in secondary amyloidosis, 60% cases present with nephrotic syndrome. Proteinuria results from damage to the glomeruli and also toxicity of SAA oligomers or profibrils. The rest may be asymptomatic. The common cause of death is chronic renal failure.

The heart is affected in 80-90% of cases of primary amyloidosis and this results in restrictive and congestive cardiomyopathy, cardiac failure, and arrhythmias. Sudden death may occur (Table 158.3).

Gastrointestinal involvement: Macroglossia may interfere with deglutition and respiration. Involvement of the intestines produces diarrhea, malabsorption, intestinal obstruction, and gastrointestinal bleeding.

Liver is commonly involved in both types of amyloidosis. The organ is enlarged and firm but functional derangement is not marked. *Spleen* is commonly enlarged and firm in secondary amyloidosis. *Adrenal gland* is affected in secondary amyloidosis and this leads to hypofunction of the gland.

Respiratory tract: Amyloid deposition may occur in the respiratory passages or in the lung parenchyma.

Nervous involvement: Common presentations are peripheral neuropathy and carpal tunnel syndrome. Primary cerebrovascular amyloidosis may occur in which

TABLE 158.3

Common sites of involvement in amyloidosis

Primary amyloidosis	Secondary amyloidosis
Heart	Kidney
Tongue	Spleen
Gastrointestinal tract	Liver
Skeletal and visceral muscles	Adrenal cortex
Nerves	Lungs
Joints, tendons	Other organs
Liver	
Skin	
Lungs	

Note: Considerable overlap may occur between the two forms.

amyloid deposits occur in the arteries and arterioles as well as adventitia of the veins and venules. This weakens the vessel wall and accounts for some cases of hemorrhagic stroke. Autonomic neuropathy affecting several organs is common.

Localized amyloidosis: Nodular masses of amyloid may occur in and around joints and tendons, particularly around the glenohumeral joints. Large deposits may occur giving rise to the “*shoulder pad sign*”.

Arthralgia and arthritis resembling rheumatoid arthritis may occur. Affection of the skin manifests as lichenoid plaques, nodules, or purpura around the orbits.

In 80-90% of persons above the age of 80 years amyloidosis of the heart may occur (*senile cardiac amyloidosis*).

Amyloid purpura occurs rarely over the chest above the nipple line, neck and eyelids. Amyloid fibrils bind to factor X and lead to factor X deficiency and purpura.

Diagnosis: Amyloidosis is confirmed by biopsy of appropriate tissues. The rectal mucosa is commonly involved in primary amyloidosis, and therefore, rectal biopsy is a rewarding procedure. Renal biopsy is usually positive when there is proteinuria. Amyloid deposits can be demonstrated in the gingival mucosa when gums are

clinically abnormal. Electron microscopy of urine and synovial fluid may reveal amyloid fibrils.

Tests to Identify the Type of Amyloid

AL amyloid: Immunofixation electrophoresis of urine and serum, bone marrow biopsy with immune histochemical staining for lambda and kappa light chains. Amyloid deposits are identified on the basis of their apple green birefringence under polarized light microscope after staining with Congo red. Under the electron microscope amyloid fibres appear as rigid non-branching fibrils 7.5-10 nm in diameter.

Familial ATTR: Serum isoelectric focussing for abnormal transthyretin, or DNA based test for mutant transthyretin gene.

Secondary AA: Elevated concentration of serum amyloid A protein, immunohistochemical staining of tissue for AA protein. Normal level of SAA fragments in blood is < 4 mg/dL. Severity of amyloidosis and prognosis correlate with blood levels of SAA.

Prognosis: Systemic amyloidosis is always fatal if untreated. Death is due to renal or cardiac failure within 1-2 years of diagnosis. Progress of amyloidosis can be arrested and the lesions may even regress with treatment of the underlying condition. AL amyloidosis (primary) has the worst progress with a median survival of 1-2 years. Patients with ATTR amyloidosis may survive up to 15 years and the prognosis for secondary amyloidosis depends upon the underlying condition.

Therapy: Treatment of the underlying cause is instituted wherever a cause can be detected. Cytotoxic drugs like melphalan are sometimes beneficial in primary and reactive amyloidosis, but not in all cases. For all forms specific therapy directed to the organs affected is essential. For primary amyloidosis chemotherapy is needed. Deflunisal is effective in familial amyloidosis. Eprosinate inhibits amyloid deposition in tissues. It delays renal damage. The dose is 800-2400 mg oral daily. Liver transplantation helps cases with familial amyloidosis. Bone marrow transplantation has been tried with varying success.

Malignant Disorders of Lymphoid Cells

K.V. Krishna Das, Mathew Thomas

Chapter Summary

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Lymphomas

GENERAL CONSIDERATIONS

These are malignant tumours arising from lymphoid tissue. In general, lymphomas remain confined to lymph nodes and other lymphoid structures in their early stages. Lymphomatous cells in varying numbers are seen later in the bone marrow and the peripheral blood. On the other hand lymphatic leukemias which are also primary malignancies of the lymphatic cells start in the marrow or in the lymph nodes and become disseminated from the beginning, even though lymph nodes and other lymphoid organs do show lesions simultaneously. Lymphatic leukemia and its variants are described in chapter 155.

Lymphomas may start unicentrically or multicentrically. They have been classified broadly into *Hodgkin's lymphoma* (HL) and *Non-Hodgkin's lymphoma* (NHL). *Hodgkin's lymphoma* is characterized by the presence of *Sternberg-Reed cells* which are absent from the latter. The course, prognosis and response to treatment are different in the two types.

In many instances lymphomas arise *de-novo* at sites not conventionally included under the lymphoreticular system, such as the brain and several other solid organs. These may remain so for long periods without manifesting any tendency for generalized spread and behaving like local tumours.

Etiology: As in the case of leukemias, several possibilities have been postulated. These include genetic predisposition, viral infections, immunological factors, long-term toxicity to drugs like cyclophosphamide, and exposure to irradiation and chemicals. There are many reports of lymphomas occurring in clusters in closed ethnic groups, and showing a seasonal prevalence. These phenomena suggest a common environmental factor.

Epidemiology: Lymphomas form 1.9% of all cancers in many general hospitals in India. Among the lymphomas 35-43% is HL and the rest is NHL. Lymphatic malignancies formed 4.3% of all cancer cases seen in Tata Memorial Hospital, Mumbai.

(Ref: Biswas et al, JAPI: 2006. 54, 24-33).

Lymphomas have been the object of intensive studies by oncologists and hematologists and based on the various parameters such as cell morphology, cytology, cytochemistry, immune markers, chromosomal characteristics, gene variation and biological behaviour, the classification, specific diagnosis, management protocols and follow-up have all assumed great importance just as in the case of leukemias.

Management of lymphomas is an equally complex exercise requiring sophisticated facilities for diagnosis and treatment. Newer and newer observations lead to changes in classification and management strategies. Only basic principles are given in this chapter.

HODGKIN'S DISEASE

SYN: HODGKIN'S LYMPHOMA

Pathology: Hodgkin's disease (HD) generally arises unicentrically and spreads to other lymphatic tissues by contiguity and later to non-lymphatic organs as well.

The pathological hallmark is the presence of **Reed-Sternberg's cells** (RS cells) which are large multinucleated cells with the nuclei being arranged in mirror image fashion in histological slides (Fig. 159.1). A causal association between EB virus infection and EBV positive subgroup of HD has been identified.

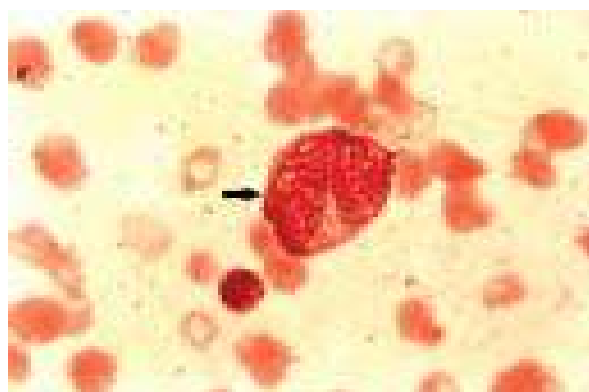


Fig. 159.1: Bone marrow Hodgkin's disease.
Note: The Reed-Sternberg's cell (arrow)

They are clones of neoplastic B-lymphocytes which originate from the germinal centres of lymphoid organs. They appear as modified germinal centre B-lymphocytes that have escaped apoptosis. They show rearrangement of the immunoglobulin variable region (V) genes. RS cells produce cytokines which promote their own growth and are also responsible for the systemic manifestations of the disease. In general RS cells form only 1% of the cell population even though they constitute the malignant tissue.

The rest of the tissue is made up of lymphocytes, macrophage and granulocytes, especially eosinophils.

The lymph node architecture is destroyed and replaced by abnormal tissue. Four histological patterns have been recognized.

Rye (1965) Classification

This classification arrived at by consensus, held its pride of place until recently. Now newer and more elaborate classifications have been introduced. The Rye classification is based on general morphology of the tissue and the cell types.

1. **Lymphocyte predominant (10%):** There is predominance of lymphocytes with a few RS cells. Nodular and diffuse patterns are recognisable. This has the best prognosis. Nodular variety of lymphocyte predominant HD is of B-cell origin.
2. **Nodular sclerosis (30-40%):** In this form the tumour is arranged as nodules which are encircled by collagenous bands extending from the capsule. A variant of the RS cells, the lacunar cell—may be present. Mediastinal lymph node enlargement is more common.
3. **Mixed cellularity (20-30%):** There are numerous RS cells and moderate number of lymphocytes.
4. **Lymphocyte depleted (10-20%):** The pattern may be reticulate or diffuse fibrosis. In the former, there is dominance of RS cells and depletion of lymphocytes. In the latter, the lymph node is replaced by disorderly connective tissue containing a few lymphocytes and a few RS cells.

The nodular sclerosis type maintains its distinct histology throughout whereas the other types may progress to one or the other or show overlap when followed up. In India mixed cellularity type is more frequent than nodular sclerosis. The prognosis becomes progressively worse as one moves from the lymphocyte predominant type to the lymphocyte depleted types.

Newer Classifications

Different newer classifications have come in. HD has been broadly classified as two distinct entities (a) nodular lymphocyte predominant and (b) the classic HD which is further divided into four subtypes 1-4.

CLINICAL FEATURES

Hodgkin's disease may be encountered at any age, but it is more common in the second decade. Males are affected twice as frequently as females. The majority of patients come in an advanced stage, the disease having been present for more than six months.

The most frequent symptom is painless asymmetrical circumscribed enlargement of the lymph nodes, which are rubbery in consistency. In over 75% cases, cervical groups are affected. Axillary, mediastinal and inguinal groups are involved less frequently. Involvement of the retroperitoneal lymph nodes is not uncommon. The lymph nodes reach moderate to large sizes. They do not soften, breakdown, or ulcerate.

Moderate splenomegaly occurs in over 50% of cases and hepatomegaly in a smaller number. These organs are firm and nontender. Hepatocellular or obstructive jaundice may occur.

Constitutional symptoms occur in the majority of cases in the later stages. Pel-Ebstein fever consists of a few days of high swinging pyrexia followed by an afebrile period. Though Pel-Ebstein type of fever has come to stay as a classic feature of Hodgkin's disease, in the vast majority the typical form is not seen. Fever is commonly due to concomitant infection, but less commonly it is due to the malignant process itself. The patient rapidly loses weight and develops toxemia. Sweating, intractable pruritus, and anemia develop in many cases.

Alcohol induced tenderness over the lymph nodes and bone is described as a diagnostic feature, but in Indian subjects it is rare. Horner's syndrome may occur due to pressure on the cervical sympathetic chain. Spinal root and cord compression and development of lymphoma in the CNS are neurological complications. Opportunistic infections such as *Herpes zoster*, *M. tuberculosis*, *cytomegalovirus*, *cryptococci* and *Candida sp.* are common.

Investigations: There may be normocytic normochromic anemia. In the advanced stage when the bone marrow is infiltrated, myelophthisic anemia develops. Mild

eosinophilia may occur frequently. In the advanced stage lymphopenia develops.

Bone marrow involvement is seen in 10-20% of cases and this is best demonstrated by trephine biopsy. As the disease progresses the immunologically competent T lymphocytes progressively diminish and this coincides with the development of anergy to tuberculin. With achievement of remission the cell-mediated immunity recovers. Humoral immunity may be normal.

Bone involvement is accompanied by hypercalcemia, hyperphosphatemia, and raised alkaline phosphatase levels. Hyperuricemia may develop. Hepatic alkaline phosphatase is raised. Serum copper is elevated during the active stages and it falls during remission. Serum LDH is elevated and it is an indicator of the tumour burden.

Several other advanced investigations such as cytochemistry, immunological tests, molecular procedures and imaging modalities such CT scan, MRI and PET studies are undertaken for full evaluation of the extent, type of tumour, and prognostic information.

Clinical staging (Ann Arbor Conference, 1971): This is based on the extent of the disease at the time of presentation.

- Stage I: Lymph node involvement in one anatomical lymph node region (I) or in a single extralymphatic organ (I_E).
- Stage II: Involvement of two or more lymph nodal regions, confined to the same side of the diaphragm (II) or localized involvement of an extralymphatic organ and one or more lymph node regions on the same side of the diaphragm (II_E).
- Stage III: Involvement of lymph nodes above and below the diaphragm (III) which may also be accompanied by splenomegaly (IIIs).
- Stage IV: Extensive disease involving nodes on either side of the diaphragm and involvement of extralymphatic tissues such as bone marrow and liver.

Each stage is further classified as B or A depending upon the presence or absence of constitutional symptoms. The important constitutional symptoms are:

- 1. Fever above 38°C and night sweats and
- 2. Loss of 10% or more of body weight within six months.

In group B the prognosis is worse compared to group A both from the point of remission and duration of survival.

Staging procedures: Since the choice of initial therapy depends on the stage, full investigation should be undertaken in all cases before deciding the therapeutic schedule. It has been established beyond doubt that proper staging and institution of appropriate therapy from the beginning are most important in bringing about a favorable outcome.

Investigation of a Case of Lymphoma

1. Full clinical examination.
2. Radiology of the chest to reveal mediastinal nodes and pulmonary involvement.
3. Complete hematological investigations.
4. Ultrasonography to detect masses of glands in the abdomen and hepatosplenomegaly.
5. Bone marrow trephine biopsy.
6. Liver function tests and liver biopsy if liver is enlarged and shows ultrasonographic changes.
7. CT scan of abdomen and chest to detect enlarged masses and wherever indicated MRI.
8. Isotopic liver scan to detect lymphomatous involvement.
9. Radio-isotopic scintigraphy of lymphnodes
10. Radio-isotopic bone scan, especially in stages III and IV.

Staging laparotomy which was a regular procedure in early stage HD has now been abandoned since the necessary information can be obtained by imaging procedures. In addition systemic chemotherapy is more commonly employed in all stages.

Diagnosis: All cases presenting with chronic local or general lymphadenopathy in which a distinct cause cannot be established should be subjected to lymph node biopsy without delay. When several groups of nodes are affected, an entire node which is moderately enlarged should be selected for biopsy.

Differential diagnosis: All other causes of lymph node enlargement such as leukemias, tuberculosis, syphilis, filariasis, secondary carcinomatosis, HIV infection, nonspecific lymphadenopathy, toxoplasmosis, sarcoidosis, and pseudolymphoma have to be excluded.

Drugs like streptomycin and phenytoin produce a type of immunoblastic lymphadenopathy (pseudolymphoma) clinically resembling lymphoma. Withdrawal of the drugs results in resolution of the node.

Treatment

Stages I and II: The treatment of choice is to give radiotherapy given up to a total dose of 4000-4500 cGy in four weeks. A total dose not below 4000 rads is curative in 90% of cases. Improved high voltage radiotherapy techniques allow safe irradiation of all lymph nodes above or below the diaphragm by upper mantle or inverted Y fields (Fig. 159.2).

Stages III and IV: These patients are treated with cyclical chemotherapy. The most popular combination is MOPP and this consists of

	Dose	Days
Mustine hydrochloride	6 mg/m ² I V	1 and 8
Oncovin (Vincristine)	1.5 mg/m ² I V	1 and 8
Procarbazine	100 mg/m ²	1 to 14
(Natulan-Roche)	oral	
Prednisolone	40 mg/m ²	1 to 14
	oral	

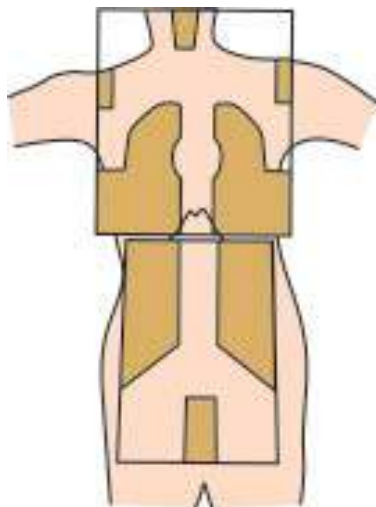


Fig. 159.2: Diagram showing mantle for radiotherapy

The 14-days treatment is followed by 14 days rest and the cycle is repeated. Usually 6 courses are given. There are many other effective regimens which use different drug combinations.

A more popular chemotherapeutic regimen consists of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD).

At present all stages of HD are given chemotherapy. For stages I and II it is short course chemotherapy preceding irradiation and for the higher stages it is the full course.

Prognosis: Approximate five-year survival rates reported from the west are:

	below 20 yrs (%)	21-40 yrs (%)	above 40 yrs (%)
Stages			
IA and IIA	94	93	78
IB and IIB	93	83	45
III and IV—A and B	80	61	22

Histologically lymphocyte predominant types show the best prognosis. Circumscribed lesions have a better prognosis than diffuse lesions. Results in Indian series are not so encouraging as these figures suggest.

In India only about 25% of cases are in stages I or II when initially diagnosed.

Other adverse prognostic factors include:

1. Age above 45 years.
2. Presence of B symptoms
3. Mediastinal width exceeding 45% of thoracic width in the skiagram.

4. Presence of extranodal disease.
5. Involvement of bone marrow.
6. PCV below 25% and ESR above 50 mm/hr.

Relapses are managed by the same or alternate schedules of chemotherapy. In resistant cases two regimens can be combined. At present more aggressive drug combinations are being used in poor-prognosis cases and relapsed cases. This has been made possible due to the availability of supportive services during the phase of neutropenia. Autologous bone marrow transplantation and stem cell transplantation have helped to institute almost curative chemo-radiotherapy.

Long-term risks: 1% of patients treated for HD may develop acute myeloid leukemia which is resistant to therapy. The risk of second malignancies is higher in treated HD patients than in the general population. Several types of second malignancies have been reported. Other complications include reversible azoospermia caused by chemotherapy, serious infective complications in splenectomized patients, amenorrhea and cumulative cardiotoxicity caused by daunomycin and related drugs. The cardiotoxicity may manifest as cardiac dysfunction even several years after recovery from the malignancy.

Advances in investigations and therapeutic modalities introduced during the past decade have made the results of therapy and prognosis much better in India as well. Institution of therapy in special institutions has helped to improve the results. Wherever possible, treatment should be undertaken in such tertiary care centres.

Non-Hodgkin's Lymphoma (NHL)

Majority of these are B cell neoplasms, though T cell NHL also occurs. Unlike Hodgkin's lymphoma, the clinical picture is more variable. Extranodal involvement is more common, so also involvement of the blood and bone marrow. The disease often starts multicentrically.

Classification

Classification of NHL has undergone considerable modification from time-to-time. Rappaport (1966) gave the histological classification as mainly 1) Nodular and 2) diffuse types. Luke and Collins based their classification on morphology and immunological characteristics.

Newer classifications have come in such as Kiel, International Working Formulation (IWF), Revised European and American lymphoma (REAL) group and WHO. Modern classification takes into account the clinical schema classifying the disease into

1. Indolent lymphoma/leukemias (with survival times measured in years, if untreated)
2. Aggressive lymphomas (survival measured in months) and

3. Highly aggressive lymphomas and leukemias (survival measured in weeks)

Each type is further subdivided into B and T cell types and also the histological pattern. For further details, refer to Hiddemann W. et al, Blood 1996; 88: 4085-4089.

The Kiel classification, which is also in vogue, makes a distinct subdivision into low grade and high grade lymphomas, the former being composed of relatively small cells, whereas the latter is composed of larger and more rapidly proliferating cells. Different institutions follow a combination of histologic, immunologic (B-cell, T-cell, etc.) and behavioral factors (Kiel) to group the lymphomas for statistical and therapeutic purposes.

Non-Hodgkin's lymphomas occur in all regions. Certain types show geographic differences, e.g. Burkitt's lymphoma is seen in Africa mainly. Kaposi's sarcoma is a cutaneous lymphoma in some cases triggered by viral infections especially AIDS.

Co-existence of NHL with Other Hematological Disorders

Diffuse well differentiated lymphoma may merge imperceptibly with chronic lymphatic leukemia and Waldenström's macroglobulinemia. Histological picture of the lymph nodes is similar in these conditions. Acute lymphatic leukemia, especially in children, presents with lymph node involvement, indistinguishable from diffuse poorly differentiated lymphoma. Histiocytic lymphomas are relatively uncommon, but when they occur, the histiocytes may phagocytose erythrocytes causing hemolytic anemia.

Majority of non-Hodgkin's lymphomas are monoclonal B-cell tumours and paraproteins of IgM or IgG classes may be demonstrable in many cases. T cell NHL presents especially with mediastinal lymph node enlargement in children.

CLINICAL FEATURES

Majority of cases occur in the second to fifth decades. The duration of illness ranges from weeks to months. More than 70% of the cases are in advanced stages at presentation.

The disease begins as asymmetric painless progressive lymphadenopathy, involving one or several lymph node regions. The cervical, axillary, inguinal, mediastinal, abdominal, and other groups of nodes may be affected. The nodes are firm, variable in size from a few to several centimeters, and are matted in the later stages. Pressure on neighbouring structures may lead to mediastinal syndrome, Horner's syndrome, and lymphedema.

Enlargement of the tonsils and Waldeyer's ring may lead to obstruction to breathing and swallowing. Liver and spleen are moderately enlarged in the majority of cases.

Mesenteric and retroperitoneal lymph nodes may be enlarged.

Systemic manifestations include early onset of fever, weight loss, and night sweats in about 30% of cases. Anemia and infections are also more common.

Comparison between Hodgkin's and Non-Hodgkin's lymphoma		
	HL (Percentages)	NHL
Lymphadenopathy	93	89
Fever	69	29
Abdominal masses	—	16
Cough and dyspnea	20	25
Skin lesions	3	15
Pruritus	14	3
Pleural effusion	6	17
(Based on 120 cases)		

Involvement of other organs: Though several organs are affected in the advanced stages of NHL, sometimes extra-nodal involvement may be the presenting symptom. Involvement of the skin leads to nodular or diffuse lesions. Intense pruritus is an early and intractable symptom in a few. Brain, spinal cord, and meninges are affected in many cases. Gastrointestinal tract, liver, lungs, respiratory tract, pleura, and bone may be the seat of primary lymphoma. Hemorrhagic pleural effusion may occur (Fig. 159.3).

Laboratory Findings

Hematology: Moderate normocytic normochromic anemia may occur in the advanced stages. The leukocyte picture is generally unremarkable but in a few cases lympho-sarcoma cells are detectable in the circulation. These cells resemble large lymphocytes with lobed or folded nuclei and may show nucleoli. The condition is termed lymphosarcoma leukemia.



Fig. 159.3: Female orbital lymphoma

Autoimmune hemolytic anemia develops in a few cases. Infiltration of the marrow results in myelophthistic anemia. Bone marrow involvement is common in stage IV NHL.

Biochemistry: Paraproteins of IgM or IgG class may be detectable in a few cases. Serum uric acid is moderately elevated in the advanced stages. Hepatic involvement is characterized by rise in alkaline phosphatase and transaminases. Obstructive jaundice results from pressure of lymph nodes at the porta hepatis.

Staging procedures are the same as for HD.

NHL is generally advanced even on first presentation.

Prognosis: Well-differentiated nodular lymphocytic lymphomas have the best prognosis and many may survive 5 years or more. Diffuse undifferentiated lesions have poorer prognosis. Extensive disease and advancing age are unfavourable prognostic factors. Females have a better prognosis than males. Prolonged survival and cure have been achieved in many cases with intensive chemotherapy.

Leukemic transformation may occur in a few cases and these behave like acute lymphoblastic leukemia.

Death is due to progressive disease, infections, liver failure, profound anemia, bone marrow failure, or drug toxicity.

TREATMENT

Stages I and II respond to radiotherapy as for HD. In the other stages chemotherapy is advocated. At present chemotherapy is given even in the earlier stages.

Single drug regimen: Continuous or intermittent therapy with chlorambucil or cyclophosphamide has been reported to give good results in patients with localized nodular and diffuse well-differentiated lymphoma. Except under special circumstances such as advanced age and general debility this is seldom followed at present.

In the vast majority of cases the disease is widespread on presentation, combination therapy is followed.

Combination therapy with cyclophosphamide, vincristine, and prednisolone (COP), as in the case of stages II and IV Hodgkin's disease, has been tried with remission rates upto 55-60%. A remission rate of 60% is obtained with MOPP regimen. In more advanced cases, adriamycin and bleomycin have been included (BACOP regimen) with remission rates upto 80%. Local irradiation with 4000-5000 cGy to control massive local disease and systemic chemotherapy give better remission rates in diffuse poorly differentiated lymphoma.

Combination chemotherapy consisting of cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) is used most frequently in the aggressive types of NHL due to its better efficacy and predictable results.

Monoclonal antibodies developed against specific CD 20 cells-rituximab (mabthera) is used to target specific

CD 20⁺ B cells which occur in several forms of NHL. The dose is 375-500 mg/m² on day-1 of the cycle. The results are considerably better.

Total body irradiation of 15 rads twice a week for 5 weeks (total 150 rads) has been used as an alternative.

Neuroprophylaxis as for acute leukemia has been advocated in stages III and IV NHL. At present depending on the type of cell and its biological behaviour, several combination chemotherapy protocols are available. These have to be given only in special treatment facilities. The modern drugs are very expensive, but when given properly, results are good.

Support by transfusion of platelets and use of growth factors have helped to tide over the leukopenic and thrombocytopenic periods. Stem cell transplantation or BMT done after chemotherapy is quite successful since these permit more aggressive and intensive regimen without causing fatal bone marrow aplasia. At present the results of treatment of NHL are being bettered. The ideal therapeutic modality is still not established.

The overall survival and disease free survival among new cases of lymphoma reported from Tata Memorial Hospital Mumbai (2006) resulting from doxorubicin based chemotherapy at five years are 62% and 50% respectively. Rituximab improved remission rate to 72%.

BURKITT'S LYMPHOMA

This lymphoma is more prevalent in Africa showing a geographical localization to areas with altitude below 1700 m and high rainfall, which are also holoendemic for malaria. Stray reports are available from all parts of the world, including several from India. Epstein-Barr (EB) virus infection is a cofactor in the development of Burkitt's lymphoma (BL), the other factor being chronic stimulation of the reticuloendothelial system by malaria.

Histology: Histology of the lesion is diagnostic and the tumour is made up of uniform type of lymphoblast-like cells, 10-25/μm in size with rounded nuclei and nucleoli. Phagocytic macrophages with large pale cytoplasm are uniformly distributed among the dark staining cells giving the appearance referred to as the "starry sky" appearance. Chromosomal abnormalities have been observed, the most frequent being a translocation between 8 and 14 (t,(8,14)(q24,q32).

Clinical features: The African cases are seen predominantly in children, mostly in the age group of 3-5 years. Multicentric tumours arise which grow rapidly affecting the jaw, salivary glands, neck, abdominal viscera, long bones and central nervous system. Spread to bone marrow and lymph nodes and the leukemic phase are uncommon.

Burkitt's lymphoma, as reported from other parts of the world affects older age groups. Lymph node and

marrow involvement is more common. Antibodies to EB virus are less pronounced.

Course and prognosis: The disease is rapidly fatal if untreated. The African cases respond dramatically to cyclophosphamide in large doses or combination chemotherapy. Response is less dramatic in cases described from other parts of the globe.

Other Rare Forms of Lymphocyte Tumours

ANGIOIMMUNOBLASTIC LYMPHADENOPATHY

This is the result of an immunological disorder seen in patients taking drugs for various conditions. The pathological process suggests a borderline between a reactive condition and a neoplasm.

Histology: The lymph node shows loss of normal architecture, pleomorphic cellular infiltrate consisting of immunoblasts, plasma cells, neutrophils and histiocytes, and proliferation of small blood vessels.

Clinical features: The disease starts as an acute or subacute illness characterized by fever, sweating, weight loss, generalized lymph node enlargement and hepatosplenomegaly. Unlike malignant lymphomas, these patients show rise in polyclonal immunoglobulins, especially IgM. If left untreated, many cases end fatally due to infective complications or supervening malignancy. The prognosis in individual cases is unpredictable.

Treatment is effective in one-third of the cases. Corticosteroids, alkylating agents, and combination chemotherapy have all been employed with variable results.

HYDANTOIN-LINKED LYMPHOMA

Syn: Pseudolymphoma

Diphenyl hydantoin may produce an allergic response characterized by fever, rash, generalized lymphadenopathy and even splenomegaly resembling angioimmunoblastic lymphadenopathy. The condition remits fully within months of drug withdrawal (Fig. 159.4).

MYCOSIS FUNGOIDES

This term has been loosely used by different workers. The consensus is to limit the term to the group showing a classical histological picture. Mycosis fungoides and Sézary's syndrome are T cell non-Hodgkin's lymphomas. These are all rare diseases.



Fig. 159.4: Hydantoin linked lymphoma

Clinical features: The onset of the disease may be as a lesion resembling pruritic erythroderma, psoriasis, seborrheic dermatitis, eczema, nonspecific exfoliative dermatitis, lichenoid dermatitis, or neurodermatitis. After several years, plaque formation or tumour formation starts. In some cases the lesions directly start as tumours which may ulcerate. The skin is red and diffusely thickened. Later the nails may be affected and they may be lost.

The course of the disease is variable. Tumour-like lesions do worse than lichenoid lesions. Advancing age worsens the prognosis. Median survival period is 5 years from diagnosis.

SÉZARY SYNDROME

This is the leukemic phase of mycosis fungoides. It is rare and is characterized by intense pruritus, erythroderma, and later on enlargement of the liver, spleen and lymph nodes. Skin shows diffuse infiltration by typical *Sézary's cells*. These cells are seen in good numbers in the peripheral blood.

Treatment: The condition responds to alkylating agents like chlorambucil or cyclophosphamide singly. Combination therapy as for NHL has been found beneficial in advanced lesions. Superficial irradiation with rays of low penetrance and surface application of mustine hydrochloride (HN_2) 10 mg dissolved in 60 mL water brings about remission in a good number of cases. Intensive electron beam therapy or photochemotherapy with psoralens and long-wave ultraviolet light are other modalities employed.

Chapter Summary

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- Polycythemia Rubra Vera (PRV) 1072
- Essential Thrombocythemia 1073

The term myeloproliferative syndrome was coined by William Dameshek in 1951. Myeloproliferative disorders are clonal hematopoietic stem cell disorders that result in overproduction of one or other of the blood cells. Myeloproliferative disorders include primary idiopathic myelofibrosis, polycythemia rubra vera (PRV), essential thrombocythemia and chronic myeloid leukemia (CML). They arise from a common precursor stem cell which can proliferate and differentiate into any one of these types. In these disorders there is a clonal proliferation of one or more cellular elements in the marrow like RBC, WBC, platelets or fibroblasts. They may show a tendency to transform into one or other type when followed up. All these have some phenotypic similarity. Around 30% of cases of PRV develop myelofibrosis but myelofibrosis transforming to PRV is rare. All these disorders show a higher tendency to transform to acute leukemia if followed up for long periods.

Ref: The myeloproliferative disorders. Peter J Compbell et al N. Eng J, Med 2006, 355 2452-2466

The JAK2 V617 F mutation Janus Kinase 2 (JAK2) which is a cytoplasmic tyrosine kinase is critical for instigating intracellular signalling by the receptors for erythropoietin, thrombopoietin, interleukin 3, granulocyte colony stimulating factor (GCSF) and granulocyte macrophage colony stimulating factor (GMCSF). JAK2 binds to erythropoietin receptors in the endoplasmic reticulum and aids in their expression on the surface. The JAK2 mutation in myeloproliferative disorders (MPD) is acquired and it is common to all the MPD.

JAK2 mutation occurs in more than 95% of cases of polycythemia vera (PV), and in 50-60% of cases of essential thrombocythemia (ET) and idiopathic

myelofibrosis (IMF). The JAK2 mutation is the first genetic marker associated with the pathogenesis of MPD and it has acquired importance in both diagnosis and follow up. The causative role of this mutation in the pathogenesis of MPD is established. The JAK2 mutation explains many of the cardinal features of MPD and it can be compared to the role played by BCR-ABL in chronic myeloid leukemia. **Cooperating mutations:** Leukemic transformation of MPD reflects the acquisition of additional mutations. One such is V617F positivity in MPD, which may even predate JAK2 mutation. The V617F somatic mutation in the JAK2 gene causes the substitution of phenylalanine for valine at position 617. Patients with 20q deletion are almost exclusively V617F positive. Mutant JAK2 protein activates multiple downstream signalling pathways with effects on gene transcription, apoptosis, the cell cycle and differentiation. Testing for JAK2 V617F mutation is now widely available and it promises to simplify the diagnostic work up. JAK2 and V617F can be identified by allele specific PCR assay, pyrosequencing, restriction enzyme digestion and real time PCR. The JAK2 mutation is also assuming importance in classification of MPDs.

Primary Myelofibrosis

(Chronic idiopathic myelofibrosis, agnogenic myeloid metaplasia, or myelofibrosis with myeloid metaplasia)

It is characterized by fibrosis of marrow without any other obvious primary cause for it. As a consequence there is massive splenomegaly due to extramedullary hematopoiesis and a characteristic leukoerythroblastic blood picture. The etiology of this disorder is not known and there are no specific cytogenetic abnormalities although abnormalities like 20q-, 13q- and trisomy 1q are often encountered. Marrow fibrosis is associated with overproduction of transforming growth factor β and thrombopoietin. The marrow is initially hypercellular with an excess of megakaryocytes which may be releasing the cytokines for proliferation of fibroblasts and as the disease

progresses the marrow becomes fibrosed and is difficult to aspirate.

Causes of Myelofibrosis

Secondary myelofibrosis
Infections e.g. tuberculosis, fungal infections
Lymphoma (NHL)
Hodgkin's disease
Acute leukemias
Chronic myeloid leukemia
Polycythemia rubra vera
Systemic mastocytosis
Systemic lupus erythematosis
HIV infection
Hypoparathyroidism
Primary myelofibrosis (Idiopathic)

CLINICAL FEATURES

Most patients are over the age of 50 years, and they usually come to medical attention for anemia and symptoms due to splenomegaly which is often massive even at presentation. Other modes of presentation include fatigue, tiredness, weight loss, night sweats and sometimes low grade fever due to the hypercatabolic state. Anemia and splenomegaly are detected during physical examination. Many patients are asymptomatic and come to attention due to accidentally detected splenomegaly or abnormal blood counts during a routine examination. The anemia is due to replacement of the hematopoietic tissue and also due to ineffective erythropoiesis or hypersplenism. The large spleen can give rise to abdominal fullness and early satiety. Splenic infarcts occur with severe abdominal pain. Sometimes portal hypertension may develop. Mild hepatomegaly is also common due to extramedullary hematopoiesis. Other sites for extramedullary hematopoiesis include lymph nodes, pleura (resulting in pleural effusion) or peritoneum (leading to ascites) or in paraspinal or epidural spaces with resultant spinal cord or nerve root compression.

Diagnosis

The erythrocytes show marked aniso and poikilocytosis with polychromasia and characteristic 'tear' drop cells. Most patients have leukocytosis at presentation with a leukoerythroblastic blood picture (Fig. 160.1). WBC count can be normal or sometimes decreased, due to hypersplenism. Thrombocytosis can occur in some, but others may have normal or even decreased platelet counts. Megakaryocytic fragments may be seen in peripheral blood.

Bone marrow aspiration often results in dry tap. Trephine biopsy of the bone marrow reveals dysplastic megakaryocytic hyperplasia, osteosclerosis and dilatation

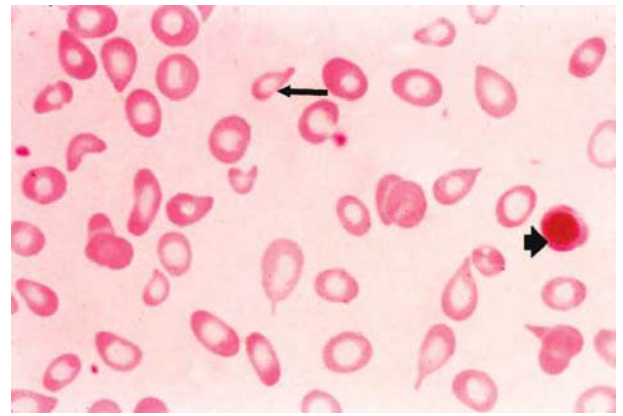


Fig. 160.1: PB myelofibrosis. Note: The teardrop cell (arrow). Normoblast (arrow head)

of marrow sinusoids with intravascular hematopoiesis. Foci of extramedullary hematopoiesis can be demonstrated in the spleen, liver and rarely lymph nodes. Radiographs of bones show osteosclerosis with obliteration of marrow cavity. Changes are most markedly seen in the vertebrae, shafts of long bones of the extremities, ribs, clavicles, and pelvis. Serum uric acid is increased. Leukocyte alkaline phosphatase is high.

Hyperuricemia and secondary gout can occur due to the hypermetabolic state.

Prognosis is good in most cases and they can be managed with supportive measures for more than 10 years but the survival is shorter than that for PRV and essential thrombocythemia. With advanced age, anemia, and WBC counts more than 30000 and blasts in peripheral blood, the survival may be much less (1-2 years). Survival is not directly proportional to the degree of splenomegaly. The common disease-related cause of death is leukemic transformation which usually occurs after 10 years.

Treatment: Treatment is mainly supportive or palliative, with supplementation of folic acid and at times, pyridoxine. Androgens have been used to correct the anemia. Erythropoietin (EPO) may help sometimes, but the anemia is usually due to ineffective erythropoiesis and hypersplenism and this may not respond to EPO. Hydroxyurea given in doses of 500 mg three times a day is used to control leukocytosis, thrombocytosis and organomegaly. Packed red cell transfusions may be given to correct severe anemia. Splenectomy may be required when the splenomegaly causes disabling symptoms or when there is severe hypersplenism. Splenectomy will be followed by rebound thrombocytosis and progressive hepatomegaly. Allopurinol can be used in doses of 100 mg tid oral to control hyperuricemia. Glucocorticoids are sometimes useful when there are co-existing autoimmune phenomena.

Thalidomide given in doses of 100-800 mg daily produces benefit in anemia and thrombocytopenia. Bone marrow transplantation may be beneficial in 50-60% of young patients.

Polycythemia Rubra Vera (PRV)

Syn: Erythremia, Vaquez's disease, Osler's disease, Cryptogenic polycythemia

The word "polycythemia" indicates excess of cells-mainly erythrocytes. In adult men hemoglobin level > 17 g/dL or PCV $> 50\%$ can be taken as abnormal. In females the corresponding values are hemoglobin level above 16 g/dL and PCV above 45%. Polycythemia may be true or apparent. In true polycythemia there is increase in red cell mass. Apparent polycythemia occurs when there is an acute reduction in plasma volume following severe dehydration, as happens in diarrhea, vomiting, use of diuretics, capillary leak syndromes and in severe burns. Polycythemia may be primary or secondary. The latter is more common. When polycythemia occurs in the absence of any physiological stimulus or without a pathological increase in EPO it is called as *polycythemia rubra vera* (PRV). This is one of the myeloproliferative disorders.

Secondary polycythemia occurs mainly due to increased amounts of erythropoietin (EPO) secreted as a physiological response to hypoxic stimulus, or abnormal secretion of EPO from the kidneys or from ectopic foci. Rarely the erythroid progenitors in the bone marrow may respond in an exaggerated manner to normal levels of EPO. All these constitute secondary polycythemia.

Causes of Secondary Polycythemia**I: Erythropoietin mediated (EPO)-hypoxia driven**

1. Chronic lung diseases
2. Chronic carbon monoxide exposure (including cigarette smoking)
3. Right to left cardiac shunts
4. High altitudes above 2500 m
5. Hypoventilation syndromes including extreme obesity
6. Sleep apnea
7. Dysfunction of the respiratory centre
8. Renal artery stenosis
9. High affinity Hb (autosomal dominant) with defective oxygen unloading in the tissues e.g.
10. Defective oxygen delivery by erythrocytes having deficiency of 2,3 diphosphoglycerate (DPG).

II: Pathologic Erythropoietin production

- A. *Malignant tumours producing excessive erythropoietin*
 1. Hepatocellular carcinoma
 2. Renal cell cancer
 3. Cerebellar hemangioblastoma
- B. *Non-malignant conditions*
 1. Uterine leiomyoma
 2. Renal cysts
 3. Hydronephrosis
 4. Adrenal tumours
 5. Atrial myxoma
 6. Post-renal transplantation

III: Miscellaneous causes

- a. Androgen abuse, erythropoietin abuse
- b. Familial polycythemia (AD)

Pathogenesis of PRV

There is clonal expansion of multipotent hematopoietic stem cells resulting in overproduction of phenotypically normal RBCs, WBCs and platelets without physiologic stimulus. The erythropoietin independent proliferation of pleuripotent stem cells, occurs possibly due to an aberrant signal transduction pathway. JAK_2 gene is a signal transduction molecule which influences several cytokine receptors including receptors for erythropoietin (EPO). Mutations of the JAK_2 gene (V617 F mutation) confers increased tyrosine kinase activity, allowing the erythroid precursors to grow even in the absence of EPO. The total red cell mass (RCM) is increased to > 36 mL/kg bw in men and > 32 mL/kg bw in women. V617 F mutation can be demonstrated by allelic specific PCR in peripheral blood nucleated cells. By an unknown mechanism there is suppression of proliferation of the normal stem cells and hence the formed elements in the patients represent the progeny of the transformed clone. The bone marrow is apparently normal, but there is increase in number of all cellular elements. Two phases of the disease can be seen. The initial one is of cellular proliferation. The latter is one of cytopenias with ineffective hematopoiesis, marrow fibrosis, and hypersplenism.

CLINICAL FEATURES

Usually it occurs in people above 40 years. Most often the disorder is picked up by noticing the eye congestion or an abnormally high hemoglobin and PCV on routine blood testing. Early symptoms are vague. These include lassitude, loss of concentration, dizziness, vertigo, tinnitus, heaviness of head or headaches, and visual disturbances. A symptom that is more specific for PRV is pruritus exacerbated by water contact (aquagenic pruritus). Sometimes they may present with the complications like vaso-occlusive diseases. These include digital ischemia, TIA, stroke, myocardial infarction, deep vein thrombosis with or without pulmonary embolism, Budd-Chiari syndrome and portal vein thrombosis. Easy bruising, epistaxis and gastrointestinal hemorrhage due to peptic ulceration may be the presenting symptoms. Hypermetabolic state can give rise to weight loss, fatigue, night sweats or hyperuricemia with features of secondary gout or even renal calculi.

On examination there is congestion of eyes and ruddy complexion and palmar erythema may be obvious in fair skinned individuals. Systolic hypertension may be present. Splenomegaly is the suggestive physical finding that helps differentiation from secondary causes. While evaluating them look also for features of the known secondary causes for polycythemia.

Features that support the diagnosis of PRV

1. Polycythemia without any known secondary cause
2. Splenomegaly
3. Elevated white blood cell count $> 12 \times 10^9/L$
4. Increased basophil count
5. Thrombocytosis $> 400 \times 10^9/L$
6. Elevated serum uric acid levels
7. Elevated leukocyte alkaline phosphatase levels
8. Elevated serum vitamin B₁₂ and vitamin B₁₂-binding protein levels.

Diagnosis

Clinically polycythemia is suspected based on symptoms and signs. Estimation of Hb, PCV and red cell count confirms the diagnosis. The features that suggest PRV are given in box above:

Presence of JAK2 is highly suggestive of polycythemia vera in patients with erythrocytosis.

In those with massive splenomegaly at times the hematocrit values may be normal due to pooling of blood in the spleen. In such cases estimation of red cell mass may be needed to differentiate PRV from primary myelofibrosis. Bone marrow study is not often required unless myelofibrosis or leukemic transformation is suspected. Leukocyte alkaline phosphatase is increased in many. Elevated levels of vitamin B₁₂ and vitamin B₁₂ binding protein may be present.

Course and Prognosis

Prognosis is good and the majority live more than 10 years after diagnosis; some live up to 20 years or more. Thrombotic complications occurring in vital tissues may contribute to morbidity and mortality. Death may occur due to fatal thrombosis or hemorrhage, and due to leukemic transformation into acute myeloid leukemia or unrelated causes. Secondary myelofibrosis may develop in some on follow-up.

TREATMENT

Aims of management include reduction of the red cell mass and thrombocytosis to normal levels, avoidance of thrombotic complications and reassuring the patient about the relatively benign nature of the disease. Management is primarily aimed at preventing the thrombotic complications by maintaining the Hb less than 15 g/dL (PCV45%) in males and less than 14 g/dL (PCV42%) in females. This is achieved by repeated venesections (300-400 mL) weekly in the initial stages, sufficient to induce a state of iron deficiency, and thereafter, done less frequently (once in 3 months). Anticoagulants and aspirin are relatively contraindicated in these patients for the control of thrombotic tendency. Allopurinol is given in doses of 100 mg tid to control hyperuricemia. Hydroxyurea (also known as hydroxycarbamide) has been used to control the splenomegaly, and thrombocytosis. But chemotherapy is not the preferred method of choice to

reduce the red cell mass. If there is severe thrombocytosis (levels above 500000/cm) anagrelide can be used to lower platelet levels. The dose is 0.5 mg/daily, the drug is expensive and not freely available in India. Interferon α has been tried with good results.

Essential Thrombocythemia

Syn: Primary (idiopathic) thrombocytosis, hemorrhagic thrombocythemia, megakaryocytic myelosis

It is a clonal disorder of unknown etiology with variable cytogenic abnormalities. There is primary proliferation of megakaryocytes in the marrow, producing apparently normal platelets but having some functional abnormalities which can predispose to either thrombosis or hemorrhage. Physiological thrombocytosis, mediated by thrombopoietin usually occurs as a response to infections, chronic inflammatory disorders, connective tissue disorders, post hemorrhagic states, iron deficiency anemia, in association with some malignancies or after splenectomy. Thrombocytosis occurring in the absence of any physiologic stimulus by thrombopoietin is called essential thrombocytosis or essential thrombocythemia. This is a myeloproliferative disorder. Apparently normal looking platelets are seen on the peripheral smear, no specific platelet function defects have been documented in spite of the bleeding tendency which may develop at times. Bone marrow biopsy usually shows megakaryocyte hyperplasia. Clonal abnormalities of the Janus kinase 2 gene (JAK₂) are demonstrable in some cases. This abnormality is seen also in polycythemia rubra vera and primary myelofibrosis.

Causes of thrombocytosis

- a. Reactive
 1. Iron deficiency anemia
 2. Infections
 3. Chronic inflammatory disorders
 4. Collagen vascular disorders
 5. Post hemorrhagic
 6. Post splenectomy
- b. Neoplastic thrombocytosis
 1. Chronic myeloid leukemia
 2. Polycythemia rubra vera
 3. Myelofibrosis
 4. Essential thrombocythemia

CLINICAL FEATURES

It is an uncommon disease seen in adults and older individuals. Patient may present with arterial or venous thrombosis at different sites. These include cerebrovascular accidents, ischemic heart disease, cortical vein thrombosis or digital ischemia and gangrene (Fig. 160.2). Hemorrhagic manifestations like mucocutaneous bleeding, easy bruising, epistaxis or GI hemorrhage may occur. Thrombotic complications are more common in



Fig. 160.2: Digital gangrene on the foot due to venous thrombosis in essential thrombocythemia

patients above 60 years of age and those with previous episodes of vascular complications. Hemorrhage is more common in those with extreme thrombocythemia. More often the disorder is identified when very high platelet count ($> 600,000$) is reported on routine investigations for other conditions. Physical findings are usually unremarkable, but sometimes mild splenomegaly may be seen. Diagnosis is established by the presence of sustained elevation of platelet counts, usually above 600,000/cmm without any underlying cause. In patients with

thrombocytosis presence of JAK2 suggests possibility of MPD. Patients without a MPD are V617F negative. Essential thrombocythemia patients with V617F mutation are more sensitive to hydroxycarbamide (but not to anagrelide) than patients who are V617F negative.

The course of the disorder is generally benign but occasionally they can have serious complications caused by thrombosis or hemorrhage. The prognosis or survival is good- rarely the disease may transform into megakaryocytic leukemia or polycythemia rubra vera.

Treatment: Asymptomatic patients below 45 years of age with platelet counts below 400000/cmm are having only low-risk. Such patients can be kept under observation without active treatment. Treatment is indicated only when the platelet count goes very high or if clinical features are attributable to the elevated platelet count. Hydroxycarbamide is effective in reducing the platelet count when given in doses of 1-2 g/day orally. Interferon α , in doses of 25 million units/week given subcutaneously as divided doses and tapered off to 8.5 million units/week is effective in bringing down the platelet count. Anagrelide given in a dose of 0.5 mg daily is an alternative. Both these drugs are more expensive. Low dose aspirin (100 to 150 mg oral daily) may have to be used to prevent thrombotic tendencies.

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Spleen and Its Disorders

K.V. Krishna Das, P.K. Sasidharan

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Functions of the Spleen

The spleen is made up of collections of lymphocytes in the white pulp performing an immune function, and reticuloendothelial cells in the red pulp performing

phagocytic function. The normal spleen weighs 120-200 g.

White pulp: It serves the following immunological functions:

1. Antibodies to circulating antigens are produced. A major function is to cull wornout, damaged or potentially dangerous cells from the blood stream. Antibodies are produced in the germinal centres of the white pulp. Milieu of the germinal centre provides specific conditions for initiating and halting the production of highly specific clinically protective antibodies by B-lymphocytes. Fc receptors help the phagocytic cells to identify the IgG-coated cells from

all others. The spleen removes spherocytes, parasitized erythrocytes and distorted erythrocytes.

- Probably a factor which increases neutrophil chemotaxis and phagocytosis (*tuftsin*) is produced. Absence of this factor is possibly responsible for the increased susceptibility to infection in asplenic subjects.

Red Pulp: It serves the following functions:

- Phagocytic functions — The cells of the red pulp remove effete red cells, antibody coated cells, and bacteria. Splenic phagocytes remove the nuclear remnants such as *Howell-Jolly bodies* from erythrocytes. This is known as “*pitting*”. Presence of numerous erythrocytes containing Howell-Jolly bodies should indicate the absence of splenic function. In the splenectomized subject, macrophages of the liver, lymph nodes and bone marrow take over most of the culling function.
- Removal of nuclear remnants, Heinz’s bodies and others from erythrocytes.
- The spleen acts as a reservoir for the formed elements of blood and these are released into the general circulation in times of stress. About 1/3 of the total platelet pool is stored in the spleen. Normal life-span of the platelets is only 9 days and out of this 1/3 is spent in the spleen. Splenectomy leads to thrombocytosis which may persist for several weeks, sometimes even up to years.
- Hematopoiesis occurs in the spleen normally in fetal life. When there is impairment of normal marrow activity the spleen takes up extramedullary hematopoiesis.

Splenomegaly

Various conditions lead to splenomegaly in the tropics. Size of the enlarged spleen is variable and when gross, the spleen may fill almost the whole abdomen. An enlarged spleen can sequester up to 25 to 30% of the total red cell mass. In splenomegaly, since the plasma volume is increased and red cells are sequestered, dilutional anemia results. Massive splenomegaly from any cause leads to secondary effects on the hemopoietic tissues known as hypersplenism.

Etiology: Some of the common causes of splenomegaly are listed below.

- Chronic infections:** Malaria, leishmaniasis, trypanosomiasis, disseminated tuberculosis, brucellosis, and systemic mycotic infections. In these conditions the spleen is considerably enlarged and generally firm in consistency.
- Acute infections:** Septicemia, enteric fever, viral hepatitis, infectious mononucleosis, infective endocarditis, exanthemata, relapsing fevers, and typhus. The spleen is moderately enlarged and often soft.

- Venous congestion:** Portal hypertension and chronic right-sided heart failure. In portal hypertension spleen enlarges considerably.
- Hematological neoplasia:** Leukemias, lymphomas, polycythemia vera, and myelofibrosis.
- Reactive splenomegaly with reticuloendothelial hyperplasia:** Hemolytic anemias, megaloblastic anemia, thalassemias and hemoglobinopathies, myelophthisic conditions, tropical splenomegaly, and acquired hypogammaglobulinemia.
- Granulomatous disorders:** Felty’s syndrome, systemic lupus erythematosus, sarcoidosis, and berylliosis.
- Infiltrative disorders:** Lipid storage disease, amyloidosis, histiocytosis-X, and gargoylism.

HYPERSPLENISM

This condition is characterized by the occurrence of anemia, leukopenia, and thrombocytopenia (pancytopenia) in a patient with moderate or massive splenomegaly of any etiology. The bone marrow is active and hypercellular. When the splenic size is increased there is increased pooling of blood in an environment with relatively decreased availability of nutrients, but full of phagocytes. This leads to exaggerated sequestration and destruction of cells. In other words it is an exaggeration of its normal function. In addition there may be humoral factors depressing cell maturation as well. The cytopenia recovers promptly on splenectomy.

Causes of Hypersplenism

All causes of moderate to massive splenomegaly like portal hypertension, lymphomas, tropical splenomegaly syndrome, myelofibrosis, hemolytic anemias, and chronic infections may lead to this situation.

Treatment: If the pancytopenia is severe, splenectomy is indicated, but the prognosis depends on the original cause of splenomegaly.

Tropical Splenomegaly Syndrome

The condition is characterized by persistent splenomegaly without any other cause in some residents of malaria endemic areas of tropical Africa and Asia. Probably it is due to an abnormal immunological response to repeated malarial infections. Malarial parasites are not seen in blood, liver or spleen but there is lymphocytic infiltration of splenic sinusoids and they show high titers of IgM Malarial antibody. Anemia and sometimes pancytopenia may occur due to the hypersplenism.

Treatment: Those in endemic areas should receive chemoprophylaxis with proguanil and those who migrate to non-endemic areas should receive antimalarial treatment.

HYPOSPLENISM

This term denotes the condition that develops after splenectomy or after splenic atrophy; Alterations of cellular and humoral immunity may develop.

Causes of Hyposplenism

- 1. Asplenia
 - i. Congenital- may be associated with fatal cardiovascular anomalies
 - ii. Splenectomy
- 2. Splenic atrophy
 - i. Infarction
 - ii. Injury
 - iii. Irradiation

Splenic atrophy is common in sickle cell disease. Rarely ulcerative colitis, Crohn’s disease and adult celiac disease may be associated with splenic atrophy.

Diagnosis: The hematologic features include presence of large number of target cells and Howell-Jolly bodies. Moderate leukocytosis and thrombocytosis are present.

Diagnosis is based on clinical suspicion and hematological features. History of splenectomy and absence of splenomegaly by physical examination and ultrasonogram help to confirm the diagnosis.

Complications: Splenectomy predisposes to infection by capsulated organisms like *Streptococcus pneumoniae*, *Haemophilus influenzae*, and meningococci. Children are more susceptible. Protozoal infections such as malaria, babesiosis and toxoplasmosis are also more common.

Management: Asplenic patients should receive bactericidal antibiotics active against pneumococci and H influenzae, at least at the first sign of infection. Prophylactic vaccination is mandatory.

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Hemostasis: General Considerations

Mathew Thomas, K.V. Krishna Das

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Normal Hemostasis

Clotting of blood is one of the host defence mechanisms which, when accompanied by inflammation and repair responses, helps to protect vascular integrity and preserve life.

Hemostasis (arrest of bleeding) takes place in two distinct stages—(1) primary hemostasis and (2) secondary hemostasis.

Primary hemostasis occurs within a few seconds after injury to blood vessels and it involves the platelets which form the platelet plug. This helps to stop bleeding occurring from capillaries, small arterioles and venules. Secondary hemostasis involves the plasma coagulation factors which help to form a stable fibrin clot and strengthen the primary hemostatic platelet plug. This may take a few minutes. This is important in the larger blood vessels. It prevents recurrence of bleeding. Both primary and secondary hemostasis are closely linked and inter-related. For example plasma coagulation is accelerated by activated platelets and products like thrombin formed by plasma coagulation reaction can induce further platelet activation.

Primary hemostasis consists of platelet adhesion, granule release and platelet aggregation.

PLATELETS

Platelet adhesion: When there is an injury to the vessel wall, platelets start adhering to the collagen fibrils of the vascular endothelium within seconds. This occurs with

the help of glycoprotein receptors (Gp) on the platelets and von Willebrand's factor (vWF) in the vascular endothelium.

Platelet activation: When agonists like epinephrine, collagen or thrombin binds to the platelet surface receptors they get activated. Thromboxane A₂ (TXA₂) is formed from arachidonic acid which is released from membrane phospholipids with the help of an enzyme cyclo-oxygenase. TXA₂ stimulates platelet activation and secretion further. Aspirin and non steroidal anti-inflammatory drugs inhibit cyclo-oxygenase.

Platelet aggregation: When activated, the platelets secrete several of their granule contents into plasma, which include ADP, serotonin, calcium, fibronectin, platelet derived growth factor (PDGF) and platelet factor 4. Released ADP binds to the glycoprotein receptors on the platelet surface. The receptors, in turn, get activated and change the conformation of the Gp II b/III a complex so that it binds fibrinogen, thereby linking the adjacent platelets and aggregating them. These aggregated platelets form the platelet plug (see Figs 148.5 to 148.8).

Once the optimum amount of clot has been formed, further extension is arrested by the antithrombic substances and the fibrinolytic enzyme plasmin, which is generated locally. Plasmin helps to remove excess of fibrin by converting it into soluble fibrin degradation products (FDP). Normal hemostasis is a well balanced system brought about by the close interaction of the vascular platelet factor, coagulation, and fibrinolysis. This can be achieved only in the presence of normal vessel walls, adequate number of functioning platelets, sufficient quantities of functional coagulation proteins, and a normal fibrinolytic mechanism (see page 979).

In peripheral blood the normal platelet count is 150-400,000/cmm. Platelets are disc-shaped non-nucleated bodies, 1.5-3 µm in diameter.

Ultrastructure of platelets—The surface of platelets is made of three layers—the glycoprotein layer, phospholipid layer and inner layer. The glycoprotein layer contains receptors for the binding of von Willebrand's factor and fibrinogen. Defects in the glycoprotein layer lead to abnormalities of adhesion and aggregation. The matrix of the platelet is made up of the sol-gel zone and the organelle zone. In the sol-gel zone the cytoplasm shows fibre systems in various stages of polymerization. These fibre systems help to maintain the shape and also account for the contractile apparatus of the platelets. The organelle zone shows various bodies—the alpha granules, dense granules and lysosomes. The alpha granules contain several secreted proteins, von Willebrand's factor, fibrinogen, fibronectin, thrombospondin, coagulation factor V, high molecular weight kininogen, platelet factor 4, beta thromboglobulin, platelet derived growth factor

(PDGF), albumin and histidine-rich glycoproteins. The dense granules contain calcium, pyrophosphate, serotonin, and adenine nucleotides. All these substances are released into plasma when the platelets are activated. Deficiency of alpha granules and dense granules lead to platelet dysfunction (see Fig. 148.4).

Platelet function requires the presence of specific receptors on the platelet surface, which interact with proteins in the plasma including those secreted by the platelets (see Fig. 148.7).

Platelets can produce many of the factors taking part in the coagulation cascade, in addition to concentrating them on their surface.

These processes collectively known as **contact interactions** consist of several processes. Platelet adherence is mediated by the interaction of platelet glycoprotein Ib/1x with endothelial von Willebrand's factor under high shear conditions, and by platelet glycoprotein Ia/IIb binding to collagen under low shear rates. Upon stimulation, adherent platelets recruit more platelets into the growing thrombus by three distinct mechanisms:

1. Platelets concentrate clotting factors on their surface and favour thrombin generation. Thrombin activates further platelets.
2. The activated platelets liberate ADP from their granules and activate further platelets.
3. Activated platelets generate thromboxane A₂ which also activates further platelets.

Activation of platelets by an agonist also activates the glycoprotein IIb/IIIa receptor conformationally. This receptor, also known as integrin binds to fibrinogen.

Fibrinogen is essential for platelet aggregation. Normal inactive platelets do not bind fibrinogen. Once activated by ADP, epinephrine or thrombin, fibrinogen receptors manifest on the surface and bind to fibrinogen. The contractile proteins of the platelets consist of actin and myosin. These help in changing shape, locomotion and extrusion of the contents to the surface.

Apart from mediating primary hemostasis (which includes the retraction and contraction of the injured vessel, and plugging of the injured vessel by platelet plug) the platelets take part in coagulation as well—this is referred to as procoagulant activity. **Platelet procoagulant activity** is mediated by the following mechanisms.

1. Protection of the coagulation factors on the platelet surface from the action of plasma inhibitors and secretion of several coagulation factors.
2. Activation of factors X, XII, and XI.
3. Platelet factor 4 antagonises heparin and other inhibitors of coagulation.

Antigenicity of Platelets

The glycocalyx layers on the external membrane of the platelets contain a series of complex glycoproteins

numbered I to X. These express several polymorphic antigenic determinants on their surfaces. These are termed platelet specific antigens (HPP, PIA I or HPAI). These antigens lead to antibody formation resulting in post transfusion purpura and neonatal autoimmune thrombocytopenia purpura (NAITP).

Coagulation

Coagulation: Nomenclature of the coagulation proteins has been accepted internationally.		
Factor	I	Fibrinogen
Factor	II	Prothrombin
Factor	III	Tissue thromboplastin
Factor	IV	Calcium ions
Factor	V	Proaccelerin-labile factor
Factor	VII	Stable factor-Proconvertin
Factor	VIII	Antihemophilic globulin (AHG, AHF)
Factor	IX	Plasma thromboplastin component (PTC), Christmas factor
Factor	X	Stuart-Prower factor
Factor	XI	Plasma thromboplastin antecedent-PTA
Factor	XII	Hageman's factor
Factor	XIII	Fibrin stabilising factor.

The numerical order does not represent the sequence of activation. In addition to the above, several other factors such as prekallikrein (PK) and high molecular weight kininogen (Kin) and several cytokines are involved in the activation of coagulation factors at several steps in the intrinsic pathway. The activated factors are represented with suffix “a”.

Molecular Basis of Blood Coagulation

All the proteins and cellular components taking part in coagulation remain in the circulation as inactive precursors. The coagulation factors are present in optimal amounts required for their efficient action. Thus fibrinogen is present in the concentration of 10 µmol/L where as factor VIII is present only in 0.2 nmol/L.

These are rapidly activated by enzymatic cleavage of one or more peptide bonds. The enzymes concerned with blood clotting are similar to digestive protease enzymes. Since the former group acts intravascularly, precise control and regulation are necessary to moderate their actions. The cascade process of blood coagulation is initiated and maintained on surface membranes of stimulated cells. Platelet surface membrane provides this critical venue for blood clotting *in vivo*. As the coagulation process proceeds, inhibiting factors such as antithrombin III, protein C and protein S are also activated and these help to arrest the coagulation process.

All the coagulation proteins are synthesised mainly in the liver. Endothelial cells including those of hepatic blood vessels secrete von Willebrand's factor polymers. von Willebrand's factor (vWF) is concerned with platelet-

vessel wall and platelet-platelet interactions. It is absent or defective in von Willebrand's disease. Factor VIII molecules form ionic bonds with vWF polymers which provide a carrier for them in the circulation and also prevent their destruction.

Factors II, VII, IX and X are produced in the liver and these are termed vitamin-K dependent factors since this vitamin is necessary for making them functional. Thrombin is produced from prothrombin and it converts soluble fibrinogen to fibrin which consists of insoluble polymers.

Natural Inhibitors of Coagulation

Antithrombin III (AT III): This is present in normal plasma and endothelial cell surfaces. It combines with thrombin and inactivates it. Heparin combines with the lysine residue of AT III and this product is more potent in inactivating thrombin. Hence AT III used to be known as heparin cofactor. AT III has got other activities as well. These include inhibition of the procoagulant factors such as IXa, Xa, XIa, XIIa, VIIa, tissue factor, plasma kallikrein, HMWK and plasmin.

Deficiency of AT III may lead to thrombotic tendencies. AT III has also antiplasmin activity.

Protein C, a vitamin K dependent protein synthesized in the liver is the key component in a physiologically important anticoagulant system. Protein C circulates in plasma as an inactive precursor which is rapidly converted into activated protein C (APC) on contact with thrombin which is bound to thrombomodulin receptors on vascular endothelial cells. APC selectively degrades factors Va and VIIIa. By inactivating these factors it controls the conversion of factor X to Xa and that of prothrombin to thrombin, thereby inhibiting the coagulation cascade.

Inherited abnormalities of factor V also known as factor V Leyden has a glutamine instead of arginine in position 506. Factor V Leyden is resistant to the section of APC. In the white population the frequency of this genetic defect is 2-15%. In India also this abnormality is present as a cause of thrombophilia. Activated protein C, antithrombin III and tissue factor pathway inhibitor (TFPI) dampen coagulation, enhance fibrinolysis and remove microthrombi. APC proteolytically inactivates factors V a and VIII a, and decreases the synthesis of plasminogen activator inhibitor -I (PAI-I).

Protein C deficiency may be inherited as an autosomal dominant. Such individuals suffer from recurrent venous thrombosis and even fatal pulmonary thromboembolism. Infants who are homozygous for protein C deficiency develop neonatal purpura fulminans. This is characterized by generalized macrovascular thrombosis. In addition to quantitative deficiency, functional abnormalities of protein C may occur as genetic defects. Resistance to APC has

been reported to occur as an inherited disorder. Sepsis reduces the levels of protein C, Protein S, ATIII, and TFP-I.

Protein S—This is also a vitamin K dependent plasma protein synthesized by the liver, which acts as a co-factor for activated protein C and this complex takes part in inhibiting coagulation cascade. Protein S exists in two forms in plasma-free and combined forms. The former is the functionally active one. Action of protein S is not fully understood. Inherited protein S deficiency leads to thromboembolic complications. Individuals who develop thromboembolic complications due to abnormalities of protein C or protein S require life-long anticoagulant therapy.

Blood coagulation occurs under two main groups of circumstances. The commonest event requiring the coagulation process to be initiated is trauma or any event that leads to disruption of a blood vessel. The extrinsic pathway is triggered and this results in prompt coagulation and arrest of bleeding. Another pathway known as the intrinsic pathway becomes operational when blood clots inside vessels or *in vitro* spontaneously. Though these two distinct processes start off differently, after the few initial steps both proceed through a common pathway. Both the processes are complementary to each other.

In 1977 a vitamin K-dependent protein circulating in bovine plasma was identified by Prowse and Eonou. The human counterpart of this protein was identified in 1984. Its structure is broadly similar to that of factors VII, IX and X and also protein C. It was named **protein Z**. It acts as a co-factor to form protein dependent proteinase inhibitor (ZPI) which inhibits the action of factor Xa.

Protein Z is synthesised in the liver. Normal levels range from 2-3 mg/L in plasma. Association between protein Z deficiency and ischemic stroke has been suggested (Protein Z and thrombosis. The Lancet; 2001, 337, 900-901).

Coagulation Pathways

The mechanism of coagulation can be considered under two heads for purposes of description, even though in real-life the whole process proceeds as a smooth continuous cascade like process.

1. Primary or extrinsic pathway end
2. Accessory or intrinsic pathway

The main pathway resulting in clot formation is the primary or extrinsic pathway. Regardless of path chosen, the final steps are the formation of prothrombinase complex which converts prothrombin to thrombin, which in turn converts fibrogen to fibrin. Fibrin is the ultimate product which forms the clot. On injury to the vessel wall, tissue factor (TF) combines with circulating factor VIIa to form extrinsic tenase. Initially this converts factors IX

to IXa and X to Xa simultaneously Factor IXa combines with factor VIIIa to form intrinsic tenase. Factor Xa with factor Va form prothrombinase complex. The intrinsic tenase also converts more of factor X to Xa.

Factor IXa is also formed from the accessory pathway with the help of factors XIIa, XIa, prekallekrein and high molecular weight kininogen (HMWK).

The combined actions of the intrinsic and extrinsic tenase and the prothrombinase, complex lead to an explosive burst of the enzyme thrombin (factor IIa). Enzyme thrombin cleaves fibrinogen to yield the fibrin clot.

Enzyme thrombin also activates factor XIII which further stabilizes the fibrin.

The next step is to terminate the activated coagulation process so that excessive clot formation will be prevented and only optimum clot will be formed. This is achieved by inhibition of the procoagulant enzyme complexes. This involves antithrombin III which inhibits thrombin and factor IXa, Xa, XIa, XIIa factor VIIa- tissue factor, plasma kallikrein and HMWK. Protein C and protein S inhibit factors Va, VIIIa. The termination phase serves to limit the coagulation process and prevent excessive clot formation (Fig. 162.1).

Thrombin

This is the key effector enzyme for converting fibrinogen into fibrin. The most crucial event in the coagulation process is the generation of thrombin from prothrombin by thromboplastin which is also known as prothrombinase. Thrombin has other actions as well.

1. Activation of platelets
2. Conversion of fibrinogen into fibrin network
3. Feedback amplification of coagulation factors.

Phosphatidylserine is a negatively charged phospholipid required for the assembly of the tenase and prothrombinase complexes. In platelets under normal conditions phosphatidylserine is present in the inner layer leaflet of the plasma membrane. When platelets are activated this phosphatidyl serine is translocated from the inner to the outer layer of the plasma membrane. In the tenase and prothrombinase complexes all the participating proteins, namely,

- a. The enzyme factor IXa and Xa
- b. The cofactors VIIIa and Va
- c. The substrate factors X and prothrombin show affinity to the phospholipid surface. The enzymes and substrates are vitamin K dependent.

Calcium binding is necessary for the molecular reactions. Antagonists of vitamin K lead to defective binding of calcium and loss of ability to interact with the phospholipid membrane. This is the mechanism of action of vitamin K antagonists employed therapeutically.

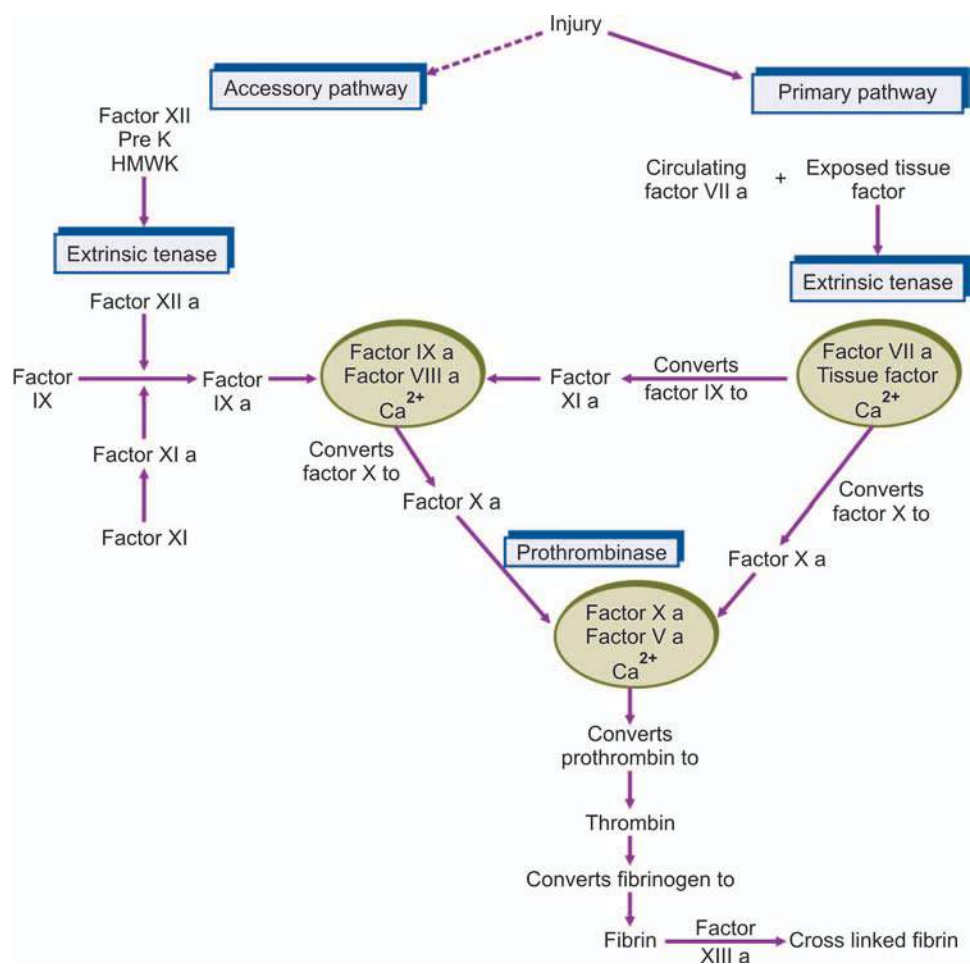


Fig. 162.1: Overview of hemostasis. Note: The term extrinsic and intrinsic 'tenase' indicate their enzymic activity

In experimental mice, lack of tissue factor, factor V and prothrombin leads to death *in utero*. Deficiency of factor VII leads to death from bleeding, shortly after birth. Deficiency of factor VIII and IX are compatible with normal growth and development, but such animals develop hemophilia like disease later on.

Polymerization of fibrin is limited by the inhibition of factors XIIa, XIa, IXa and Xa, and thrombin by anti-thrombin III (heparin cofactor) present in blood and endothelial cell surfaces. At this stage the other inhibitors of coagulation—protein C and protein S—also come to play their roles in limiting further thrombosis.

Fibrinolysis

This is the process by which fibrin polymers are lysed by the enzyme plasmin derived by partial proteolysis of the zymogen-plasminogen which is adsorbed to fibrin polymers. The main fibrinolytic components of plasma are plasminogen, alpha-2 antitrypsin, tissue plasminogen activator (tPA) and urinary type plasminogen. The

formation of plasmin-resistant stable fibrin clot is the ultimate result in the coagulation process.

Coagulation factor XIII acts on fibrin to convert it into polymerized form which is resistant to plasmin. Tissue plasminogen activator facilitates the conversion of plasminogen to plasmin. Plasminogen activators are derived from the lysosomes of disrupted endothelial and tissue cells. These bind to fibrin polymers and convert fibrin-bound plasminogen into plasmin.

Plasmin remains bound to fibrinogen and degrades it into soluble fragments—the fibrin degradation products (FDP). D-dimer is also produced in excess. In addition to splitting fibrin, plasmin is also capable of splitting fibrinogen and factors V and VIII. Fibrinolysis is inhibited by plasminogen activator inhibiting type I (PAI-I) and increased plasma concentrations of factor VII, fibrinogen and von Willebrand's factor. PAI-I is produced by vascular endothelium. It is also seen on platelets. Increase in PAI-I occurs in syndrome X which is associated with diabetes mellitus and increased tendency to atherosclerotic vascular occlusions.

GENERAL CLINICAL CONSIDERATIONS

In general, primary hemorrhagic disorders are rare, in the majority of cases abnormal bleeding is due to secondary causes, either localized (surgical conditions) or generalized, e.g. hepatic failure, renal failure and anticoagulant overdose. In any patient who gives a history of easy bruising or excessive bleeding from childhood, a congenital hemostatic defect is likely. The acquired form starts at a later age. Even in congenital defects which are mild, clinical onset may be delayed.

Congenital Hemorrhagic Disorders are Characterized by

1. Purpura, ecchymosis, hematoma, or spontaneous bleeding from multiple sites or following minor trauma.
2. Excessive bleeding after trauma or minor surgery.
3. Bleeding into joints, gums, and mucous membranes of the gastrointestinal and the genitourinary tracts.
4. Positive family history in many cases.
5. History of previous episodes of hospitalization and blood transfusions to control the hemorrhage.
6. Abnormality involving one or only a few coagulant factors.

On the other hand, acquired hemorrhagic tendencies set in at a later age, may be temporary and may reveal deficiencies of multiple coagulation factors.

Broadly the hemorrhagic disorders can be divided into two groups.

1. **Purpuric disorders:** These affect the process of primary hemostasis, i.e. platelet and/or vascular functions are abnormal. These are characterized by bruising, ecchymosis, and bleeding from mucous membranes, especially of the gastrointestinal and genitourinary tracts. Bleeding starts soon after injury and it is brisk initially. It is relieved by local pressure. The capillary resistance test (*Hess' test*) is positive. Bleeding time is prolonged. Unless there is severe thrombocytopenia (less than 20000/cmm), coagulation time is not prolonged.
2. **Coagulation defects:** These may be congenital or acquired. In the majority of cases the primary coagulation disorders are congenital. They are characterized by deep tissue bleeding, bleeding into joints, progressive deformity of joints, prolonged coagulation time, and normal bleeding time and a negative Hess-test. If the platelets and capillaries are normal, post-traumatic bleeding stops temporarily to be followed by prolonged and gradually increasing bleeding, which may even threaten life.

LABORATORY INVESTIGATIONS IN HEMORRHAGIC DISORDERS

A. Screening tests

1. *Platelet count* and morphology.

2. *Prothrombin time* (to test the extrinsic coagulation pathway).
3. *Partial thromboplastin time* (to test the intrinsic coagulation pathway).
4. *Thrombin time* to test the common coagulation pathway.

A *stained blood film* should show clumped and single platelets at the rate of 1 for 20-25 erythrocytes. Absence of clumping may suggest thrombasthenia.

B. Further tests for platelet function

1. *Bleeding time (Ivy):* Prolongation beyond 12 minutes is definitely abnormal. In dysfunction of platelets and capillaries, the bleeding time is prolonged. Common causes of prolongation of the bleeding time are thrombocytopenia (platelet count below 100,000/cmm), thrombopathies, von Willebrand's diseases and scurvy.
2. *Hess tourniquet test:* Appearance of more than 30 spots (when examined with a hand lens) within a circle of 2.5 cm diameter is considered a positive test. Hess' test is positive in thrombocytopenia, thrombocytopathy, and diseases of the capillaries. This test is less reliable than the bleeding time and hence abandoned in many centres.
3. *Platelet aggregometry:* This is an *in vitro* test to determine the ability of the platelets to aggregate in platelet-rich plasma. This phenomenon can be studied spectrophotometrically or using an aggregometer. Platelet aggregation in response to ADP, epinephrine, collagen or thrombin is absent in thrombasthenia.

Interpretation of findings on platelet aggregation

Normal	Thrombocytopenias von Willebrand's disease
Absent	Thrombasthenias, especially Glanzmann's disease
Diminished	Disorders of platelet release reaction and afibrinogenemia.

4. *Tests for platelet adhesion:*

C. Tests for coagulation

Clotting time (coagulation time-Lee and White): 1 mL blood is drawn into each of three clean dry test tubes and clotting time for each test tube at room temperature is noted and the values are averaged. Normally clotting occurs in 5-7 min. Prolongation beyond 10 min is abnormal. Clotting time is prolonged in hemophilia, Christmas disease, presence of circulating anticoagulants, hypofibrinogenemia, and secondary deficiencies of coagulation factors. Clotting time is prolonged only when the defect is gross, and therefore, it is not reliable when the disorder is mild.

Clot retraction: When kept at room temperature the clot retracts and the serum separates within two hours. When the platelet number is grossly deficient or platelet function

is defective, clot retraction is impaired. Normally the serum expressed measures 55-65% of the total quantity of blood.

Prothrombin time (Quick's): This test evaluates the production of thrombin and fibrin polymers by the extrinsic coagulation pathway. Prothrombin time is prolonged whenever factors VII, X or V, prothrombin, or fibrinogen are reduced to levels below 30% of normal. Normal prothrombin time is 10-12 seconds. In order to standardize the test results and avoid inter laboratory variations, internationally standardized thromboplastin is used and the results are expressed as International Normalized Ratio (INR).

Partial thromboplastin time (PIT): Activated partial thromboplastin time (APTT) measures the time required for the formation of thrombin and fibrin polymers by the intrinsic pathway. Normal APTT is 35 sec. Value of APTT rises whenever the levels of one or more of the coagulation factors other than factor VII is reduced below 30% of the normal. When the common pathway is impaired both PTT and APTT are prolonged.

Substitution Test and Factor Assays

Identification of deficiencies of coagulation factors is done by estimating APTT in the patient's plasma and repeating the test with added plasma with known defects, till APTT is corrected. Assay of factors XII, XI, IX and VIII-C, prekallikrein, and high molecular weight kininogen is done by modified APTT test.

Thrombin time: This helps to identify abnormalities in the quantity and quality of fibrinogen. It is prolonged in hypofibrinogenemia and dysfibrinogenemia. Normal level of fibrinogen in plasma is 150-400 mg/dL.

Estimation of fibrin degradation products (FDPs): Increase in FDPs in serum and urine indicate increased fibrinolysis.

Euglobulin lysis time: This indicates the amount of fibrinolytic activity in the serum, and therefore, it is an indirect indication of plasmin activity. In disseminated intravascular coagulation (DIC) and primary hyperfibrinolytic states, euglobulin lysis time is shortened and serum levels of FDPs are increased.

D-dimer Elevated levels of D-dimer in plasma are more specific indicators of thromboembolic episodes followed by fibrinolysis. D-dimer is the fibrin fragment in plasma which is a marker of fibrin formation and reactive fibrinolysis. Normals levels of D-dimer in plasma is < 500 ng/mL.

Rusven (Russels viper venom) clotting time is employed to assay factor X and also for the detection of lupus anticoagulant.

At present test kits are available from many sources, and therefore, these tests can be done even in moderately equipped laboratories.

Detection of Circulating Anticoagulants

In conditions where the abnormality of coagulation is due to deficiency of one or more of the clotting factors, addition of 10-30% by volume of normal plasma corrects the abnormal laboratory tests.

In conditions where circulating anticoagulants or antibodies to coagulation factors are present, substitution with normal plasma fails to correct the abnormality, until very large quantities are added.

Automated testing machines are available for performing coagulation tests and platelet function tests. If properly serviced and calibrated using standard specimens, they are reliable and more accurate than manual methods.

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Platelet and Vascular Disorders

K.V. Krishna Das, Mathew Thomas

Chapter Summary

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General Considerations

The term purpuric disorder is applied to a hemorrhagic state characterized by bleeding into the skin in the form of dot like purpura, ecchymosis, or deep hemorrhages, and often associated with bleeding from the mucous membranes of the mouth, nose, gastrointestinal tract, uterus, and urinary tract. Purpuras are caused by primary disorders of blood vessels or thrombocytopenia or thrombocytopathy. Purpura has to be distinguished from macular rashes. The former does not blanch on pressure whereas the latter does. Palpable purpura occurs in vasculitis, e.g. Henoch-Schönlein syndrome (Table 163.1).

When the platelet count falls below 100,000/cmm (1010/L) it is designated as thrombocytopenia. Even at this level mild bleeding tendency may start, but bleeding becomes pronounced when the platelet count falls below 50,000 per cmm. Severe bleeding occurs when the platelets fall below 20,000 per cmm. The severity of the bleeding does not always correlate with the degree of thrombocytopenia. Bleeding may be spontaneous or may follow minor trauma. Purpuric bleeding usually stops within 24 hours either spontaneously or on local compression.

Causes of thrombocytopenia: Thrombocytopenia may result from either diminished production or increased destruction of platelets. In some both may operate. It may also occur in disseminated intravascular coagulation and massive transfusion of stored blood.

TABLE 163.1

Causes of thrombocytopenia

- A. **Diminished production of platelets**
 - 1. Aplastic anemia
 - 2. Selective hypoplasia of megakaryocytes or inhibition of platelet production by antibodies
 - 3. Dyshemopoietic states, e.g. megaloblastic anemia
 - 4. Myelophthistic conditions, e.g. acute and chronic leukemia, lymphoma, myelofibrosis, disseminated carcinoma, and multiple myeloma
 - 5. Heavy alcoholism (ethanol leads to inhibition of megakaryocytes)
- B. **Increased destruction**
 - 1. Idiopathic (immune) thrombocytopenic purpura
 - 2. Chronic or acute secondary immune thrombocytopenia following viral infections, systemic lupus erythematosus, lymphomas, and chronic lymphatic leukemia, acquired hemolytic anemias, AIDS and others.
 - 3. Drugs like sedormid, quinine, quinidine, para aminosalicylic acid, sulphonamides, rifampicin, stibophen, digoxin, streptomycin, alpha methyl dopa, heroin, carbimazole, chloramphenicol, tetracycline, mesantoin, troxidone, and phenylbutazone
 - 4. Sequestration of platelets, e.g. splenomegaly, giant hemangioma, arteriovenous fistulae, disseminated intravascular coagulation.
- C. Dilutional thrombocytopenia, e.g. transfusion of massive quantities of stored blood poor in platelets

Immune Thrombocytopenic Purpura (ITP)
Syn: Idiopathic thrombocytopenic purpura

This is one of the common hemorrhagic disorders seen in clinical practice in India. In the vast majority of cases antibodies develop which coat the platelets and lead to their destruction in the reticuloendothelial system in the spleen, liver, bone marrow and other sites. These antibodies are demonstrable by direct or indirect methods. Though the exact antigenic stimulus for production of the antibodies is not clear, it is seen that they are directed against many of the components of the platelets. Most of the autoantibodies are directed against epitopes on

glycoproteins on the platelet surface. The antibody-coated platelets are sequestered in the spleen, liver, bone marrow and other reticuloendothelial organs, and selectively destroyed by macrophages. The antibodies are produced in the spleen and bone marrow. They are IgG in 70%, IgM in 5% and IgG and IgM in 20% of cases. In the circulation they are attached to the platelets. Most of the auto-antibodies are directed against epitopes on glycoproteins on the platelets surface. Life-span of the platelets is reduced and the reduction is inversely related to the amount of platelet associated IgG.

There is compensatory increase in platelet production brought about by increase in the number of megakaryocytes to 3-5 times the normal, but platelet destruction exceeds the regeneration and ultimately the platelet count falls. The antibody has also action in inhibiting the production and release of platelets from megakaryocytes and in some cases platelet production may be suppressed. In the bone marrow many megakaryocytes are seen to possess hyaline cytoplasm and entire margins, indicating absence of platelet production. In small doses the antibodies lead to platelet dysfunction. In larger doses they lead to platelet destruction. Many of the platelets formed under stress are larger than normal. These megathrombocytes have the same diameter as red cells. They have reduced life-span which is inversely proportional to their diameter. Presence of antibodies may also contribute to their morphological abnormality.

CLINICAL FEATURES

Idiopathic thrombocytopenic purpura (ITP) may occur at any age, but younger subjects are affected more. The disease may present as the acute and the chronic varieties. In chronic ITP duration of the disease exceeds three months. Acute ITP is more common in children whereas the chronic variety is more common in young women. Both sexes are equally affected below the age of 12 years, but after that age females are affected about four times more frequently than males.

In many cases of ITP in children, purpura may be preceded by an upper respiratory infection or other specific diseases like measles or mumps. Viral infections trigger the formation of antiplatelet antibodies. The acute form is characterized by rapid onset of bleeding from the gums, purpura, ecchymosis, and bleeding into deeper tissues. Majority of these patients seek medical help within 1-2 weeks of onset. In the chronic form the onset is insidious and the course is prolonged over several weeks or months, sometimes even years, before they seek medical help. Periods of exacerbations and remissions occur. In women one of the common presentations is menorrhagia and intermenstrual bleeding. The menorrhagia tends to be severe and in some cases blood loss may be considerable so as to necessitate blood transfusion.



Fig. 163.1: Female purpura over legs

Due to this complication ITP tends to be more severe in women than in men. Subdural hematoma may occur in chronic ITP.

Physical examination reveals the typical purpuric spots and ecchymosis, particularly over the limbs, chest, and sometimes over the neck. Areas of pressure by clothing or minor trauma of rubbing as in the axillae and thighs show more purpuric spots. Spontaneous bleeding is seen from the mouth, nose, urinary tract and genital tract in women. In severe cases hemorrhagic bullae develop in the mucous membrane of the mouth. The extravasated blood undergoes clotting. Hematemesis and melena may occur. Ordinarily the bleeding stops within a few days either spontaneously or with treatment. Retinal bleeding occurs in severe cases. Bleeding into the central nervous system may present as spontaneous subarachnoid hemorrhage or cerebral hemorrhage. Central nervous system bleeds are likely when the platelet counts fall below 20,000/cmm. As a rule, there is no palpable splenomegaly. Presence of moderate or marked splenomegaly should suggest the possibility of leukemia, systemic lupus or other disorders (Figs 163.1 and 163.2).

Laboratory investigations: Platelet count is reduced in all cases. It may be below 20,000 per cmm in severe cases. Under light microscopy the platelets appear normal, except for the presence of a few large forms—the *megathrombocytes* (Fig. 163.3). The presence of megathrombocytes indicates disordered thrombopoiesis and possibly the effect of antibodies. Though there is no

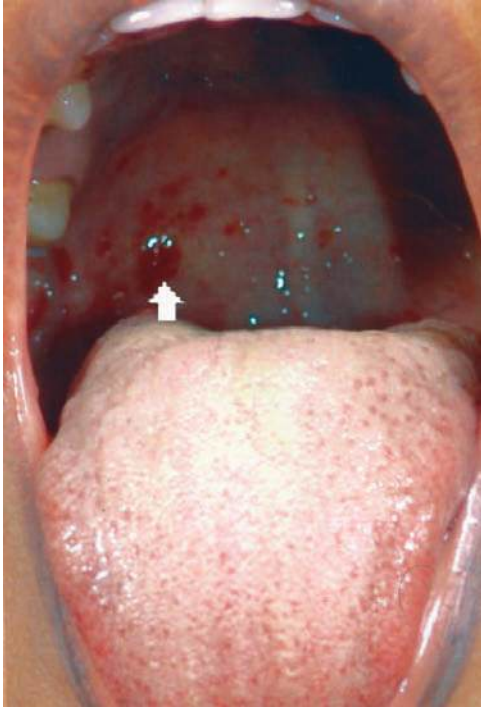


Fig. 163.2: Purpura over the palate

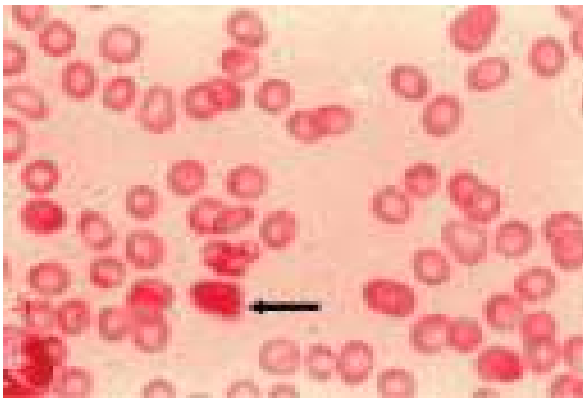


Fig. 163.3: PB ITP megathrombocytes

gross impairment of platelet function, the antibody leads to impairment of platelet release reaction which can be demonstrated *in vitro*. The hemorrhagic manifestation is mainly due to thrombocytopenia, it is aggravated by platelet dysfunction as well. Bleeding time is prolonged whereas the whole blood clotting time is normal. Clot retraction is deficient if the platelet count is below 50,000/cmm. Hess' test is positive. Examination of the bone marrow is basically normal but it may show increased number of megakaryocytes. Many of them have hyaline cytoplasm, entire margins and are devoid of budding activity. In over 75% of cases antiplatelet antibodies can be demonstrated by direct or indirect tests. The degree of anemia is proportional to the blood loss which may be visible externally or deep into tissues.

Differential diagnosis: This includes allergic purpura, drug induced thrombocytopenia, systemic lupus erythematosus, acute leukemias, aplastic anemia, thrombocytopathies, vascular disorders, HIV infection and septicemias. Systemic lupus erythematosus may clinically present as thrombocytopenic purpura for a considerable period of time before other florid features develop.

Presence of mild or moderate splenomegaly should suggest the possibility of acute leukemia, lupus erythematosus, or hemolytic anemia. Sometimes ITP may be associated with other autoimmune disorders such as hemolytic anemia (*Evan's syndrome*). Rarely ITP may coexist with autoimmune thyroid diseases.

Course and prognosis: Acute ITP runs a short course and may remit spontaneously in a few of the cases. It may result in serious bleeding with rapid development of anemia. Fulminant cases may be fatal if untreated. Death is due to severe blood loss or bleeding into vital organs such as the brain. Platelet counts below 10,000/cmm, hematuria, retinal hemorrhages and signs of meningeal irritation are grave prognostic signs. Mortality is about 2-3% in large series.

Among the acute ITP cases, 7-28% go into the chronic form. In the chronic form periods of remissions and exacerbations alternate and the patient suffers only minor disability. Infections, menstruation, or drugs like aspirin may precipitate bleeding episodes. Menstrual and intermenstrual blood loss in women may be severe and even life-threatening and they seek medical help earlier due to this factor. During pregnancy the bleeding episodes may aggravate in many cases, though in some cases the condition may remit. Risk of intra-uterine death of fetus and perinatal fetal loss are high.

TREATMENT OF ITP

All treatment modalities available at present are only supportive or palliative. Therefore, prolonged treatment may have to be given in chronic ITP. Acute ITP may remit and relapse and therefore treatment also may have to be repeated. Rest in bed is essential to reduce the severity of bleeding. If blood loss is severe blood transfusion is indicated. Platelet transfusions have been satisfactory in some cases, but when antibody titre is high the transfused platelets are also destroyed rapidly.

Corticosteroids form the mainstay of treatment in the acute stage. Prednisolone given orally in the dosage of 1 to 2 mg per kg body weight (about 40 mg in divided doses) brings about relief within hours. The effect is brought about by immediate inhibition of macrophage function and a long-term effect on antibody production. The dose is reduced after the first or second week, when clinical severity comes down. Steroids can be withdrawn when the platelet count returns to normal. In fulminant ITP

hydrocortisone or its analogues are given intravenously in a dose equivalent to 100 mg every 8 hours. In resistant cases methylprednisolone given IV in a dose of 1 g daily for a few days may bring about remission. Steroids should be withdrawn only gradually to avoid exacerbation. In many cases the remission is permanent.

Immunoglobulin given in a dose of 0.4-0.8 g/kg IV daily for 4-6 days brings about rapid relief in 60-70% of cases. IVIG helps to raise the platelet counts rapidly. In many cases it is life-saving and may help to avoid emergency splenectomy. The preparation—*Sandoglobulin* (Sandoz, NJ) is ideal. The daily dose is 0.4-0.5 g/kg bw. It is given IV as a 3-4% solution daily for 6 days consecutively. As the condition improves gammaglobulin is repeated in smaller doses at 1-6 week intervals. Heavy expense and non-availability of the drug limit its widespread use.

In large doses, immunoglobulin may increase the viscosity of blood and thereby increase the risk of myocardial infarction and strokes in susceptible individuals.

Plasmapheresis may be employed as an emergency measure to remove antibodies from the plasma.

Chronic ITP: As in the case of acute ITP steroids are started on a moderate dose and withdrawn on getting remission. Corticosteroids are reintroduced in a dosage necessary to maintain clinical remission, if the platelet count falls on their withdrawal. Steroids are effective in 50-60% of cases.

The clinical benefit and rise in platelet count are not uniform in all cases. Though it is ideal to raise the platelet count above 100,000/cmm, often it may not be possible and therapy has to be aimed at clinical improvement. More emphasis should be given to the clinical condition than to the absolute platelet count alone (Fig. 163.4).

Splenectomy: Since the spleen is the major source of production of antibody and also platelet destruction,

removal of the spleen produces dramatic benefit in over 75% of cases. Following are the indications for splenectomy.

1. Acute ITP non-responsive to corticosteroids or immunoglobulin—emergency splenectomy is indicated, especially if there is a danger of intracranial bleeding.
2. Chronic ITP in which the bleeding recurs frequently on reduction of steroid dosage below 15 mg/day.
3. Exacerbation during pregnancy or when pregnancy is to be allowed in a case of chronic ITP requiring moderate or high doses of corticosteroids.

Soon after splenectomy the platelet counts shoot up and severe thrombocytosis may lead to thrombotic episodes in the postoperative period. In such cases antiplatelet drugs and heparin may be necessary. The platelet count gradually returns to normal over weeks and remains so in most cases. In some cases small doses of corticosteroids may be required even after splenectomy. In general, splenectomy is effective in 80% of cases. Splenectomy is not undertaken in children below the age of ten years due to the risk of severe infections. Appropriate immunizations are indicated in splenectomized patients. Accessory spleens occur in about 10% of cases. If these are left behind, these impair the effectiveness of splenectomy. Accessory or persistent splenic tissue can be confirmed by radionuclide scan.

Immunosuppressants: Cyclophosphamide in a dose of 1-2 mg/kg or azathioprine in a dose 1-4 mg/kg are effective adjuvants when used along with corticosteroids. They are contraindicated in pregnancy. Vincristine in a dose of 1 mg/m² once a week given for three to four weeks helps to bring about remission in intractable cases. Mycophenolate mofetil may be used in resistant cases of ITP.

Alternate drugs: *Danazol*, an androgen with only low virilizing activity, commonly used in gynecological practice, when given in doses of 100-300 mg/day brings about clinical improvement in 50% of cases. After control of the acute episode the drug may be given as a maintenance dose for 2-3 months. It probably enhances suppressor T cell function and reduces antibody levels. It acts synergistically with corticosteroids.

Anti-Rh-D immunoglobulin (Rhogam) when given in a dose of 25 µg/kg IV on two consecutive days is effective, especially in Rh-D positive individuals. This may be tried as a cheaper substitute for IV immunoglobulin. Anti Rh-D leads to immune hemolysis and this secondarily overloads the phagocytic cells, thereby reducing the phagocytosis of antibody coated platelets.

Dapsone causes oxidative hemolysis and this process overloads the phagocytic cells, thus rendering them less effective to destroy antibody coated cells. In dose of 50-100 mg/day given orally it can be used for maintenance

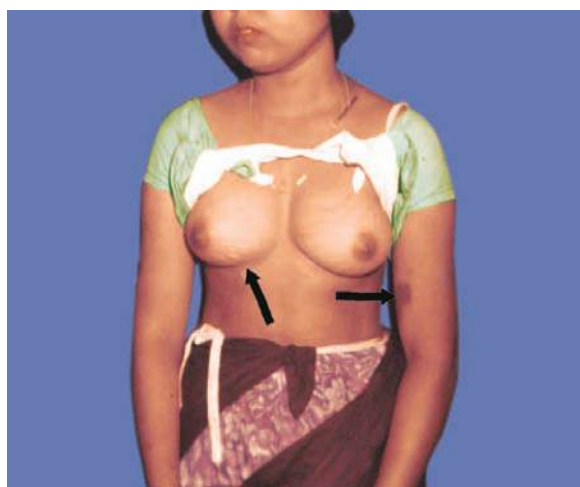


Fig. 163.4: ITP figure female long-term steroid therapy striae

therapy. About 50% of mild chronic ITP patients respond favourably.

Rituximab (Mabthera) which is an anti-CD20 monoclonal antibody, eliminates B lymphocytes that produce platelet antibodies. It has been found to be useful in resistant cases with severe symptoms. The drug is very expensive.

Neonatal Thrombocytopenia

In women suffering from ITP IgG antibodies cross the placenta to reach the fetus. The neonate may develop thrombocytopenia and bleeding. Common manifestations include bleeding from the umbilical stump and ecchymosis. The majority of infants recover spontaneously. The risk of fetal bleeding during vaginal delivery is high. During delivery or soon after, the fetus may die from intracranial bleeding. Maternal platelet count below 100,000/cmm and/or fetal platelet count below 50,000/cmm are associated with high risk of intracranial bleed during vaginal delivery. In severe cases intravenous hydrocortisone 2-3 mg/kg body weight and platelet transfusions are necessary to tide over the crisis. Judicious use of immunoglobulin will help to tide over a crisis if other measures fail. Since the risk of intracranial bleeding is high during vaginal delivery, cesarean section is indicated if the platelet count in the fetus is below 50,000/cmm or the maternal platelet count is below 100,000/cmm. Neonatal thrombocytopenia may develop even when the mother is in remission.

Neonatal Alloimmune Thrombocytopenia

It is a rare fetomaternal incompatibility in which maternal IgG antibodies directed against fetal platelets reach the fetus transplacentally. The mother is clinically normal. In most children the platelet count is low at birth, it declines further during the first 48 hours of birth, to reach a nadir below 10,000/cmm in almost 50%. Hemorrhagic manifestations develop in 90% of cases. Neonatal alloimmune thrombocytopenia follows a benign course in 90% of cases and spontaneous recovery is the rule. Recurrence rate in subsequent pregnancies is 50%. Central nervous system bleeding may occur in 15% of cases, it may be intracerebral or rarely subarachnoid.

Treatment: Corticosteroids, transfusion of maternal platelets and immunoglobulins have been tried with good results. Treatment of choice is the transfusion of maternal platelets, washed free from antibody—containing plasma and suspended in A B blood group plasma. Intravenous immunoglobulin therapy should be tried in cases resistant or not fully responding to corticosteroids.

Anti-D immunoglobulin is a less effective alternative. It is given in doses of 25 µg/kg IV on two consecutive days.

ITP and Pregnancy

50% of women develop mild asymptomatic gestational, thrombocytopenia during term. If the platelet counts go below $70 \times 10^9/L$ in early gestation, ITP is the probable diagnosis.

Mild or moderate asymptomatic cases are monitored without intervention. If the platelet count goes down further and symptoms occur, treatment is on the same lines as ITP.

Women with ITP should be counselled regarding the risks before they opt to become pregnant. There is higher risk for both the mother and the fetus. Aggravation of bleeding tendency in the mother and risk of fetal loss has to be anticipated. These patients should be monitored every month. Corticosteroids can produce adverse side effects.

Splenectomy should be delayed up to the second trimester in order to avoid abortion. Drugs like vinca alkaloids and cyclophosphamide are teratogenic. Azathioprine is possibly safe. IV IG is safer and may have to be used more frequently in order to raise maternal platelet counts above 30000 throughout pregnancy and above 50000 during labour. Platelet transfusions may have to be given to maintain these levels. Cesarean section should be undertaken based on the obstetric indications, in order to avoid trauma to fetal head during delivery.

Pre-eclampsia (PE) is associated with thrombocytopenia in 15% of cases. In addition, some women with PE develop microangiopathic hemolysis and liver dysfunction—known by the **acronym HELLP** (hemolysis, elevated liver-enzymes, low platelet) counts. If severe, plasma exchange may be needed. In the ordinary cases the platelet abnormality clears after delivery.

Secondary Thrombocytopenia

Thrombocytopenia may develop as part of the clinical picture in acute leukemia, aplastic anemia, myelodysplastic syndromes, systemic lupus erythematosus, AIDS, viral hemorrhagic fevers and several virus infections. In these the major clinical manifestations are those of the primary condition.

Drug induced thrombocytopenia may be a result of toxic damage to the bone marrow. In this case, the thrombocytopenia is a manifestation of marrow hypoplasia. Drugs may lead to immune mediated thrombocytopenia. Heparin, sedormid, quinine, vancomycin and others may lead to immunologically mediated platelet destruction. The antibodies can be demonstrated by flow cytometry, or ELISA.

In **drug-induced thrombocytopenias**, very often other signs of drug toxicity may be evident but thrombocytopenia may be the sole manifestation at times. The drug or its metabolites act as haptens which bind

noncovalently with albumin or other serum proteins in the plasma to form complete antigens. Antibodies are produced which combine specifically with the protein-bound haptenic drug or its metabolites to form antigen-antibody complexes. These are absorbed on to the platelet glycoproteins such as IIb/IIIa fibrinogen receptor or glycoprotein 1b/1x (vWF receptor or both).

In some cases, e.g. quinine the thrombocytopenia may be accompanied by other phenomena such as immune neutropenia and disseminated intravascular hemolysis. They activate complement and this leads to complement-mediated lysis of platelets in the circulation. If the amount of antibody coating the platelets is small, such platelets are destroyed by the macrophages of the spleen and liver. Drug induced thrombocytopenia is generally severe. Since presence of the drug or its metabolites is essential to perpetuate the immune mechanism, withdrawal of the drug relieves the thrombocytopenia promptly. In severe cases platelet transfusions are required. Corticosteroids help to arrest platelet destruction by inhibiting macrophage function in the spleen and liver.

Thrombocytopenia occurring as an isolated abnormality in otherwise healthy persons.

Thrombocytopenia detected on routine platelet count may remain asymptomatic in many cases. Sometimes congenital thrombocytopenia may occur. Asymptomatic thrombocytopenia may precede myelodysplastic states or immune mediated diseases like SLE for considerably long periods.

Congenital thrombocytopenia is rare. Commonly it is associated with morphological abnormalities such as giant platelets.

Pseudothrombocytopenia

This is a falsely low platelet count due to platelet agglutination caused by the anticoagulant EDTA used during blood collection, with the frequency of 1/1000 samples.

Thrombocytopathies

These are conditions associated with functional defects of platelets. Platelet counts are normal or even increased in many. The defects may be either congenital or acquired. A classification of thrombocytopathies is given in the Table 163.2.

Thrombopathies are common, though many may be asymptomatic.

Storage Pool Disease

This disease is inherited as an autosomal dominant. In this condition there is no store of ADP in the granules of the platelets and so ADP is not released for further aggregation and platelet functions.

TABLE 163.2

Classification of thrombocytopathies

I. Hereditary conditions

1. Storage pool disease
2. Wiskott-Aldrich syndrome
3. Albinism
4. Hermansky-Pudlak syndrome
5. Hereditary thrombasthenia (Glanzmann's disease)
6. May-Hegglin anomaly
7. Bernard-Soulier syndrome

II. Acquired

1. Drug effects—anti-inflammatory drugs e.g. aspirin, phenylbutazone, indomethacin, other NSAIDs, dextran, clofibrate, dipyridamole, beta-lactam antibiotics and antihistamines, clopidogrel.
2. Uremia, hepatic failure, scurvy
3. Paraproteinemias—myelomatosis, Waldenström's macroglobulinemia
4. Articles of food such as excess of ginger, garlic and onion

Bleeding disorder associated with *albinism* and **Wiskott-Aldrich syndrome** is also due to deficiency of nucleotides in the platelets. *Wiskott-Aldrich syndrome* which is inherited as a sex linked recessive is usually associated with bleeding from various sites, thrombocytopenia, overwhelming infection, eczematous dermatitis and a tendency to develop lymphomas.

In **Hermansky-Pudlak syndrome** there is lack of storage of adenine nucleotides and a deficiency of serotonin. The associated hemorrhagic disorder is clinically mild.

HEREDITARY THROMBASTHENIA

Hereditary thrombasthenia (Glanzmann's disease) is a rare autosomal recessive disorder occurring in both sexes. The platelet membrane glycoproteins Gp II b/IIIa are deficient or defective. The platelets do not bind fibrinogen and cannot aggregate. Bleeding manifestations are purpura, epistaxis, bleeding from wounds and cuts, menorrhagia and excessive bleeding during delivery. The characteristic laboratory finding is the failure of platelets to aggregate in presence of ADP, adrenaline, noradrenaline, thrombin or 5-hydroxytryptamine. Platelet adhesion and clot retraction also are poor. There is deficiency of fibrinogen on the platelet, and it does not bind to the platelet surface membrane. Therefore aggregation is not initiated. Bleeding may be mild or sometimes severe. Platelet transfusion may be required to arrest bleeding.

Diagnosis: Clinical suspicion can be strengthened by examining a stained blood film. Normally platelets should be seen in clumps. In thrombasthenia the platelets are seen singly in large numbers, without any tendency to form clumps.

Morphological abnormalities of platelets such as larger size may suggest immunological and functional abnormalities. Diagnosis is confirmed by studying platelet aggregation. Positive family history may be obtained in the majority of cases.

The May-Hegglin anomaly: In this anomaly, a mild bleeding disorder is associated with basophilic and pyroninophilic inclusion bodies in the leukocytes and an abnormality of the megakaryocytes. Thrombocytopenia may develop. Megathrombocytes may be seen in peripheral blood.

BERNARD-SOULIER SYNDROME

This is a rare autosomal recessive disorder which may lead to mild or severe bleeding. This is characterized by the presence of larger platelets in peripheral blood which fail to adhere to vessel wall. The abnormality is in the surface glycoprotein coat. The platelets have deficient or defective glycoprotein Gp Ib/Ix complex. They cannot bind to vWF and therefore platelet adhesion to vascular endothelium is defective.

Paraproteinemias

Platelet dysfunction may develop in Waldenström's macroglobulinemia and myeloma. The abnormal protein in circulation may coat the platelets and lead to dysfunction resulting in disorders of adhesion, aggregation and release reaction.

Acquired disorders of platelet function: Drugs such as aspirin, clopidogrel and sulphinyprazole inhibit platelet activities and they are used as antiplatelet drugs. Several drugs and articles of food produce platelet dysfunction, sometimes leading to mild or even moderate bleeding tendency. These are used as antiplatelet drugs.

Other drugs such as NSAIDs, beta-lactam antibiotics and antihistamines and articles of food such as *ginger, onion, garlic* and fish oils may give rise to purpura.

Except thrombocytopenia, drug induced thrombopathies rarely give rise to serious generalized bleeding tendency in normal subjects. In persons who have congenital or acquired defects of hemostasis more serious bleeding manifestations develop. Withdrawal of the drug for a week may be essential if surgery or similar procedures are to be undertaken. The platelet defect can be compensated by platelet transfusions. Recently DDAVP (arginine vasopressin) has been reported to reverse the platelet abnormality.

Platelet adhesiveness is diminished in scurvy and this factor also contributes to the hemorrhagic tendency.

Metabolic disorders: The bleeding diathesis in uremia is partly attributable to defects of platelet function. Several

abnormalities may be seen. These defects are reversible when the metabolic abnormalities are corrected. In liver failure also variable platelet defects may be encountered.

VASCULAR PURPURAS (NON-THROMBOCYTOPENIC PURPURA)

These are a group of heterogenous disorders characterized by bruising and spontaneous bleeding from small vessels. In these the bleeding is due to abnormality in the capillaries. Except for a prolongation of bleeding time, other tests may be normal.

The number and function of platelets are usually normal, though occasionally platelet dysfunction may co-exist. The defects may be hereditary as in *Ehlers-Danlos syndrome* or acquired as in *scurvy*.

ANAPHYLACTOID PURPURA Syn; Henoch-Schönlein syndrome, Hypersensitivity angiitis, Rheumatic purpura

This is an immune complex disease caused by type III hypersensitivity reaction similar to that of rheumatic fever and acute glomerulonephritis. This is an acute small vessel leucocytoclastic vasculitis. This is not a primary hematological disorder. It belongs to the group of vasculitic disorders, described in Section: 12. This particular entity is described here since, often it is mistaken for thrombocytopenic purpura clinically. Although the cause is unknown, IgA has a pivotal role in the pathogenesis of HSP. Among the two subclasses of IgA-(IgA₁ and IgA₂) only IgA₁ is involved in HSP. IgA₁ is deposited in vessel walls and renal mesangium. The IgA₁ molecules are altered so that they aggregate into macromolecular complexes which activate the alternate pathway of complement and then deposit in the renal mesangium.

Histology shows vasculitis involving the small blood vessels. This syndrome is more common in children but occasionally it may be seen in young adults. Males predominate. In a small proportion of cases there is history of preceding B-hemolytic streptococcal infection 10 to 20 days prior to the onset of purpura. Other precipitating causes are allergic reactions to drugs and food materials. In many there may be no evidence of a precipitating cause (Fig. 163.5).

Clinical features: A purpuric rash develops acutely over the skin of the extensor surface of the forearms, elbows, buttocks, and legs distally. The lesions may be urticarial, blotchy, and pruritic. Only rarely lesions develop over the trunk and face. Cutaneous purpura in the distal parts of the body is the essential feature. Joint lesions occur in 75%, gastrointestinal involvement occurs in 50-75%, and renal involvement occurs in 40-50%. They share many of the features of IgA nephropathy.

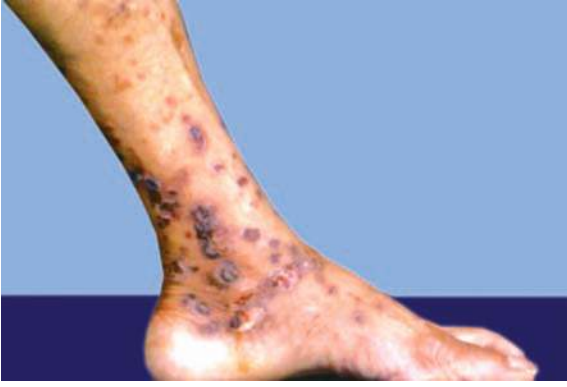


Fig. 163.5: Pitted lesions persisting after relief of anaphylactoid purpura

Abdominal symptoms such as colicky pain and vomiting are usual. Hematemesis and melena may develop in severe cases.

Involvement of joints is common and many large joints are affected. Polyarthralgia, polyarthritis, and peri-arthritis may occur. Hematuria, albuminuria, edema, and hypertension are indicative of renal involvement which may develop in 10 to 30% of cases. The renal lesions may manifest as acute glomerulonephritis. Some of the cases may develop acute renal failure. A small proportion develops persistent and progressive renal lesions. Diagnosis is clinical. There are no pathognomonic laboratory tests. Serum IgA levels are raised in 50% of cases. Blood shows neutrophil leukocytosis. Mild eosinophilia may occur at times. Tests of platelet and capillary function are usually normal. HSP is a self-limited disease. In a third, recurrence may occur. Majority of patients recover completely but recurrence may occur on exposure to the allergen.

Treatment: Symptomatic treatment is adequate in most of the cases since the condition is self-limiting in the majority. Prednisolone 1 mg/kg per day gives symptomatic benefit. Steroids should be withdrawn after a short course. Antispasmodics relieve abdominal pain. Steroids have no effect on the skin lesions. If streptococcal sore throat is evident, a course of penicillin is indicated. For persistent nephritis IV pulse dose is methylprednisolone (30 mg/kg for 3 consecutive days followed by oral corticosteroids may help to arrest the nephropathy. Immunosuppressive drugs like azathioprine and cyclophosphamide have been employed when the glomerulonephritis proves to be resistant to steroid therapy. Response to therapy is unsatisfactory.

Drug induced vascular purpura: Exposure to drugs like penicillin, sulphonamides, atropine, phenacetin, aspirin, and sedatives may produce vascular purpura.

Senile purpura: This condition occurs as a chronic disorder of thin elderly people above the age of seventy

years. Purpuric and ecchymotic spots occur on the extensor surfaces of the forearms which arise spontaneously or after unnoticed trauma. The purpura is due to traction injury to the small capillaries of the dermis due to loss of dermal collagen and subcutaneous fat. No therapy is effective in this condition. It is important to distinguish this benign disorder from other diseases which may require therapy.

Hereditary Hemorrhagic Telangiectasia

Syn: Rendu-Osler-Weber syndrome

This hereditary bleeding disorder is transmitted as an autosomal dominant and affects both sexes. Endoglin is a transferring growth factor B (TGFB) receptor which is normally present abundantly on endothelial cells. TGFB is member of a family of dimeric polypeptide growth factors. TGF regulates the proliferation and differentiation of cells, embryonic development, wound healing and angiogenesis. Endoglin is mutated in patients with hereditary hemorrhagic telangiectasia. Multiple telangiectasia are found in the tongue, nasal mucosa, face, lips, conjunctiva, mucous membrane of the gastrointestinal tract, kidneys, solid organs and over other parts of the skin. Any of these sites may bleed recurrently since the vessels are fragile. Smaller lesions on exposed parts lead to cosmetic problems and bleeding. Larger ones lead to bleeding, embolic manifestations and high output cardiac failure. At the sites of bleeding there is increased fibrinolytic activity (Fig. 163.6).

Ocular complications include bleeding from the conjunctiva, retinal hemorrhage and retinal detachment. Neurological hepatic and pulmonary complications may develop. These include cerebral or subarachnoid hemorrhage, development of mycotic aneurysms, hepatic cirrhosis, portal hypertension, biliary disease and pulmonary arteriovenous fistulae. Primary pulmonary hypertension occurs in 15%.

High output cardiac failure, embolization and digital clubbing may follow. As age advances, the number of

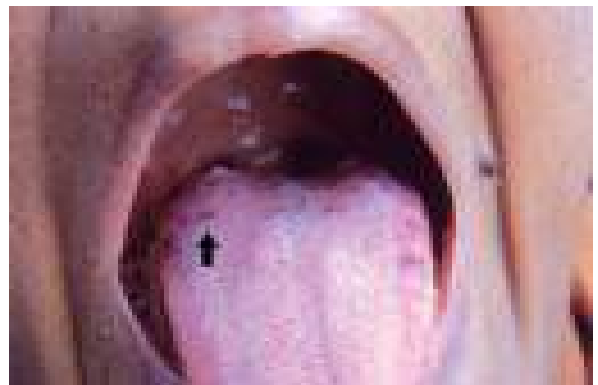


Fig. 163.6: Woman with telangiectasia oral cavity and tongue. Note: The telangiectasias (arrow)

lesions increases and bleeding becomes more marked. Diagnosis is made from the typical telangiectasis, bleeding episodes, and the family history.

Treatment: Local pressure and application of thrombin help to arrest bleeding. Cauterization and surgical treatment of arterio-venous fistula are of limited value but may be required at times. Hematinic therapy is indicated to prevent anemia. Antifibrinolytic drugs have been tried with benefit.

Symptomatic purpura: Several infections cause purpuric manifestation.

1. **Bacterial infections:** Meningococcal septicemia, bacterial endocarditis, leptospirosis and the gram-negative septicemias.
2. **Viral infections:** Measles, influenza, hemorrhagic fevers, and smallpox.
3. **Rickettsial infections:** Typhus and spotted fevers.
4. **Protozoal infections:** Falciparum malaria.

Bleeding is caused by the direct injury to the vascular endothelium by the infecting agent, bacterial embolism, or due to vasculitis as in bacterial endocarditis. The toxins of infective agents inhibit thrombopoiesis and also accelerate platelet destruction. Other factors like thrombocytopenia and diffuse intravascular coagulation may also be contributory.

Antiplatelet Drug Therapy

Antiplatelet drugs to prevent thrombosis of the coronary, cerebral and peripheral arteries widely employed. Antiplatelet drugs acting at different levels of platelet activation are available at present. On many occasions they are used

singly. Often they are combined in order to improve the efficacy. All of them lead to some degree (often minor) of hemorrhagic tendency.

Aspirin	blocks synthesis of thromboxane A2
Ticlopidine and clopidogrel	inhibits ADP binding to receptor on platelets irreversibly
Glycoprotein IIb/IIIa antagonists	blocks aggregation in response to all agonists by preventing cross-linkage of fibrinogen-mediated activity

Different types of glycoprotein IIb/IIIa receptor antagonists are available. These include:

Abciximab	a monoclonal antibody against IIb/IIIa receptor. It blocks receptor action and also blocks the binding of vitronectin to its receptors on endothelial cells. It inhibits platelet aggregation and the template bleeding time.

Synthetic inhibitors	
Eptifibatide	This is a heptapeptide
Tirofiban	These are non-peptides
Lamifiban	
All inhibit IIb/IIIa receptors.	

Combination of different antiplatelets drugs produce enhanced activity than using a single drug.

This type of different combinations of anti-platelet drugs improves the success rate of stenting in coronary and other arteries and prevents postangioplasty thrombosis.

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Defects of Coagulation

Mathew Thomas, K.V. Krishna Das

Chapter Summary

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- Vitamin K Deficiency 1096
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Inherited Disorders

HEMOPHILIA-A (Factor VIII Deficiency)

Hemophilia comprises of two clinically indistinguishable coagulation defects-hemophilia A due to deficiency of factor VIII, and hemophilia B due to deficiency of factor IX—both inherited through the X-chromosome. The pathogenesis and basic defects in the two conditions are

different; therefore treatment schedules are also different. Hemophilia is the most common among the inherited coagulation defects. The disease is worldwide in distribution. In India it forms two thirds of all the inherited coagulation defects. About 25-50% of cases may not give any family history and it is presumed that in them the disease arises due to spontaneous mutation either in the patient or his mother. The clinical picture varies widely in affected subjects.

Prevalence of hemophilia in the developed world is around 6/10000 population. India should have about 50000 patients with severe hemophilia. In addition about 1300 new patients will be added each year.

Hemophilia is transmitted as a sex-linked recessive disorder and the genetic defects is located in the X-chromosome. The gene locus for factor VIII is at the tip of the long arms of X chromosome at Xq-24q tcr. It consists of 186 kilobases and has a molecular weight of 267000. It constitutes 0.1% of the bulk of the X-chromosome. Factor VIII gene is very susceptible to undergo abnormalities such as deletion, mis-sense mutation and non-sense mutation. Due to the variability of genetic abnormalities hemophilia is a heterogeneous disorder varying in severity and clinical behaviour. In about 50% of hemophiliacs factor VIII C is below 5% of normal. In the others the level ranges from 5-20%. It is transmitted by females who act as carriers, but it manifests almost exclusively in males. Half of the daughters of female carriers possess the trait and half of the sons suffer from the disease. Male hemophiliacs pass the trait to all their daughters but their sons are not affected. Carriers of hemophilia (A and B) have only 50% of the normal levels of factor VIII/or factor IX respectively. Clinically they have no bleeding, but they have decreased coagulability. This may even protect them against fatal ischemic heart disease. They may show higher bleeding tendencies when exposed to anti-platelet drugs.

The basic defect is deficiency, defective function or absence of factor VIII. Levels of factor VIII as low as 0.2 units/ml of plasma ensures adequate coagulation activity. The bleeding tendency depends to a great deal on the levels of factor VIII in the plasma.

When the level of factor VIII falls below 30% of normal, bleeding tendencies start. Spontaneous bleeding occurs only when the level falls below 5%. In a severe case, there may be no detectable factor VIII C during episodes of bleeding (Table 164.1).

Factor VIII molecule: This is a protein of large molecular size $1.5-2 \times 10^6$ daltons. Factor VIII is synthesized primarily by the hepatocytes, but kidneys, sinusoidal endothelial cells and lymphatic tissue can also synthesise small amounts. Its half-life in circulation is 12 hours in adults. It circulates in plasma as a covalent complex with von Willebrand's factor (vWF) which is synthesized by

TABLE 164.1

Shows the relationship between the levels of factor VIII and clinical severity

Mild hemophilia	5-40% of normal factor VIII levels (i.e.)	0.05-0.4 u/mL.
Moderate	1-5%	0.01-0.05 u/mL
Severe	< 1%	< 0.01 u/mL

endothelial cells. vWF forms the major bulk of the circulating factor VIII complex. It used to be known as factor VIII related antigen (VIII RAG) since it could be precipitated by heterologous antisera developed in animals. Combination of vWF with factor VIII helps to increase the synthesis, protect factor VIII from proteolysis and concentrate factor VIII coagulant activity at the required site. Factor VIII has to be released from vWF to enable it to take part in the process of coagulation and form the complex consisting of factor VIIIA, IXa and phospholipid. Factor VIIIA accelerates the rate of cleavage of factor X through IXa. Activated factor VIII is short-lived.

CLINICAL FEATURES

The bleeding tendency is noticed early in life. Sometimes the umbilical stump may bleed. Though bleeding can occur from any site, the common presentations are hematomas, deep tissue bleeding, hemarthroses, or hematuria. Bleeding may be spontaneous, may follow trivial trauma or undue physical exertion. Following cuts or wounds, bleeding is arrested initially, but may start soon and proceed unchecked, leading to fatal blood loss. The extravasated blood does not clot for long periods. Recurrent painful swelling of the knees when the child walks should suggest the possibility of hemophilia.

Bleeding into joints occurs frequently in moderate and severe cases. The knees, ankles, elbows, shoulders, and hips are commonly affected. Bleeding may be spontaneous or follow unaccustomed exertion. The joints show features of acute inflammation. Repeated hemorrhage into joints and deep tissues lead to crippling ankylosis and contractures. Chronic synovitis is seen in 10% of hemophiliacs in India. 64% of such patients showed the presence of HLA B₂₇ and this is statistically significant. Bleeding can occur in the central nervous system in severe cases (Fig. 164.1).

The disease shows remissions and exacerbations. Physical exertion, infections, trauma, or psychological stress lead to exacerbations. With the passage of time the severity and frequency of bleeding diminishes. Death may result from uncontrolled blood loss or bleeding into vital organs.

Diagnosis: Hemophilia should be suspected from the history, evidence of heredity, and from the prolonged



Fig. 164.1: Male: Hemophilial arthritis knees

coagulation time or APTT. Clinical hallmarks are joint and muscle hemorrhages, easy bruising and prolonged potentially fatal hemorrhage following trauma or surgery, but no excessive bleeding after abrasions or minor cuts. Bleeding time, platelet count, and prothrombin time are normal but PTTK (APTT) is prolonged. Assay of factor VIII helps to establish the diagnosis and assess the severity. Factor VIII assay also helps to monitor replacement therapy.

Hemophilia has to be differentiated from Christmas disease, von Willebrand’s disease and acquired coagulopathies.

TREATMENT

Rest in bed is essential during a bleeding episode. The inflamed joint should be splinted and cooled with ice packs. Sedatives like diazepam or phenobarbitone or analgesics like dextropropoxyphene may be used to relieve insomnia and pain. Local measures to stop the bleeding include pressure, adrenaline packs, and local dressing with fibrin-foam or thrombin. Bleeding sites from gums, tooth-sockets, or nose should be plugged with adrenaline packs. Aspiration of joint should be done only after AHG is administered. Early mobilization prevents ankylosis.

The mainstay of the treatment is administration of factor VIII concentrate. Factor VIII is available as cryoprecipitate or as freeze dried AHG. Cryoprecipitate contains factor VIII (both factor VIII: vWF and factor VIII: C portions), fibrinogen and fibronectin. The dose is determined by the severity and site of bleeding. The aim is to elevate factor VIII levels to 50% or above. The usual dose is to administer 1 pack for every 10 kg body weight as IV infusion and repeated 12-hourly, for 2 days, and thereafter, depending upon the requirement. To prepare for major surgery and in life-threatening hemorrhage, factor VIII level should be raised to 100% and factor VIII preparations are ideal.

Freeze dried AHG is available from several laboratories. Factor VIII is prepared from human blood and by recombinant DNA technology. Each vial contains 250 to 1000 units and the shelf-life is 18 months. In the ordinary case the initial dose should be 250-1000 units depending on the severity of the bleeding. Larger initial doses are more effective. The half-life of administered AHG is 10-12 hours. The total dose of AHG required to elevate the AHG level to the desired level is given by the formula.

Percentage increase in factor desired × weight in kg

2

The whole quantity has to be given as an IV push dose or a rapid infusion, after dissolving the freeze dried preparation in the diluent. Correction of the bleeding tendency occurs immediately and this persists for 8-12 hours. The dose has to be repeated 8-12 hourly.

1 mg of AHG ≡ 15 units of factor VIII. Infusion of 1 unit/kg bw of AHG will raise the plasma level by 0.02 unit/mL (2%). For minor bleeds the factor VIII level should be raised to 0.3 unit/mL of plasma and for major bleeds it should be raised above 0.5 unit/mL. This level has to be maintained for 36-48 hours till hemostasis is firmly established (Table 164.2).

In febrile and actively bleeding patients, the half-life of AHG will be considerably shorter.

TABLE 164.2 Showing dosage of factor VIII			
Condition	Initial dose U/kg	Repeat doses U/kg	Total duration of therapy
Life/limb-threatening bleed	50	25-30 every 8-12 h or 3-4 U/kg/bw as IV infusion	14-21 days
Intracranial bleed			
Major tissue bleed			
Major surgery			
Hemarthrosis	20-30	20 every 12 h	1-2 days
Hematomas – not life-threatening	20-30	20 every 12 h	Do
Dental extraction, minor surgery	20	20 every 12 h	1-2 days

The factor VIII level in whole blood is 0.3 unit/mL and in (fresh frozen plasma it is 0.8 unit/mL.

In cryoprecipitate factor VIII level is 6-8 units/mL. One unit of cryoprecipitate is 15 mL. Several units may be required for a moderately severe patient. All available commercial preparations of factor VIII have to be free from HIV, HBV and HCV. Still it is advisable to immunize hemophiliacs against hepatitis B. The cost of AHG is around Rs. 5-6/unit and it can be obtained from the office bearers of Hemophilia Society which has branches in several places in India.

Other Supportive Measures

Antifibrinolytic drugs like epsilon-aminocaproic acid (EACA) given in doses of 24 g daily orally have been used along with AHG to prevent dissolution of the clots formed as a result of therapy. EACA should be avoided in urinary bleeding due to the risk of clotting of blood in the urinary tract with the production of urinary obstruction and clot colic.

Mild cases of hemophilia with factor VIII activity of 10% or above respond to 1-deamino-8-D arginine vasopressin (DDAVP). The functional levels of AHG and vWF increase 3-5 times. The dose is 0.3 µg/kg/IV slowly. Though expensive, and not freely available in India, DDAVP provides a reasonably good alternative for the management of mild hemophiliacs. DDAVP can be used prophylactically as a nasal instillation. It helps to reduce the bleeding episodes and the requirement of AHG.

Inhibitors of Factor VIII

20-52% hemophiliacs receiving factor VIII repeatedly, develop antibodies which neutralize factor VIII activity and thereby make further treatment ineffective. Plasma from such patients inactivates factor VIII in normal subjects as well. The level of inhibitors can be assayed and expressed as Bethesda units. Genetic mutation in which there is absence of endogenous factor VIII predisposes to the development of anti-factor VIII antibodies more readily when replacement therapy is given. Less commonly antibodies to AHG may occur *de novo* as part of an immunological disorder such as systemic lupus erythematosus.

Management of Patients with Antibodies to Factor VIII

1. Higher doses of factor VIII may be given – 100 units/kg/bw.
2. Use of porcine factor VIII- as a temporary measure.
3. Factor VIII bypassing activity- (a) use of prothrombin complex concentrates (PCC) (b) infusion of recombinant factor VIIa, which directly activates factor X, thus bypassing factor VIII action.

4. Removal of antibodies by plasma exchange or protein A sepharose affinity column.
5. Use of immunosuppressant drugs.

Recombinant factor VII (Novo seven) is the treatment of choice for severely bleeding patients with factor VIII antibodies. Factor VII activates factor X directly and bypasses the inhibitor induced defect.

Prophylaxis: All hemophiliacs should carry identification cards showing their blood groups to enable emergency treatment without delay. They should be made aware of the nature of the disease and its management. Children should attend ordinary schools but avoid games and strenuous physical training. Special care should be taken to avoid all trauma. Intramuscular injections and anti-platelet drugs should be avoided in all hemophiliacs. Dental care should be instituted to avoid dental caries and the need for extractions.

The modern approach is to prevent bleeding into joints by early administration of AHG. The patient or his near relative is instructed to identify bleeding episodes and self-administer AHG early at the first sign of bleeding or joint pain. This prevents further bleeding and joint deformity which is the most disabling complication (home care programme). Administration of factor VIII at least 2-3 times a week will help to maintain AHG levels above 0.01-0.02 units/mL and this serves to avoid spontaneous bleeding into joints and tissue spaces.

In developed countries all hemophilia patients are provided with adequate amounts of AHG with a view to prevent painful episodes of bleeding and permanent disability.

Prognosis: The ultimate prognosis depends on the severity of the disease, facilities for early diagnosis and specialized management and the availability of factor VIII concentrates. If diagnosed early and joint bleeding is avoided, these patients can lead to near-normal life under supervision. If early diagnosis is missed and repeated joint bleeds occur, permanent or remediable deformities may result. The development of antibodies to AHG gives rise to serious problems in subsequent management. In general, more than 2/3 of the patients can be managed with general measures, moderation of activities and limited use of factor VIII or cryoprecipitate. Mortality is generally due to uncontrolled external bleeding or bleeding into vital organs, such as the brain.

Prenatal diagnosis of hemophilia is possible by estimating factor VIII in fetal blood obtained by fetoscopy. Fetuses in the first trimester of pregnancy can be subjected to genetic analysis and the diagnosis established. Affected pregnancy can be aborted. Carrier females can be detected by VIII assay. Such females show only half the VIII activity expected for the level of vWF.

Future prospects: With effective replacement therapy all surgeries can be performed on hemophiliacs. Effective

home care programmes help to prevent disability and ensure quality of life.

Implantation of genetically altered fibroblasts which are capable of producing factor VIII have been tried successfully. Such grafts secrete factor VIII for long periods.

Christmas Disease
Syn: Hemophilia B

This is also a X-linked recessive disease, caused by deficiency or abnormality of factor IX. Transmission is similar to that of hemophilia. Factor IX is a 415 aminoacid serine protein, synthesized in the liver. It is the largest among the vitamin K dependent proteins. Plasma concentration of factor IX is 50 times that of factor VIII and its half-life is 24 hours. Factor IX gene is located in the long arm of chromosome X at Xq27. The gene for factor IX is smaller and less complex than that of factor VIII. More than 2100 mutations of the gene have been identified.

Preliminary coagulation tests are similar to those of hemophilia. Frequency is 1/4 of that of hemophilia A. The diagnosis can be confirmed by demonstration of reduced levels of factor IX. Fifty percent of daughters of carrier females are carriers. Carriers of hemophilia B have lower levels of factor IX activity compared to normals. Normal level of factor IX activity is 1 unit/mL. Levels less than 0.1 unit/mL indicate severe disease. The clinical spectrum resembles that of hemophilia, and it varies depending on the levels of factor IX. Inhibitors to factor IX develop only in 1.5-3% of cases.

Treatment: Factor IX can be administered as the concentrate, prothrombin complex concentrates, recombinant factor VII (Novo seven), or fresh frozen plasma. Since the distribution volume of factor IX in the tissues is twice the plasma volume, the dose of factor IX for therapy should be twice that of factor VIII. This has to be administered as IV bolus twice a day.

von Willebrand's Disease
Syn: Pseudothrombophilia

von Willebrand's disease (vWD) is a primary vascular hemostatic defect, transmitted as an autosomal dominant, affecting both sexes. Next to hemophilia this is the most frequent inherited hemostatic defect. vWF is encoded by a gene spanning 178 Kb of genomic DNA of chromosome 12. More than 250 mutations of the vWF gene have been identified. vWF is synthesized by endothelial cells and megakaryocytes and secreted into plasma and subendothelial extracellular matrix.

Functions

- 1. It acts as an adhesion protein and helps in the formation of the platelet plug.
- 2. It forms a non-covalent complex with factor VIII in plasma thereby protecting it from inactivation and clearance.

Laboratory tests for VW disease show prolonged bleeding time, reduced levels of factor VIII, reduced levels of vWF antigen and reduction of ristocetin cofactor.

The basic defect is reduction of the amount of subendothelial factor VIII: vWF polymers or the presence of abnormal or inadequately polymerized subendothelial factor VIII: vWF. Normal vWF contains multimers of varying molecular sizes ranging from 850,000 to 12 million daltons. Von Willebrand's factor is normally secreted from endothelial cells as extra large polymers of a peptide bound by disulphide bonds. In the plasma the peptide bonds are cleaved by a metalloproteinase enzyme. This results in the formation of dimers of 176 kd and 140 kd fragments. This protease enzyme is inactive in circulation unless it is unfolded by high shear force or other factors. Inhibition of this enzyme and abnormal configuration of this enzyme leads to abnormalities of function of vWF. The defective vWF leads to impairment of platelet adhesion to sites of vascular injury. There is also impairment in function of factor VIII leading to defects of coagulation, even despite normal factor VIII levels. Depending on the genetic defect the disease has been divided into three types.

Genetic Transmission of von Willebrand's Disease

Phenotype	Mechanism	Transmission
1 (1)	Partial quantitative deficiency of vWF and factor VIII	Autosomal dominant (AD)
2 (A)	Defect in platelet dependent vWF and lack of large multimers	AD
2 (B)	Heightened platelet dependent vWF functions associated with lack of large multimers	AD
2M	vWF functions and multimers reduced	AD
2N	Defective vWF binding to factor VIII	AD
3	Severe or complete deficiency of vWF and moderately severe factor VIII deficiency	Autosomal recessive

CLINICAL FEATURES

These are similar to that of ITP, i.e. excessive post-traumatic bleeding, menorrhagia, and mucosal bleeding, especially from the nose, gums, gastrointestinal tract, and genitourinary tract. Bleeding time is prolonged. Platelet counts are normal in Types I and IIA, but may be

moderately decreased in II B. In those with factor VIII C levels below 1% of normal, manifestations of a coagulation defect may also be prominent. Bleeding manifestations are most marked in homozygous type IIA which is rare.

Diagnosis of the specific defect of factor VIII : vWF is made by electrophoresis. Another *in vitro* test is to determine the capacity of plasma to aggregate platelets in the presence of the antibiotic-ristocetin. Ristocetin partially neutralizes negative charges on factor VIII: vWF polymers to induce platelet aggregation.

This phenomenon is called ristocetin cofactor activity. Ristocetin cofactor activity is diminished in types I and II A disease.

In patients with type I or II A vWD, the diminution of ristocetin cofactor activity correlates with the defective platelet adhesion to subendothelium *in vitro*. But in type II B disease this is not so. In type II B the factor VIII: vWF polymers are abnormally formed and these are incapable of inducing platelets to adhere to vascular endothelium. But even in the presence of small amounts of ristocetin, these abnormal polymers present in platelet poor plasma attach to platelets and induce aggregation *in vitro*.

In homozygous type II A vWD patients with severe bleeding tendency, endothelial polymerization of factor VIII: vWF monomers is defective and only small factor VIII: vWF polymers are present in plasma. In these patients bleeding time is prolonged and plasma levels of factor VIII : vWF antigen, ristocetin cofactor activity, and factor VIII: C are extremely low. Being heterozygous, the majority of cases of vWD have only mild bleeding tendency.

Factor VIII: C is also reduced in the plasma of majority of patients with vWD. Unlike hemophilia in which the synthesis of factor VIII : C is diminished, in vWD, though factor VIII: C is synthesized, it is not transported effectively in the systemic circulation without adequate levels of polymerized factor VIII : vWF. Further, factor VIII : C molecules which enter the circulation unbound to VIII: vWF polymers are rapidly removed.

Treatment: Cryoprecipitate infusions arrest bleeding promptly and these are employed to arrest bleeding episodes and to prepare the patient for surgery. The largest factor VIII : vWF polymers in the cryoprecipitate get deposited on the injured subendothelial surface and this favours platelet adhesion and hemostasis. The therapeutic effect lasts only for 4 hours and hence cryoprecipitate has to be repeated. Lyophilized factor VIII preparations are not as effective as cryoprecipitate as they do not contain the largest plasma factor VIII:vWF polymer forms.

In type I vWD where synthesis of factor VIII : vWF within the endothelial cells is normal, infusion of **deamino-8-D arginine vasopressin** (DDAVP) causes

release of VIII: vWF polymers from endothelial cells. DDAVP attaches itself to vasopressin receptors on the endothelial cells and helps in releasing factor VIII: vWF polymers. Both factors VIII and vWF can be temporarily raised. Optimal dose is 0.3 µg/kg bw IV. If given intranasally the dose is 300 µg in adults and 150 µg in children. The concentration of factor VIII and vWF are doubled or quadrupled within 10-30 minutes of IV use and 60-90 minutes of intranasal use. Side effects include facial flushing, headache and arterial thrombosis. In heterozygous type II A and II B and homozygous type II A vWD, DDAVP is not very effective.

Acquired vWF Disease

vWF is excessively cleaved by increase in concentration of the metalloprotein ADAMTS 13 which is produced in valvular heart diseases such as aortic stenosis, VSD and PDA. Reduction or absence of large multimers of vWF causes bleeding from mucus membranes and skin.

Correction of the cardiac defect abolishes the bleeding as well. Acquired vWF does not respond to DDAVP or replacement of coagulation factors.

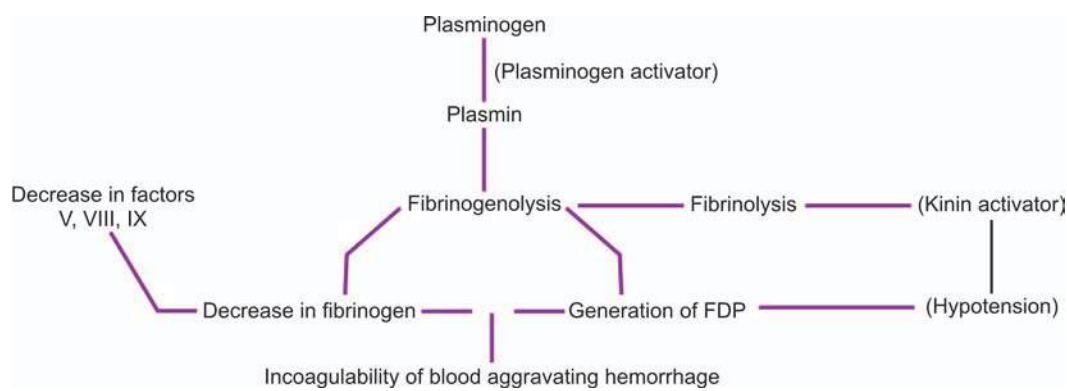
Vitamin K Deficiency

Vitamin K is essential for the production of functional prothrombin, factor VII, factor IX and X in the liver. In the absence of vitamin K, the blood contains nascent non-functional forms of these factors. Nascent nonfunctional forms of protein C also exist in the circulation in vitamin K deficiency. Since the body stores are small, deficiency of vitamin K leads to hypoprothrombinemia within two weeks. Clinically it manifests as ecchymoses, bleeding from injection sites, bruises, gum bleeding, hematemesis, melena, or hematuria. Both the prothrombin time and activated partial thromboplastin time are prolonged. Administration of vitamin K in a dose of 5-10 mg stops the bleeding promptly within 1-2 days. Either the oral water-soluble preparation or parenteral forms may be used. Natural preparations are preferable, being more effective. If blood loss is severe or response to vitamin K is inadequate, fresh blood transfusion or fresh frozen plasma is also indicated. See also Chapter 30.

Circulating Anticoagulants

Sometimes hemorrhagic manifestations develop on account of the presence of anticoagulants in the circulation. Many of these anticoagulants are antibodies to fibrinogen and the other specific clotting substances like factors VIII, IX, V, X, XI, and XIII. Antibodies may develop due to repeated transfusions, or as part of an immunological disorder like SLE, rheumatoid disease, or generalized penicillin allergy.

Flow chart 164.1: Sequence of events in accelerated fibrinolysis



Clinical features are similar to those of the primary coagulation disorders with the exception that replacement therapy may be ineffective as long as the antibody persists in the circulation. This can be overcome by giving large doses of the missing factor and removal of the circulating antibodies by plasmapheresis or by immunosuppressant therapy.

Other rare coagulation disorders: Several other inherited deficiencies of coagulation factors exist, though they are rare. These include deficiencies of fibrinogen and defects in the composition of fibrinogen, deficiency of prothrombin, factors XII, X and XI and XIII. These crop up infrequently and may be mistaken for the more common hemorrhagic disorders. Diagnosis is by specific laboratory tests. Therapy consists of the administration of fresh frozen plasma, specific factors if available or prothrombin complex concentrate.

Pathological Fibrinolysis

Healthy individuals may show minor variations in fibrinolytic activity without any deleterious effects, but gross increase in fibrinolytic activity causes hemorrhage. Excessive fibrinolysis may be a primary phenomenon or develop as a consequence of disseminated intravascular coagulation (DIC).

Causes of Excessive Fibrinolysis

- a. *Obstetric causes:* Abruptio placentae and amniotic fluid embolism.
- b. *Surgical causes:* Gastrectomy, lung resection, nephrectomy, prostatectomy, cardiopulmonary bypass, splenectomy, and pancreatectomy.
- c. *Medical causes:*
 - i. Liver diseases such as cirrhosis of liver.
 - ii. Leukemias, especially in acute leukemia and chronic granulocytic leukemia.
 - iii. Anaphylactic shock.
 - iv. Autoimmune diseases such as systemic lupus erythematosus.

Pathogenesis: Fibrinolytic activity may be enhanced as a result of excessive release of plasminogen activator or reduction in the inhibitor. The sequence of events is given in Flow chart 164.1.

Clinical features: The clinical features depend on the predominant mechanism. If thrombocytopenia is also pronounced, capillary bleeding predominates. If coagulation mechanism is defective the bleeding is more serious. The severity and clinical presentation may vary from case-to-case.

Diagnosis: Normal bleeding time, slightly prolonged clotting time, and poor quality of the clot should suggest the possibility of excessive fibrinolysis. Primary fibrinolysis has to be distinguished from disseminated intravascular coagulation (DIC). In primary fibrinolysis, platelet count is normal and this distinguishes it from DIC in which platelet count is reduced. It is important to distinguish these two conditions since treatment is different (Table 164.3).

TABLE 164.3		
Differentiation between DIC and primary fibrinolysis		
Tests	Acute DIC	Primary fibrinolysis
Platelet count	Decreased	Normal
Bleeding time	Prolonged	Normal
Clot retraction	Defective	Clot is dissolved
Red cell fragmentation	Present	Absent
Clotting time	Prolonged	Prolonged slightly
Prothrombin time	Prolonged	Prolonged
Activated partial thromboplastin time	Prolonged	Slightly prolonged
Euglobulin lysis time	Shortened	Shortened
Fibrin split products (FDP) estimation	High titre	High titre
D-dimer levels	Raised	Raised
Thrombin time	Prolonged	Prolonged

Laboratory tests: The tests for fibrinolysis are:

1. Euglobulin lysis time for detecting the presence of increased levels of circulating plasminogen activator.
2. The detection of excess of fibrin degradation products (FDP) by immunological methods.
3. D-dimer levels in plasma are elevated. D-dimer is the fibrin fragment in plasma which is a marker of fibrin formation and active fibrinolysis.
4. Circulating levels of plasminogen which will be low in fibrinolysis.

Treatment: Primary fibrinolysis can be readily controlled by the use of antifibrinolytic agents.

Commonly used antifibrinolytic agents are epsilon-aminocaproic acid (EACA) and tranexamic acid which are synthetic amino acids, and aprotinin (Trasylol) which is a polypeptide. Both EACA and tranexamic acid bind reversibly to plasminogen and thereby block its binding to fibrin and fibrinolysis. Aprotinin inhibits the action of trypsin, chymotrypsin, plasmin and tissue kallikrein. By inhibiting kallikrein it indirectly blocks the activation of factor XII and thereby prevents the initiation of both coagulation and fibrinolysis. Activity of aprotinin is expressed as kallikrein inactivation units (KIU).

When given orally, EACA is rapidly absorbed and a single oral dose is effective for 4 hours. It is contraindicated in advanced renal disease. For immediate effect, 5

to 10 g is given intravenously in the first hour followed by 2 g hourly for the next 2 to 3 hours. This is then followed by oral therapy with 4 g every 4 hours. The total dose in 24 h should not exceed 30 g. Since the drug is excreted by the kidneys, its concentration in urine is higher than in plasma. Aprotinin (Trasylol) used for reducing intra operative blood loss in cardiac surgery may lead to serious nonfatal cardiovascular events and renal toxicity.

In disseminated intravascular coagulation (DIC), fibrinolysis occurs as a defence mechanism helping to remove the clots formed, and inhibition of fibrinolysis is harmful since it may lead to widespread thrombosis. Administration of EACA should not be undertaken without concurrent heparin therapy if the distinction between primary fibrinolysis and DIC is not clear. Thrombotic complications, particularly renal cortical necrosis may develop when EACA is used alone in patients with DIC.

Dose of tranexamic acid is 20-25 mg/kg bw orally bd or tds. The parenteral dose is 0.5 to 1 g IV tds or also as an infusion.

Aprotinin is used mainly as an intraoperative infusion to reduce surgical blood loss. The dose is 0.5-1 million units given over 10 minutes, repeated in doses of 0.2 million units till the bleeding is arrested.

Since aprotinin inhibits pancreatic trypsin and chymotrypsin it is also useful in acute pancreatitis.

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Therapeutics of Anticoagulants

Mathew Thomas, K.V. Krishna Das

Chapter Summary

Heparin 1099

Oral Anticoagulants 1100

Direct Thrombin Inhibitors (DTI) 1101

Anticoagulants inhibit the coagulation pathway in one or other step, thereby preventing thrombus formation. They are indicated in the prevention and treatment of thromboembolic disease.

Indications

- Recurrent venous thromboembolism,
- Ischemic heart disease
- Cerebral venous thrombosis,
- Prevention of thromboembolism in atrial fibrillation
- Implantation of prosthetic heart valves, arterial conduits
- Recurrent pulmonary embolism
- Follow-up therapy after thrombolysis

Available drugs

1. Heparin and its derivatives which are given parenterally.
2. Oral anticoagulant drugs—coumarins and indanediones.
3. Thrombin inhibitors

HEPARIN

Heparin is present naturally in mast cells and the liver, but in health there is no free heparin detectable in plasma. Commercially available heparin is produced from animal lungs. Standard heparin (SH) is a mixture of compounds with molecular weights ranging from 2000-20000 (mean 5000) and their anticoagulant activity is also variable. By physico-chemical methods low molecular weight heparin (LMWH) having molecular weights ranging from 2000-10000 is produced e.g. Dalteparin sodium.

SH and LMWH show difference in their actions and chemical effects.

Action

Heparin inhibits coagulation both *in vitro* and *in vivo*. SH acts mainly through the medium antithrombin III (AT III) which acts as cofactor. AT III is part of the natural defence mechanism of the body against thrombosis. The major ultimate actions of heparin are to inhibit the formation of thrombin from prothrombin and aggregation of platelets caused by thrombin. Heparin produces a conformational change in AT III. This accelerates and augments the effects of AT III against thrombin and factor Xa about 1000 folds. SH binds to plasma proteins and platelets in varying degrees and therefore its action is less consistent when compared to LMWH which has more bioavailability. LMWH acts more as anti-factor Xa and this effect is 2-4 times that of SH. LMWH is more expensive than SH, still its advantage in special situations makes it the drug of choice in cardiovascular and neurovascular indications.

Indications

1. As prophylactic and curative in venous and arterial thromboembolic disease. The anticoagulant effect is rapidly achieved by parenteral administration of heparin. Simultaneously oral anticoagulants are also started. The latter takes 2-3 days for their effect to be established. By this time the heparin is withdrawn and anticoagulation is continued for prolonged periods, depending on the indication.
2. Disseminated intravascular coagulation: heparin inhibits the widespread intramuscular thrombotic process and thus arrests the vicious circle from developing.

Side effects: These include bleeding from the gastrointestinal and urinary tracts, intracranial bleeding, thrombocytopenia and purpuric bleeding, allergic manifestations, alopecia, osteoporosis and prolonged administration. Heparin leads to thrombocytopenia by an immune mechanism, on repeated administration.

Preparation: Vials—5000-25000 units (1000 units/mL to 5000 units/mL) 1 mg is approximately 100 units.

Dose

1. 5000-10000 units every hour or as IV infusion 20000 units, diluted in 5% glucose solution or normal saline, run over 12-24 hours. The dose and rate of administration depend on the indications and degree of anticoagulation desired.
2. Repeated deep IM or sub-adipose injections of 2000-10000 units 6th hourly.

The dose is titrated by keeping the clotting time 2-3 times the normal. A more reliable parameter is the activated partial thromboplastin time (APTT) which should be maintained at 1½-2 times the normal.

Dose for small adults and children

15-25 units/kg/bw IV infusion continuously or 2.5 units/kg/bw every 12 h by sc injection is quite effective.

In general the doses required to prevent venous thrombosis are considerably less in comparison to those required for arterial thromboembolism (2000 units once or twice a day v/s 5000-10000 units 6h).

Low molecular weight heparin

Note: LMWH has distinct advantages over SH. These are:

1. Smaller dose and longer duration of action.
2. Once or twice a day administration.
3. More consistent clinical effects.
4. Less chance of thrombocytopenia.
5. No need to have regular laboratory monitoring when given in the usual dosage.
6. Can be given as outpatient therapy and at home.

Preparation: Solution containing 2500 iu/mL-4 mL ampoules.

Dose: 2000-5000 units given SC once or twice a day.

Antidote to Heparin**Protamine Sulphate**

This is available as 5 mL ampoules, each mL $\equiv$ 10 mg.

Dose: Protamine sulphate 1% solution given IV neutralizes heparin and rapidly reverses its effect. 1 mg protamine sulphate for every 100 units (1 mg) of heparin is given as the last dose. If given after 3-4 h of the last dose of heparin, only smaller amounts of protamine are needed. It is effective in neutralizing dalteparin as well. Adverse effects include allergy, flushing and hypotension.

HEPARIN INDUCED THROMBOCYTOPENIA (HIT)

It is an immunologically mediated adverse drug reaction characterized by platelet activation, thrombocytopenia and a high risk of thrombotic complications. It is characterized by the paradox in which thrombosis occurs in a thrombocytopenic patient who is anticoagulated. HIT is caused by heparin- dependent IgG antibodies that activate platelets. Platelet derived micro particles are formed which are highly procoagulant. Two clinical syndromes have been identified and HIT type I and HIT-type II.

HIT type I: This occurs in 20% of patients. It is not antibody mediated. These patients develop thrombocytopenia within the first four days of starting therapy. Despite continuance of heparin the platelet count recovers.

HIT type II is mediated by IgG. It is associated with mild to severe symptoms, fall of platelet count to < 50% of normal and thrombotic tendencies. Clinical features correlate with the type of heparin, its dose and route of administration. Acute thrombotic events include occlusion of peripheral arteries, mesenteric artery, ischemic heart disease, cerebrovascular accidents and deep vein thrombosis, pulmonary embolism and venous limb gangrene. Systemic features like fever and chills develop. Heparin induced platelet agglutination test (HIPA) is positive. ELISA test detects heparin-PF4 complexes.

Management

Thrombotic complications have to be reversed. Heparin and LMWH are contraindicated. Warfarin is contraindicated since it may lead to deep vein thrombosis and limb gangrene. Ancrod which is obtained from defibrinating snake venom has been used with success. Danaparoid sodium is a mixture of low molecular weight glycosaminoglycans such as heparan sulphate, dermatan sulphate and chondroitin sulphate. It specifically inhibits platelet aggregation caused by HIT. The dose is 2250 units I V as a loading dose, followed by 400 units/hour for four hours. Other thrombin inhibitors such as lepirudin, argatroban and bivalirudin are also useful.

Note: The association of physicians of India has published Consensus Development Recommendations for the role of LMW. Heparins in the prophylaxis of venous thromboembolism - an Indian perspective: Supplement to JAPI. January 2007. www. japi. org

Guest editor: Rajiv Prakash

Oral Anticoagulants

The two classes of drugs in this group are the coumarins and indanediones. They are effective when given orally, but they do not possess any anticoagulant activity *in vitro*.

Mode of Action

They prevent the activation of vitamin K-dependent coagulation factors, i.e. VII, IX and X in the liver. When given orally they are well absorbed and peak serum levels are obtained in 2-3 hours. They are concentrated in the liver which is their main site of action. Their action is slow, taking 2-3 days for maximal effect, but once established, the anticoagulant effect persists for 4-7 days even after withdrawal of the drug.

Coumarin Group of Drugs

Warfarin Sodium

Preparations: When given orally it is absorbed rapidly. Its half-life is 15-70 hours. Tablets of 1 mg, 2 mg, and 5 mg, are available.

Therapy is started with a loading dose of 10-15 mg daily along with heparin. The dose is tapered off daily to 3-5 mg/day in order to maintain the prothrombin time as 2 to 3.5 times the control value, or international normalized ratio (INR) as 2-3 depending upon the underlying indication.

Indanediones

The commonly used drug in this class is Phenindion.

This is an effective anticoagulant. When given orally it is rapidly absorbed. Its half-life is 5-10 hours.

Preparations: Tablets 10 mg, 25 mg, and 50 mg

Dose: The initial loading dose is 200-300 mg/day. It is rapidly tapered off daily to 100 mg and later to 50 mg daily. The maintenance dose is around 50 mg in order to maintain optimal anticoagulation.

Oral anticoagulants are contraindicated in pregnancy, lactation.

Side effects: Hemorrhagic manifestations—gastrointestinal, urinary and intracranial.

Drug interactions: Oral anticoagulants produce several important drug interactions which lead either to enhancement or blunting of their effects.

Drugs which enhance anticoagulants effects

1. Sulpha drugs, clofibrate, ethacrynic acid, nalidixic acid. The anticoagulant is displaced by these drugs from its plasma protein binding sites and therefore the anticoagulant activity is enhanced.
2. Further depression of vitamin K related clotting factors by quinine, quinidine, thyroxine.
3. Anabolic steroids—impairment of hepatic function.

Drugs which impair the anticoagulant action

Barbiturates, phenytoin, haloperidol, griseofulvin and rifampicin will cause microsomal enzyme induction in the liver and rapid destruction of the anticoagulant.

TABLE 165.1

Showing the properties of available DTIs

Parameter	r. Hirudin	Bivalirudin (HIRULOG)	Argatroban (NOVASTAN)	Ximelagatran and melagatran (EXANTA)	Dabigatran
Route of administration	IV, SC	IV	IV	xymelagatran po melagatran oral IV and SC	Oral
Plasma half-life	IV-60 mts SC- 120 mts	25 mts	45 mts	Oral 3-5 hrs IV and SC-2-3 hrs	12 hrs 50-225
Dose	15 mg per day for 8-12 days	-	-	ximelagatran 24 mg bd x 7-12 days oral melagatran 3 mg/day SC	50-225 mg bd for 6-10 days
Main site of clearance	Kidney	Kidney, liver other sites	Liver	Kidney	Kidney

Since oral anticoagulants are administered over long periods for prophylaxis and treatment of life-threatening conditions, it is important to elicit drug history which should suggest drug interactions.

Antidote to Oral Anticoagulants

The first step is to withdraw the anticoagulant. If the prothrombin time is only 3 times the normal this measure is enough. If the PTT is further prolonged, *phytomenadion* (Vitamin K₁) 5 mg given by slow IV injection corrects the hemorrhagic tendency within a few hours. If the condition is life-threatening or the hepatic function is unsatisfactory, concentrates of factors II, IX, X and VII have to be given. If the concentrates are not available, fresh frozen plasma is infused, approximately 1000 mL for an adult.

Other Anticoagulants

Fondaparinux: It is a synthetic anticoagulant with anti-Xa activity. The effect is similar to that of heparin. The dose is 50-100 mg daily to be given by subcutaneous injection. Monitoring is not required.

Direct Thrombin Inhibitors (DTI)

Thrombin is inhibited by low molecular weight heparin directly. DTIs can inhibit thrombin bound to fibrin or

fibrin degradation products in addition to free thrombin. By inhibiting thrombin, DTIs exert an indirect antiplatelet effect as well. DTIs include recombinant hirudins, lepirudin or bivalirudin, argatroban, xymelagatran, melagatran and dabigatran (Table 165.1).

Overdose of these drugs can be managed by either hemodialysis or administration of activated prothrombin complex concentrates.

Indications

- 1. Acute coronary syndromes with and without precutaneous coronary interventions
- 2. Myocardial infarction
- 3. Non-valvular atrial fibrillation
- 4. Prevention of venous thromboembolism in patients undergoing major orthopedic surgery
- 5. Recurrent deep venous thrombosis
- 6. Heparin induced thrombocytopenia

Guidelines for Correcting Over Dose of Anticoagulants

The target INR to be achieved is given below:	INR
Moderate bleeding, with high risk of thrombosis	2-2.5
Serious bleeding with moderate risk of thrombosis	1-1.5
Serious or heavy bleeding with low risk of thrombosis	1.0

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Disseminated Intravascular Coagulation, Microangiopathic Hemolytic States

K.V. Krishna Das, Mathew Thomas

Chapter Summary

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Disseminated Intravascular Coagulation (DIC)

Syn: Defibrination syndrome, consumption coagulopathy

Pathogenesis: This is an example of consumptive thrombohemorrhagic disorders in which excessive consumption of the factors needed for hemostasis leads to their depletion in circulation resulting in widespread hemorrhagic tendency. All the components—platelets, fibrinogen and coagulation factors are consumed. Widespread thrombosis develops leading to the occlusion of the microcirculation in several organs. The capacity of the system to replenish the coagulation factors and platelets is exceeded and this leads to their reduction in circulating blood.

The basic pathophysiology consists of:

1. Systemic formation of fibrin due to increased generation of thrombin
2. Simultaneous suppression of physiological anticoagulant mechanism, and
3. The delayed removal of fibrin as a consequence of impaired fibrinolysis.

Several cytokines act as procoagulant mediators. Prominent among them is interleukin-6. All major physiological anticoagulants such as antithrombin III, protein-C and tissue factor-pathway inhibitor are to be affected in DIC.

Formation of widespread thrombi in different situations triggers off excessive secondary fibrinolysis

which results in the formation of large amounts of the degradation products of fibrin and fibrinogen, detectable in plasma and urine. These in turn also act as anti-thrombotic agents which tend to aggravate the hemorrhagic tendency. Initially the acceleration of fibrinolysis is a protective mechanism, but when it becomes excessive it is harmful.

DIC is triggered off by the liberation of large amounts of thromboplastic substances into the circulation.

Common causes of Disseminated Intravascular Coagulation (DIC)

1. Obstetric: Abruptio placentae, intra-uterine fetal death, septic abortion, and amniotic fluid embolism.
2. Infections: Falciparum malaria, gram-negative septicemia, meningococcemia, septic shock, rickettsial infections, viral infections and several others.
3. Malignant disease: Diseases of prostate, breast, lung, pancreas and others.
4. Hematological malignancies: Acute promyelocytic leukemia.
5. Mismatched blood transfusion with hemolytic transfusion reaction.
6. Cavernous hemangioma.
7. Miscellaneous: Trauma, fat embolism, burns, hypothermia, viper bites, and scorpion bite.

CLINICAL FEATURES

There is a wide spectrum of presentation ranging from chronic mild bruising and bleeding tendencies as is seen in intrauterine fetal death, to fulminant bleeding from sites of injections, mucous membranes, tissue spaces and vital structures as is seen in acute DIC. In many cases DIC is a primary disorder. In others such as burns and septicemia DIC occurs as a complication. DIC is a very frequent complication of the sepsis syndrome and shock.

Laboratory findings: Diagnostic findings are reduction in platelets, fibrinogen, and factors II, V and VIII. The prothrombin time and partial thromboplastin time are prolonged.

Fibrin degradation products (FDP) are markedly increased in blood and urine. Euglobulin lysis time is

increased due to excessive fibrinolysis. D-dimer levels are increased in blood. Normal levels of D-dimer in plasma is < 500 ng/mL.

Normal fibrinogen in plasma is 150-400 mg/dL

Diagnostic Criteria

- A. Presence of the triggering factor
- B. Laboratory diagnosis
 1. Platelet count below 100,000 and rapidly falling further.
 2. Clotting time, prothrombin time and APTT are all prolonged.
 3. Increase in FDP levels and D- dimer in plasma.
 4. Coagulation inhibitor levels reduced.

Differential diagnosis: DIC has to be distinguished from primary hyperfibrinolytic states, thrombocytopenias, vasculitis, microangiopathic hemolytic states, septicemias and overdose of therapeutically administered anticoagulant and fibrinolytic drugs. Severe hepatic failure may resemble DIC clinically.

Prognosis: Mild chronic cases subside promptly when the primary cause is attended to. Fulminant DIC is fatal due to bleeding and dysfunction of vital organs. Prompt recognition of the condition and management are needed to save life.

Management—Principles

1. Identify the underlying causes and correct them.
2. Restore normal hemostasis by blocking the activation and excessive consumption of the coagulation factors and platelets.

This is achieved by the administration of heparin in moderate doses (i.e.) 300-500 unit/kg bw as continuous infusions. Indication of heparin

1. Chronic DIC of malignancy,
2. Dermal necrosis due to vascular occlusion and
3. Retained dead fetus with hypofibrinogenemia.

Heparin can act only in the presence of normal levels of AT III which is also deficient. AT III has to be administered if the level is below 70% of normal. A dose of 11units/kg/bw produces rise in plasma AT III level to 80% or more, at which level it is effective. AT III is replaced by giving AT III concentrates containing 120-250 units/day for 2-3 days, given as IV infusions.

Once this level is reached, maintenance is continued with half this dose given at 4-6 hours intervals.

3. If the plasma levels of coagulation factors and platelets are deficient, replacement of these components with fresh frozen plasma is indicated under close supervision. The dose in 15 mL/kg bw. Cryoprecipitate which contains the coagulation factors is very effective. It is indicated when the plasma fibrinogen

level is < 80 mg/dL. Usually 6 units are required. This raises the blood fibrinogen levels to 100 mg/dL or more. Platelet concentrates are required when there is thrombocytopenia.

Antifibrinolytic drugs are generally contraindicated, since fibrinolysis automatically comes down, once the DIC is corrected.

4. The general condition of the patient and the dysfunction of vital organs have to be managed on appropriate lines.

MICROANGIOPATHIC HEMOLYTIC STATES

Microangiopathic Hemolytic Anemia (MHA)

This comprises thrombotic thrombocytopenia purpura (TTP), hemolytic uremic syndrome (HUS), chemotherapy induced microangiopathic hemolytic anemia, malignant hypertension and the HELLP syndrome (hemolysis, elevated liver enzyme levels and a low platelet count occurring in association with pre-eclampsia).

1. Formation of microthrombi initiated and perpetuated by platelet adhesion and aggregation in the microcirculation of vital organs with the consequent development of thrombocytopenia and organ dysfunction, and
2. Development of microangiopathic hemolytic anemia, which results from damage to erythrocytes traversing the platelet thrombi and adhesion to endothelium of the affected vessels. The hallmark of microangiopathic hemolytic anemia is the presence of fragmented and damaged erythrocytes in circulation (schistocytes) at least two in a high power field (Fig. 166.1).

Unlike as in DIC, there is no gross alteration in the process of coagulation and fibrinolysis. The serum levels of prothrombin and fibrinogen are near-normal and *in vitro* tests of coagulation are normal.

Pathogenesis: The condition is triggered off by events which alter platelet adhesiveness to endothelium and also

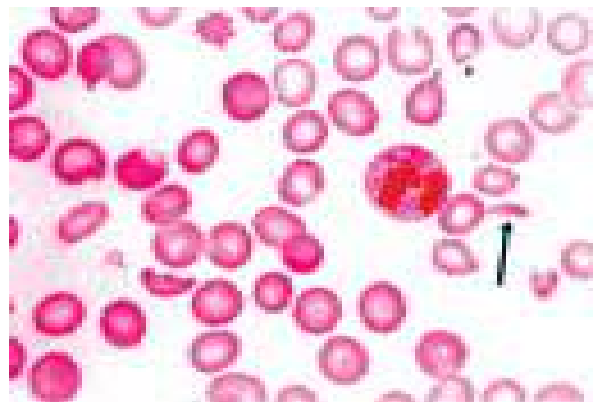


Fig. 166.1: Blood smear –schistocytes in microangiopathic hemolytic anemia (arrow)

damage the capillary endothelial cells. The common precipitating factors are gastrointestinal infections, sepsis, malignant diseases, immune complex disease, vasculitis, malignant hypertension and others. The common feature of microangiopathic hemolytic anemia seems to be endothelial damage which causes adhesion and aggregation of platelets, the formation of thrombin and the impairment of fibrinolysis. In both TTP and HUS, aggregates of platelets form and these reversibly obstruct the capillaries of various organs, leading to fluctuating ischemia and at times, infarction.

TTP: The major pathogenic factor in TTP is the activation of platelets by large multimers of vWF leading to the formation of disseminated platelet thrombi. Normally large vWF multimers are cleaved into smaller fragments by the protease enzyme known as ADAMTS13 (an acronym for a disintegrin and metalloprotease with thrombospondin-1-like domain). In TTP this enzyme level is only < 5% of normal.

HUS: Activation of platelet glycoprotein IIb and IIIa and adhesion to fibrinogen under high shear forces lead to their deposition in microvessels and these microthrombi occlude the circulation. This is the main pathogenic factor in HUS. The pathogenesis of TTP and HUS are different.

THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)

The main lesions are in the brain, kidneys and other organs. It is a multisystem disease characterized by fever, fluctuating central nervous system abnormalities, renal failure and thrombocytopenia. In many cases there may be overlap of symptoms between TTP and HUS. Peak incidence is in the third decade of life and females are more affected.

The characteristic symptom complex includes;

1. Microangiopathic hemolytic anemia
2. Thrombocytopenia
3. Neurological lesions
4. Renal lesions and
5. Fever.

The hemorrhagic manifestations include petechiae, ecchymosis, gastrointestinal bleeding, hematuria or epistaxis. More than 80% of cases show hemolysis and thrombocytopenia. The neurological features include headache, confusion, delirium, coma, convulsions and focal neurological deficits. Renal manifestations occur in 80% of cases. These include proteinuria, varying grades of hematuria and renal failure. Abdominal pain and tenderness along with nausea and vomiting may be mistaken for gastroenteritis.

Untreated, the mortality is high, reaching upto 75%.

Laboratory findings: The hemoglobin is reduced, often to 7 g or less. Thrombocytopenia is demonstrable and it may persist for 7-20 days. There is no constant relationship between the severity of thrombocytopenia and the clinical picture. Microscopic, or rarely macroscopic hematuria may occur. Lactic dehydrogenase (LDH) in serum is grossly elevated. LDH is derived from ischemic and necrotic vascular cells and not mainly from lysed erythrocytes.

Coombs' test is negative. Osmotic fragility is normal.

Prognosis: The mortality may reach upto 75% if the condition is not recognized and managed properly.

Treatment: In addition to attention to the causative event, and appropriate supportive measures, plasma exchange is done using 1-1.5 times of the patient's predicted plasma volume. FFP is used, starting with 30 mL/kg bw on the first day, thereafter 15 mL/kg daily till the platelet count rises above 150,000/cmm. Plasma LDH levels help to monitor progress and recognize relapse early.

Recurrence: At times, TTP may relapse. Drugs such as glucocorticoids, cyclophosphamide, vincristine and monoclonal antibodies such as rituximab have been employed to prevent relapse.

Hemolytic Uremic Syndrome (HUS)

In this condition renal endothelial injury is the primary event. HUS may follow two clinical patterns—diarrhea associated and non-diarrhea associated. The exotoxins of shigella and *E. coli* (particularly verotoxin of *E. coli* 0157:H7) are the triggering factors in the former group.

In the diarrhoea associated group intraluminal platelet thrombi and fibrin occlude glomerular capillaries and afferent arterioles. In the other group thrombi are seen in the arterioles and small arteries. Unlike TTP, vWF multimers do not play a major role in the pathogenesis. LDH levels are grossly elevated.

Major occlusion of the capillaries may lead to necrosis of glomeruli and tubules. Late complications such as hypertension and end-stage renal disease may follow.

Clinical features: HUS is more common in children and the illness starts abruptly after an episode of diarrhea or upper respiratory tract infection. Sixty percent of patients develop acute renal failure which resolves with treatment. About 10% go to the chronic stage. Laboratory findings include evidence of renal failure, microangiopathic hemolytic anemia and thrombocytopenia. Mortality ranges from 10-20%. In adults mortality is higher.

Treatment: In many, supportive measures may be the only form of therapy required. Infusion of fresh frozen plasma, plasma exchange, corticosteroids and anti-platelet drugs have been employed with considerable benefit.

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Thrombophilia

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Chapter Summary

Definition 1105

Definition

This term denotes an abnormally increased tendency to undergo thrombosis *in vivo* either spontaneously or due to trivial reasons. Venous system is affected more often. This is a pathological state caused by several inherited and acquired abnormalities. Broadly the causes may be grouped as below:

1. *Increases in hemostatic components*
e.g. increase in coagulation factors VIII, VII, fibrinogen. A mutation in the 3' untranslated region of the prothrombin gene G to A at position 20210 (PT 20210 A) is associated with increased plasma levels of prothrombin.
2. *Abnormalities of coagulation factors to*
e.g. factor V Leyden which is resistant to activated protein C
3. *Reduction or absence of natural inhibitors of coagulation*
e.g. AT III deficiency, protein C and protein S deficiency
4. *Abnormal metabolites in the system*
e.g. hyperhomocysteinemia. This leads to venous and arterial thrombosis
5. *Presence of coagulant factors in the circulation*
e.g. (a) tumour metabolites in several cancers leading to migrating and recurrent phlebothrombosis
(b) antiphospholipid antibody syndrome
6. Endothelial factors which favour thrombosis.

Pregnancy is associated with a five-fold risk of venous thromboembolism caused by venous stasis, rise in factors II, VII and X and decreased fibrinolysis. Obesity is a predisposing factor for venous thrombosis. The risk of venous thrombosis in the various thrombophilic conditions is given below.

	Risk of venous thrombosis
AT III deficiency	70%
Protein C deficiency	33%
Protein S deficiency	17%

Patients with antiphospholipid antibody syndrome have several complications during pregnancy.

Patients with thrombophilia are candidates for long-term anticoagulant therapy.

Venous thrombosis is 3-6 times more frequent in women taking oral contraceptives (OC). Those drugs raise the levels of prothrombin, factor VII, VIII and X and also fibrinogen. Oral contraceptives also confer an acquired resistance to activated protein C. Venous thrombosis is more common in the young, whereas arterial thrombosis is also more frequent in older age groups. Previous history of myocardial infarction and concurrent tobacco smoking are associated with higher risk. Persons undertaking long haul flights in aircrafts develop predisposition to venous thrombosis.

Antiphospholipid Antibody Syndrome (APAS)

Note: see Section: 12, Chapter 106.

DEEP VEIN THROMBOSIS (DVT)

Risk of deep vein thrombosis can increase when patients with thrombophilia are exposed to temporary risk factors such as surgery or trauma.

Quantitative risk of DVT in thrombophilic conditions compared to normals

Factor V Leyden	7 fold in heterozygotes 80 fold in homozygotes
Factor II G 20210 A	2.8 fold
Antithrombin III deficiency	8 fold
Protein C deficiency	7 fold
Protein S deficiency	8 fold
High clotting factor levels	
Factor VIII > 150 Iu/ dL	4.8 fold
Factor IX > 129 Iu/ dL	2.8 fold
Factor XI > 121 Iu/ dL	2.2 fold

mild hyperhomocysteinemia	2.7 fold
Pregnancy and puerperium	2-14 fold

Ref: Paul A Kyrle and Sabine Eichin Deep vein thrombosis
The Lancet 2005 365 1163-1174

Management of Acute DVT:
Dose of Anticoagulant

LMWH (enoxaparin) 40 mg daily or daltaparin 50000 units.

In patients undergoing major orthopedic surgery—Fondaparinux 2.5 mg daily, started 6 hours after surgery is an effective alternate to LMWH.

Long-term prevention is by warfarin therapy, given in doses to keep INR at 2-3. The duration of prophylaxis depends upon the underlying condition, varying from a few months to life-long.

Nephrology

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Development of the Kidneys and Urinary System

Nephrogenesis starts from the 4th week of intrauterine life. Three sets of excretory organs are formed in mammalian embryos from the intermediate mesoderm. They are the pronephros, mesonephros and metanephros. The pronephros and mesonephros are tubular structures that involute before birth. Only the caudal portion of the mesonephric duct which opens into the cloaca persists. Metanephros is the direct precursor of the adult kidneys. Nephrons, the excretory units of the kidneys, develop from metanephros. Collecting system of the kidneys develop from the ureteric bud which starts as an outgrowth of the mesonephric duct close to its entrance to the cloaca (Fig. 168.1).

The ureteric bud penetrates the metanephric tissue (blastema) and is appears as a cap moulded over its blunt end. The ureteric bud dilates and splits into branches. These develop ultimately into the collecting ducts, minor and major calyces, the renal pelvis ureter and the trigone of bladder. The metanephric blastema differentiates into the glomeruli, proximal convoluted tubule, loop of Henle and the distal convoluted tubule and renal interstitium. Nephrogenesis is complete at 36 weeks of intrauterine life. The number of nephrons does not increase once the development is complete. At birth the kidneys have a lobulated appearance (Fig. 168.2). During infancy the lobulation disappears as a result of further growth of the nephrons.

The development of urinary bladder and urethra starts with the formation of a membrane called the urorectal septum. This membrane divides the cloaca into two compartments: The dorsal rectal compartment and ventral urogenital compartment. The urogenital compartment

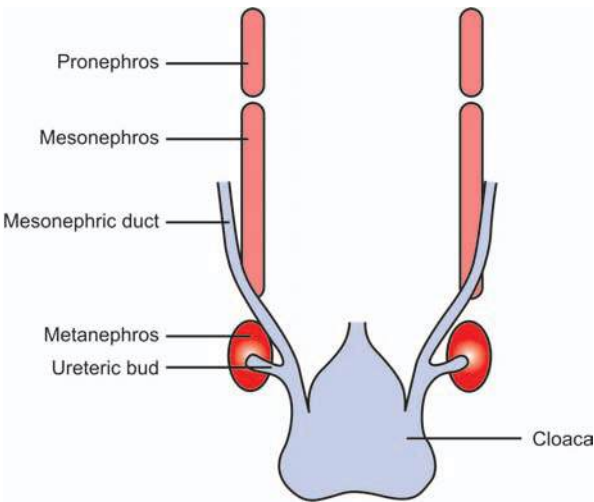


Fig. 168.1: Schematic diagram showing relationship of cloaca, ureteric bud, pronephros, mesonephros and metanephros

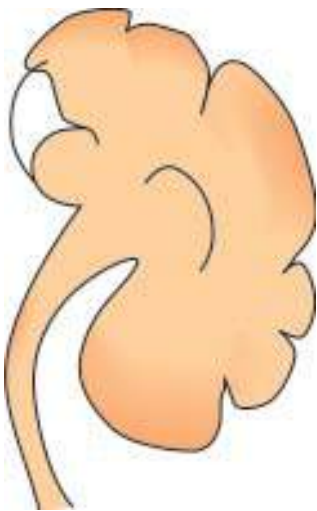


Fig. 168.2: Lobulated appearance of kidney

communicates with the allantois. The caudal portion of the mesonephros forms the urogenital sinus. The urinary bladder develops from the urogenital sinus and allantois. The trigone of the bladder develops from the ureteric bud.

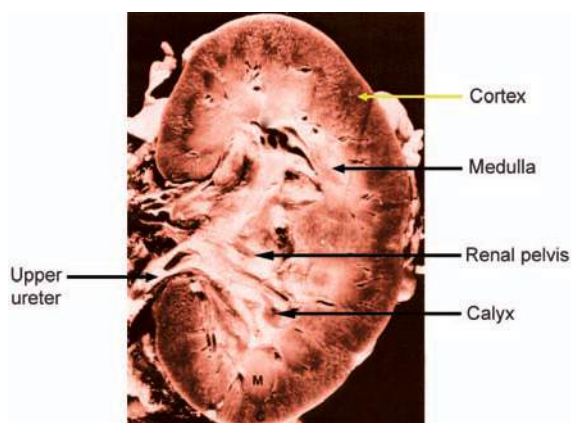


Fig. 168.3: Cut section of kidney showing cortex, medulla, renal pelvis and upper part of ureter

Structure of the Kidney

The kidneys are paired bean shaped organs situated in the retroperitoneum on either side of the vertebral column against the psoas major muscle. Each kidney weighs about 120-170 gram, and is about 12 cm in length, 6 cm in breadth and 3 cm in thickness. At the concave medial border of each kidney, there is a slit-like aperture—the hilum. The renal artery, renal vein, nerves, lymphatic and the expanded funnel shaped renal pelvis pass through the hilum. Surrounding each kidney is the tough fibrous capsule, the perinephric fat and perirenal fascia (Gerota's fascia). The kidneys play a major role in maintaining the internal environment (milieu interior).

The cut section of the kidney reveals an outer dark zone – the cortex and the inner pale zone, the medulla (Fig. 168.3).

Corticomedullary distinction can be clearly made out. The cortex is 2-3 cm thick. It is divided into an outer cortex and juxtamedullary cortex. The cortex contains the glomeruli, proximal and distal tubules, blood vessels and interstitium.

The medulla is divided into outer and inner parts. The outer medulla adjacent to the cortex is divided into an outer stripe and inner stripe (Fig. 168.4).

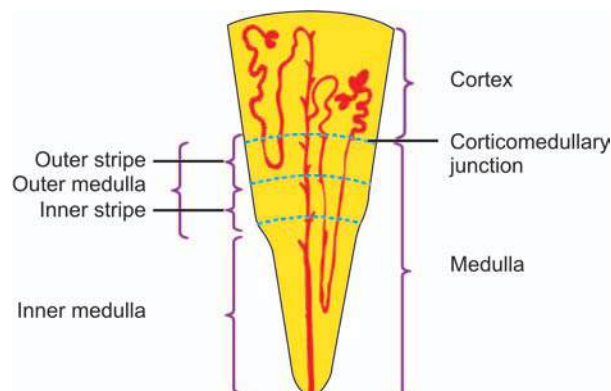


Fig. 168.4: Subdivisions of renal parenchyma

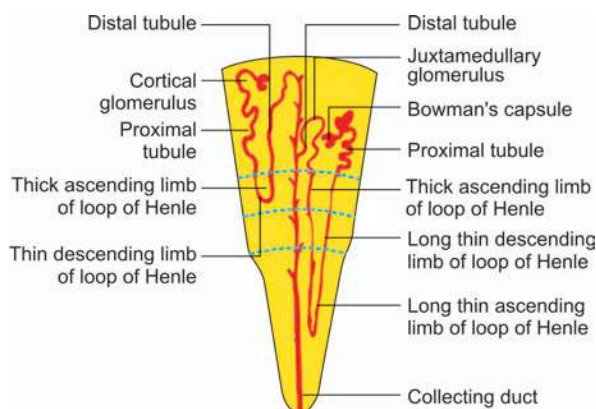


Fig. 168.5: Arrangement of cortical and juxtamedullary nephrons

The medulla consists of the limbs of the loop of Henle, collecting tubules, vasa-recta and interstitium. There are about 8-18 pyramid like projections in the medulla with their base adjacent to the cortex. The apex of each pyramid is called the papilla. The collecting ducts open into the papilla. Each renal papilla is surrounded by the minor calyx, which receives the urine from the collecting ducts. 3-5 minor calyces open into the major calyx, which join to form the renal pelvis.

Nephron is the functional unit of the kidney and consists of renal corpuscle or glomerulus and a system of tubules called proximal tubule, loop of Henle and distal tubule. The spatial arrangement of different parts of the nephron in the different zones of the renal parenchyma plays an important role in their function. There are mainly 2 types of nephrons – cortical and juxtamedullary nephrons (Fig. 168.5). The juxta-medullary nephrons are near the corticomedullary junction and have long loops of Henle which turn back in the inner medulla. Cortical nephrons have short loops of Henle which turn back in the outer medulla.

The glomerulus consists of the central mesangial frame work surrounded by a specialized capillary net work. This globular structure is encircled by the Bowman's capsule all around except at the vascular pole. The afferent arteriole enters the glomerulus at the vascular pole and divides into the capillary net work. This network of capillaries reunites and form the efferent arteriole which leaves the glomerulus. The blood is filtered and the ultrafiltrate moves through the basement membrane into the Bowman's capsular space. The mesangium is the central skeletal frame work of the glomerulus. The mesangium consists of the mesangial cells and the matrix. The mesangial cells contain contractile elements like actin, and myosin which enable them to regulate the ultrafiltration. The macrophage derived cells in mesangium exhibit reticuloendothelial function and remove the trapped macromolecules. The wall of the capillary loop is lined by endothelial cells. The endothelial

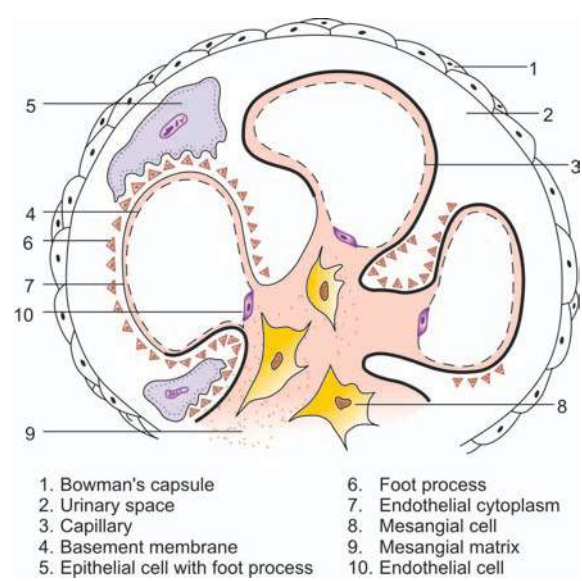


Fig. 168.6: Electron microscopy of the glomerulus

cell cytoplasm is stretched into thin sheets completely encircling the lumen. On electron microscopy, fenestrations are seen in this thin sheet of endothelial cell cytoplasm. Outside the endothelium is the glomerular capillary basement membrane and a layer of specialized visceral epithelial cells called podocytes. The basement membrane consists of a central dense layer called lamina densa with two less dense layers on either side, lamina rara interna on the endothelial side and lamina rara externa on the epithelial side. It is made up of collagen and negatively charged sialoglycoproteins (Fig. 168.6).

Podocytes are specialized visceral epithelial cells. They resemble an octopus with a central nucleus and numerous cytoplasmic prolongations. The divisions and subdivisions of these cytoplasmic prolongations

interdigitate with the neighbouring podocytes. The term podocyte is derived on account of the presence of the foot processes which are in contact with the basement membrane. The space between two foot processes has a slit pore membrane. The slit in this membrane is the ultimate ultrafiltration barrier which permits only substances with less than 60 daltons to pass through. The whole glomerular capillary network is surrounded by the Bowman's capsule. The parietal epithelial cells line the outer surface of the Bowman's capsule. The space between the visceral and parietal cell layers is the urinary space. The urinary space communicates with the lumen of the proximal tubule (Fig. 168.7).

The renal tubules consist of a long tubular system with 3 main segments, which differ in their structure and functions. They are the proximal tubule, loop of Henle and distal tubule. The proximal tubule consists of a convoluted and a straight portion. The glomerular basement membrane continues as the basement membrane of the proximal tubule. The proximal tubule is lined by a single layer of columnar cells with prominent brush border on the luminal side. These cells contain several mitochondria and are metabolically very active and highly oxygen dependent. Thus this region is very vulnerable to ischemic injury. The capillary net work arising from the efferent arteriole surrounds the proximal tubule. Loop of Henle, is a hairpin like segment of the tubule which connects the proximal and distal tubules. It consists of the descending limb, the bend and the ascending limb. The descending limb and the 'U' bend of the loop of Henle is lined by a single layer of flat cells with clear cytoplasm. Cortical nephrons have short loops of Henle with short thin descending limbs. The 'U' bends stop short at the outer stripe of the medulla. The juxtamedullary nephrons have long thin descending and ascending limbs

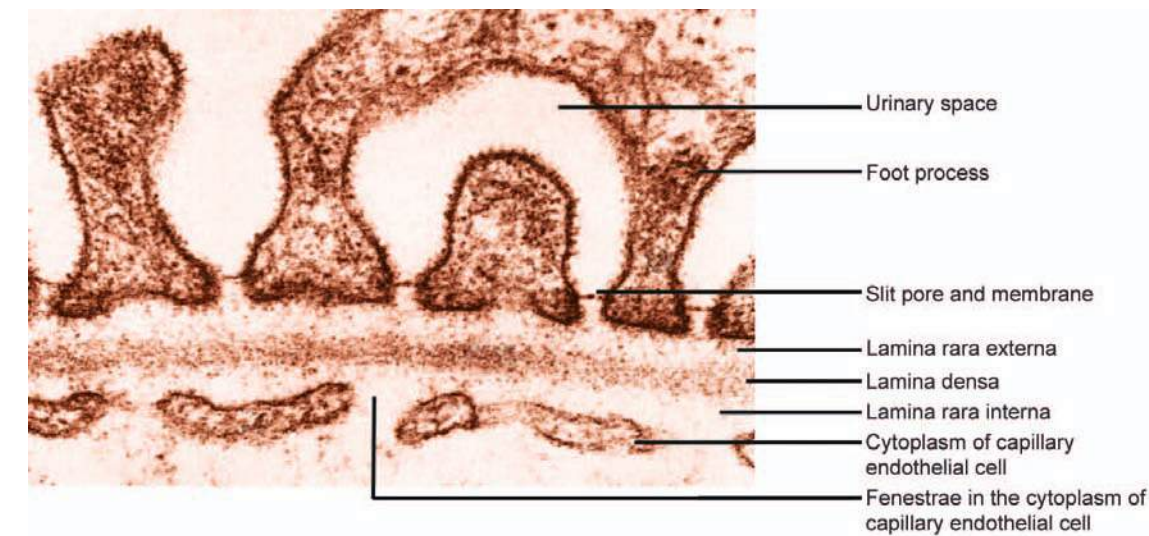


Fig. 168.7: Glomerular capillary filtration barrier

with the 'U' bend reaching deep into the inner medulla. A portion of the ascending limb is thick and it is called the thick ascending limb. The thick ascending limb is lined by columnar cells and it has specialized function. At the junction of the ascending limb and the distal tubule, the glomerulus, afferent and efferent arterioles and the distal tubule are close together to form the juxtaglomerular apparatus.

The juxtaglomerular apparatus (JGA) consists of macula densa at the initial part of the distal tubule, the afferent and efferent arterioles of the parent glomerulus and the glomerular mesangium at the vascular pole (Fig. 168.8).

The modified smooth muscle cells of the afferent arteriole contain renin stored as granules. The macula densa consists of specialized cells in the tubular wall at the junction between thick ascending limb of loop of Henle and distal tubule. These long and narrow cells have densely packed large nuclei (macula densa). The structural organization of JGA suggests a regulatory function. The macula densa senses the composition of the tubular fluid reaching it. This information is used to regulate the release of renin from the modified smooth muscle cells of the afferent arteriole.

The distal tubule is the continuation of the thick ascending limb of loop of Henle. The lining cells of the distal tubule are cuboidal with microvilli on the luminal side. Unlike proximal tubular cells, they do not have brush

border. The collecting ducts are formed by the union of several distal tubules. They pass through part of the cortex and the whole length of the medulla to open into the calyces through slit like openings into the renal papillae. The lining cells of the collecting ducts are of two types – the principal cells and intercalated cells. The principal cells are simple polygonal cells. The intercalated cells are of two types: Alpha (Type A) and Beta (Type B) cells. Alpha cells secrete acid and beta cells secrete bicarbonate.

The renal interstitium increases in volume progressively from cortex to medulla. The interstitium contains fibroblasts with many lipid droplets especially in the medulla. These are called lipid laden interstitial cells. They produce prostaglandin and vasodilatory hormones called *medullipin*. The peritubular fibroblasts secrete *erythropoietin*. The interstitium also contains dendritic cells of macrophage origin.

The kidney receives about 20% of the cardiac output and each gram of renal tissue receives 3.5 to 4 mL of blood every minute. Near the renal sinus, the renal artery divides into 6-8 interlobar arteries. At the junction between cortex and medulla they divide into numerous arcuate arteries which run along the corticomedullary junction. Interlobular arteries arise perpendicularly from the arcuate artery and traverse the renal cortex. The afferent arterioles arise from the interlobular arteries. The afferent arterioles divide to form the glomerular capillary network and reform as the efferent arterioles. They break up to form the peritubular capillary plexus or vasa recta and ultimately form the interlobular veins, arcuate veins, interlobar veins and renal veins.

Functions of the Kidney

Kidneys are important in maintaining the internal milieu. Major functions of the kidney include excretion of nitrogenous waste products, maintenance of acid base, electrolyte and water balance. Kidney also functions as an endocrine organ. It produces chemicals with which have endocrine and paracrine functions. The formation of urine contributes to the excretory and metabolic functions of the kidney.

The glomeruli filter about 120 mL ultrafiltrate from nearly 1500 mL of blood every minute. The ultrafiltrate contains all the solutes such as glucose, sodium, potassium, calcium, phosphate, bicarbonate, small molecules such as urea, creatinine, uric acid and amino acids. The ultrafiltrate flows from the Bowman's space through the urinary pole into the proximal convoluted tubule (PCT). About 60-70% of water and solutes are reabsorbed from PCT. Glucose, bicarbonate, amino acids and phosphate are completely reabsorbed. The proximal tubule is capable of reabsorbing large amounts of fluid. As the fluid reabsorption is iso-osmotic, the concentration of the fluid and osmolality do not change. The proximal

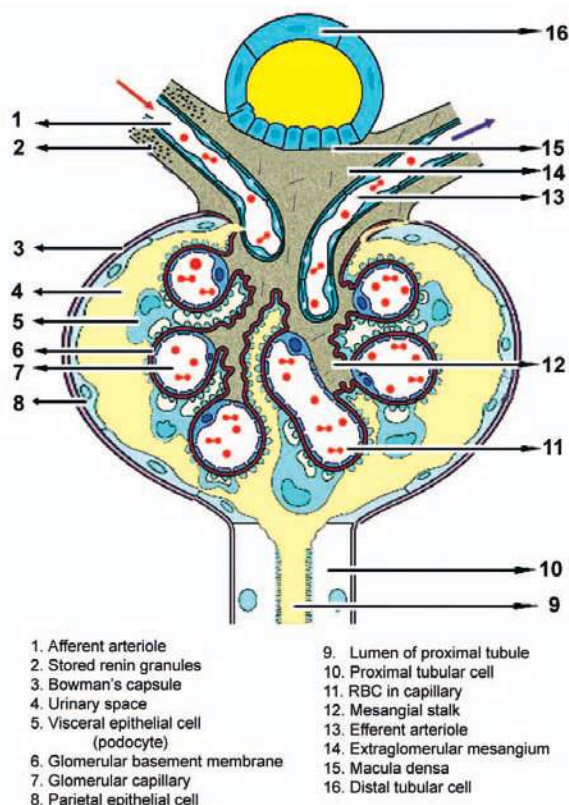


Fig. 168.8: Juxtaglomerular apparatus

tubular cell is also involved in the metabolism and elimination of metabolites like ammonium, drugs and toxic chemicals. The proximal tubule is particularly vulnerable to injury by toxins which reach in high concentrations.

The thin portion of the descending and ascending parts of the loop of Henle are freely permeable to water and urea. Since the medullary interstitium is maintained hyperosmotic (1100-1200 mOsm/kg water), there is reabsorption of water and urea from the tubular fluid. Consequently the osmolality of the tubular fluid progressively increases as the fluid moves down the thin portion, reaching a maximum of approximately 1200 at the 'U' bend of the loop. The thick ascending limb of loop of Henle is impermeable to water. There is an active chloride pump which helps to remove chloride and sodium from the tubular fluid into the interstitium. Approximately 20–25% of the sodium filtered by the glomerulus is reabsorbed in this segment without reabsorption of water. Thus the tubular fluid leaving this segment is always hypotonic with osmolality of 50-100 mOsm/kg. So, this segment is also called the *diluting segment*.

In the distal tubule, reabsorption of sodium in exchange for potassium occurs and is regulated by aldosterone. In the distal tubule, ammonia (NH_3) is converted to ammonium NH_4 by H^+ in secreted into the tubule. This segment is permeable to water and the permeability is partly regulated by the anti-diuretic hormone (ADH). ADH completely controls the water reabsorption in the collecting duct. In the presence of ADH, water transport channels called *aquaporin 2 channels* are inserted into the tubular cell membrane. Thus the cell becomes freely permeable to water and reabsorption occurs resulting in formation of smaller volumes of concentrated urine. In the absence of ADH, the aquaporin channels are stored inside the cell and the cell wall becomes impermeable to water. Thus larger volumes of dilute urine are formed.

The kidney functions as an endocrine organ. It produces hormones with local and systemic effects.

The main hormones are

1. Renin-angiotensin
2. Metabolites of Vitamin D
3. Erythropoietin
4. Prostaglandins
5. Kallikrein – Kinin system

Angiotensinogen is an alpha globulin produced by the liver and which circulates in the plasma. This is converted by the renin which is released by the modified smooth muscle cells of the afferent arterioles into *angiotensin I*. This in turn is converted by the angiotensin converting enzyme (ACE) to *angiotensin II* which is a powerful

vasoconstrictor. It is a trophic hormone for the zona glomerulosa of the adrenal cortex stimulating the release of aldosterone. By selective action of angiotensin II on the smooth muscle cells of the afferent and efferent arterioles, the glomerular filtration can also be regulated by the juxtaglomerular apparatus (JGA). This interaction between the tubule and the glomerulus is called the tubuloglomerular feed back. The renin angiotensin system controls the blood pressure and electrolyte balance through the coordinated effects on the heart, blood vessels and kidney.

Vitamin D obtained from different sources is converted to 25 hydroxy vitamin D in the liver. This is further converted to 1, 25 dihydroxy vitamin D in the proximal tubular cells of the kidney. This conversion is under the influence of parathormone which is the rate limiting factor. The most active biological product which acts as a hormone is 1, 25 dihydroxy vitamin D. Renal osteodystrophy may occur in chronic renal disease due to inadequate formation of active vitamin D. Administration of conventional or even high doses of vitamin D may be ineffective in such patients. Administration of 1, 25 dihydroxy vitamin D is therapeutically effective.

Erythropoietin is a glycoprotein with a molecular weight of 36,000 produced mainly by the interstitial cells of the kidney and to a lesser extent by the liver. Erythropoietin is secreted in response to hypoxia. It stimulates the proliferation of committed stem cell precursors in the bone marrow and induces differentiation as erythroblasts. Deficiency of erythropoietin causes regenerative anemia in chronic renal failure. Recombinant human erythropoietin is now used for the management of anemia in chronic renal failure.

Vasodilator prostaglandins produced in the renal medulla play an important role in autoregulation of renal blood flow. Even in times of hypotension and early shock they help to maintain glomerular blood flow and filtration. Nonsteroidal anti-inflammatory drugs (NSAIDs) which suppress prostaglandins render the kidney susceptible to hypoperfusion and damage even with mild or transient hypotension. These drugs should be avoided especially in those with compromised renal blood flow and when other nephrotoxic drugs are concurrently used.

The renal kallikrein-kinin system also produces renal vasodilatation and plays important roles in renal hemodynamics and excretory function. They are important in the pathogenesis of essential hypertension. In addition to the primary renal hormones already listed, kidney is also acted upon by other hormones like parathormone, prolactin, estrogen, progesterone, aldosterone, ADH, growth hormone and several others. Kidney also plays a key role in the metabolism of hormones like insulin.

169

Clinical Approach—
Evaluation and Investigations

Jacob George

Chapter Summary

Symptomatology in Renal Disease 1113

Clinical Syndromes in Nephrology 1113

Investigations in Renal Disease 1114

SYMPTOMATOLOGY IN RENAL DISEASE

An underlying renal disease may be suspected if a patient presents with any of the following symptoms:

1. *Oliguria*: The urine output is less than 400mL/24 hours. This is usually seen with renal failure, though some cases of renal failure may be non-oliguric.
2. *Anuria*: The urine output is less than 50 mL/24 hours and may be seen with severe renal failure, total urinary obstruction, bilateral renal artery occlusion, acute cortical necrosis, rapidly progressive glomerulonephritis, etc.
3. *Edema* can occur with acute nephritis, nephrotic syndrome, renal failure, etc. Periorbital edema is more often seen in renal edema rather than cardiac edema as patients with cardiac failure have orthopnea and hence have more of dependent or pedal edema (Fig. 169.1).



Fig. 169.1: Acute glomerulonephritis: woman 30 years
Note: Puffiness of face and moderate edema

4. *Hematuria* can signify a pathology occurring anywhere in the genitourinary tract and may be due to a urological problem. Cola colored urine is however more often seen with glomerular diseases.
5. *Anorexia, nausea and vomiting* may signify underlying renal failure.
6. *Dysuria, frequency and urgency* should raise the possibility of a lower urinary tract infection.

CLINICAL SYNDROMES IN NEPHROLOGY

A constellation of symptoms, signs and abnormal investigation results can constitute a renal syndrome. The following are some of the syndromes often seen in nephrology practice:

1. *Acute nephritic syndrome* (acute glomerulonephritis): This is characterized by varying combinations of edema, hypertension, hematuria and oliguria. Acute postinfectious glomerulonephritis, IgA nephropathy, lupus nephritis and membranoproliferative nephritis can present with this syndrome.
2. *Nephrotic syndrome* is associated with massive edema, proteinuria exceeding 3.5 gm/1.73 m², hypoalbuminemia, hypercholesterolemia and lipiduria. Minimal change disease, focal segmental glomerulosclerosis, membranous nephropathy, diabetic nephropathy, amyloidosis and other systemic diseases can present with this syndrome (Fig. 169.2).
3. *Rapidly progressive glomerulonephritis*: There is a doubling of serum creatinine within a period of weeks to months with associated glomerular hematuria or RBC casts in urine. Post-infectious glomerulonephritis, Goodpastures syndrome, lupus nephritis and vasculitis can present with this syndrome.
4. *Acute renal failure* is characterized by a rapid fall in glomerular filtration rate (GFR) with accumulation of nitrogenous waste products and can be seen in prerenal, renal and obstructive causes.
5. *Chronic renal failure* is associated with a gradual but often progressive decline in GFR of more than 3 months. There can be various signs and symptoms in this disorder which are however individually



Fig. 169.2: Nephrotic syndrome boy

nonspecific so that several of these patients can present to various other specialities of medicine. The term chronic kidney disease (CKD) is used to represent chronic involvement of kidney with normal or subnormal kidney function lasting for over 3 months.

6. Other syndromes include *urinary tract infections, urinary tract obstruction, nephrolithiasis, hypertension*, renal tubular disorders, etc. which are covered in detail in the subsequent chapters.

Investigations in Renal Disease

Investigations in renal diseases are intended to diagnose the type of renal involvement, quantify the severity, identify the underlying etiology, plan management strategies as well as predict the outcome. Investigations start with routine urinalysis and more sophisticated tests are done as needed.

Urine Examination

This is the most rewarding investigation in renal disease. It is essential, therefore, that the clinician familiarises himself with all the tests and their critical interpretation. Fresh urine collected directly in a clean container is examined macroscopically and is subjected to biochemical and other tests. The centrifuged deposit is examined under the microscope. Gram staining of the deposit, cytology and urine culture is undertaken depending on the indication.

The first voided sample in the morning is usually preferred for routine test. For estimating urinary loss of proteins, electrolytes and for calculating creatinine clearance, 24-hour urine is collected in appropriate containers with preservative. If collection and transport of the 24-hour urine sample is difficult, timed samples for 4, 6 or 12 hours is collected. In females, the labia are

separated and in males, prepuce is retracted during micturition to ensure a clean catch specimen. For microbiological culture, urine is collected directly into the culture bottle after cleaning the genitalia with water. Since this procedure may not always be practical in children, suprapubic aspiration of bladder may be necessary to get an uncontaminated sample.

A detailed urinalysis includes numerous tests from which the appropriate ones are chosen.

1. **Volume** is determined by accurate 24 hour urine collection.
2. **Colour:** Normal urine is amber coloured. The color can vary widely in normal persons depending on the concentration or dilution of urine. Presence of substances like bilirubin, blood, drugs, dyes or other coloring agents impart different colours.
3. **Odour:** Normally, freshly passed urine is odourless. On standing, a pungent ammoniacal odour develops due to splitting of urea to ammonia. In urinary infections even freshly passed urine may be foul smelling. Excretion of substances such as metabolites or other malodorous substances may impart characteristic smells to the urine, e.g. fruity odour of acetone.
4. **Turbidity:** Turbid urine may occur in pyuria, chyluria, or hematuria. Amorphous phosphate may precipitate on standing and lead to turbidity, which disappears on adding acetic acid. *Chyluria* has a milky appearance due to fat droplets which clears on addition of ether or chloroform. In pyuria, centrifugation of the urine leaves the supernatant clear.
5. **Reaction / pH:** The pH of urine ranges from 4.5 to 8.0. Strongly alkaline urine may denote infection with urea splitting organisms such as proteus, or renal tubular acidosis. Estimation of the pH of urine is important in the diagnosis and management of urinary tract infections, renal calculi and others.
6. **Specific gravity and Osmolality:** Specific gravity (sp.gr.) and osmolality are indirect indicators of the solute content of urine. Normal sp.gr. of urine may vary from 1002 to 1030. Sp.gr. increases during water deprivation, presence of excessive solutes, excessive fluid losses, and in some cases of acute glomerulonephritis. Increase in specific gravity may occur due to presence of sugar, proteins or radiographic contrast dyes in urine. Sp.gr. is low in the diuretic phase of acute tubular necrosis, diabetes insipidus, during clearance of edema and in normal subjects after excessive fluid intake. In chronic glomerulonephritis where the tubules lose their capacity to concentrate and dilute the urine the specific gravity becomes fixed around 1010 (isosthenuria). This is approximately the specific gravity of protein free plasma. Osmolality indicates

the amount of osmotically active particles and it is expressed as milliosmoles/kg. Normal urine osmolality can vary from 50 to 1200 mOsm/kg.

7. **Water deprivation test:** This assesses the concentrating capacity of the kidney and is employed in polyuric states. On withholding fluids for a period of 6-8 hours normally the hourly urine output falls and the kidneys produce concentrated urine with a specific gravity of 1022 or more. In diabetes insipidus the concentrating power of the kidney is lost and therefore large volumes of dilute urine with sp.gr. less than 1004 are passed. If the diabetes insipidus is due to reduced production of vasopressin (central diabetes insipidus), injection of vasopressin will correct the urine volume and concentration. In nephrogenic diabetes insipidus where the renal tubules are unresponsive to vasopressin, this does not happen.
8. **Water loading test:** This tests the diluting ability and is rarely done in clinical practice. The patient is given one litre of water to drink within 20 minutes. A normal person excretes 80% of this water within 4 hours and the specific gravity of at least one sample should be around 1002. A normal test suggests that the ability of the kidney to dilute the urine is preserved. Apart from primary renal disorders, which impair the excretory capacity of the kidney, deficiency of glucocorticoids (Addison's disease) leads to impairment of diluting function.
9. **Proteinuria and albuminuria:** Proteinuria and albuminuria are not synonymous terms. Normally, urine may contain upto 150 mg proteins in 24 hours. In health, two-thirds of the urinary proteins is constituted by protein of tubular origin, particularly the *Tamm-Horsfall mucoprotein*. This protein is secreted into the tubular lumen by the distal tubular cells and it forms the basic ingredient of urinary casts. Proteins derived from plasma namely albumin, immunoglobulins, light chains and beta-2 microglobulin constitute the remaining third. Albumin may constitute only upto 10 mg in 24 hours. Such small amounts of albumin are not detectable by the usual side room tests. Specific dipstick tests or radioimmunoassays are needed for detecting albumin in such small quantities.

In glomerular diseases, the proportion of albumin lost in urine increases. In addition, small quantities of lipoproteins may also be present. Proteinuria may result from renal disorders, lesions in the urinary tract or extra renal causes like cardiac failure and fever. Gross proteinuria associated with the presence of casts is invariably due to renal disease. Presence of blood in urine gives rise to considerable amounts of protein in urine and this has to be excluded before attributing proteinuria to a primary renal lesion.

Selectivity of proteinuria can be used to assess the extent of glomerular damage and predict response to drugs such as corticosteroids in diseases like nephrotic syndrome. The ratio of IgG excretion to albumin forms the basis for identifying selectivity. In highly selective proteinuria, more of albumin and less of IgG are excreted, suggesting milder glomerular damage and good response to steroids. If the proportion of IgG is high, it suggests greater damage and poorer therapeutic response. A *globulin albumin ratio of <0.1% suggests highly selective proteinuria. Gross proteinuria, above 3.5 g in 24 hours or 2 g/m² body surface occurs in nephrotic syndrome.* Serial quantitative estimation of urinary proteins helps to monitor the progress of nephrotic syndrome and other renal diseases. Proteinuria can be assessed from a spot urine sample by estimating the protein – creatinine ratio. A value of 3.5:1 indicates a 24-hour urinary protein of 3.5 g. Estimation of this ratio is useful in children and in situations where an accurate 24-hour urine collection is difficult. In about 50% patients with multiple myeloma, light chains of immunoglobulins called *Bence Jones protein* is detected in urine. It may also be seen in other conditions like macroglobulinemia, lymphoma, leukemia, amyloidosis and other malignancies. The dipstick test does not detect Bence Jones protein. Immunoelectrophoresis of urine is the ideal method to detect and quantify Bence Jones protein.

Several terms are used to denote specific types of proteinuria.

Fixed proteinuria: >1 g/24 hours mostly of glomerular origin and mainly albumin.

Tubular proteinuria: <1g/24 hours mostly proteins other than albumin.

Overflow proteinuria: light chains of myeloma.

Orthostatic proteinuria: This occurs only when the patient assumes erect posture.

Physiological proteinuria: (transient proteinuria) This may occur transiently even in normal persons after heavy exertion.

Among the pathological proteinurias approximately $\frac{2}{3}$ rd is of glomerular origin and $\frac{1}{3}$ rd is of tubular origin.

10. **Reducing substances:** Presence of glucose in urine often suggests a diagnosis of diabetes mellitus. Rarely, glucose may appear in urine in the presence of normal blood sugar and this occurs in renal glycosuria. **Glucose oxidase test** is specific for glucose and can be used in test stripes for rapid detection of glucose.
11. **Other biochemical tests:** Specific tests are available for detection of ketone bodies, bile pigments, bile salts, urobilinogen and others. Other tests which

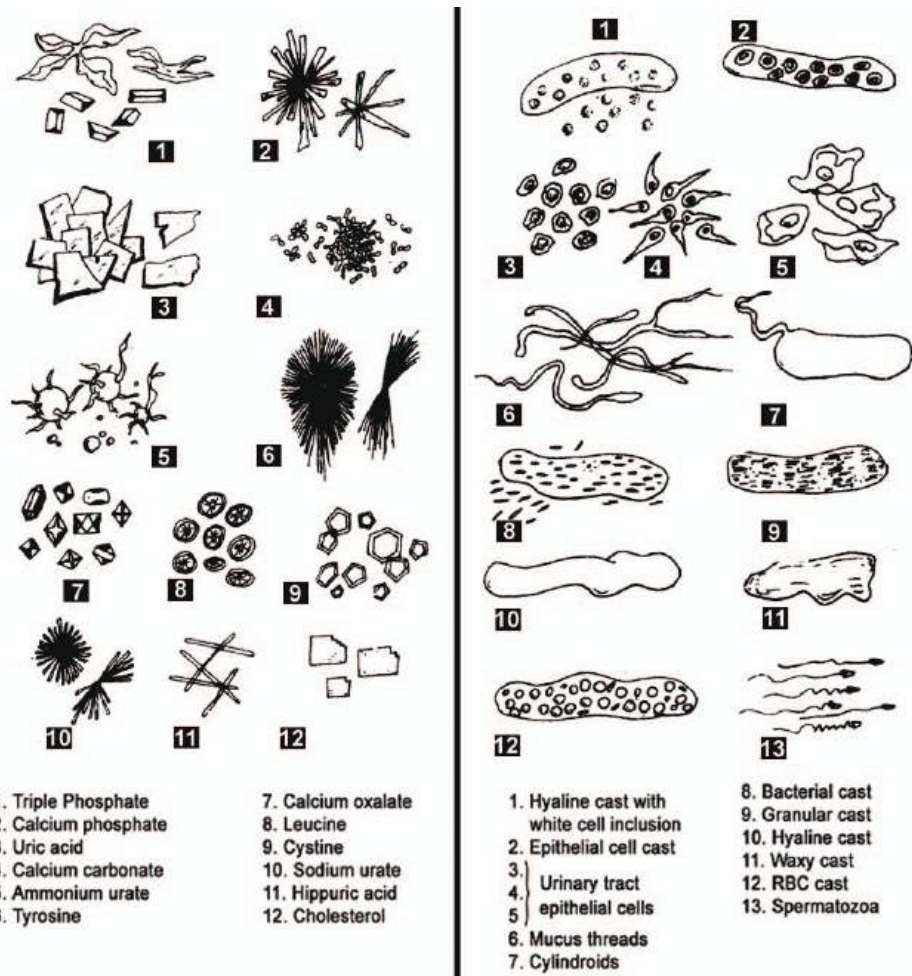


Fig. 169.3: Urinary sediments

are occasionally employed include urinary electrolytes, urea, creatinine, uric acid, calcium, amino acids, phosphates, oxalate, metabolites of hormones, drugs or toxic substances.

12. **Microscopic examination:** This is done to study the formed elements consisting of various cells, casts, crystals, lipid droplets, micro-organisms and parasites. The cells are derived from blood or may be acquired from any part of the urinary tract (Figs 169.3 to 169.6).

Erythrocytes: Presence of more than 2 erythrocytes in every high power field should suggest microscopic hematuria. Gross hematuria occurs in acute glomerulonephritis, infections, tumours, renal infarction, ulceration in the urinary tract, bleeding disorders and others.

Leucocytes: Neutrophils constitute the majority. They are numerous in urinary tract infections, urologic disorders and in patients with interstitial nephritis. Lymphocytes may appear in urine in smaller numbers. Eosinophils also may occur

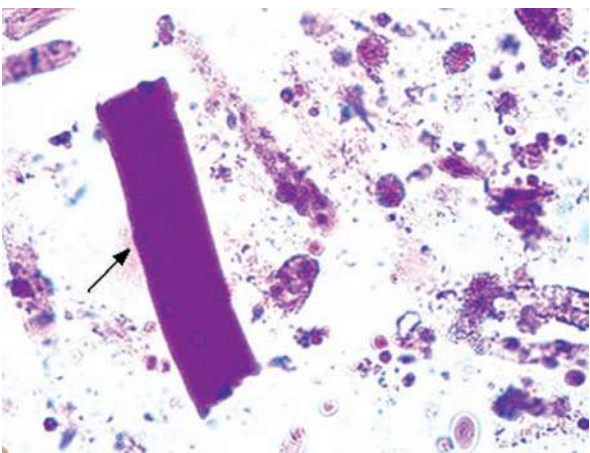


Fig. 169.4: Waxy cast

particularly in acute interstitial nephritis or athero-embolic renal diseases.

Renal tubular cells: These can be differentiated from leucocytes only by transmission electron microscopy.

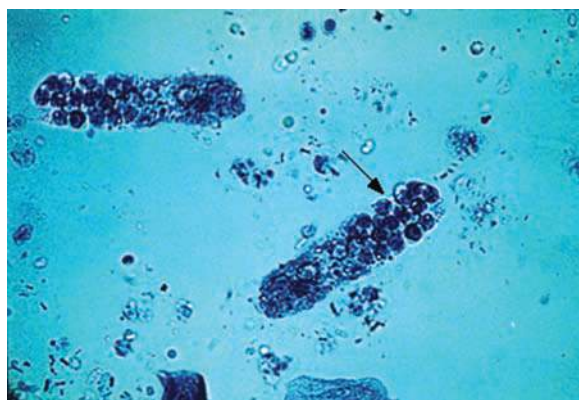


Fig. 169.5: White blood cell cast

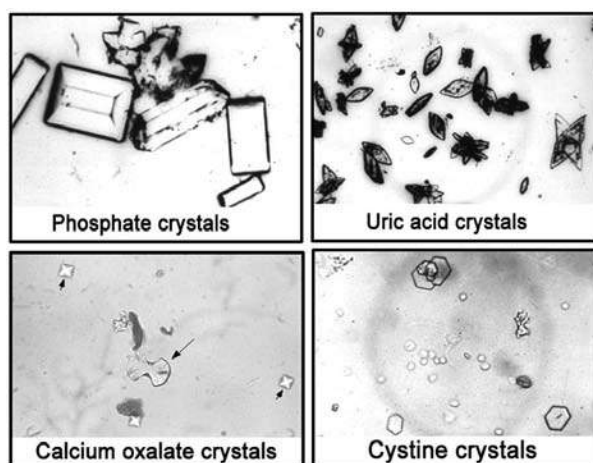


Fig. 169.6: Urinary sediments crystals

Urothelial cells: These may be present in small numbers. The cells are derived from the urinary tract. Excessive number of vaginal squamous cells should suggest contamination during collection of urine.

Cancer cells from malignancy of the urinary tract or renal carcinoma can be identified by special stains.

Casts: Casts are elongated and cylindrical shaped moulds formed in the lumen of the distal tubules where aggregation and gel formation of Tamm-Horsfall glycoprotein occurs. The casts may be hyaline, granular or cellular. *Hyaline casts* contain mainly Tamm-Horsfall protein and they may be seen even in normal urine. They have low refractive index and hence they are visible under dim lighting. *Granular casts* contain either fine or coarse granule like substances. These granules may represent ultrafiltered protein or degenerating cells. Normal urine may show only a few fine granular casts. *Waxy casts* are large and refractile with clean-cut edges (Fig. 169.4). *Broad casts* are formed in the dilated tubules of the surviving hypertrophied nephrons in

chronic kidney disease. *Fatty casts* contain lipids and are characteristic of nephrotic syndrome. *Pigment casts* may contain hemoglobin, myoglobin, bilirubin or other pigments. *Cellular casts* may contain erythrocytes, leucocytes, and renal epithelium in varying numbers.

Crystals: Various types of crystals are seen in the urine and can be identified by their characteristic morphology (Fig. 169.6). Normal urine may contain several crystals depending on the concentration and pH. Under abnormal conditions such as gout, oxaluria and urolithiasis specific crystals may be present in large numbers and may even suggest the diagnosis. Presence of cystine, leucine, isoleucine and other amino acid crystals occurs in metabolic errors and in hepatic failure. These are always pathological.

Gram-staining and acid-fast staining are done with centrifuged deposit of fresh urine. If there is likely to be delay in transport to the laboratory, the urine should be preserved with boric acid to give a final concentration of 1.8%. Conventional Ziehl-Neelsen staining can identify AFB in urine. *Mycobacterium smegmatis*, which is also acid fast may be seen as a contaminant in males.

Phase contrast microscopy helps to identify dysmorphic (abnormal) and isomorphic (normal) erythrocytes. This helps to identify the site of bleeding. Dysmorphic erythrocytes such as crenated or budding forms and acanthocytes suggest glomerular disease. Bleeding from sites below the renal parenchyma show normal erythrocytes.

Scanning or transmission electron microscopy can be used to distinguish between leucocytes and tubular epithelial cells in the urine sediment.

13. **Culture:** A clean catch midstream specimen of urine is generally satisfactory for microbiological examination. Urinary catheterization should not be routinely performed for this purpose due to risk of introducing infection. In addition to routine culture, quantitative determination of the colony count helps to decide whether the organisms exist as contaminants or as active invaders. Bacterial counts below 10^4 colony forming units (CFU/mL) of urine is suggestive of contaminants whereas those above 10^5 /CFU/mL is in favour of active infection. For doing colony counts and to facilitate culture, dipsticks coated with the culture media are available commercially. These can be directly inoculated by immersion to the urine and incubated straight away.
14. **Hematological tests:** Hemoglobin and packed cell volumes are often low in patients with chronic renal disease. Patients with nephrotic syndrome who develop contraction of plasma volume may have high hemoglobin and PCV. Polymorphonuclear

leucocytosis occurs when there is acute infection. High ESR often above 100 mm should suggest the possibility of lupus erythematosus, other forms of dyscollagenoses, renal tuberculosis or myeloma. In chronic renal failure, the erythrocytes are normocytic and normochromic. This is due to deficiency of erythropoietin. In addition to this mechanism, several other factors may also contribute to the development of anemia.

Biochemical Tests

Investigations of the blood and urine are necessary to assess the renal function. These tests also help to determine selectively the functions of the different parts of the nephron.

Blood urea (BU) or blood urea nitrogen (BUN): Urea is the principal end product of nitrogen metabolism. It is excreted by the kidney and it accounts for 50% of total urinary solutes. Amount of urinary urea is primarily determined by dietary protein intake and it depends upon the amount of urinary flow. Urea is filtered, reabsorbed and secreted by the tubule. Normal blood urea is 20-40 mg/dL and BUN is 10-20 mg/dL. Blood urea nitrogen is approximately 50% the value of blood urea. Blood urea or BUN gives an approximate estimate of the glomerular filtration rate (GFR). In addition to changes in GFR, several other factors like the state of hydration, urine flow rate and protein intake alter the serum levels of BU or BUN. Hence blood urea level or BUN is a less reliable parameter of glomerular filtration compared to creatinine.

Serum creatinine and creatinine clearance: Creatinine is the end product of muscle breakdown and is normally excreted by the kidney. The normal level of serum creatinine is 0.8-1.3 mg/dL (70-113 μmol/L). Creatinine is filtered by the glomerulus and is not reabsorbed from or secreted into tubular lumen in large amounts. Therefore, for all practical purposes, the clearance of creatinine closely reflects the GFR. The normal creatinine clearance is 115 ± 15 mL/min. The clearance of a substance is the amount of plasma that is completely cleared of the substance in unit time and can be calculated from the formula:

$C = UV/P$

- Where C = Clearance of the substance in mL/min.
U = Concentration of the substance in the urine (mg/dL)
V = Volume of urine formed (mL/min)
P = Concentration of the substance in plasma at that time (mg/dL)

Given the 24-hour urinary creatinine in mg/day and serum creatinine in mg/dL, the clearance can be calculated at the bedside as follows:

Creatinine clearance =

$$\frac{24\text{-hr urinary creatinine (mg)} \times 5}{\text{Serum creatinine in mg/dL} \times 72}$$

(This is derived from the formula: Clearance = UV/P)

e.g. If 24 hour urinary creatinine is 1200 mg and serum creatinine level is 1.0 mg/dL.

Creatinine clearance =

$$\frac{1200 \times 5}{1.0 \times 72} = 83.66 \text{ mL/min}$$

The creatinine clearance reduces with age even though the serum creatinine levels remain within normal range. This is due to the reduction in muscle mass which occurs with age. It is possible to calculate the creatinine clearance from serum creatinine, age and body weight using the following formula (Cockcroft-Gault formula):

Creatinine clearance =

$$\frac{(140 - \text{age in years}) \times \text{body wt (kg)}}{72 \times \text{Serum creatinine (mg/dL)}} = 83.66 \text{ mL/min}$$

Note: for females, multiply by 0.85, because the creatinine clearance is only 85% of this value in females.

This formula helps to calculate the approximate creatinine clearance at the bed side, particularly for adjusting drug dosages. There is a fixed relationship between serum creatinine and creatinine clearance in the same person. When the creatinine clearance falls to 50% the serum creatinine doubles. Therefore, serial estimations of serum creatinine can give an approximate idea about creatinine clearance. For example, if the creatinine clearance is 120 mL/minute and the serum creatinine is 1.2 mg/dL, when the creatinine clearance comes down respectively to 60mL/min, 30mL/min and 15 mL/min. the corresponding values of serum creatinine would be 2.4, 4.8 and 9.6 mg/dL in the same patient. Therefore, if the relationship between serum creatinine levels and the corresponding creatinine clearance is known, it will be possible to estimate the creatinine clearance by serial monitoring of serum creatinine alone.

Cystatin C: This is an endogenous substance produced at a constant rate by all nucleated cells and is removed only by glomerular filtration. It is possible to estimate the GFR by measuring cystatin C blood level. This test eliminates the need for 24-hour urine collection.

Serum electrolytes: Estimation of serum sodium, potassium, bicarbonate and pH helps to assess acid base status and renal function.

Serum cholesterol and lipids are elevated in some types of nephrotic syndrome and in chronic renal failure.

Uric acid: Hyperuricemia may be the cause or result of renal failure. High serum uric acid level can itself produce renal damage. In renal failure caused by hyperuricemia, the excretion of uric acid (spot sample) exceeds that of creatinine.

Serum calcium levels are low in chronic renal failure. Secondary hyperparathyroidism may cause bone changes.



Fig. 169.7: Plain X-ray abdomen: right renal area showing branched radio-opaque stag-horn calculus

In advanced cases, tertiary hyperparathyroidism may develop, resulting in elevation of serum calcium and metastatic calcification. Serum phosphorus levels are increased in acute and chronic renal failure.

Radiological Investigations

- a. **Plain X-ray of the abdomen** to include kidney, ureter, bladder and urethra (KUB) taken after suitable bowel preparation gives a good picture of the kidney and urinary tract. For getting a good skiagram, it is better to ensure proper bowel movement, if necessary by giving anti-flatulents like activated carbon and laxative for the previous 2 days and asking the patient to be ambulant so as to avoid excess of gas in the intestines.

Abnormalities of size, presence of calculi and calcification can be seen (Fig. 169.7). The bipolar length of the normal kidney is about the width of 3 ½ lumbar vertebrae. The left is about 1 cm longer and is situated higher than the right. In health, the two kidneys do not differ in length by more than 2 cm. An atrophic kidney may be smaller than its normal counter part. Tumours may lead to enlargement. In addition, bone changes occurring in the spine and pelvis can be seen. Tumours of the kidney may give rise to larger renal shadows. Hydronephrosis and polycystic kidney, though palpable as abdominal masses, may not be seen in the plain X-ray picture. Larger tumours, polycystic kidneys and hydronephrosis may give indirect evidences of their presence such as the displacement of gas-filled bowel.

- b. **Ultrasonography:** This has become the most popular and easily available imaging procedure for the preliminary assessment of the excretory organs. This is an investigation of choice for assessing renal size and the presence of obstruction, tumour, cysts, and calculi. Moreover, ultrasonography being noninvasive



Fig. 169.8: Ultrasonogram showing stone in renal pelvis (arrow) Note the 'acoustic' shadow due to the stone

is used more and more extensively. Ultrasonography is not useful for assessing renal function (Fig. 169.8).

- c. **Intravenous urography (IVU):** Intravenous urogram helps to assess the renal structure, anatomy of the collecting system and function by using radio-contrast agents, which contain iodine. These agents are selectively concentrated and excreted by the kidneys. Originally, hyperosmolar agents like meglumine and iothalamate were used. At present safer and non-ionic low osmolar agents like, iohexol, iopamidol and ioxglate are used. They produce adverse side effects only infrequently. Hypersensitivity to iodine is an absolute contraindication for IVU. Risk of renal failure is high in impaired renal function, concurrent use of other nephrotoxic agents, multiple myeloma with proteinuria and those with and diabetic nephropathy. The risk of contrast nephrotoxicity can be reduced by good hydration with intravenous saline and agents like N-acetyl cysteine (Fig. 169.9).

A plain X-ray of the abdomen is taken for comparison. Then films are taken at 5, 10, 20 and 30 minutes after administration of the contrast agent intravenously and a final picture after complete micturition.

Points to be noted on the IVU are summarized below

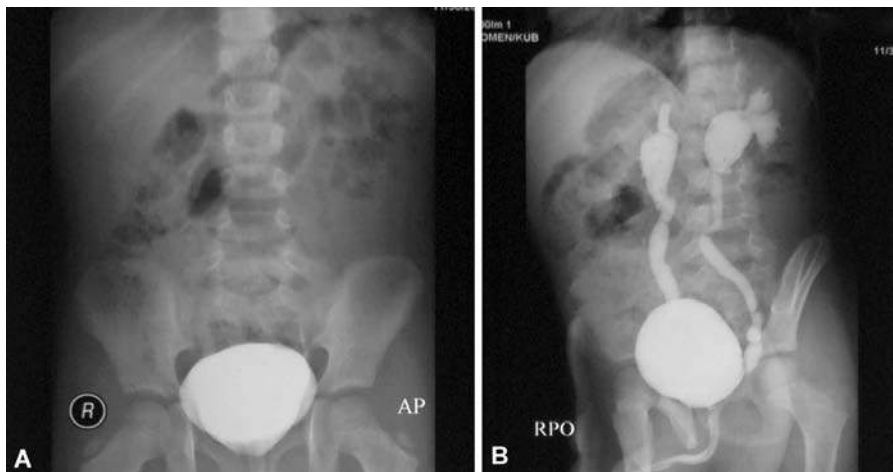
1. Time of initial visualization of the renal outlines. This depends upon renal circulation and glomerular filtration.
2. Time for maximum opacification of kidneys and visualisation of pelvicalyceal system. This depends upon the excretory function of the kidneys.
3. Size, shape and presence of negative contrast (stones, tumours, etc.) in the pelvicalyceal system.
4. Flow of the dye along the ureters, their size and presence of obstruction.
5. Time taken for the renal and pelvicalyceal shadow to disappear. This is usually complete within 20-30 minutes and this gives an idea about the efficacy of the drainage system, as well as vascularity of the kidneys.
6. Size and shape of the bladder, presence of filling defects caused by calculi, tumours or enlarged prostate and completeness of bladder emptying, as is seen in the post-micturition film.



Fig. 169.9: Intravenous urogram showing right renal area with sloughed papilla appearing as a rounded shadow in the middle calyx—arrow (from a case of analgesic nephropathy)

Several modifications of the IVU have been devised. These include:

- a. **Minute sequence pictures.** When pictures are taken every minute for the first five minutes, delay in appearance of nephrogram on one side, decrease the size of the kidney, higher concentration of the contrast in the collecting system and delayed drainage on the same side are all suggestive of unilateral renal artery stenosis.
- b. **Diuretic urogram** is performed by administration of a diuretic in cases with upper ureteric ballooning or obstruction to confirm or rule out obstruction. A functional obstruction of the pelvi-ureteric junction is relieved by the use of diuretic whereas the ballooning persists if there is a mechanical block.
- c. **Infusion urogram** is undertaken in the presence of renal failure and delayed pictures are taken at intervals of 6 hours upto even 96 hours to delineate the urinary tract in some cases of obstructive uropathy.
- d. **Retrograde pyelography** is the procedure by which the ureter is catheterized and the pelvicalyceal system is visualized by direct instillation of radiographic agent.
- e. **Cystourethrography** helps in studying the bladder, urethra, and vesicoureteric junction.
- f. **Micturating cystogram:** X ray is taken while the patient passes urine after introducing radiopaque contrast into the bladder. This helps to visualize the urethra, identify lesions such as posterior urethral valve or other obstructions and to establish the presence of vesicoureteric reflux (Figs 169.10A and B).
- g. **Aortography** performed by injecting dye into the aorta delineates clearly the aorta, renal arteries and the renal vascular pattern. Selective angiography can be done after catheterizing the renal arteries. Renal venograms can be obtained by injecting the dye into the renal veins (Fig. 169.11).
- h. **Isotope renography** helps to assess renal perfusion and excretory function. It is particularly useful to diagnose renovascular hypertension, assess individual kidney function, renal scarring and to confirm pelvi-ureteric junction obstruction. The radiopharmaceutical agents include technetium labeled DTPA (diethylene triamine penta acetic acid) (Fig. 169.12). Diuretic renogram is performed after administering frusemide and helps to differentiate between organic and functional ureteric obstruction. The functional obstruction clears after diuretic. Captopril renogram is performed after administration of 12.5 mg captopril



Figs 169.10A and B: A. Cystourethrogram: AP view showing bladder filled with dye before patient tries to pass urine. Note that there is no filling of the ureters. B. Oblique view of the same case when the patient (child) is passing urine. Note the flow of urine through the urethra and simultaneous filling of both ureters and the dilated renal pelvis and calyces (Grade V vesicoureteric reflux)

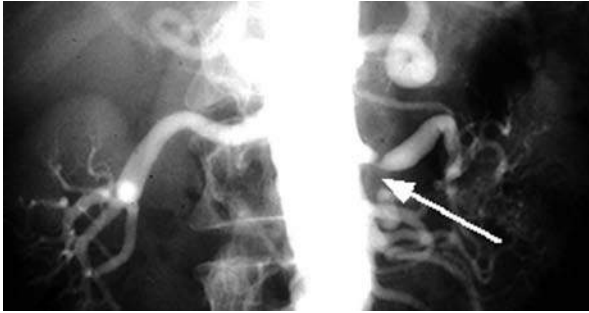


Fig. 169.11: Abdominal aortogram showing aorta and both renal arteries. Note the narrowing of proximal left renal artery (arrow) and post-stenotic dilatation

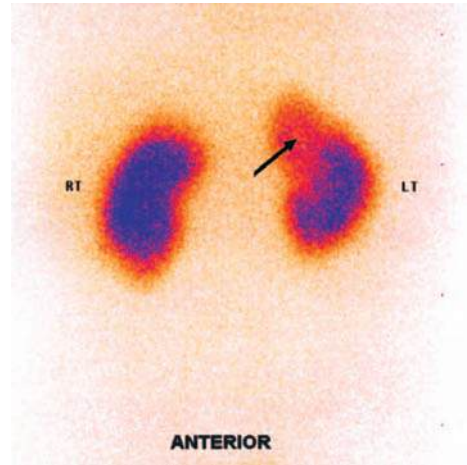


Fig. 169.13: DMSA scan showing scar in the upper pole of left kidney (arrow)

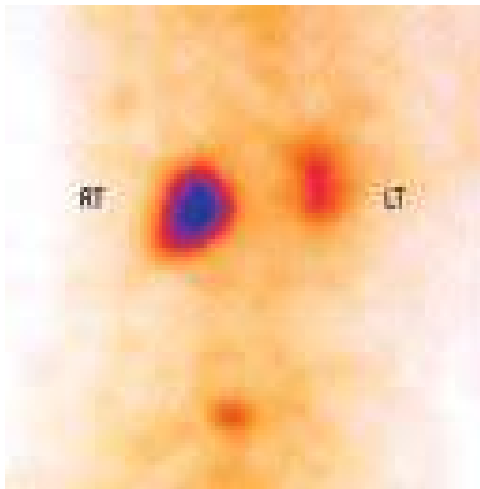


Fig. 169.12: DTPA renogram showing retention of radiopharmaceutical in the renal pelvis of right kidney (From a case of congenital pelviureteric obstruction)



Fig. 169.14: CT scan showing bilateral enlarged kidneys due to numerous cysts of varying sizes in both kidneys (arrows). (Autosomal dominant polycystic kidney disease)

orally and it helps to identify renal artery stenosis. The radiopharmaceutical DMSA (dimercapto succinic acid) is concentrated in the renal parenchyma and it is used to identify scars in the parenchyma (Fig. 169.13).

- i. **CT scan** helps to delineate the structural and morphological abnormalities in the kidney, details of tumour, and the relationship to other organs. In the vast majority of cases, CT scan will give adequate information (Fig. 169.14).
- j. **MRI** is employed at times. The advantages are a clear delineation of the corticomedullary junction and better visualization of the renal artery, vein and inferior vena cava.

Renal Biopsy

Renal tissue can be obtained by closed needle biopsy. The tissue is processed for histology, microbiological studies, electron microscopy and for immunofluorescence microscopy. Histological diagnosis is necessary for

determining the management and prognosis of several renal disorders like acute glomerulonephritis, nephrotic syndrome, lupus erythematosus, amyloidosis, and transplant rejection. Since clinical pattern of several different pathological entities may be similar, the ultimate diagnosis in many diseases has to rest on renal biopsy.

Serological Tests

These have to be done in selected cases depending on the clinical picture to confirm the diagnosis. These include ANA, Anti-dsDNA, ASO Titre, Complement (C3 and C4) levels anti-neutrophil cytoplasmic antibodies (pANCA and cANCA), Anti-GBM antibodies, screening for hepatitis viruses (esp. HCV and HBV) and HIV.

Urologic Investigations.

Urological investigations such as cysto-ureteroscopy help to visualize the urinary tract and enable endoscopic procedures.

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Glomerulonephritis

Acute Nephritic Syndrome and Nephrotic Syndrome

R. Kasi Visweswaran, Ramdas Pisharody

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Acute Nephritic Syndrome

R. Kasi Visweswaran

Acute nephritic syndrome is characterized by hematuria, red blood cell casts, proteinuria, oliguria, hypertension, fluid retention and sometimes, renal failure.

Common Causes

1. Post-streptococcal acute glomerulonephritis
2. Other post-infective acute nephritic syndromes following staphylococcal, pneumococcal, and viral infections.
3. Focal glomerulonephritis and membranoproliferative glomerulonephritis.
4. Collagen disorders, especially systemic lupus erythematosus and polyarteritis nodosa.
5. Miscellaneous group: Henoch-Schönlein syndrome, infective endocarditis, hypersensitivity angitis, hemolytic uremic syndrome and early stages of Goodpasture's syndrome.

POSTSTREPTOCOCCAL GLOMERULONEPHRITIS

Pathogenesis and pathology: Poststreptococcal acute glomerulonephritis is a common form. It is an example

of immune-complex mediated glomerulonephritis. Following streptococcal infection, the streptococcal antigens stimulate the production of antibodies. The antigens and antibodies combine to form immune complexes. These get deposited in tissues, particularly in the kidney and initiate acute inflammatory reaction in the glomerulus. The kidneys are enlarged. The Glomeruli are swollen and show proliferation of the endothelial cells. Glomerular tuft is infiltrated by polymorphonuclear cells. Immune complex deposits can be demonstrated as electron dense deposits when seen under electron microscopy. These can also be demonstrated by immunofluorescence staining which shows a granular pattern of distribution of immune complexes in the glomeruli.

Clinical features: The illness starts about 2-3 weeks after streptococcal infection of the skin, throat or respiratory tract. It is more common in children but can occur in any age. In India the most common precipitating cause was infected scabies or other skin infections. Both sexes are affected. The onset is often abrupt with puffiness of the face, oliguria, reddish smoky-urine, hypertension and edema. Small outbreaks may occur in closed communities due to the presence of nephritogenic strains of streptococcus. Severity of the disease is variable. Mild cases may go unnoticed (subclinical type). Severe cases present acutely with life-threatening complications like hypertensive encephalopathy, acute left ventricular failure or uremia. Majority of cases of poststreptococcal glomerulonephritis in children are self limited and more than 90% recover completely without complications or sequelae. After a week or so of the oliguric phase, diuresis starts. Though gross hematuria and casts disappear promptly, proteinuria and microscopic hematuria may persist for up to 6 months. In most cases, the blood pressure returns to normal with recovery. Some cases may require anti-hypertensive drugs.

Investigations

Urine examination: The urine volume is reduced, it is reddish-brown and contains protein. At this stage, the specific gravity is normal or raised. Numerous red cells

are seen. The presence of red cell casts indicates active glomerulonephritis.

Blood chemistry is altered depending on the severity of the disease and the presence of renal failure. During the oliguric phase, biochemical features of renal failure may be evident. The ASO titre is elevated above 200 Todd units and in many cases hemolytic streptococci may be obtained by culture of the skin lesion or throat swab. Levels of C3 complement are low in 95% of cases in the first two weeks of illness, C5- or C9 are also low. Classical pathway complement components C1, C4 and C2 are usually normal. This indicates that the alternate pathway is activated.

Diagnosis: Any patient presenting with abrupt onset of puffiness of face, oliguria, hematuria, hypertension and edema should be investigated to exclude acute nephritic syndrome.

Differential Diagnosis of Acute Glomerulonephritis

1. Angioneurotic edema
2. Nephrotic syndrome
3. Membranoproliferative glomerulonephritis (MPGN)
4. Chronic renal failure with acute exacerbation.

Angioneurotic edema involving the face may occur in children. This may superficially resemble acute glomerulonephritis. In angioneurotic edema, puffiness is asymmetrical. Often there is pruritus and other signs of allergy. The blood pressure is not elevated and urine is normal.

Nephrotic syndrome may present with edema of the face, though edema is more prominent in the dependent parts. The long duration, less dramatic onset, and urinary findings should suggest the diagnosis. The blood pressure is normal in the majority of cases of nephrotic syndrome.

MPGN with nephrotic syndrome may have an onset similar to acute nephritis but with massive proteinuria, hypertension, hematuria and renal failure. MPGN is more common in children and it may occur due to various causes, including streptococcal infection. 20-30% present as acute nephritic syndrome, whereas the others follow the nephrotic pattern. Majority progresses to persistent nephritic state and renal failure. The complement levels of both classical and alternate pathways are reduced in Type I MPGN whereas in Type II MPGN only C3 complement is lowered. Renal biopsy is indicated in order to confirm the diagnosis in all cases where the course is atypical. Chronic renal failure may present with acute exacerbations due to causes such as infection, electrolyte imbalance or cardiac failure. Though clinically they may suggest acute nephritic syndrome, the long history, urinary findings such as isosthenuria, presence of granular casts and evidence of uremic features should suggest the diagnosis.

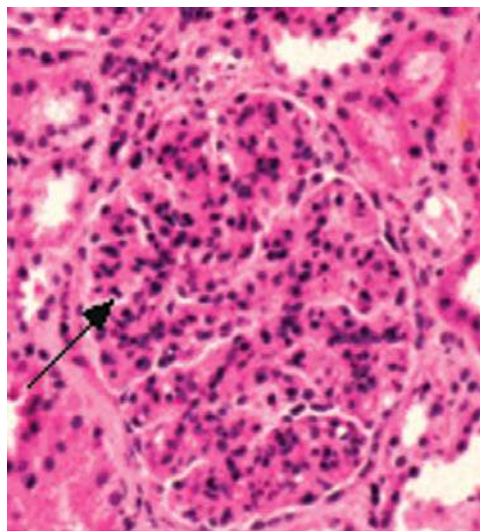


Fig. 170.1: Renal biopsy poststreptococcal glomerulonephritis: Note enlargement of the glomeruli, increase in cellularity and occlusion of capillary lumen, polymorphonuclear infiltrates

Diagnosis is confirmed by urinary findings and biochemical examination of blood. Etiological diagnosis is made by estimating serum complement levels, isolation of the organisms, estimation of ASO titer and renal histology. Reduction in serum complement levels and demonstration of the pattern of immune complex deposition in histological specimens by immunofluorescence microscopy are diagnostic of the different types of immune mediated glomerulonephritis. Poststreptococcal glomerulonephritis is usually associated with coarse granular immune deposits. In conditions like Goodpasture's syndrome, linear ribbonlike immune deposits are seen along the glomerular basement membrane.

Renal biopsy is not routinely indicated in all cases of acute post-streptococcal glomerulonephritis especially in children. It is indicated under the following conditions: (1) failure to recover promptly, (2) persistence of hypertension, azotemia and hematuria and (3) possibility of systemic diseases like vasculitis and collagen diseases (Fig. 170.1).

Course and prognosis: In 90% of children recovery is uneventful and complete even though the proteinuria and microscopic hematuria may persist for a few weeks or months. Some children develop nephrotic syndrome or chronic glomerulonephritis. Advanced irreversible renal failure may develop in 2-5% of cases in the acute phase. During recovery any intercurrent infection may precipitate transient exacerbation of the clinical and urinary abnormalities. In adults uneventful recovery occurs only in 50%. In the rest, acute renal failure, hypertension, nephrotic syndrome or chronic glomerulonephritis progressing to renal failure develop in varying proportions.

Management: Since in the vast majority of patients, acute nephritic syndrome is self-limiting, only fluid restriction and close observation are required. As in the case of acute renal failure, bed rest, maintenance of fluid and electrolyte balance and adequate nutrition with carbohydrate and fat calories form the basic principles of therapy.

Complications arising during the course of the disease, such as hypertensive encephalopathy, cardiac failure with pulmonary edema, hyperkalemia and uremia demand active intervention.

The hypertension occurring in acute nephritic syndrome is often self-limiting and in most cases does not require any long-term treatment. If the diastolic blood pressure is over 90 mmHg and hypertensive complications are imminent, hydralazine, methyldopa, nifedipine, amlodipine or atenolol have to be used in adequate doses. If blood pressure rises rapidly or hypertensive encephalopathy occurs, parenteral labetalol or nitroglycerine has to be given. Nifedipine administered through buccal mucosa helps to bring down the blood pressure rapidly and smoothly. The blood pressure can be maintained by the same drug or other drugs given orally. If convulsions continue in spite of antihypertensive therapy more aggressive measures to control the convulsions may be needed. Pulmonary edema is to be treated on the usual lines of left ventricular failure. Sedation with diazepam 10 mg given intravenously, oxygen inhalation, frusemide in large doses (100-200 mg IV) and slow intravenous injection of aminophylline are helpful. If the diuretics do not bring about diuresis, pulmonary congestion can be effectively relieved by physiological venesection by applying tourniquets to the proximal parts of the limbs to prevent venous return. Dialysis or ultrafiltration should be employed to remove the excess of fluid in these cases. A course of penicillin is indicated if there is active infection by streptococcus.

SPECIAL TYPES OF ACUTE NEPHRITIC SYNDROME

Goodpasture's Syndrome

This is a typical example of anti-GBM-antibody mediated glomerulonephritis. Antibodies against the glomerular basement membrane (GBM) and pulmonary capillary basement membrane are produced. These attach to the respective basement membranes and set up inflammatory reaction. In the glomerular capillary basement membrane the antibody appears as a linear deposit on immunofluorescence microscopy. This stands out in sharp contrast to the granular deposit of immune complexes seen in post-streptococcal acute glomerulonephritis. Renal histology shows proliferation of the epithelial cells of the Bowman's capsule giving rise to the appearance of crescents. The disease presents with pulmonary symptoms such as

hemoptysis and features of acute glomerulonephritis. The prognosis is generally unfavorable. Large doses of corticosteroids and immunosuppressive drugs have been tried but the results are not uniformly good.

Other Conditions

Systemic lupus erythematosus, polyarteritis nodosa, Henoch-Schönlein syndrome, and infective endocarditis may give rise to acute nephritic syndrome during their course. Other evidences of the underlying disease are generally present. Treatment is for the primary disorder. Renal manifestations also usually subside when the primary condition resolves. In lupus and Henoch-Schönlein purpura, the renal lesion may persist in many and lead to renal failure later. Renal involvement is a major factor deciding long-term prognosis in these disorders.

Nephrotic Syndrome

Ramdas Pisharody, M. Sreelatha

Definition

Nephrotic syndrome (NS) is a condition characterized by heavy proteinuria of $>3.5 \text{ g/1.73m}^2$ body surface area in 24 hours, often associated with hypo-albuminemia, edema, hyperlipidemia and a hypercoagulable state.

ETIOLOGY

NS can be due to primary (idiopathic) glomerular diseases, or may be secondary to a large number of identifiable diseases (Table 170.1).

PATHOPHYSIOLOGY

The glomerular filtration barrier consists of 3 layers: fenestrated endothelial cells, the GBM and epithelial slit diaphragms. Movement of molecules across this barrier depends on the size, electrical charge, configuration, shape and deformability of the molecule. The structural integrity of GBM and glomerular hemodynamics are the other factors controlling the filtration. Under normal conditions, the GBM has an electronegative charge and this repels the negatively charged albumin molecules. Thus, leakage of albumin is prevented. In minimal change disease (MCD), there is loss of the negative charge of GBM allowing more of albumin to be filtered. This is known as *charge selective proteinuria*. In most other glomerular diseases, there is structural damage to GBM leading to alteration in the size selective barrier function. Thus, all substances below a particular molecular size are filtered. This is known as *non-selective proteinuria*.

Hypoalbuminemia is a cardinal feature of NS. This is due to urinary loss of albumin and albumin catabolism in

TABLE 170.1

Etiology of NS

1. Primary glomerular diseases (Idiopathic NS)
1. Minimal change disease (MCD)

2. Focal segmental glomerulosclerosis (FSGS)

3. Membranous nephropathy (MN)

4. Membranoproliferative glomerulonephritis (MPGN)

5. Mesangioproliferative glomerulonephritis (Mes. PGN)

6. IgA Nephropathy
2. Secondary nephrotic syndrome
1. Infections

Bacterial: Post streptococcal glomerulonephritis, infective endocarditis, shunt nephritis, syphilis, tuberculosis, chronic bacterial infections

Viral: Hepatitis B, hepatitis C, cytomegalovirus, Epstein Barr virus, HIV

Protozoal: Quartan malaria, toxoplasmosis

Helminthic: Schistosomiasis, trypanosomiasis, filariasis

2. Neoplasms

Solid tumours: Lung, colon, stomach and breast, leukemia, lymphoma

3. Drugs: Penicillamine, gold, mercury, nonsteroidal anti-inflammatory drugs (NSAIDs), captopril, probenecid, trimethadione, alpha-interferon, lithium

4. Multisystem diseases: Systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), dermatomyositis, rheumatoid arthritis (RA), Henoch Schonlein purpura (HSP), mixed cryoglobulinemia, sarcoidosis, light chain and heavy chain diseases, amyloidosis

5. Heredo-familial and metabolic diseases: Diabetes mellitus, myxedema, Graves' disease, Fabry's disease, congenital nephritic syndrome, Charcot-Marie-Tooth syndrome, Hurler's syndrome, familial nephrotic syndrome, lipoprotein glomerulopathy

6. Miscellaneous: Pre-eclampsia, malignant nephrosclerosis, chronic allograft nephropathy, obesity, reflux nephropathy, Castleman's disease, Kimura disease.

the proximal tubule. Hepatic albumin synthesis is increased in nephrotic patients. Along with albumin several other plasma proteins are also lost in urine. These include IgG, erythropoietin, complement, thyroxine Vit D binding globulins, some of the procoagulant factors and also anticoagulant factors like antithrombin III. This predisposes the patients with nephrotic syndrome to repeated infections, hypothyroidism, anemia and thrombosis.

Generalized edema and facial puffiness are the cardinal symptoms of nephrotic syndrome. Effusions into serous cavities occur. The severity of edema depends on severity of proteinuria, duration of disease, type of glomerular disease, dose of diuretic and intake of salt and fluid by the patient. Oliguria due to renal hypoperfusion is common especially in the acute phase. The edema formation in nephrotic syndrome is explained by the ‘underfill and overfill’ hypothesis. In the ‘underfill’

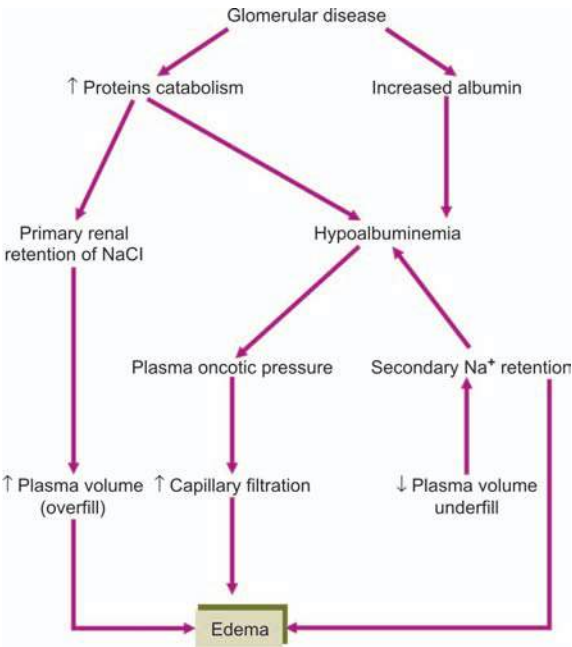
hypothesis the hypoalbuminemia and decreased plasma oncotic pressure cause underfilling of the vascular system. Fluid accumulates in the interstitial space. The rennin-angiotensin-aldosterone system is stimulated causing further salt and water retention and aggravation of edema. In ‘overfill’ hypothesis there is primary reabsorption of sodium and chloride by the renal tubules with resultant edema. This is further aggravated in the setting of reduced GFR (Flow chart 170.1).

Hyperlipidemia is common in NS with marked elevation of plasma LDL, VLDL, intermediate density lipoproteins (IDL) and lipoprotein-a (Lp(a)) and lowering of HDL concentration. LDL and VLDL increase as a result of increased synthesis in liver and this is linked to lipoprotein synthesis. The urinary loss of lipoprotein lipase, an enzyme involved in degradation of lipids contributes to an increase in VLDL. HDL levels are lowered due to losses in urine. Hyperlipidemia not only leads to early atherosclerosis but also contributes to the progression of renal disease. Hyperlipidemia reverts to normal when nephrotic syndrome undergoes remission. *Dietary restriction does not improve the lipid abnormalities in nephrotics.* Lipid lowering therapy is indicated only if the course of nephrotic syndrome is prolonged or if the patient has steroid resistant nephrotic syndrome. Statins are preferred as lipid lowering agents in nephrotic syndrome.

Minimal Change Disease

This disease first described in 1913 was called “*Lipoid Nephrosis*” or “*Nil Disease*”. It constitutes 80-90% of nephrotic syndrome in children under the age of 10 and

Flow chart 170.1: Showing the pathogenesis of edema



about 20% of primary NS in adults. The male: female ratio is 3:2 in children and 1:1 in adults. The exact pathogenesis is not known. Immunological injury with involvement of both cell mediated and humoral immune mechanisms are responsible.

The cardinal clinical feature of MCD is generalized edema. Facial edema is noted first. Edema becomes clinically evident when more than 5 liters of fluid accumulate in the interstitial compartment. Since the intravascular volume is low or normal, the patients are not dyspneic or orthopneic except when they have serous effusions. Usually there is no hypertension, hematuria or renal failure. Reversible acute renal failure may occur due to acute tubular necrosis caused by extreme intravascular volume contraction; diuretic (frusemide) induced acute interstitial nephritis, renal vein thrombosis or severe renal interstitial edema.

Ideally all adults with nephrotic syndrome should be subjected to renal biopsy before starting treatment. However, a patient with nephrotic syndrome may be given a course of treatment with corticosteroids before considering renal biopsy in the absence of hematuria, hypertension and renal failure. Biopsy should be done if response to steroids is inadequate and more powerful drugs are to be used.

The renal biopsy is essentially normal on light microscopy (Fig. 170.2). Immunofluorescence (IF) studies show absence of immune deposits in MCD. Faint mesangial staining for IgM and component C1q may be encountered in variants of MCD. These are catagorized as 'IgM mesangial nephropathy', and 'C1q nephropathy', respectively. The only structural abnormality seen under electron microscopy (EM) is the extensive effacement of foot processes of the podocytes (Fig. 170.3).



Fig. 170.2: The glomeruli appear normal under light microscopy in minimal change disease. Note the normal cellularity, open capillary lumen, normal capillary wall and normal Bowman's capsule

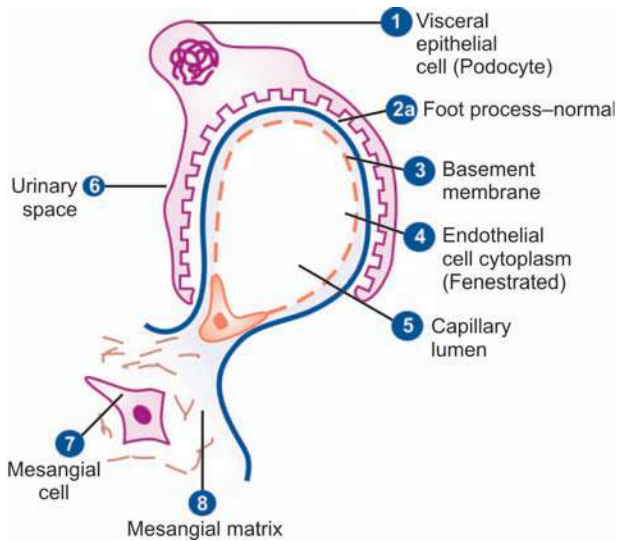


Fig. 170.3A: Line drawing showing normal capillary loop

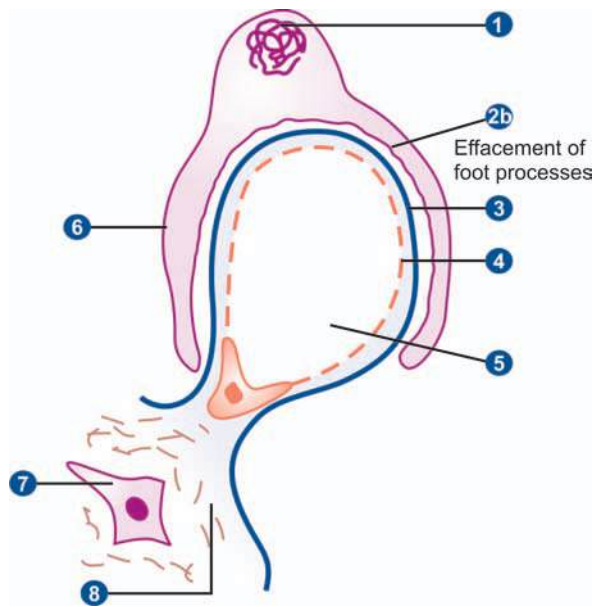


Fig. 170.3B: Line drawing showing effacement of foot process in minimal change disease

MANAGEMENT

General treatment measures for the control of edema include, fluid restriction, low sodium diet and rest in recumbancy. Rest helps to mobilize the fluid from the extracellular to the intravascular compartment. Aggressive diuretic therapy is avoided since it may precipitate intravascular volume depletion, hypotension and acute tubular necrosis. If the patient has very low intravascular volume, intravenous administration of plasma or IV albumin with frusemide will help to temporarily improve the intravascular volume and make the diuretic more effective. Human albumin is given as a 20% solution

100-200 mL IV as slow infusion until the plasma albumin rises above 2.5 g/dL or diuresis is established. Other temporary measures to relieve resistant edema include standing neck deep in water for about one hour in the morning and evening (head-out water immersion) and graded pressure elastic stockings. Both procedures result in increase in the interstitial fluid hydrostatic pressure causing movement of fluid from the extravascular to the intravascular compartment.

The diet should be of normal protein with low fat. Salt and water should be restricted. The total allowance of fluid should be 400-600 mL less than the previous 24-hours urine volume so as to effect a weight reduction of 400-600 g/day. Long-term anticoagulation is required in those who had episodes of venous thrombosis or even a single episode of arterial thrombosis.

Specific Treatment

The drug of choice for the treatment of minimal change disease (MCD) is corticosteroid. The accepted guidelines for the treatment of the first attack are as follows.

Prednisolone 60 mg/m²/day (maximum dose 80 mg per day) is given as a single morning dose for a period of 4-6 weeks. If the patient goes into remission, the dose is reduced to 40 mg/m² on alternate days and continued for 4-6 weeks. The dose is then tapered stepwise every 2 weeks and discontinued by 8-12 weeks. About 80% of adults and 95% of children undergo complete remission of proteinuria within 6-8 weeks. In some adults the response may be delayed up to 16 weeks even on full dose of daily steroids.

Depending on the response to steroids, the nephrotic patients can be classified as *primary responder*, *frequent relapser*, *steroid dependent* and *steroid resistant*. The term *steroid response* is defined as reduction of proteinuria to less than 4 mg/kg/day (<200 mg/day) for 3 consecutive days. Early responder is one who goes into remission within 4 weeks of standard steroid therapy. Late responder is one who undergoes remission within 16 weeks. The term persistent remission indicates sustained remission for 18-24 months. The term relapse indicates occurrence of proteinuria of more than 3+ for 3 consecutive days even without edema or more than 1 g per day after achieving remission. If two or more relapses occur within 6 months or more than three relapses occur in a year, it is termed frequent relapse. The term infrequent relapse indicates occurrence of less than 2 in 6 months or less than 3 in a year. Steroid dependence is defined as the occurrence of relapse within 2 weeks of stopping steroids or while tapering steroids on at least 2 consecutive occasions. In primary steroid resistance there is no response in spite of 16 weeks of full dose daily steroids. The term secondary steroid resistance indicates the condition in which a primary responder fails to respond during a subsequent relapse despite 16 weeks of full dose steroids.

In adults with MCD, 40% are frequently relapsing, 30% steroid dependent and 10% steroid resistant. Patients with frequently relapsing NS and steroid dependent NS must be treated with a combination of low dose steroids and cytotoxic drugs like cyclophosphamide (2-3 mg/kg/day) or chlorambucil (0.1-0.2 mg/kg/day) given for 12 weeks. Cyclosporin in doses of 5-6 mg/kg/day may be considered if response to steroid is inadequate. It is expensive and withdrawal may be associated with relapse. Levamisole is used as an adjunct to low dose maintenance steroids in children with frequently relapsing NS. Steroid resistant MCD occurs in less than 7% of children and 15% of adults. They should be treated with antiproteinuric drugs like angiotensin converting enzyme inhibitors or angiotensin receptor blockers. Progression of MCD to renal failure is rare. Spontaneous remissions may occur in 25% of cases on long-term follow-up.

Focal Segmental Glomerulosclerosis (FSGS)

FSGS accounts for 30% of nephrotic syndrome in adults and 50% of all steroid resistant cases. Most cases of FSGS eventually develop kidney failure over a period of 10 to 20 years. When end stage renal disease occurs within 3 to 5 years, it is termed malignant FSGS.

Classification of FSGS

- Primary (idiopathic) FSGS
- Familial FSGS
- Secondary FSGS
 1. Due to glomerular maladaptation and reduced nephron number
 - Reflux nephropathy
 - Oligomeganephronia
 - Obesity
 - Unilateral renal agenesis
 - Sickle cell disease
 - After removal of one kidney
 2. HIV associated nephropathy
 3. Heroin induced nephropathy
 4. Secondary to focal proliferative GN
 5. Treatment with palmidronate, interferon and sirolimus.

Pathogenesis of FSGS

The pathogenesis of focal segmental glomerulosclerosis is poorly understood. Injury to the visceral epithelial cell (podocyte) in the glomerular tuft is an important factor. A circulatory factor which increases the permeability of the glomerular filter leading to sclerosis has been identified. The same factor is responsible for the recurrence of original disease in the transplanted kidney in some cases of FSGS. HLA associations and aberrations of single genes have been identified in familial forms of FSGS.

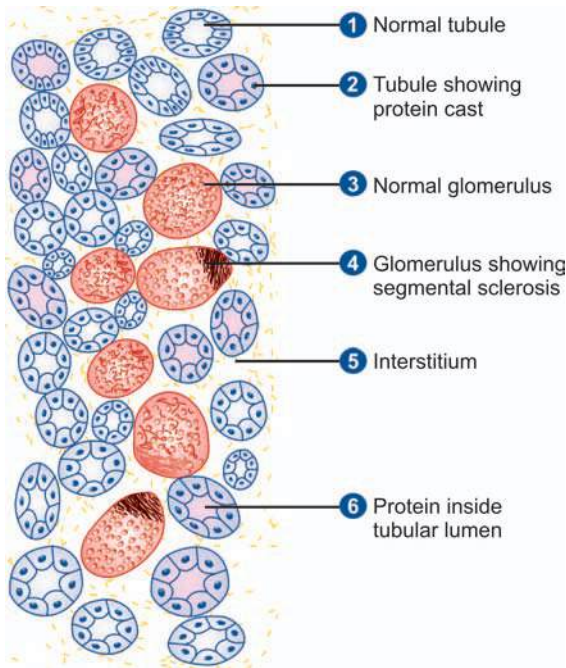


Fig. 170.4: Diagram showing focal and segmental glomerular involvement

Note: 3 out of 7 glomeruli are affected. They show sclerosis involving < 50% of the glomerular capillary tuft

Pathology

In 'classic FSGS', sclerosis is focal involving < 50% of the glomeruli and segmental involving < 50% of the glomerular tuft (Fig. 170.4). The remaining part of the glomerular tuft and the other glomeruli are normal (Fig. 170.5). If the biopsy sample does not contain adequate number of glomeruli, the diagnosis of FSGS may be missed. Two important clues in the biopsy favour the diagnosis. They are abnormally enlarged glomeruli, presence of interstitial fibrosis and tubular atrophy. Immunofluorescence study may show nonspecific IgM deposits. Under EM there is foot process effacement in sclerotic and nonsclerotic glomeruli. Depending on histological variations, FSGS is subclassified as (a) classic (b) collapsing (c) cellular (d) tip lesion and (e) peri hilar FSGS.

Adverse prognostic factors are elevated serum creatinine, hypertension at the onset, massive proteinuria exceeding 10 gm/day, steroid non-responsiveness, persistent nephrotic state, cellular lesions and interstitial scarring involving more than 25% of the biopsy tissue.

Clinical Features and Treatment

Most patients present with sub-nephrotic or nephrotic proteinuria. Nearly half of the patients have microscopic hematuria, hypertension or elevated serum creatinine at presentation. Treatment is with steroids given in daily

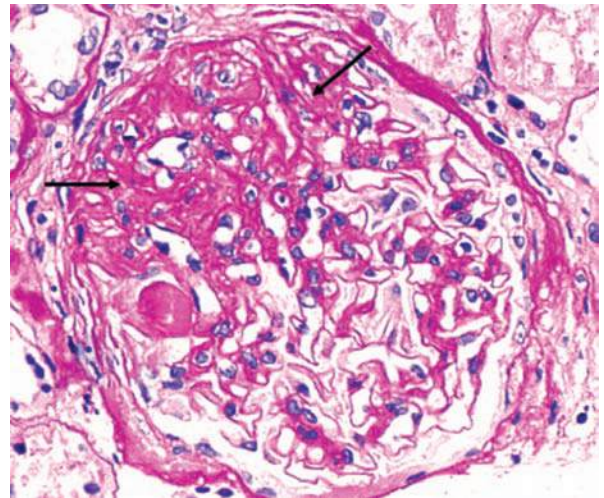


Fig. 170.5: Light microscopy of focal and segmental glomerulosclerosis showing a segment (< 50%) of glomerular capillary tuft showing sclerosis (arrows) and the remaining part of the glomeruli remaining normal

doses of 1 mg/kg body weight for at least 6 months. Steroid response rate is only 30%. In resistant cases, immunosuppressive drugs like cyclosporine have to be added. ACEI and ARB have anti-proteinuric effect and are useful in steroid resistant cases.

Recurrence of FSGS in the transplanted kidney may occur in 30-40% of patients. Recurrence often occurs within 3 months of transplantation. Secondary FSGS may occur when there is loss of more than 70% of the functioning nephrons. The remaining nephrons hypertrophy and hyperfilter and undergo progressive damage.

Membranous Nephropathy

Membranous nephropathy (MN) is the most common cause of adult-onset NS accounting for about 50% of the cases. In children the frequency is 5-7%. The peak incidence is in 4th and 5th decades of life. Male to female ratio is 2:1.

Causes of Membranous Nephropathy

1. Idiopathic MN
2. Secondary MN

Infections: Hepatitis B, Hepatitis C, syphilis, *Plasmodium malariae*, leprosy, filariasis, chronic suppurative infections.

Neoplasia: Solid tumours: Colon, lung, rectum, sarcomas, lymphomas, leukemias.

Drugs: Penicillamine, gold, mercury, probenecid, lithium, NSAIDs.

Autoimmune disorders: Systemic lupus erythematosus, rheumatoid arthritis, mixed connective tissue disease,

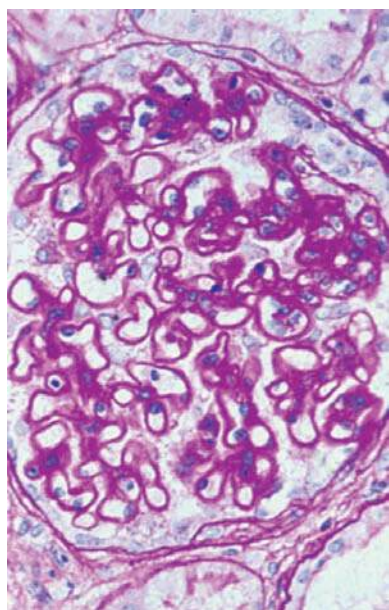


Fig. 170.6: Membranous nephropathy. Note thickened capillary wall due to immune deposits on the subepithelial side of the BM. Over growth of BM between the deposits as spikes

autoimmune thyroiditis, sarcoidosis and dermatitis herpetiformis.

Miscellaneous: Renal transplantation, diabetes mellitus, Sjögren's syndrome, renal vein thrombosis, bullous pemphigoid.

Pathophysiology

The characteristic histologic abnormality under light microscopy is diffuse global capillary wall thickening in the absence of significant glomerular hypercellularity (Fig. 170.6). The capillary wall thickening is due to subepithelial immune deposits and overgrowth of the basement membrane around it. This is best demonstrated with silver-methanamine staining as 'spike and dome' appearance (Fig. 170.7). It shows diffuse granular capillary wall staining for IgG and C3. Clq staining is uncommon. Electron microscopy demonstrates the typical subepithelial immune deposits. Tubular basement membrane staining for IgG or complement and occurrence of mesangial dense deposits under EM suggest the possibility of secondary MN.

Clinical Features and Natural History

NS is of insidious onset. Hypertension and microhematuria are present in 30-50% cases. Most patients present with normal or slightly decreased renal function. The adverse prognostic factors in MN are male gender, age >50 years, severity of NS, persistence of NS for >6 months, low GFR at presentation, significant

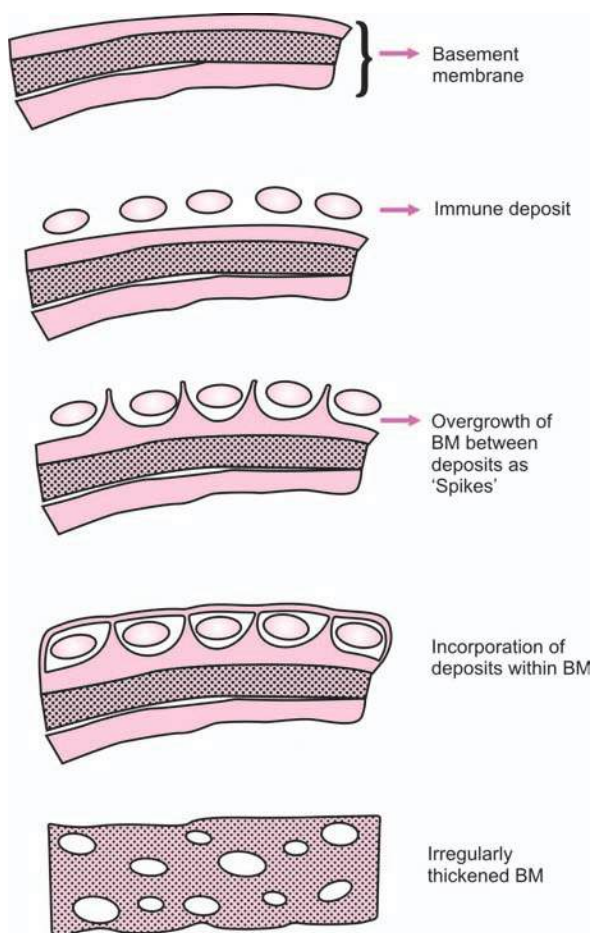


Fig. 170.7: Diagram showing the processes in the basement membrane thickening

tubulointerstitial damage, crescents and segmental sclerosis. Of these, persistence of the nephrotic state for over 6 months is the most serious adverse factor. Women, children and young adults have relatively better prognosis. About 30% of patients undergo spontaneous remission, 30% progress to renal failure and 30% have variable degrees of proteinuria, but stable renal function. Ten percent die of non-renal causes. Rarely, spontaneous remission may occur after 36-48 months.

Treatment

Low risk patients with normal renal function and proteinuria < 4 g/day require only blood pressure control and anti-proteinuric measures. ACEI or ARBS are the drugs of choice since they act in both ways. Medium risk patients with normal or near normal renal function and proteinuria between 4-8 g/day are treated with the 'Ponticelli regimen'. This consists of pulse doses of IV methyl prednisolone 1 g/day for the first 3 days of every month for 6 months and daily oral methyl prednisolone 0.4 mg/kg/day or prednisolone 0.5 mg/kg/day in the first

month. During the next month, chlorambucil 0.2 mg/kg/day is given in place of prednisolone. Oral prednisolone and chlorambucil are used every alternate month for 6 months. More patients attain remission or remain with stable renal function with this regimen. Cyclophosphamide in a dose of 1.5-2.5 mg/kg/day can be used as an alternate drug instead of chlorambucil. Alternatively, cyclophosphamide and prednisolone are given simultaneously for 6 months.

High risk patients who have deteriorating renal function and/or proteinuria >8 gm/day should be treated with prednisolone and immunosuppressants. Cyclosporin is given in a dose of 4-5 mg/kg/day for a period of 6-12 months.

All the patients should be given supportive treatment with dietary protein restriction, control of hypertension, hyperlipidemia, and use of ACEI or ARBS as anti-proteinuric agents, oral anticoagulant therapy is also used as primary prevention for venous thrombosis in high-risk patients with serum albumin < 2 g/L. Immunosuppressive therapy is not indicated in patients with serum creatinine >4.5 mg and in those with severe chronic changes in biopsy.

Membranoproliferative Glomerulonephritis (MPGN) (Mesangio-capillary GN)

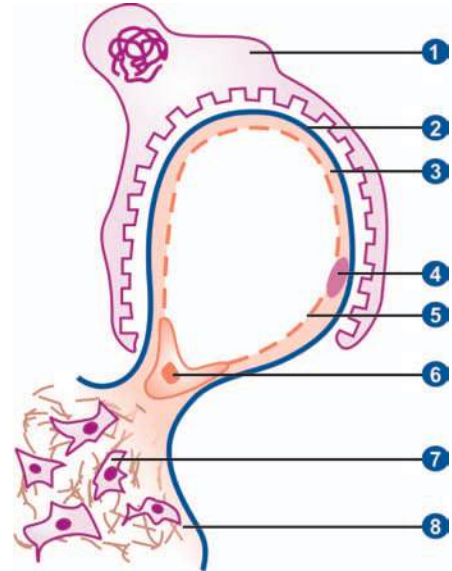
MPGN is common in children between ages of 8-16 years. There is an equal proportion of males to females.

Causes of MPGN

- I. Idiopathic MPGN → Type I, II, III
- II. Secondary MPGN:
 - Infection: Hepatitis B and C, chronic deep seated abscesses, infective endocarditis, shunt nephritis, malaria, schistosomiasis.
 - Rheumatologic diseases: SLE, scleroderma, Sjögren's syndrome, sarcoidosis, essential mixed cryoglobulinemia.
 - Malignancy: carcinoma, lymphoma, leukemia.
 - Inherited disorders: Deficiencies of α_1 antitrypsin and complements C2 and C3.

Pathogenesis

Type I MPGN is an immune complex disease but specific antigens have not been identified. The immune complex formed leads to inflammation through complement activation and proliferation of mesangial cells, endothelial cells and infiltration by inflammatory cells. In MPGN Type II, the pathogenesis is related to IgG auto-antibodies known as C3 nephritic factor (C3 NeF) which is directed against the enzyme C3 convertase. In the alternate



1. Visceral epithelial cell
2. Basement membrane
3. Interposition of mesangium between endothelial cell and basement membrane—causing thickening a capillary wall. Basement membrane is not thickened
4. Mesangial cell invading capillary wall
5. Fenestrated capillary endothelial cell cytoplasm
6. Endothelial cell
7. Increase in number of mesangial cell
8. Increase in mesangial matrix

Fig. 170.8: Line drawing showing interposition of mesangium between basement membrane and endothelium in MPGN

pathway of complement activation, C3 NeF mediates C3 breakdown leading to persistent activation of complement cascade. Hypocomplementemia is a characteristic feature of all types of MPGN. In Type I, C3 is used up for immune complex formation, and in Type II, it is continuously broken down by C3NeF.

Histology shows glomerular hypercellularity with 'double contour' appearance of GBM due to mesangial overgrowth and interpositioning in the subendothelial space of the capillary wall (Fig. 170.8). The glomeruli are enlarged and there is lobular accentuation. The proliferation is typically uniform and diffuse in idiopathic MPGN. In a few patients, crescents involving >50% of glomeruli are seen. On immunofluorescence, IgG, IgM and C3 are present on the capillary wall and mesangium.

Type II MPGN also known as 'Dense Deposit Disease', is characterized by thickening of the basement membrane due to deposition of highly refractile and eosinophilic intramembranous deposits. These deposits give the appearance of a 'string of sausages'. Immunofluorescence (IF) shows C3 deposits on the capillary wall. Type II MPGN is rarer than Type I, accounting for 15-25% of all MPGN cases. Type II MPGN may show crescentic glomerulonephritis and chronic tubulointerstitial changes on biopsy (Table 170.2).

TABLE 170.2

Differences between Type I and Type II MPGN

Type I	Type II
Mainly nephrotic presentation	Nephritic presentation more common
C3 NeF in 20%	C3 NeF in 70-80%
Terminal nephritic factor +ve in 30%	Terminal nephritic factor – Not present
Circulating immune complex in 60-70%	Circulating immune complex in 30-40%
Classical pathway of complement activation	Alternate pathway of complement activation
Recurrence in graft 30%	Recurrence in graft 100%

Type III MPGN shows, in addition to subendothelial and mesangial deposits, numerous subepithelial deposits as well.

Clinical Features and Natural History

MPGN constitutes 10 to 15% of NS in childhood and adolescence. Patients present with combined features of acute nephritic and nephrotic syndrome. It usually presents with edema, hypertension, hematuria and renal insufficiency. Respiratory tract infections may precede MPGN in 50% of patients. Persistent hypocomplementemia is the hallmark of MPGN. Partial lipodystrophy is sometimes seen in patients with complement deficiency and MPGN.

Course and Prognosis

Usually MPGN has a downhill course. The prognosis of Type II disease is worse compared to that of Type I.

Clinical remissions are very rare in Type II and patients reach ESRD by 8-10 years from onset.

Treatment

A third of patients with Type I MPGN may have spontaneous remission, a third has progressive disease and the rest show a waxing and waning clinical course without full recovery. Drug treatment offers only limited success.

Guidelines for the Treatment of MPGN

In children with non-nephrotic proteinuria and normal renal function, a trial of prednisolone 1mg/kg on alternate days is given for 3 months. If the renal function is abnormal, steroids may have to be continued for a longer period.

In adults, no specific treatment is recommended, but the patient is kept under periodic follow-up. If renal failure is present, aspirin 325 mg daily may be given for 6-12 months. ACEI and ARB help to reduce proteinuria.

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Tubulointerstitial Nephritis

A. Vimala

Chapter Summary

- Introduction 1131
- Classification 1132
- Pathogenesis and Pathology 1132
- Acute Tubulointerstitial Nephritis 1133
- Chronic Tubulointerstitial Nephritis 1133

Introduction

Tubulointerstitial nephritis (TIN) includes a spectrum of diseases of different etiologies that primarily involve the interstitium. This is different from the changes occurring in the interstitium secondary to glomerular disorders. The patient can present with acute or chronic

interstitial nephritis. Many forms of tubulointerstitial injury may result from exposure to drugs or other nephrotoxic agents and infections.

Classification

Tubulointerstitial nephritis may be broadly classified as acute and chronic (Table 171.1).

Pathogenesis and Pathology

The pathogenetic mechanism in acute and chronic TIN is the same. Lethal or sublethal injury to renal cells leads to expression of new local antigens, inflammatory cell infiltration, and activation of proinflammatory and chemoattractant cytokines. These cytokines are produced by inflammatory cells such as macrophages and lymphocytes and also by the renal cells such as proximal tubular cells, vascular endothelial cells, interstitial cells and fibroblasts. The outcome can be acute or chronic TIN. The histopathology of acute TIN is shown in Figure 171.1. The interstitium shows inflammatory cell infiltrate. In chronic TIN there is tubular atrophy, interstitial scarring and fibrosis (Fig. 171.2). Glomeruli are normal in primary TIN till advanced stages of the disease.

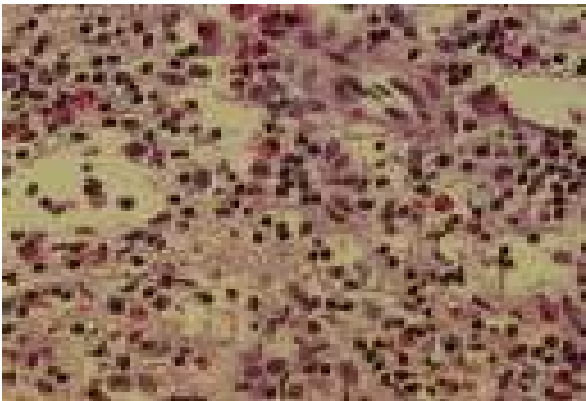


Fig. 171.1: Acute interstitial nephritis in renal biopsy. Note: Interstitial edema with infiltration with eosinophils and some cells even in the lumen of renal tubules. No glomeruli are seen in this high power view. They appear normal in acute interstitial nephritis

TABLE 171.1

Causes of tubulointerstitial nephritis	
1. Acute tubulointerstitial nephritis	
Drugs	
•	Nonsteroidal anti-inflammatory drugs [NSAIDs] nimuselide, ibuprofen, diclofenac, indomethacin, Cox2 inhibitors
•	Antibiotics – rifampicin, penicillins, sulfa drugs
•	Diuretics – thiazide, frusemide
•	Anticonvulsants – phenytoin, valproate
•	Miscellaneous – indinavir, captopril, allopurinol
Infections	
•	Spirochetes: leptospirae
•	Bacterial: acute bacterial nephritis
•	Viral: cytomegalovirus [CMV], Hantavirus, HIV
•	Fungal: histoplasmosis
•	Parasitic: lymphatic filariasis
•	Immunologic diseases – Lupus erythematosus, Goodpasture's syndrome, Sjögren's syndrome, acute transplant rejection
2. Chronic tubulointerstitial nephritis	
•	Analgesic nephropathy, cyclosporin nephrotoxicity
•	Drugs: lithium, tacrolimus
•	Heavy metals: lead, cadmium, mercury
•	Obstructive nephropathy, nephrolithiasis, reflux nephropathy
•	Immunologic diseases: lupus erythematosus, Sjögren's syndrome, amyloidosis
•	Primary glomerulopathies, sarcoidosis, vasculitides such as - antineutrophil cytoplasmic antibody vasculitis and Wegener's granulomatosis
•	Chronic transplant nephropathy
•	Neoplasia: myeloma, leukemia
•	Sickle cell anemia
•	Atherosclerotic kidney disease (ischemic) - cholesterol microembolism
•	Metabolic diseases: hypercalcemia, cystinosis, hypokalemic nephropathy, hyperoxaluria
•	Genetic disorders: Alport's syndrome, medullary cystic disease
•	Miscellaneous: Balkan endemic nephropathy, Chinese herbal/Aristolochia nephropathy and other toxins.

Clinical consequences of functional disturbances of interstitium is shown in Table 171.2.

TABLE 171.2

Clinical consequences of TIN	
Functional disturbance	Clinical consequence
Damage to proximal tubule	Type II renal tubular acidosis (RTA), Fanconi's syndrome (phosphaturia, renal glycosuria, aminoaciduria, bicarbonaturia and RTA
Damage to distal tubule	Type I renal tubular acidosis, salt wasting, hypokalemia
Damage to medullary tubules and vasculature	Polyuria, isosthenuria
Obstruction to tubules	Reduction in GFR



Fig. 171.2: Chronic interstitial nephritis in renal biopsy. Note: The glomerulus is near an area of interstitial scar and shows segmental area of sclerosis (arrow). There is scarring and tubular atrophy. Some tubules are relatively normal

Acute Tubulointerstitial Nephritis

Acute renal failure is the most common presentation of acute tubulointerstitial nephritis. Renal failure is usually non-oliguric but rarely can present with anuria. Patients commonly present with rash, fever, arthralgia, arthritis, eosinophilia, eosinophiluria, and elevated immunoglobulin E (IgE) levels. Renal involvement can be subtle and the only manifestation may be hematuria or Fanconi's syndrome. Urinalysis may show microscopic hematuria and/or sterile pyuria with or without eosinophils. Proteinuria is usually less than 2 g in 24 hours. Nephrotic syndrome does not occur. Renal biopsy is required to make a definite diagnosis. Withdrawal of the offending agent usually results in complete recovery. In some patients renal failure persists for many weeks before improvement occurs.

Acute Tubulointerstitial Nephritis Caused by NSAIDs

Pathogenesis NSAIDs block the cyclooxygenase pathway and hence cause preferential conversion of arachidonic acid to leukotrienes. This will activate helper T cells, release various inflammatory mediators like cytokines and result in inflammation of the interstitium.

All NSAIDs including specific Cox2 inhibitors can result in TIN. This should be differentiated from hemodynamically mediated ARF which is more common in patients with renal impairment.

Clinical features include rash, fever, arthralgia, arthritis, eosinophilia and eosinophiluria. Patients may have nephrotic proteinuria due to glomerular involvement. Renal biopsy is diagnostic and may show granulomas. Spontaneous recovery occurs within weeks to months of withdrawal of the drug. Topical preparations of these drugs should be stopped as they can be absorbed. Relapse may occur with subsequent administration.

Treatment – If the renal function is markedly deranged, dialysis support is given till recovery occurs. If renal failure persists for more than 2 to 3 weeks after stopping the drug, a short course of steroids may be tried.

Antibiotic-induced Acute TIN

This is usually observed during antibiotic treatment and occurs after initiation of antibiotic therapy. Renal failure develops along with rash, eosinophilia, and eosinophiluria. Sterile pyuria, hematuria, and proteinuria usually <1 g/day occurs. Nephrotic range proteinuria is very rare. Renal biopsy may show eosinophils in the interstitium.

Rifampicin: Intermittent therapy with rifampicin is associated with TIN. It occurs when the antibiotic is reintroduced after an interval. Usually it presents with flu-like syndrome such as fever, arthralgia, skin rash, flank pain, hypertension and oliguria. Some patients may have circulating anti-rifampicin antibodies and immunoglobulin G (IgG) deposits along the tubular basement membranes.

Acute TIN Caused by Miscellaneous Agents

Infections by spirochetal, viral, bacterial and fungal infections may be occasionally associated with acute TIN. Pathogenetic species of leptospirae - *L. interrogans* is a common cause of ARF in several parts of India.

Leptospirosis: ARF in leptospirosis is due to multiple causes. Hypoperfusion of the kidneys from hypovolemia is the most common cause. Leptospirae can traverse the glomerular capillaries, enter the interstitium and cause TIN. The renal failure is usually reversible and it does not progress to chronicity.

Hantavirus, CMV, and HIV are associated with acute interstitial nephritis. In HIV disease, acute interstitial nephritis is usually observed in conjunction with glomerular disease (i.e., focal segmental glomerulosclerosis). Parenchymal invasion by the virus is not always present and other characteristic features such as eosinophilia and fever, are usually absent.

Acute bacterial nephritis: This is due to direct bacterial infection of the kidneys. Patients present with high grade fever, rigor loin pain and anuric renal failure. Kidneys are enlarged and palpable. Ultrasonography shows large kidneys, but CT scan and MRI are diagnostic. It shows micro-abscesses in the medulla. Patients improve with appropriate antibiotic therapy.

Chronic Tubulointerstitial Nephritis

The chronic form is an insidious disease which progresses slowly. Clinical presentation may be as anemia, and /or bone disease. Children may present

TABLE 171.3

Differences between interstitial and glomerular diseases		
Clinical feature	Interstitial disease	Glomerular disease
Edema	Usually absent till late	Edema early
Blood pressure	Normal or low	High
Anemia	Disproportionate to decline in GFR	Proportional to decline in GFR
Bone disease	Rickets / osteomalacia	Not common
Neuromuscular symptoms	More common	Not common
Nephrotic proteinuria	Absent	Pathognomonic
Hematuria	Rare	Dysmorphic RBCs / RBC casts
WBCs in urine	Sterile pyuria, pus cell casts	Usually absent

with failure to thrive, growth retardation and rickets. Evaluation for anemia or rickets may reveal elevated renal parameters.

The differentiating features between glomerular and interstitial disease is shown in Table 171.3.

Analgesic Nephropathy

Analgesic nephropathy is the most common category of chronic interstitial nephritis worldwide. There is higher incidence in women in the sixth and seventh decades of life. This disorder occurs with long-term ingestion of combinations of phenacetin, aspirin, and caffeine or phenacetin-acetaminophen or NSAIDs and acetaminophen. In its most severe form, it is associated with papillary necrosis. The amount of phenacetin-acetaminophen combination required to cause chronic interstitial nephritis has been estimated to be at least 5-6 kg over many years . Clinically, patients with analgesic nephropathy present with renal insufficiency, modest proteinuria, sterile pyuria, and anemia. Diagnosis can be supported by history of heavy analgesic use and features of chronic interstitial nephritis. Microcalcifications at the papillary tips may be demonstrated on CT. It is often associated with uroepithelial malignancies and eventually progresses to end stage kidney disease. Extrarenal manifestations include psychosis, accelerated atherosclerosis, and acid peptic disease. Treatment is supportive and includes discontinuation of analgesic use.

Cyclosporin- and tacrolimus-induced nephropathy:

Chronic tubulointerstitial nephritis is associated with long- term use of cyclosporin. Most kidney transplant recipients have a stable course with mild impairment of renal function, up to 10% of heart transplant recipients develop progressive renal insufficiency and eventually require dialysis. Patchy striped interstitial fibrosis on renal biopsy is diagnostic.

Lead nephropathy: The major consequence of chronic lead poisoning is chronic tubulointerstitial disease usually in the third to fourth decades of life. This is an occupational hazard in painters, welders, smelters and battery workers. The diagnostic triad is chronic TIN, gout and hypertension.

Chinese herb nephropathy and TIN due to drugs from alternative systems of medicine:

Chinese herbal medicines used for weight reduction containing aristolochic acid can produce chronic TIN. Renal biopsies show severe interstitial fibrosis. Some drugs from alternate systems of medicine contain unknown quantities of various heavy metals or other toxic substances which may lead to chronic TIN.

Miscellaneous causes like obstructive uropathy, atherosclerotic kidney disease, cholesterol microembolic disease and metabolic disorders are other causes of chronic TIN.

Chapter Summary

Introduction 1135

Uncomplicated Urinary Tract Infection 1135

Complicated Urinary Tract Infection 1136

Investigations 1136

Introduction

Urinary tract infection (UTI) is a common problem in the community. It is more common in women of childbearing age and in older individuals. Normally, colonization of bacteria in the urinary tract is prevented by numerous defense mechanisms. The flow of urine, the presence of mucus coat in the stratified squamous epithelium, the high concentration of urea in the urine, osmolality, lack of nutrients like glucose in the normal urine and certain normal ingredients like Tamm Horsfall protein prevent the adherence of bacteria to the urothelium. When any of these defense mechanisms are defective, bacteria may adhere to the urothelium, colonise and cause bacteriuria. Depending on the virulence of the organism, manifestations of UTI vary.

UTI is defined as the presence and multiplication of bacteria in the urinary tract. Since contamination of urine with peri-urethral flora occurs, urine collection must be meticulous.

Significant bacteriuria is defined as the presence of 10^5 or more colonies of the same organism per mL of urine in females. In males, since the chances of contamination is less likely, presence of even 10^4 or more of same organism per mL of urine is taken as significant.

Rarely infections of urinary tract without bacteriuria may occur in pyogenic renal abscess, perinephric abscess, prostatitis or infection of renal cysts.

Urinary tract infection may be uncomplicated or complicated, upper or lower. The clinical features, diagnosis, treatment and prognosis vary depending on the organism, site of infection and structural and functional integrity of the urinary tract.

Uncomplicated Urinary Tract Infection

This term denotes the occurrence of infection in a normal urinary tract, unassociated with diseases like diabetes mellitus, analgesic abuse and immunosuppression or recent urological interventions. Females in the reproductive age are more often affected. 80% of the infections are due to *E. coli*. The colonisation of vagina and urethra occurs from the perianal region. They ascend to the bladder and from there to the upper tract. Factors predisposing to infection in women of child bearing age include migration of bacteria from the peri-urethral region to the bladder during sexual intercourse. The use of spermicidal jellies may alter the normal vaginal flora and predispose to infection. Some women have genetically determined increase in the number of receptors for *E. coli* in the urothelial cells. In addition, bacterial fimbriae and production of bacterial products enable adherence of bacteria to the urothelium.

Acute Bacterial Cystitis

This is the most common type of urinary infection in females. In addition to *E.coli*, *Staph. saprophyticus* infection may be encountered in few cases. The typical symptoms are dysuria, increased frequency, urgency, voiding small volumes of urine and lower abdominal and suprapubic pain. The urine may be foul smelling and blood stained. Systemic symptoms like fever, loin pain and tenderness may be absent and does not lead to renal damage.

Urethral Syndrome

These patients have symptoms similar to cystitis, but without significant bacteriuria. This is because the common organisms that produce urethral syndrome like *Ureaplasma urealyticum*, *Mycoplasma hominis*,

lactobacilli and other microaerophilic bacteria do not grow in the conventional cultures.

Urethritis and Vulvovaginitis

The combination of urethritis with vulvovaginitis occurs in sexually transmitted infections like *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Herpes simplex virus*, *Candida* or *Trichomonas* infection. The onset of symptoms is gradual and is often mild in severity. The patient may have foul smelling vaginal discharge and dysuria for a long time. The sexual partners may also have lower urinary symptoms.

Acute Pyelonephritis

This is due to infection of the upper urinary tract. Pathologically the kidneys are swollen. Microscopically they show focal inflammatory reaction with neutrophil and monocyte infiltration, tubular damage and interstitial edema.

It presents characteristically with constitutional symptoms such as high grade fever, chills and rigor, headache, nausea and vomiting. Local symptoms include flank pain, loin tenderness and burning micturition. In severe cases, gram-negative septicemia, shock and renal failure may supervene.

Complicated Urinary Tract Infection

In this condition, there is pre-existing anatomical or functional abnormality of the urinary tract or presence of systemic diseases like diabetes. UTI occurring in males is invariably complicated.

Factors associated with complicated UTI are:

- 1. Diabetes mellitus
- 2. Pregnancy
- 3. Nephrolithiasis
- 4. Neurogenic bladder
- 5. Urinary tract obstruction
- 6. Renal failure
- 7. Vesico-ureteric reflux
- 8. Foreign body in the urinary tract
- 9. Renal transplant recipient
- 10. Instrumentation of urinary tract.

Investigations

Urinalysis: The urine may be turbid, blood stained and foul smelling. The pH of the freshly voided urine depends on the pathogenic bacteria. *E.coli* and *klebsiella* infections cause acid urine. *Proteus* infection causes alkaline urine. Mild proteinuria may be present. Urine microscopy often shows pus cells and pus cell casts. A clean catch

midstream urine specimen is taken before starting treatment. If such specimens are difficult to obtain as in small children a suprapubically aspirated bladder urine specimen is used for culture. Hemogram, blood glucose and renal function tests are done in all cases.

Ultrasonography is performed routinely for all patients since in 5% of patients structural abnormalities are detectable. Such patients require more detailed evaluation. Imaging during the acute phase is necessary mainly to rule out conditions like pyonephrosis, abscesses, perinephric lesions, urinary tract obstruction or presence of air in parenchyma or collecting system. Repeat ultrasonogram done 3-6 weeks after cure of infection helps to identify renal scars.

Other investigations include plain X-ray abdomen to rule out stones or calcifications. Intravenous urography is done to localise calculi in the calyces or pelvis, delineation of the collecting system, obstruction to the drainage system and the presence of papillary necrosis. Medullary sponge kidney, scars developing in reflux nephropathy and congenital abnormalities like cysts and others can be visualized. In addition, the IVU also gives reliable information about renal functional parameters. Computed tomography is required in selected cases to identify small renal abscess, minimal pelvicalyceal dilatation and detection of air and small radiolucent calculi. Isotope renography using Technetium (⁹⁹Tc) labelled dimercaptosuccinic acid (DMSA) is useful to detect severe parenchymal infections and scars. Scans using ⁹⁹Tc labelled diethylenetriamine penta-acetic acid (DTPA) are useful to study the vascularity, function and obstruction to the upper tract. The other investigations which are useful are micturating cystourethrography to rule out vesicoureteric reflux (VUR), urodynamic studies to assess the bladder pressure, sphincter tone, and cystoscopy to visualize the bladder.

Cystoscopy is indicated in older patients with severe hematuria in order to exclude bladder cancer. Patients with recurrent or persistent unexplained frequency and dysuria who have sterile urine also require this investigation.

Treatment

Regimen is shown in Table 172.1.

Relapsing infection is defined as recurrence of symptoms and bacteriuria with the same organism within three weeks of treatment. The urine culture at the end of treatment is usually negative. Relapse indicates failure to eradicate the organism. Such patients have to be investigated further and carefully followed up. Patients given single dose therapy may harbor the organisms in the periurethral area

Reinfection is defined as infection with a different organism after 7-10 days of treatment. This is more common than relapse. Reinfection with the same bacterial

TABLE 172.1

Treatment of bacterial urinary tract infection				
Condition	Common pathogens	Associated conditions	Treatment schedules	Duration
Uncomplicated acute cystitis in women	<i>E.coli</i> , <i>Staph.saprophytics</i> , <i>Proteus mirabilis</i> , <i>Klebsiella pneumoniae</i>	Nil	Trimethoprim + sulphamethoxazole, fluoroquinolones	3 days
Uncomplicated acute pyelonephritis in women	<i>E.coli</i> , <i>Klebsiella</i> <i>Staph.saprophyticus</i>	Nil	Amoxycillin, nitrofurantoin, cephalosporins	7 days
Complicated acute cystitis in women	<i>E.coli</i> , <i>Staph. saprophyticus</i> , <i>Proteus mirabilis</i> , <i>Klebsiella pneumoniae</i>	DM, symptoms > 7 days, recurrent UTI	Trimethoprim + sulphamethoxazole, fluoroquinolones	7 days
Complicated acute cystitis in pregnancy	<i>E.coli</i> , <i>Staph. saprophyticus</i> , <i>Proteus mirabilis</i> , <i>Klebsiella pneumoniae</i>	Pregnancy	Amoxycillin, nitrofurantoin, cephalosporins	7 days
Complicated UTI	<i>E.coli</i> , <i>Klebsiella</i> , <i>Proteus</i> , <i>Pseudomonas</i>		Oral amoxycillin, fluoroquinolones, cephalosporins (as out patient)	14 days
Complicated UTI	<i>E.coli</i> , <i>Klebsiella</i> , <i>Proteus</i> , <i>Pseudomonas</i>	Severe infection, pregnacy	Parenteral antibiotics – ampicillin, aminoglyco- sides, fluoroquinolones, cephalosporins (as inpatient)	14 days
Acute urethral syndrome	Urea plasma urealyticum Mycoplasma hominis	Sexual activity Non-gonococcal urethritis 'Dysuria-pyuria'	Doxycycline	5 days

Note : Fluoroquinolones are to be avoided in pregnancy

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Nephrolithiasis

A. Vimala, Susan Uthup

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species can occur if the organism persists in peri-urethral area or in the fecal reservoir.

Chapter Summary

- Introduction 1137
- Types of Renal Stones 1138
- Clinical Features 1138
- Diagnosis 1139
- Management 1139

Introduction

Renal stone disease occurs worldwide and has been recognised as a medical problem even from the BC era. Urine contains various solutes dissolved in water. The concentration of urine changes depending on the amount of water and the solutes. When the concentration of solutes in urine increases, it reaches a state of saturation. Saturation is the point at which the water and the minerals dissolved in the urine are in equilibrium and precipitation does not occur below this level. Further increase in solute load leads to supersaturation. Supersaturation is the level beyond which addition of further solute invariably results in crystallisation. The stage between saturation and supersaturation is the metastable zone. In this stage, crystallisation occurs if other factors are favorable.

The term nephrocalcinosis suggests calcification of renal parenchyma. Nephrocalcinosis may be cortical or medullary. Nephrolithiasis is defined as the occurrence of stones in the collecting system of the kidney. Nephrocalcinosis and nephrolithiasis may coexist. Often nephrolithiasis starts by the aggregation of crystals on a nidus. The Nidus can be glycoprotein matrix, injured epithelium, foreign body or another crystal. Once such a nidus is formed and the urine saturation remains in the metastable zone or it is supersaturated, aggregation of crystals occurs over the nidus and the crystal grows in size to form a stone. There are inhibiting factors in normal urine which prevent stone formation.

The natural inhibitors include citrate, Tamn–Horsfall protein, glycosaminoglycans, nephrocalcin and uropontin.

Deficiency of natural inhibitors in urine is an important factor contributing to formation of urinary stones. Stone disease is more common in adults, particularly males. It shows variability in incidence from region to region. The geographical peculiarities and quality of drinking water in areas with arid climate favor stone formation. This stone belt includes areas of northwestern part of India, Pakistan, Afghanistan, Iran, Iraq and Turkey, eastern Europe and the Middle East countries. Idiopathic renal lithiasis accounts for 60-80% of stone disease. The inherited tubular or enzymatic abnormalities constitute only less than 1% of the stone forming population. Etiologic classification of urolithiasis is shown in Table 173.1.

Types of Renal Stones

Renal stones can be broadly classified into *radiopaque* and *radiolucent stones*. The commonest radiolucent stone is uric acid stone. Less common radiolucent stones include xanthine and hypoxanthine stones. Radiopaque stones constitute the majority of renal stones. All calcium

TABLE 173.1

Etiologic classification of urolithiasis

1. Hypercalcemic states
 - i. Primary hyperparathyroidism
 - ii. Immobilization
 - iii. Hypervitaminosis D
 - iv. Neoplasia
 - v. Milk alkali syndrome
 - vi. Sarcoidosis
2. Uric acid lithiasis
 - i. Idiopathic uric acid stones
 - ii. Gout
 - iii. Myeloproliferative disorders
 - iv. Acidic urine and oliguric states
3. Idiopathic renal lithiasis
 - i. With hypercalciuria
 - ii. Without hypercalciuria
 - iii. Hyperuricosuria
 - iv. Hyperoxaluria
 - v. Hypocitraturia
 - vi. Increased urine alkalinity
4. Renal tubular syndrome and enzyme abnormalities
 - i. Distal renal tubular acidosis
 - ii. Carbonic anhydrase inhibitors
 - iii. Hyperoxaluria
 - iv. Cystinuria
 - v. Xanthinuria
5. Drugs
 - i. Triamterene
 - ii. Acyclovir
 - iii. Indinavir
 - iv. Sulphonamides

Secondary Nephrolithiasis

1. Cystic renal diseases
2. Urinary diversion procedures
3. Stents, suture materials
4. Catheters

containing stones are radiopaque. Hypercalcemia, hypercalciuria, hyperoxaluria, hyperuricemia, hypocitraturia, high protein intake and low liquid intake are the risk factors for calcium stones. It is also common in those consuming large volumes of carbonated beverages. Stones are more common in persons with urinary tract infection and in those taking drugs like triamterene, acyclovir, indinavir and sulpha drugs. For unknown reasons, it is more common among vasectomized individuals and in hypertensives.

Clinical Features

Patients may remain asymptomatic and stones may be detected incidentally on X-ray or during ultrasound examination. The most common symptom is colicky pain often associated with macroscopic or microscopic hematuria. Increased WBC excretion may be seen in many cases of stone disease. The pain due to stone in renal

pelvis is often abrupt in onset, intense in severity, intermittent and radiates from groin to loin. The colic due to mid-ureteric stone is characterized by radiation to testes or labia. Bladder stone are usually associated with frequency, strangury, urgency or dysuria. The lower urinary symptoms are due to irritation of the trigone of the bladder by the stone. The patient may experience dull dragging suprapubic or perineal pain as well. Interrupted urinary stream may occur if the stone is moving freely in the bladder or partially impacted in the lower urinary tract. General symptoms like sweating, nausea and increased frequency also occur. Stone can cause obstruction, secondary infection, pyonephrosis and renal failure. Anuria may occur when the obstruction is bilateral and complete or if the urethra is totally blocked. When a patient presents with a history of not passing even a drop of urine, total obstruction should be ruled out by appropriate procedures. Even in the most severe forms of glomerulonephritis or tubular necrosis the urine output may be at least a few milliliters in 24 hours. Strangely a person with partial obstruction to urinary system will present with polyuria rather than oliguria. This is due to associated tubular abnormality resulting from the back pressure due to obstruction.

In secondary urolithiasis, infection or obstruction appear to be the primary cause of stone formation. Infection with bacterial organisms that produce urease, results in the breakdown of urea to ammonia resulting in liberation of bicarbonate. Thus the urine is alkalinized. Alkaline urine favours the precipitation of calcium, magnesium and ammonium phosphate resulting in triple phosphate stones (*struvite stones*). These stones are less radiodense than pure calcium oxalate stones. They are often laminated and have branched or staghorn configuration. The stones that are formed in the dilated collecting system due to partial obstruction often contain phosphate. *Cystine stones* occur in cystinuria. It is a genetic disorder of amino acid metabolism with autosomal recessive inheritance. Abnormal transport of the amino acids – cystine, ornithine, arginine and lysine (COAL) results in increased urinary excretion and stone formation. In homozygous individuals, cystine stones are more common. These stones are moderately radiopaque and appear homogenous. They are usually large and surrounded by smaller satellite stones.

Primary hyperoxaluria is an inherited disorder of glyoxalate metabolism resulting in increased urinary excretion of oxalate. Two types of enzyme abnormalities are recognized. Type I (glycolic aciduria) due to deficiency of peroxisomal alanine glyoxalate aminotransferase (PAGA) and Type II (L glyceric aciduria) due to deficiency of D glyceric dehydrogenase. Both enzyme disorders results in hyperoxaluria, stones, nephrocalcinosis and renal failure. Oxalate stones are extremely radio-dense and non-branching.

Diagnosis

In nephrolithiasis and urolithiasis, metabolic or secondary causes for stone formation should be excluded. The recognition of stone forming risk factors is also important.

Laboratory evaluation includes urinalysis, urine culture and determination of antibiotic sensitivity. If urine culture is sterile, fasting urine pH is done to assess acidification ability of the kidney. A 24 hours urine chemistry of calcium, phosphorus, uric acid, oxalate, cystine, citrate and creatinine are also assessed to rule out hypercalciuria, hyperuricosuria, hyperoxaluria and hypocitraturia. Other investigations include estimation blood urea, serum creatinine, serum calcium, phosphorus, uric acid, sodium, potassium, chloride, and bicarbonate. Ultrasound examination of kidneys and urinary system not only detects the presence of stones but also the site of obstruction if any. Ultrasound examination is the most useful investigation to detect the presence, severity and site of obstruction due to stone. It is non-invasive and can be performed repeatedly. Plain X-ray abdomen for kidney, ureter, bladder and urethra (KUBU) will detect the radio-paque stones. Intravenous urography (IVU) helps to assess the renal function apart from detecting the radiolucent stones as filling defect and the level of obstruction. Biochemical analysis of stone helps to plan treatment. CT scan abdomen may be used as needed. Once the diagnosis is made the activity of the stone is assessed by the criteria in Table 173.2.

Management

Management of stone depends on the position, size, symptoms and the ‘activity’. When a patient presents with acute or severe colicky pain, the management includes hydration and administration of analgesics, antispasmodics and relief of obstruction. Often the small calculi in the urinary tract are washed off, if the urine flow rate is

TABLE 173.2	
Classification of the ‘activity’ of stone	
1.	Surgically active stones Stone associated with colic, obstruction, infection or bleeding
2.	Indeterminate metabolic activity All stones which are not surgically active are initially classified as indeterminate metabolic activity
3.	Metabolically active stones Evidence of new stone formation or stone growth within one year
4.	Metabolically inactive urolithiasis No evidence of stone formation or growth in one year of follow-up
5.	Secondary urolithiasis

increased with oral or intravenous fluid administration combined with antispasmodics and diuretics. The general measures for the medical management of stone disease include.

Dietary Modification

The fluid intake is increased so that the urine volume is more than 2.5 litres in 24 hours. High fluid intake is encouraged to reduce the recurrence or growth of urinary stone. Animal proteins, dietary sodium, oxalate rich foods such as leafy vegetables, spinach, rhubarb, chocolate and nuts, carbonated beverages and excessive vitamin C intake should be avoided. Normal calcium intake should be encouraged. Patients with hypercalciuria benefit from treatment with thiazide diuretic combined with potassium citrate. Thiazides decrease calcium excretion in urine. The administration of citrate or citrus fruits is also beneficial in patients with hypocitraturia. Hyperuricosuria is commonly encountered in patients with stone disease. If hyperuricemia and uricosuria are present, allopurinol 200-300 mg a day combined with potassium citrate is given so as to maintain an alkaline urine pH. Long-term alkalinisation of urine helps to dissolve uric acid stone by increasing its solubility. High protein intake in the form of red meat is avoided in such cases. In stone disease with hyperoxaluria, in addition to dietary modifications, oral calcium citrate is used to bind citrate in the gut. Oral pyridoxine is also beneficial. In cystinuria alkalinisation of urine, reduction of dietary sodium and meat combined with measures to increase the urine output to more than 3 liters per day may help to reduce recurrence rate. D-penicillamine, captopril or Vit. B₆ may also be useful. In infection related stones treatment of infection and modi-

fication of urine pH (acidification if initial pH is alkaline and vice versa) and long-term antibiotic prophylaxis are beneficial.

For those with family history of stones, bone disease, gout, chronic UTI and nephrocalcinosis, more extensive investigations are required. The presence of a silent stone detected by X-ray or ultrasonogram alone is not an indication for aggressive investigation and / or treatment. A surgically active stone which is not passed spontaneously or with hydration or following various modalities of minimally invasive nature may be considered for surgical removal. The minimally invasive procedures for stone powdering and removal include:

- 1. **Extracorporeal shock wave lithotripsy (ESWL):**
It is useful for small stones less than 2.5 cm in diameter, stones in the renal pelvis and those in the upper third of the ureter. The stones are powdered or pulverized using shock waves administered from outside the body and directed to the stone.
- 2. **Ureteroendoscopy for stone in ureter:**
In ureteroendoscopy an ultrasound probe is passed 'through the cystoscope and sound energy is used to pulverize the stone. Usually a stent is also placed to enable the smooth passage of the stone fragments.
- 3. **Percutaneous nephrolithotomy (PCNL)** is another procedure whereby the stones are approached through the loin through an ultrasound guided nephrostomy. This procedure is usually undertaken if there is significant hydronephrosis and the stone is sufficiently large and incapable of passing through the ureter.
Open surgical methods are used only if other minimally invasive procedure fail or are not possible. A systematic approach in the diagnosis and management of stone disease helps to avoid long-term renal complications like the kidney failure and infections.

174

Kidney in Systemic Diseases

M. Thomas Mathew

Chapter Summary

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Kidneys are often involved in many metabolic, immune mediated, infective, neoplastic and congenital diseases. Kidney involvement may be the predominant manifestation or it may be a minor part of the systemic illness. A brief outline of the renal involvement in important systemic diseases affecting the kidney is given below. The student should also refer to the appropriate chapters where the diseases are described in detail.

DIABETIC NEPHROPATHY (DN)

The renal involvement in diabetes can be related to duration of diabetes, glycemic control, genetic susceptibility, atherosclerosis, hypertension and pattern of hyperlipidemia. Diabetes mellitus is the leading cause of End Stage Renal Disease (ESRD). Most cases of Type 1 (IDDM) and Type 2 (NIDDM) diabetes mellitus eventually develop diabetic nephropathy and to ESRD over the course of many years. Hyperglycemia is the most important factor inducing glomerular and mesangial injury through different mechanisms like formation of advanced glycation end products (AGE), activation of protein kinase-C (PKC) and generation of reactive oxygen species (ROS). The most common lesions involve the glomeruli and include capillary basement membrane thickening, expansion of the glomerular mesangium and increased secretion of mesangial matrix leading to diffuse or nodular sclerosis of the glomeruli. This is the hallmark of diabetic nephropathy. Exudative lesions like capsular drops, formation of fibrin caps and hyalinosis or arteriosclerosis of afferent arterioles are also seen. Slight increase in urinary albumin excretion called 'microalbuminuria' can be measured only by sensitive methods and is the earliest clinical manifestations of involvement of kidney in diabetes. In healthy normal adults, urinary albumin excretion in 24 hours is less than 30 mg/day (20 microgram/minute). Microalbuminuria is diagnosed when at least 2 out of 3 urine samples examined within a 6 weeks period shows more than 30 mg/24 hrs. The range for microalbuminuria is 30-300 mg/24 hours. When urinary albumin excretion is > 300 mg, it can be detected by the conventional laboratory tests for albumin or by 'albustix'. It is established that those with microalbuminuria have increased risk of developing overt diabetic nephropathy, renal failure and cardiovascular complications in future. The urine sample for microalbuminuria should be collected only when the diabetic state

is well controlled, hypertension is controlled, and the patient has no urinary infection.

The course of diabetic nephropathy often pass through five different stages. Any one who is having clinical diabetes is already in:

Stage I: Soon after the onset of diabetes, the kidney size enlarges (nephromegaly), renal blood flow increases, GFR increases. Blood pressure is typically normal at this stage. This is the stage of hypertrophy and hyperfunction. Tight control of diabetes arrests of progression to the next stage.

Stage II: Once diabetes has been present for more than 5 years or more, patient may pass on to a stage of incipient latent diabetic nephropathy which is characterized by reversible microalbuminuria of >30 mg/24 hrs particularly when the diabetic and hypertensive states are poorly controlled, or the patient undergoes physical exertion. This is the stage of intermittent microalbuminuria. In this clinically silent stage, there is thickening of glomerular and tubular basement membrane, expansion of mesangial matrix and increase in blood pressure. The illness may progress to stage III within 5-7 years.

Stage III: This stage typically occurs 10-15 years after the onset of the diabetic state and it is characterized by the progression of microalbuminuria to "overt" proteinuria or macroalbuminuria, i.e. with urinary albumin excretion of at least 300 mg/24 hours, corresponding to overt proteinuria of >500 mg/24 hours. Patient may become nephrotic and the blood pressure is elevated. The natural history of the disease is progressive with gradual fall in GFR. Histologically, there is diffuse or nodular glomerulosclerosis as well as arteriosclerosis and tubulointerstitial fibrosis.

Stage IV: In the next 4-5 years, progression to advanced nephropathy takes place. This stage is marked by nephrotic range of proteinuria (>3.5 g/24 hr), overt hypertension and rapid fall in GFR with elevated urea and creatinine, the stage of Kimmelstiel-Wilson syndrome.

Stage V: In another 1-3 years' time, the disease progresses further to end stage renal disease (ESRD) with severe hypertension and cardiac failure requiring dialysis or renal transplantation.

More than 60% of patients with diabetic nephropathy also have diabetic retinopathy and neuropathy—the so called "triopathy" of the microvascular complication of diabetes. Patients may also have other renal and genitourinary manifestations of diabetes. These include tubular proteinuria, fluid-electrolyte disorders, hypercalciuria, hyperkalemia, hypoaldosteronism, type IV distal renal tubular acidosis (RTA), papillary necrosis, emphysematous pyelonephritis, xanthogranulomatous pyelonephritis and others.

Treatment

Tight glycemc control with strict diet, insulin and oral antidiabetic drugs is the mainstay in the prevention and treatment of diabetic nephropathy. Normalization of blood pressure is equally important and is achieved by using a combination of angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin-receptor blockers (ARBs). Lipid lowering agents, diuretics and antioxidants also help in retarding the progression of nephropathy. It is prudent to avoid high protein diet in overt nephropathy or ESRD. The average nonvegetarians and all vegetarians may continue to take their ‘normal’ protein intake. Once patient develops ESRD, renal replacement therapy should be initiated. Kidney transplantation is preferable to dialysis therapy because of the risk of infection and vascular access problems due to the atherosclerotic vessels in these patients. In most of the nephrology centers in India, diabetic nephropathy accounts for a major portion of the work load and renal replacement services. Combined pancreas – kidney transplantation achieves the best medical rehabilitation.

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

(See also Section 12, Chapter 108)
Renal involvement occurs in over two-third of patients with SLE. Although the immunologic abnormalities of lupus can virtually affect any organ system, renal involvement is a major cause for morbidity and mortality. Renal involvement is extremely diverse ranging from asymptomatic urinary findings to nephrotic syndrome or fulminant renal failure.

The pathogenesis of SLE is complex and multifactorial. Immunologic dysregulation leads to production of autoantibodies to nuclear and other cellular antigens. The term “lupus nephritis” or “lupus glomerulonephritis” is commonly applied to the many patterns of glomerular involvement in SLE. This includes mesangial lesions, membranous patterns and proliferative lesions. The World Health Organization (WHO) has classified lupus nephritis on the basis of histopathology for proper diagnosis and uniformity in the management.

Modified WHO Classification of Lupus Nephritis

Class I	Normal Glomeruli (by LM, IF, EM)
Class II	Pure mesangial alteration a. Normal by LM, mesangial deposits by IF, EM b. Mesangial hypercellularity and deposits by IF, EM

Class III	Focal segmental glomerulonephritis a. Active necrotizing lesions b. Active and sclerosing lesions c. Sclerosing lesions
Class IV	Diffuse glomerulonephritis (severe mesangial, endocapillary or mesangiocapillary proliferation or with crescents)
Class V	Diffuse membranous glomerulonephritis a. Pure membranous b. Associated with sclerosis c. Associated with focal or segmental proliferative lesions
Class VI	Advanced sclerosing glomerulonephritis
LM – Light Microscopy, IF – Immunofluorescence, EM – Electron microscopy	

The clinical presentation varies from mild or moderate proteinuria, microhematuria and telescoped urinary sediments or with hypertension and renal insufficiency. Class I and II often present with significant proteinuria. Class III may present with nephrotic syndrome and moderate renal failure. The most active form of lupus nephritis is the Class IV group. They present as nephritic syndrome with hematuria, hypertension and moderate to severe renal failure. Class V and Class VI present with nephrotic syndrome, hypertension and renal failure.

Diagnosis

Apart from the clinical diagnostic criteria of SLE, the presence of LE cells, ANA, Anti-dsDNA and hypocomplementemia and the renal histology as per the WHO classification are helpful in diagnosis, prognosis and treatment.

Treatment

The general recommendations for treatment of lupus nephritis are guided by the activity of lupus and the classification as per WHO. In general, Class I and mostly Class II do not require any specific aggressive treatment apart from general measures for SLE. Often symptomatic treatment is given for the systemic manifestations. For Class III and IV, prednisolone in a dose of 1-1.5 mg/kg/day alone or in combination with cyclophosphamide 2 mg/kg/day is given for a period of 4 to 6 weeks or till remission is achieved. Thus the drugs can be given on alternate days for another 4 to 6 weeks. A more effective and safe method of administering cyclophosphamide is to give 0.5-0.75 g/m² as an IV infusion in 500 mL of normal saline over 4 hours. The infusion may be preceded by a bolus dose of ondansetron 4 mg in order to prevent vomiting. This should be followed by 20-40 mg frusemide IV in order to reduce the toxic effects of cytophosphamide. Such ‘pulse’ doses cyclophosphamide are given at

monthly intervals for 6 doses, and 3 monthly intervals thereafter for 6-9 more doses. The blood counts are monitored before and 5 days after each pulse dose. Plasmapheresis has been tried in severe cases of lupus nephritis. Plasma exchange involving one plasma volume daily for 7-10 days has been recommended. Other immunosuppressive drugs like cyclosporine, azathioprine, and mycophenolate mofetil, thromboxane antagonists and IV gammaglobulin have all been used. In spite of treatment, 20-30% of patients of Class III and IV progress on to ESRD and require renal replacement therapy. Often SLE becomes quiescent with the development of ESRD and recurrence of nephritis is not common after renal transplantation.

Rheumatoid Arthritis (RA)

(see also Section 12 Chapter 105)

Kidney involvement is uncommon in rheumatoid arthritis. However, in 10 to 20% of patients, there could be direct involvement or the kidneys could be affected by the treatment given for RA. The changes resulting directly due to RA are membranous glomerulonephritis, mesangial proliferative nephritis, diffuse proliferative nephritis or necrotizing vasculitis. Renal amyloidosis (AA type) may develop secondary to the chronic inflammatory state due to RA. Drugs used in the treatment of RA like NSAIDs, methotrexate azathioprine, cyclosporine, and others can indirectly produce kidney damage. Treatment is usually symptomatic, but in a rare patient with renal insufficiency steroids or cyclophosphamide may be useful.

Sjögren's Syndrome (SS)

(see also Section 12 Chapter 105)

Distal renal tubular acidosis, Fanconi's syndrome, impaired urinary concentrating ability, interstitial nephritis, nephrogenic diabetes insipidus, hypercalciuria and nephrolithiasis may occur in 20 to 25% of patients. Urinary tract infection is more common especially in women who have vaginal sicca symptoms. Some patients may progress to chronic renal failure due to interstitial fibrosis or glomerular sclerosis. Use of steroids and immunosuppressive drugs in the early stages, followed by symptomatic treatment and renal replacement therapy when the patient is in ESRD are advocated.

Progressive Systemic Sclerosis (PSS)

(see also section 12 Chapter 107)

Kidney involvement is the most common cause of death in PSS and is present in 40 to 70% of cases. The renal blood vessels are predominantly involved with marked intimal thickening, intimal cell proliferation and fibrinoid necrosis which are indistinguishable from malignant hypertension. There is slowly progressive renal insuffi-

ciency accompanied by hypertension and moderate proteinuria. However, manifestation such as acute renal failure with or without malignant hypertension (scleroderma renal crisis) is not uncommon. There is no specific treatment. However, energetic management of hypertension with ACE inhibitors and renal replacement therapy will be required in ARF or if the patient goes on to ESRD. In spite of advanced renal failure, ACE inhibitors are the drug of choice in scleroderma renal crisis.

Mixed Connective Tissue Disease (MCTD)

(see also Section 12 Chapter 107)

Mixed connective tissue disease has overlapping clinical manifestation of SLE, polymyositis, systemic sclerosis and the presence of a distinctive antibody profile. Kidney disease occurs in approximately 25% of patients with MCTD. It may be clinically silent or mild consisting of proteinuria or haematuria. Serious kidney involvement is common in children. Membranous or focal proliferative glomerulonephritis is common. Malignant hypertension can be a presentation with proliferative vasculopathy similar to the vasculopathy seen in systemic sclerosis. Some patients may end up with ESRD or may develop renal involvement due to treatment with NSAIDs. There is no specific treatment. Patients with hypertension will require antihypertensive medication including ACE inhibitors.

VASCULITIDES

The kidneys may be involved in systemic vasculitis in different ways. Refer also to Section 12 Chapter 108.

Polyarteritis Nodosa (PAN)

Renal involvement is seen in more than 80% of patients. The glomerular lesions are those of ischemia with collapse of the glomeruli and fibrinoid necrosis. Renal infarctions may be seen because of the ischemia produced by vascular blocks and necrosis. Diagnosis is based on anemia, raised ESR, leukocytosis and supportive clinical features. Definite diagnosis can be made by angiography or tissue biopsy.

A combination of steroids in dose of 2 mg/kg/day and cyclophosphamide in doses of 1 to 2 mg/kg body weight is given for 4-6 weeks and tapered off gradually over 6-12 months. Hypertension has to be controlled adequately.

Churg-Strauss Syndrome

Churg-Strauss syndrome is a granulomatous vasculitis affecting small arteries especially of the lungs and marked by eosinophilic tissue infiltration. cANCA is positive in these patients. Renal involvement is less

common and may consist of granulomatous nephritis and focal necrotizing granulomatosis. Treatment is with corticosteroid and cyclophosphamide.

Microscopic Polyarteritis

Renal involvement is common and it manifests with proteinuria, hematuria and RBC casts. Hypertension is usually mild. The most striking feature is rapidly progressive renal failure. When extrarenal features are inconspicuous or missing it is called *renal-limited vasculitis*. Renal histology shows involvement of small vessels in the form of polymorphonuclear infiltration, fibrinoid necrosis and extravasation of erythrocytes. Glomeruli show focal necrotizing lesions and there may be variable degree of crescent formation. Endocapillary proliferation is uncommon. Immunofluorescence shows scanty deposits of immunoglobulins and complement (pauci-immune glomerulonephritis).

Treatment is similar to PAN, consisting of steroids and cyclophosphamide. Plasma exchange has been shown to be of benefit in some patients. Intravenous immunoglobulins and monoclonal antibodies directed against CD4 or CD52 have been used in patients who are resistant or intolerant to the conventional treatment.

Wegener's Granulomatosis (WG)

(see Section 14, Chapter 143)

Renal involvement occurs in 85%. GFR is reduced in about half of the cases at the onset of the disease. cANCA is positive in 90-95% and is sensitive and specific. Prominent features include hematuria, variable degree of proteinuria and progressive renal insufficiency.

Renal histology is that of diffuse or focal necrotizing glomerulonephritis. Crescentic glomerulonephritis may be seen in patients presenting with rapidly progressive renal failure. Immunofluorescence shows a lack of immune deposits and electron microscopy may show scattered electron-dense deposits in capillary walls. The prognosis of untreated WG is dismal, and 1-year survival may be <20%. Treatment with prednisolone 1 mg/kg/day and cyclophosphamide 2 mg/kg/day is effective. Steroid dose is reduced after 6 weeks and may be discontinued once clinical remission is achieved. Cyclophosphamide should be continued in the same dose for at least 1 year after achieving quiescence of disease activity. Plasma exchange may be tried in patients who do not respond quickly to conventional therapy and dialysis undertaken for renal failure.

Henoch-Schönlein Purpura (HSP)

(see also Section 15, Chapter 163)

Renal involvement is seen in 50-80% of cases, and is usually apparent within 4 weeks of diagnosis. The findings

include gross or microscopic hematuria, proteinuria and rarely rapidly progressive renal failure. Nephrotic syndrome is seen in 50% of cases. The most striking histopathological lesion in the kidney is segmental mesangial proliferation. The degree of proliferation is variable and may be associated with glomerular capillary tuft necrosis and crescent formation. HSP is a leucoclastic vasculitis. The renal lesions resemble IgA nephropathy. Predictors of renal involvement are available. HSP is usually a benign condition with an overall mortality rate of 10% on 10 years follow-up. If the renal functions are normal 5 years after the onset of clinical symptoms, the chances of progressive renal failure are less. However, poor prognostic factors include older age, acute nephritic syndrome with renal failure and persistent nephrotic range proteinuria. Treatment is symptomatic. Steroids or immunosuppressive agents are unhelpful in altering the course of renal disease. Patients with rapidly progressive renal failure in association with crescentic glomerulonephritis may be benefited by intensive plasma exchange along with immunosuppressive drugs and dialysis.

Mixed Cryoglobulinemia

This condition is characterized by the presence of cold agglutinins in blood. They are a mixture of monoclonal IgM and polyclonal IgG in the circulation which precipitate in cold and give rise to clinical symptoms like purpura, necrotizing skin lesions, arthralgias, hepatosplenomegaly and Raynaud's phenomenon.

Renal disease is seen in about 50% of cases and is more common if circulating cryoglobulin concentration exceeds 1 g/dL. Clinical features may be precipitated by dehydration or exposure to cold and include nephrotic syndrome (30%), asymptomatic proteinuria (30%), acute nephritic syndrome (20-30%) and acute renal failure (5%). Light microscopy shows endocapillary proliferative glomerulonephritis and infiltration by monocytes. Crescents may be seen in a few glomeruli. Large eosinophilic PAS- positive deposits are seen within the capillary lumen (intraluminal thrombi). There is uneven thickening of the GBM. Vasculitis is observed in 33% of cases. Treatment includes IV pulse doses of methyl prednisolone (500-1000 mg/ day for 3 days) followed by a combination of oral prednisolone (30-60 mg/day) and cyclophosphamide (2 mg/kg/day). In patients with crescentic glomerulonephritis with rapidly deteriorating renal function plasma exchange may be required to bring down cryoglobulin levels.

Takayasu's Arteritis

Various patterns of arterial lesions have been described. In India, the main seat of pathology is found in abdominal aorta and renal arteries as compared to Japan where aortic

arch and its branches are involved more frequently. Presentation with renovascular involvement is common with hypertension, chronic renal failure, congestive cardiac failure, stroke or limb ischemia. General features of toxemia like fever, malaise, arthralgias, anemia are not common in Indian patients. There is no specific treatment. Glucocorticoids or other immunosuppressive drugs are tried for cases with arterial inflammation during acute phase. Strict control of hypertension is the mainstay in treatment. Stenotic lesions of most arteries can be treated by angioplasty, stenting and by surgical correction.

Amyloidosis

(See also Section 15)

Amyloidosis is characterized by deposition of abnormal protein consisting of immunoglobulins or its fractions. Amyloidosis occurs in two forms AL and AA types. The fibrils consist of immunoglobulin light chains in AL and serum amyloid A in AA. Besides amyloid it includes light and heavy chain deposition disease, cryoglobulinaemia and fibrillary glomerulonephritis. Amyloidosis involves the kidney among several other organs as well. Kidney is involved in over 80% of the patients. Other organs like liver, spleen, lymph nodes, heart and others are also involved. The amyloid associated with chronic hemodialysis and Alzheimer's disease usually does not involve the kidneys. The involvement of kidney is commoner in AL amyloidosis as compared to AA variety. The renal presentation is with proteinuria progressing to nephrotic syndrome. Relatively low frequency of hypertension and enlargement of the kidney are the hallmark of amyloid renal disease. Progression to renal failure is slow and the severity of primary disease or the intervening complications decide the outcome. Some patients may present with amyloid deposition in the renal tubules and present as tubular syndromes like diabetes insipidus and renal tubular acidosis. Diagnosis can be made by renal biopsy. Demonstration of green birefringence in biopsy tissues stained with congo red and examined under polarized light is diagnostic. Abdominal fat biopsy and rectal biopsy are also useful. There is no satisfactory treatment of this condition. AL variety of amyloidosis may show regression with treatment of the primary disease. Both dialysis and renal transplantation are not very rewarding because often the involvement of extrarenal organs decide the outcome of the disease.

Multiple Myeloma

(See also Section 15, Chapter 158)

Almost 50% of patients have overt renal insufficiency at some time during the course of the disease. In many instances, renal disease may be the first indicator of multiple myeloma. Virtually, all parts of the renal

parenchyma can be damaged by light chain deposition. Symptomatology varies widely.

1. *Glomerular involvement*
 - a. Amyloid, type AL
 - b. Granular light chain deposition disease
 - c. Fibrillary glomerulopathies
2. *Tubulo-interstitial involvement*
 - a. Fanconi's syndrome
 - b. Acute tubular necrosis or tubulopathy
 - c. Cast nephropathy (myeloma kidney)
 - d. Tubulointerstitial nephritis
3. Vascular lesions
4. Asymptomatic Bence Jones proteinuria
5. Hypercalcemic nephropathy
6. Hyperviscosity syndrome
7. Pyelonephritis
8. Neoplastic cell infiltration
9. Obstructive nephropathy.

The common urinary abnormality is the detection of light-chains or Bence Jones proteinuria, in 65-100% of patients. Proteinuria may rarely precede the development of systemic symptoms of myeloma by a few months. The quantity of protein excreted often exceeds 3 g/day and these patients may be misdiagnosed to have nephrotic syndrome. Acute renal failure occurs in some patients even in the absence of pre-existing renal insufficiency. Precipitating factors of ARF include hypercalcemia, dehydration, increased plasma viscosity, hyperuricemia, radio-contrast administration and infection. The pathogenetic mechanism is thought to be intratubular obstruction by casts due to precipitation of myeloma proteins. In some cases of multiple myeloma, the acute renal failure may be irreversible.

Slowly progressive chronic renal failure occurs often in light chain and IgD myeloma associated with Bence Jones proteinuria. Hypertension and hematuria are rare and non-light chain proteinuria is mild. Renal histology shows dilated tubules containing "fractured glassy eosinophilic casts" surrounded by multinucleated giant cells. There is widespread tubular atrophy, interstitial fibrosis and inflammation. On immunofluorescence, the casts exhibit kappa or lamda chains beside immunoglobulins, Tamm-Horsfall protein and complement. Tubular defects involving both proximal and/or distal segments may occur in myeloma and sometimes precede it. Secondary amyloidosis occurs in 6-15% of myeloma patients, leading to proteinuria and nephrotic syndrome. Presence of renal insufficiency shortens the survival of patients with multiple myeloma.

The main principles of prevention of ARF are maintenance of adequate hydration, vigorous control of hypercalcemia and hyperuricemia, and avoidance of potentially nephrotoxic drugs. The specific treatment using standard chemotherapeutic regimen with melphalan and prednisolone ameliorates renal lesions in more than

50% of the patients. In those with severe renal failure, improvement in renal function has sometimes been observed with peritoneal dialysis or plasmapheresis, both of which can remove significant amounts of light chains. Only 50% of myeloma patients survive for over 1 year on maintenance dialysis. Renal transplantation is considered on rare occasions when the tumor growth is well controlled and the myeloma state is in prolonged remission.

Renal Lesions Associated with Neoplasia

Lymphoreticular malignancies, solid tumours of the lung, gastrointestinal tract, breast and ovary lead to mild proteinuria or even nephrotic syndrome. Renal lesions may antedate the diagnosis of the primary malignancy. The treatment is directed towards the primary tumour and symptomatic management for the nephrotic syndrome.

Minimal change disease is common in Hodgkin's lymphoma. Crescentic glomerulonephritis has been reported in non-Hodgkin's lymphoma. Other types of renal involvement like focal segmental glomerulosclerosis, membranous or membranoproliferative

glomerulonephritis have been described. Kidney may also be involved by direct infiltration in leukemias and lymphomas. The presentation could be with hematuria, proteinuria or might even manifest as ARF. Treatment is symptomatic and supportive. Dialysis may be required to tide over the crisis in ARF.

Tumour Lysis Syndrome

The tumour lysis syndrome is a complication of cancer chemotherapy in extensive rapidly growing and sensitive tumours due to rapid breakdown of tumour tissue. This results in the release of large quantities of cellular products into the circulation. The blood concentrations of uric acid, xanthine, phosphate and potassium increase very rapidly due to large scale cell destruction. The subsequent filtration and the intratubular precipitation of these substances result in ARF. This condition can be prevented by good hydration in order to ensure urine flow rate of about 120 mL/hr. Alkalinization of urine and use of allopurinol before commencing cancer therapy and maintaining the same during the treatment period helps to reduce renal failure. Patients may require dialysis to tide over the crisis if ARF develops.

175 The Kidney and Hypertension

S. Krishnakumar, Jacob George

Chapter Summary

- Introduction 1146
- Renal Parenchymal Hypertension 1147
- Renovascular Hypertension 1147

Introduction

There is a close interrelationship between the kidney and hypertension. Normally, the kidneys influence the blood pressure by several mechanisms and several kidney diseases produce hypertension. Hypertension *per se* can also cause kidney disease or worsen kidney damage. Thus hypertension can be caused by kidney

disease and hypertension can involve and damage the kidney. The primary determinants of blood pressure are blood volume and the peripheral vascular resistance, and both are influenced by the kidney. Salt and water retention can increase the blood volume resulting in hypertension in several kidney diseases. In addition, the peripheral vascular resistance is influenced by several hormones produced by the kidney. Renin, which is secreted from the kidney can cause vasoconstriction. The renal medulla may produce certain vasodilatory lipids, and their deficiency in renal disease could contribute to hypertension.

Secondary hypertension accounts for less than 5% of all hypertensive patients. The most common cause of

secondary hypertension is either a renal parenchymal disease or a renovascular disease. Endocrine diseases also cause secondary hypertension. Even in essential hypertension, the kidneys play an important role.

RENAL HYPERTENSION

Renal hypertension could be due to renal parenchymal disease or renovascular disease.

Renal Parenchymal Disease

Renal parenchymal disease can initiate and sustain hypertension. At the same time, hypertension can accelerate the progression of renal disease. The various mechanisms by which the kidney produces hypertension are shown in Table 175.1.

TABLE 175.1
Mechanism of hypertension in renal disease
1. Salt and water retention (seen in acute nephritis, renal failure, etc).
2. Activation of renin angiotensin aldosterone system.
3. Reduced renal (vasodilator) medullary lipids.
4. Stimulation of sympathetic nervous system due to increased renal afferent activity in renal parenchymal disease.

The common causes of renal parenchymal hypertension are shown in Table 175.2.

TABLE 175.2
Causes of renal parenchymal hypertension
1. Acute glomerulonephritis.
2. Diabetic nephropathy.
3. Chronic glomerulonephritis.
4. Reflux nephropathy (chronic pyelonephritis).
5. Polycystic kidney disease.
6. Hemolytic uremic syndrome
7. Collagen disorders
8. Pre-eclampsia.

Hypertension resulting from renal parenchymal disease may be of recent onset or long standing. Common causes of recent onset of hypertension include acute glomerulonephritis, hemolytic uremic syndrome, scleroderma renal crisis and pre-eclampsia. Such patients are more prone for complications such as hypertensive encephalopathy and may need hospitalization at comparatively lesser levels of hypertension than those with long standing hypertension. When a patient presents with hypertension, some clinical clues which point to renal hypertension should be looked for Table 175.3.

Investigations

TABLE 175.3
Clinical clues to suspect renal parenchymal hypertension
1. Age < 30 or > 55 years.
2. History of edema/hematuria/oliguria.
3. Palpable kidneys.
4. Difficult-to-control hypertension (three or more anti-hypertensive medications).
5. Hypertensive neuroretinopathy (striate hemorrhage/soft exudates).
6. Hypertensive encephalopathy.

Such patients are investigated to ascertain the cause. The relevant investigations include the following:

Significant proteinuria will be present in glomerulonephritis, diabetic nephropathy and reflux nephropathy. Microhematuria/granular casts are seen in glomerulonephritis. Hemoglobin may be low in chronic kidney disease, hemolytic uremic syndrome and Goodpasture’s syndrome. The erythrocyte sedimentation rate may be raised in vasculitis, SLE or multiple myeloma. Blood urea and serum creatinine may be elevated. Ultrasound of kidney may show enlarged echogenic kidney in acute glomerulonephritis or small irregular echogenic kidneys with loss of corticomedullary differentiation in chronic glomerulonephritis and chronic tubulointerstitial nephritis. Serological tests like ASO titre, C₃ and C₄ level, ANA and ANCA may be requested when warranted. Renal biopsy helps to confirm the nature and identify the underlying kidney disease, gives an idea regarding prognosis and helps in deciding the management.

Treatment

Although in essential hypertension a blood pressure less than 140/90 may be considered adequate, in secondary hypertension due to renal parenchymal disease, the aim is to bring the blood pressure below 130/80 mm Hg or even below 125/75 if there is associated proteinuria. A lower blood pressure retards the progression of renal disease and could delay the onset of end stage renal disease. Often two or more antihypertensive drugs may be needed. If the glomerular filtration rate is below 30 mL/mt, thiazide diuretics are ineffective and loop diuretic may be needed to control salt and water retention. Angiotensin II converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta blockers and calcium channel blockers are usually used. If ACEIs or ARBs are used, serum creatinine and serum potassium should be monitored at least twice weekly for the first two weeks after the drug is initiated and thereafter once in 4-6 weeks. If the serum creatinine rises more than 20% of baseline soon after initiation, or if hyperkalemia develops these drugs have to be withdrawn.

RENOVASCULAR HYPERTENSION

TABLE 175.4

Clinical clues for suspecting renovascular hypertension

1. Onset of hypertension before 35 and after 55 years of age.
2. Requirement of 3 or more antihypertensive drugs.
3. Systolodiastolic renal bruit/femoral bruit.
4. Asymmetric blood pressure recording in the limbs.
5. Evidence of generalised atherosclerosis like coronary artery disease, peripheral vascular disease, cerebral infarcts etc.
6. Worsening of renal function following exposure to ACEIs or ARBs.
7. 'Flash' pulmonary edema.
8. Malignant hypertension/hypertensive neuroretinopathy.
9. Chronic smokers/diabetics.

Renovascular hypertension develops when the blood supply to the kidney is impaired. This may be either due to unilateral renal artery stenosis which is usually a renin dependent hypertension or due to bilateral disease which is more often due to salt and water retention. The common causes of renovascular hypertension are atherosclerotic renovascular disease, aortoarteritis (Takayasu's arteritis) and fibromuscular dysplasia. Rare causes are coarctation of aorta, dissecting aortic aneurysm and external compression of the renal artery by tumours or lymph nodes.

The clinical clues to suspect renovascular hypertension is given in Table 175.4.

CLINICAL FEATURES

Altherosclerotic renovascular disease is suspected in those having evidence of generalised atherosclerosis like thickened vessel walls, absent peripheral pulsations, associated carotid or femoral bruits and those with coronary artery disease. It predominantly affects the proximal renal arteries and the ostia. Takayasu's arteritis occurs in those below 40 years of age and is prevalent in all parts of India. It is similar to reversed coarctation and the upper limb pulsations may be decreased where as the lower limb pulsations are normal. The ocular fundus may show a wreath like appearance of the retinal vessels near the optic disc. Fibromuscular dysplasia is seen in young females and is mostly seen in the Western countries. Renal failure is rare and the renal artery shows a characteristic beaded appearance on angiogram. Occurrence of sudden onset of pulmonary edema ("flash pulmonary edema") points to the presence of bilateral renovascular disease. Such patients have a sudden worsening of renal function or drop in urine output when ACEIs or ARBs are used.

Often when flash pulmonary edema occurs, the clinician

should suspect bilateral renovascular disease and proceed with further investigations. Today with the availability of angioplasty or stenting the results of treatment are highly rewarding.

Investigations

Urinalysis is relatively normal with no significant proteinuria or urinary sediments. When mild degrees of proteinuria occur, it represents the action of angiotensin II on the glomerular capillary permeability. The hemogram and renal function test are unremarkable. Rise of urea or creatinine when the patient is treated with ACEI or ARBs is a strong indicator of bilateral renovascular disease. Ultrasound examination of abdomen may reveal a smaller sized kidney in unilateral renovascular disease. However the cortical echotexture and corticomedullary differentiation are normal. Ultrasound duplex scan combines pulsed doppler with B mode scanning. Colour Doppler helps to identify the origin of the renal arteries. The peak systolic velocity is proportional to the degree of stenosis. Criteria for diagnosis are peak systolic velocity of 2.5 standard deviations more than the normal range and ratio of change of velocity to that recorded in the aorta (RAR) of more than 3.5. This suggests a degree of stenosis of 60 to 99%. This test is highly sensitive. A high resistivity index (>80%) suggests poor diastolic flow and indicates poor response to intervention. Although, it is a good screening test, it is highly operator dependent. Rapid sequence intravenous urogram was used as a screening test. A size difference of >1.5 cm between the affected and normal kidneys, delayed appearance of nephrogram and increasing concentration on subsequent films on the affected side are suggestive of unilateral renal artery stenosis. This test is seldom employed now because more reliable tests such as isotope renogram are available.

Isotope renogram: In this test ⁹⁹Tc (Technetium) DTPA is administered and the transit of the radio pharmaceutical through the kidney and urinary system is recorded by a gamma camera. Delay and decrease in the uptake of the DTPA and delay in excretion are the usual findings on the side of renal artery stenosis, compared to the normal side.

In captopril renography 25 mg of captopril is administered one hour before the test. The uptake and excretion of the isotope are delayed further compared to the study without captopril suggesting a fall in the GFR due to captopril on the side of renal artery stenosis. Captopril renography has a sensitivity of 90% and hence it is a good screening test. Selective catheterization of renal veins and measurement of the renin levels from each side and aorta will help to identify the side of disease. Renin levels will be high on the affected side and low on the normal side. This is an invasive test. It may be useful to predict response to angioplasty and revascularization of the renal artery.

Captopril test: Administration of captopril 25 mg further elevates renin secretion from the affected kidney. Measurement of basal levels of PRA and after captopril stimulation helps to diagnose renal artery stenosis.

Renal angiogram is the gold standard for diagnosing renal artery stenosis. This will demonstrate the stenotic area, post stenotic dilatation and a gradient across the stenosis. Digital subtraction angiography and spiral CT has the advantage of using lesser contrast. Magnetic resonance angiography (MRA) using gadolinium can be used especially in those with renal failure as there is no risk of contrast nephrotoxicity. Therapeutic procedures like balloon angioplasty or stenting can also be undertaken in the same session as angiography.

Table 175.5 summarises the diagnostic test in renovascular hypertension.

MANAGEMENT

There are three types of management for renovascular hypertension.

- 1. **Medical management:** This includes use of anti-hypertensive medication, antiplatelets and statins. Beta blockers, calcium channel blockers and occasionally diuretics are used. ACEIs and ARBs are the drug of choice in unilateral renovascular hypertension but should be used cautiously, especially in those with associated involvement of the other kidney with frequent monitoring of serum creatinine and serum potassium. It would be safer to withdraw them if the serum creatinine increases by more than 20% soon

TABLE 175.5	
Diagnostic tests in renovascular hypertension	
1.	Screening tests
a.	Rapid sequence IVU
b.	Duplex ultrasound
c.	Captopril renogram
2.	Demonstrating anatomical stenosis
a.	Conventional renal angiogram
b.	DSA
c.	MRA
d.	Spiral CT
3.	Tests suggesting response to intervention.
a.	Captopril test
b.	Renal vein renin assay.

after its introduction. Medical treatment should be advocated in the elderly, those unfit for angioplasty or intervention and in those unlikely to benefit from intervention procedures.

- 2. **Percutaneous transluminal angioplasty:** This can be used with or without stenting. They are most useful in fibromuscular dysplasia and when stenosis involves the distal renal artery. It can also be tried in patients who have unilateral or bilateral renovascular narrowing. It is relatively less invasive, compared to the surgical revascularisation procedures.
- 3. **Surgical revascularisation procedures:** These include endarterectomy, aorto-renal bypass, spleno-renal anastomosis or hepatorenal bypass. The revascularization is done using either saphenous vein as grafts or prosthetic grafts. It may be useful in patients in whom the lesion is likely to progress, as in high grade stenosis (75-99%) with kidney size more than 7.5 cm. It should be performed only in centers with experience in vascular surgery.

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Pregnancy and Medical Disorders

Jacob George

Chapter Summary

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- Hypertension 1150
- Pre-eclampsia/Eclampsia 1151

- Pregnancy and Renal Diseases 1152
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- Acute Pyelonephritis 1154
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- Systemic Lupus Erythematosus (SLE) 1154

Pregnancy is a physiological state and a safe outcome is often the rule. However, medical complications can occur either due to occurrence of pregnancy in a patient with a pre-existing illness or development of a new medical disease during pregnancy. The commonly encountered medical problems during pregnancy are diabetes mellitus, hypertension, acute renal failure, chronic kidney disease, liver dysfunction, urinary tract infection, and systemic lupus erythematosus.

Diabetes Mellitus

(see also Chapter 91)

When diabetes occurs *de novo* during pregnancy, it is called gestational diabetes mellitus. In pre-gestational diabetes, mellitus pregnancy supervenes on type 1 and type 2 diabetes mellitus. The prevalence of pre-gestational diabetes is lower (0.1-0.3%) than gestational diabetes mellitus (2-5%). Some patients may develop impaired glucose tolerance during pregnancy. A decrease in insulin sensitivity and a failure to achieve a higher insulin production are mainly responsible for gestational diabetes mellitus. Those with gestational diabetes mellitus have a six fold increased risk of developing type 2 diabetes mellitus subsequently.

Screening for diabetes in pregnancy is important as uncontrolled diabetes can affect both maternal and fetal health. Hyperglycemia in first trimester is associated with fetal anomalies and miscarriages. In later pregnancy, hyperglycemia causes large for gestational age infants, macrosomia (birth weight > 90th percentile), shoulder dystocia, birth injuries and neonatal hypoglycemia. There is also an increased risk of maternal hypertension and pre-eclampsia.

Risk Factors for Gestational Diabetes Mellitus

1. Body Mass Index (BMI) > 25 kg/m²
2. Waist hip ratio > 1
3. Family history of diabetes
4. Age > 25 years
5. Multiparity
6. Ethnic predisposition

In those at risk, screening with 50 g glucose challenge test at the first prenatal visit and then at 24th and 32nd weeks is recommended. In those without risk factors, screening once between 24th and 28th week is adequate. If the test is positive, a 3-hour oral glucose tolerance test with 100 g glucose should be performed after 10 hours fasting. The diagnostic values for venous plasma in 3 hour oral 100g GTT are

FBS	≥ 95 mg/dL
1 hr	≥ 180 mg/dL
2 hr	≥ 155 mg/dL
3 hr	≥ 140 mg/dL

Two abnormal values are needed for diagnosis.

Management

Dietary management is on the same lines as for non-pregnant women. Extra calories and proteins should be provided to fulfill the needs of the fetus also. It is safer to start insulin early. Oral hypoglycemic agents are avoided as most of them can cross the placental barrier and affect the fetus. Pregnancy is a state of relative insulin resistance. So, maternal nutrients are shunted to the developing fetus and the normal range of blood glucose is lower by approximately 20%. The target fasting blood sugar should be between 60-95 mg/dL and 2 hours postprandial should be less than 120 mg/dL. At fasting blood sugar levels of more than 95 mg/dL the risk of macrosomia is more. Since blood sugar should be kept in the normal range, frequent self-monitoring is recommended.

Generally, spontaneous delivery is desirable. However, with presence of maternal hypertension, history of previous stillbirth, poor metabolic control and macrosomia, delivery is planned around 37-38 weeks of gestation. If fetal weight is greater than 4 kg, cesarean section is done. The fetal loss and perinatal mortality are higher in diabetic compared to non-diabetics pregnancies.

Hypertension

(see also Chapter 123)

Hypertension is a major problem during pregnancy. The guidelines for diagnosis and management of hypertension are different in pregnant subjects compared to the general population. As there is no clear-cut dividing line between normal and abnormal blood pressure during pregnancy, certain arbitrary BP levels have been established for clinical purposes. The Committee on Terminology of the American College of Obstetricians and Gynecologists suggested any one of the following criteria for the diagnosis of hypertension in pregnant women.

1. A sustained rise of 30 mmHg or more in systolic BP;
2. A sustained rise of 15 mmHg or more in diastolic BP;
3. A sustained systolic BP of 140 mmHg or more and;
4. A sustained diastolic BP of 90 mmHg or more.

“Sustained” refers to elevated BP observed on two different occasions, at least six hours apart. To apply the above criteria, the BP in the prepregnant state or soon after conception must be known. Since these BP readings are often not available, the diagnosis of pregnancy-induced hypertension becomes difficult. To overcome this difficulty, it is also suggested that the upper limit of normal diastolic BP should be taken as 75 mmHg in midtrimester and 85 mmHg in last trimester. The clinical classification of the hypertensive disorders of pregnancy recommended by the committee of the American College of Obstetricians and Gynecologists is shown in Table 176.1.

TABLE 176.1

Hypertensive disorders of pregnancy

1. Pregnancy-induced hypertension (pre-eclampsia / eclampsia).
2. Chronic hypertension of whatever cause.
3. Chronic hypertension with superimposed pre-eclampsia.
4. Late or 'transient' hypertension.

1. **Pregnancy Induced Hypertension (PIH) - Pre-eclampsia/eclampsia:** Pre-eclampsia is characterised by a constellation of signs and symptoms including new onset of hypertension after 20 weeks of gestation, proteinuria, edema and occasionally complicated by coagulation and liver function abnormalities. The term pre-eclampsia is used synonymously with pregnancy induced hypertension (PIH). Several factors may predispose to the development of pre-eclampsia. These include primigravida, extremes of age, multiple pregnancy, hydatidiform mole, diabetes, polyhydramnios, fetal anomalies, hydrops fetalis and family history of pre-eclampsia/eclampsia.
2. **Chronic hypertension of whatever cause:** This group includes those patients with essential or secondary hypertension who subsequently become pregnant. Those who have hypertension before twenty weeks of pregnancy are more likely to fall into this group.
3. **Chronic hypertension with superimposed pre-eclampsia:** Almost three quarters of those with severe hypertension develop superimposed pre-eclampsia in the second-half of pregnancy. Pre-eclampsia in this group is often more severe than those without pre-existing hypertension.
4. **Late or transient hypertension:** This group includes those who develop hypertension in the last trimester or immediate puerperium which normalises by the tenth postpartum day.

PRE-ECLAMPSIA/ECLAMPSIA

Pregnancy induced hypertension is a multisystem disease characterised by vascular endothelial dysfunction and damage. Placenta plays a central role in the pathogenesis and shows evidence of hypoperfusion, ischemia and scars. Various theories have been proposed on its pathogenesis including the role of superficial placentation, immune maladaptation, and reduced angiogenic factors. Normally, during pregnancy, the decidua part of spiral arteries are invaded by the cytotrophoblast and there is loss of muscle layer and endothelium of blood vessels. This results in failure of the blood vessels to respond to vasomotor stimuli. Thus the vascular supply of the placenta is transformed from a high pressure, low flow system to a low pressure, high flow system. In PIH, the trophoblastic invasion is partial and the preservation of the muscle

layers makes the vessels sensitive to vasomotor stimuli. Thus the high pressure low flow system persists leading to reduced placental blood flow and generalized endothelial damage with multi-organ involvement. Plasma volume is found to be significantly decreased in patients with PIH compared to pregnant women with normal BP. The salient pathological changes in the kidneys include enlargement of the glomeruli with no increase in the number of cells. The endothelial cells are swollen and fill up the capillary loops. These changes have been termed 'glomerular capillary endotheliosis.'

Diagnosis

Pre-eclampsia is suspected clinically by noting blood pressure elevation after 20th week of pregnancy. This may be associated with headache, epigastric or right upper quadrant abdominal pain and visual abnormalities such as scotoma, cortical blindness or spasm of retinal arterioles. Symptoms like epigastric discomfort and visual disturbances may precede the development of generalized convulsions. If convulsions occur, it is termed eclampsia. Examination of urine reveals proteinuria. The important hematologic abnormalities include rise in hematocrit and hemoglobin due to hemoconcentration and thrombocytopenia. Blood levels of aspartate aminotransferase, alanine aminotransferase and lactic dehydrogenase enzymes may be elevated, but they return to normal within ten days of delivery. The normal values for blood urea nitrogen (BUN) (8 mg/dL equivalent to blood urea of 17 mg/dL) and serum creatinine 0.4 mg/dL during pregnancy are markedly lower than the pre-pregnant levels. This is because of an increase in glomerular filtration rate. In pre-eclampsia if BUN or creatinine levels are equal to pre-pregnant values, it indicates impaired renal function. Similarly, serum uric acid is low (2.5 mg/dL) and elevation of serum uric acid to > 4.5 mg/dL indicates pre-eclampsia. Thus hyperuricemia helps to distinguish women with pre-eclampsia from those with chronic hypertension. Presence of hypertension before conception or detection of hypertension before 20 weeks of gestation is suggestive of pre-existing hypertension and not pre-eclampsia. Pre-eclampsia is uncommon in multiparous women. The blood pressure usually decreases dramatically following delivery. Severe pre-eclampsia has to be distinguished from acute fatty liver of pregnancy, thrombotic microangiopathy, glomerulonephritis or systemic lupus erythematosus.

Management

- Regular antenatal check up should include the following:
- i. To limit maternal weight gain to less than 12.5 kg.
 - ii. Control of blood pressure. The blood pressure should be maintained below 125/75 in the second trimester and 135/85 in the third trimester.

- iii. Aggressive salt restriction and diuretic therapy should be avoided since they will cause further reduction of intravascular volume.
- iv. The pre-eclamptic woman is hospitalized early and encouraged to rest on the left lateral position.
- v. Fetal growth parameters are monitored clinically and by ultrasound scans.

The fetal prognosis improves by judicious and deliberate pre-term delivery and the care given in a good premature nursery. The chances of survival of the infant improve by judicious pre-term delivery. Delivery should be planned by 37th week in mild cases and by 34th week in more severe cases. Antihypertensive treatment should be instituted if diastolic blood pressure exceeds 84 mmHg in the second trimester and 94 mmHg in third trimester. If the fetal maturity and weight are satisfactory at the time of detection of hypertension, labour may be induced. Depending on the facilities in the premature baby unit, labor is induced when the fetal weight is 1.5-1.8 kg. Prescription of antihypertensive drugs to hypertensive pregnant women should be done with caution.

Centrally-acting alpha-2 receptor agonists, e.g. methyldopa; vasodilators, e.g. hydralazine; beta adrenergic blockers, e.g. atenolol; combined alpha-beta receptor blocking agents, e.g. labetalol and calcium channel blockers, e.g. nifedipine are safe. Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor antagonists are not safe. Diuretics are generally avoided. In case of hypertensive emergency, hydralazine is given IV/IM in doses of 10-50 mg every 4-6 hours or orally in doses of 25-50 mg tid or qid. Labetalol given orally in doses of 100-200 mg bd or in doses of 20-80 mg IV bolus every 10 minutes or 0.5 to 2 mg/min as infusion is a good alternative. Sodium nitroprusside is avoided since thiocyanate levels in blood increase, leading to cyanide toxicity and reduction in placental blood flow. This increases the risk to fetus.

Once pre-eclampsia is confirmed, the expectant mother is hospitalized and the condition is assessed as mild, moderate or severe. In mild and moderate PE, if pregnancy is close to term (36 weeks or later) and fetal maturity is acceptable, delivery should be induced. If the period of gestation is less than 36 weeks, the mother is closely observed and parameters like blood pressure, urine output, proteinuria, optic fundi, neurologic status, blood urea, serum creatinine, serum uric acid, lactic dehydrogenase, platelet count and aspartate amino transferase are monitored. Attainment of fetal lung maturity is the most important factor which influences the decision for pre-term delivery. Fetal lung maturity can be assessed by estimation of lecithin/sphingomyelin ratio. The normal ratio is > 3.5:1. If the ratio is > 2:1, it indicates adequate lung maturity for induction of labour.

Convulsions can be arrested and further occurrence prevented by the timely use of parenteral magnesium

sulphate. Dose of magnesium sulphate is 4 g given as IV injection of 20 mL of 20% solution given over 5 minutes. This is followed by deep intramuscular injection of 10 mL of 50% solution on the buttock. This can decrease risk of eclampsia. The loss of patellar jerk is the earliest warning sign of impending magnesium toxicity. Administration of magnesium sulphate is often continued for 24 hours postpartum. It acts at the neuromuscular junction. Long-term use of diazepam as an anticonvulsant is not favourable for the fetus, since it may cause hypotonia, drowsiness and apnea for several hours after birth.

Those who develop pre-eclampsia may be predisposed to endothelial injury and they have an eight-fold increase in the risk of cardiovascular disorders, hypertension and stroke in later life. They have also an increased risk of dyslipidemia, insulin resistance, anemia and lung diseases.

Rollover test is a simple, nonspecific, noninvasive test performed between 28 and 32 weeks. It can be used to detect patients at risk of PE. The blood pressure is recorded repeatedly 15 minutes after the subject assumes lateral recumbent posture till consistent readings are obtained. Then she rolls over to the supine position and blood pressure is checked after one minute. Any increase in diastolic blood pressure of more than 20 mmHg indicates as positive test. A negative test indicates less likelihood of developing PE.

Antiplatelet agents like aspirin have a prophylactic role in high risk individuals even though it cannot be recommended as routine prophylaxis. Low dose aspirin therapy may be used in the following situations: (1) A positive family history of pregnancy induced hypertension, (2) previous history of pre-eclampsia, (3) teenage pregnancy, (4) pregnancy above the age of 35 years, (5) pre-existing renal disease with hypertension, (6) multiple pregnancy, (7) Rh negative mother, diabetic mother and (8) a positive roll-over test.

The syndrome of hemolysis, elevated liver enzymes and thrombocytopenia (HELLP syndrome) has been recognized as a complication of pre-eclampsia and eclampsia. It's frequency is 0.1%. The typical hepatic lesion associated with HELLP syndrome is periportal or focal parenchymal necrosis, in which large hyaline deposits of fibrin-like materials can be seen in the sinusoids. Renal dysfunction is also common. Prompt induction of delivery within 24 hours of the diagnosis is the treatment of choice. Delay in delivery may lead to high maternal and fetal morbidity and mortality.

PREGNANCY AND RENAL DISEASES

Renal diseases may develop *de novo* in pregnancy or a latent renal disease may manifest during pregnancy. Pregnancy may supervene on pre-existing overt renal

disease. When proteinuria is first discovered after the twentieth week of pregnancy, the differential diagnosis is between pre-eclampsia and underlying renal disease. Proteinuria, hypertension, edema and renal insufficiency occur in both settings. Elevated serum uric acid out of proportion to the severity of renal insufficiency suggests the diagnosis of pre-eclampsia. Presence of glomerular capillary endotheliosis is specific for pre-eclampsia.

Kidney diseases during pregnancy can affect both the mother and fetus. Women with moderate or advanced renal failure generally have anovulatory cycles or amenorrhea. If they conceive, the outcome is unfavorable. Women with mild renal failure (serum creatinine < 2.3 mg/dL) can conceive and go through the pregnancy successfully. The overall fetal outcome depends on the degree of renal functional impairment, degree of control of hypertension and severity of proteinuria on conception.

Generally, pregnancy does not influence the natural course of renal disease adversely if renal function is well preserved and the blood pressure is normal at conception. Those with lupus nephritis, IgA nephropathy, membranous glomerulopathy or focal and segmental glomerulosclerosis may have further deterioration of the original disease during pregnancy or puerperium. The important risk factors are nephrotic range proteinuria, hypertension and impaired renal function. Renal disease complicated by pregnancy must be considered as “high risk” pregnancy and managed by an experienced team of nephrologists and obstetricians.

Acute Renal Failure (ARF) in Pregnancy

Acute renal failure may complete pregnancy rarely. The frequency has been brought down by improved prenatal care, better management of maternal complications and decrease in illegal abortions. The incidence of ARF in pregnancy has a bimodal pattern. The causes in the first trimester are:

- Illegal abortion practices induced by crude methods
- Nephrotoxic abortifacients
- Dehydration due to hyperemesis gravidarum
- Shock due to bleeding
- Urinary infection and
- Septicemia.

During the third trimester, ARF results from

- Severe pre-eclampsia/eclampsia
- HELLP syndrome
- Abruptio placentae
- Postpartum hemorrhage
- Hypotension
- Intrauterine death
- Amniotic fluid embolism and
- Disseminated intravascular coagulation.

Multiple factors may operate in the same patient and result in severe ARF. Bilateral renal cortical necrosis occurs more frequently in women with placental abruption. Pre-existing nephrosclerosis, renal ischemia, and disseminated intravascular coagulation predispose to development of renal cortical necrosis.

Idiopathic postpartum acute renal failure, follows an apparently normal pregnancy and manifests usually between one day to several weeks after delivery. The onset is a “flu-like” illness followed by rapidly developing renal failure. The blood pressure is usually normal. Congestive cardiac failure and convulsions may occur in some cases. The cause of the syndrome is not clear. Retained placental fragments, oral contraceptives, oxytocin, ergot alkaloids, prostaglandin deficiency and immunologic basis have all been incriminated. Circulating large multimers of von Willebrand’s factor (vWF) lead to platelet aggregation and thrombosis in renal circulation, resulting in renal damage. The management consists of bringing the blood pressure to normal and supportive measures. The renal function may not recover fully. Specific measures include plasmapheresis done daily or on alternate days for the initial 2 weeks. Plasmapheresis helps to remove the toxins and vWF multimers.

Management of Acute Renal Failure in Pregnancy

The general management of acute renal failure in pregnant and nonpregnant subjects is essentially similar. Prerenal factors are corrected. In case of blood loss, the appropriate quantity is replaced under supervision. In case of established renal failure, early or prophylactic dialysis is advocated since the uremic toxins cross the placenta and reduce the chances of fetal survival. The choice of dialysis therapy is individualized and both peritoneal and hemodialysis can be undertaken. Excessive fluid shifts during dialysis should be avoided. If the fetus is viable, it should be delivered as soon as the maternal condition improves. The neonate will have higher blood levels urea and creatinine at birth leading to osmotic diuresis. This should be recognized and managed with prompt hydration.

Urinary Tract Infections

Asymptomatic Bacteriuria

Asymptomatic bacteriuria is characterized by absence of urinary symptoms in spite of significant bacteriuria. Because of the anatomical and functional changes in the urinary tract and increased urinary excretion of amino acids, protein, calcium, glucose and vitamins during pregnancy, asymptomatic bacteriuria may occur in 5-10% of all pregnancies. It is more common when pre-existing conditions like diabetes mellitus, sickle cell disease, renal

diseases, multiparity, low socioeconomic background or hypertension are present. Although asymptomatic bacteriuria may be a relatively benign disorder not requiring active treatment in nonpregnant subjects, 30-50% of pregnant women with asymptomatic bacteriuria develop symptomatic urinary tract infection. Asymptomatic bacteriuria may be associated with increased incidence of pre-eclampsia, premature delivery, anemia and low birth weight. Therefore, routine screening of all pregnant mothers during the first trimester for bacteriuria is advocated. If detected, any one of the following antibiotics should be administered orally for 14 days.

Amoxycillin 500 mg 8 h, ampicillin 500 mg 6 h, cephalexin 500 mg 6 h or cefixime 200 mg 12 h.

The patient should be followed up with urine cultures every month till delivery. In women in whom asymptomatic bacteriuria is difficult to eradicate, continuous antibiotic therapy during pregnancy and detailed investigations to rule out urinary tract obstruction in the postpartum period are warranted.

Acute Pyelonephritis

Symptomatic renal parenchymal infection with fever, rigor, chills, loin pain and pyuria may occur in about 1% of all pregnancies. Severe infections may lead to renal cortical abscess, renal carbuncle, sepsis, shock and fetal loss. Those with asymptomatic bacteriuria, having previous episodes of urinary tract infections or congenital abnormalities of the urinary tract are more prone to develop acute pyelonephritis. The patient should be hospitalized and prompt treatment instituted. Urine and blood samples should be sent for culture, and treatment with intravenous fluids, antipyretics and antibiotics started. In severe infections, antibiotics which reach high concentrations in the renal parenchyma and which have no adverse effects on the fetus should be started immediately, e.g. amoxycillin 500 mg 8 h or cefotaxime 1g 6 h or ceftazidime 1 g 6 h IV. When the fever is controlled for 48-72 hours, antibiotics have to be continued orally for a total period of three-weeks to ensure eradication of infection. During follow-up, urinalysis and cultures are essential. Tetracycline should be avoided during

pregnancy. Co-trimoxazole should not be given near term because of the risk of kernicterus in the newborn. Aminoglycosides may cause ototoxicity and hence they should be avoided.

Acute Fatty Liver of Pregnancy

This occurs in the third trimester and is characterized by rapid development of jaundice, bleeding, seizures and hepatic encephalopathy. Serum bilirubin and liver enzymes are elevated but the serum alkaline phosphate is usually normal. More than 50% of these patients develop acute renal failure. The cause of ARF may be prerenal and hemodynamic factors as in the hepatorenal syndrome. The mortality is high due to hepatic rather than renal failure. Prompt delivery usually improves the liver function. The subsequent pregnancies may be normal.

Systemic Lupus Erythematosus (SLE)

(see also Chapter 106)

This increases the risk both to the mother and the fetus. The effect of gestation on lupus and the effect of lupus on gestation are variable. If the disease is not active for at least one year prior to conception and renal functions are normal, the chances for uneventful pregnancy are good and postpartum aggravation of lupus activity is unlikely. If the woman had active lupus at the time of conception or the symptoms develop during pregnancy for the first time, the outcome may be unfavorable. Flare up of lupus occurs during pregnancy, especially in those having thrombocytopenia and hypertension, but the episodes are usually mild to moderate. In about 10% of patients, there is exacerbation of lupus activity postpartum leading to acute renal failure. For this reason, the dose of steroids may be increased prophylactically after delivery and tapered off over the next three months.

The autoantibodies may cross the placenta and result in repeated abortions. In particular, the presence of antiphospholipid antibodies considerably worsens the fetal outcome. Such patients require special therapy for successful outcome. The presence of antinuclear antibodies may lead to the lupus syndrome in the neonate characterized by transient skin rash, pancytopenia and transient heart block.

Chapter Summary

General Considerations 1155

Clinical Features 1156

Diagnosis 1156

Management 1156

GENERAL CONSIDERATIONS

Obstruction of the urinary tract (obstructive uropathy) may occur anywhere between the renal tubule and the urethral meatus. The impedance to the normal flow of urine results in complex structural and functional changes in the kidneys and urinary tract. Based on the site of obstruction, it can be classified as intrarenal and extrarenal. The extrarenal obstruction may be upper urinary tract obstruction (obstruction above vesicoureteric junction VUJ) or lower urinary tract obstruction below the VUJ. Urinary obstruction may be unilateral or bilateral, complete or partial, acute or chronic and may be caused by extraluminal or intraluminal causes.

Obstructive uropathy is defined as the structural and functional changes in the urinary tract that impede the normal flow of urine. Changes in the kidney secondary to the obstruction of the urinary tract are termed obstructive nephropathy. The terms hydronephrosis and hydroureterosis denote only dilatation of the drainage system and does not mean obstruction.

Causes of Urinary Tract Obstruction**A. Upper urinary tract obstruction**

1. Causes in the lumen
 - Crystals and stones
 - Sloughed renal papillae
 - Blood clots
2. Causes in the wall
 - Functional - Pelviureteric junction (PUJ) or vesicoureteric junction (VUJ) obstruction
 - Tumours (transitional cell carcinoma)

- Infections (tuberculosis)
 - Strictures (tuberculosis, radiation, other granulomas)
3. Causes outside the wall
 - Retroperitoneal fibrosis
 - Pelvic tumours – fibroid, carcinomas of uterus, cervix, ovary and prostate
 - Radiation sequel
 - Lymph nodes
 - Crohn's disease
 - Aneurysm of abdominal aorta
 - Aberrant arteries
 - Retrocaval ureter
- B. Lower urinary tract obstruction**
1. Causes in the lumen
 - Stones
 - Blood clots
 2. Causes in the wall
 - Urethral stricture
 - Posterior urethral valve
 - Phimosis, paraphimosis, meatal stenosis
 - Carcinoma of bladder
 - Trauma
 - Functional causes – neurogenic bladder
 - Anticholinergic drugs
 - Levodopa
 3. Causes outside the wall
 - Prostatic enlargement,
 - Infiltrating pelvic malignancies.

Pathophysiology

When the urinary system is obstructed, changes occur in both glomerular and tubular function. The GFR declines progressively depending on whether the obstruction is complete or partial, unilateral or bilateral and acute or chronic. Abnormalities in tubular function include impairment of concentrating and acidifying function. If the obstruction is relieved within 1-2 weeks, there is normalization of glomerular and tubular functions. Chronic obstruction for more than 12 weeks results in irreversible destruction of renal parenchyma. **1155**

In such cases, functional recovery may be incomplete even after relief of obstruction. Eventually, the nephrons and renal parenchyma are replaced by extracellular matrix. When prolonged obstruction is relieved, there is temporary inability to concentrate urine or reabsorb solutes. This leads to polyuria, salt wasting and hypokalemia. This may last for variable periods. This is referred to as '*post-obstructive diuresis*'. Pathologically, marked thinning of cortex occurs over many months with atrophy of tubular structures, obliteration of nephrons, progressive sclerosis and fibrosis of the renal parenchyma.

CLINICAL FEATURES

The clinical manifestations depend on the site, degree and duration of obstruction. Pain is a common presenting symptom and is due to distension of the bladder, collecting system or renal capsule. Pain is more severe in acute, compared to chronic obstruction. The location and quality of pain often help to determine the site of obstruction. Obstruction at pelviureteric junction causes colicky pain in the loin. Mid-ureteric obstruction usually produces sudden lumbar pain with radiation from loin to groin. In lower ureteral obstruction the pain radiates to the ipsilateral testicle, labia or inner part of the upper thigh. Distension of the bladder with stretching of the trigone leads to frequency, strangury and radiation of pain to tip of the penis. In lower urinary obstruction, the patient often complains of poor stream, intermittency, hesitancy, urgency, precipitancy, dribbling, nocturia or urinary incontinence. Urinary obstruction predisposes to resistant urinary infection. Infection can be eradicated only when the obstruction is cleared. In a chronically obstructed urinary system infection with proteus group of organisms and secondary stone formation are common. In neonates and children with posterior urethral valve, secondary vesico-ureteral reflux may occur and lead to progressive renal damage. Obstruction due to calculi or neoplastic lesions may lead to hematuria. Complete lower urinary tract obstruction, bilateral ureteric obstruction or obstruction to a single functioning kidney leads to anuria. In partial obstruction, the urine output may be normal or even increased.

One or both kidneys may be enlarged and palpable depending on the site of obstruction. In the case of lower

tract obstruction, the distended bladder may be palpable and tender. Enlarged prostate is identified by rectal examination. In females, pelvic examination is required to detect local malignancy. Hypertension may occur in some cases due to salt and water retention or renin release.

Proteinuria, hematuria, pyuria and bacteriuria may be present. Rarely urine examination may be 'normal'. In chronic obstruction, the specific gravity of urine is less than 1.010. Bilateral obstruction is associated with features of renal failure. There is impaired excretion of acid and potassium and this leads to type IV renal tubular acidosis (hyperchloremic hyperkalemic metabolic acidosis).

Diagnosis

Diagnosis is often made by history and physical examination. After the preliminary evaluation including urinalysis, urine culture, hemogram, assessment of renal function and electrolytes, imaging studies are undertaken. Ultrasonography detects dilatation of the urinary tract in almost all cases. Other investigations include X-ray of the abdomen for KUB, intravenous urogram, retrograde pyelogram, CT Scan and magnetic resonance imaging. Non-contrast enhanced helical CT is now used as the primary imaging modality for assessment of acute flank pain. Isotope renography with IV frusemide (diuretic renogram) is helpful in the diagnosis of obstruction in patients with good renal function.

Management

This depends on the site and cause of obstruction and the degree of renal impairment. In acute obstruction, rapid intervention helps to salvage the kidney.

Methods used for relief of obstruction include—

- Urethral catheters or suprapubic cystostomy for urethral obstruction: Relief of obstruction should be gradual in chronic obstructive lesions.
- Cystoscopy and passage of retrograde ureteral catheter or nephrostomy for upper urinary obstruction.

These procedures are undertaken with appropriate antibiotics. Specific therapy is decided depending in the cause of obstruction after the patient is stabilized. Relief of obstruction and further management of the causative lesions is the realm of the urologist.

Chapter Summary

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Definition

Acute renal failure (ARF) is defined as a potentially reversible rapid decline in the excretory function of the kidney which develops over hours to days leading to retention of nitrogenous waste products and the consequent clinical complications. ARF occurs due to various etiological factors.

Epidemiology

ARF complicates the clinical course of upto 5% of all hospital inpatients and nearly 30% of Intensive Care Unit (ICU) admissions. The annual incidence of adult ARF in the general population is 200 /million.

Classification

ARF can be classified based on epidemiology, etiology or pathophysiology.

Epidemiologic Classification

- 1. Community Acquired ARF (CAARF)
- 2. Hospital Acquired ARF (HAARF)
ARF acquired in the community behaves differently in its etiology, severity and outcome from that acquired in hospitals. Generally, CAARF has a better outcome and lower mortality compared to HAARF - 15% Vs 25%.
The common causes of CAARF include gastro-enteritis, diarrheal disease, viperine snake envenomation, leptospirosis, herbal toxins, falciparum malaria, copper sulphate poisoning, obstructive nephropathy and others.

The etiology varies from place to place depending on local characteristics. Most cases of HAARF result from pre-renal factors. Sepsis, postsurgical ARF and iatrogenic factors such as nephrotoxic drugs are important causes in the hospital setting.

Pathophysiologic Classification

- 1. Prerenal
- 2. Intrinsic renal
- 3. Postrenal

Prerenal	Decreased extra-cellular fluid volume Low cardiac output Impaired renal autoregulation Alteration in systemic to renal vascular resistance ratio
Intrinsic renal	Acute tubular necrosis Glomerular diseases Interstitial nephritis Vascular (macro-and microvascular) causes
Postrenal	Ureteric obstruction Bladder neck obstruction Urethral obstruction

Pre-renal Causes of ARF

Prerenal ARF is the most common form. The term ‘pre-renal’ is used when renal dysfunction is caused by decrease in renal perfusion. Restoration of renal perfusion results in rapid recovery of renal function in the early stages, before irreversible changes develop. Prerenal ARF occurs in diseases associated with reduction in extracellular fluid volume as is seen in gastrointestinal fluid loss (vomiting, diarrhea), burns, hemorrhage, third space fluid sequestration or excessive renal fluid losses. Conditions associated with a reduction in the ‘effective arterial blood volume’, seen in low cardiac output states such as myocardial, pericardial or valvular diseases, pulmonary hypertension and others, account for many cases. Other causes include drugs interfering with the autoregulation of renal blood flow and GFR such as COX

inhibitors and ACE inhibitors. Systemic to renal vascular resistance ratio is altered when there is systemic vasodilatation or intra-renal vasoconstriction. This may occur in sepsis, anesthesia and anaphylaxis leading to prerenal failure.

ARF may be broadly classified into medical ARF, surgical ARF, obstetric ARF

Intrinsic Renal Causes of ARF

The most common cause of intrinsic ARF is ‘acute tubular necrosis’ (ATN). ATN may be caused by ischemic or nephrotoxic injury. However in a large number of cases the cause is multifactorial. Conditions which cause prerenal failure may lead to renal ischemia and ATN. Substances toxic to the renal tubule are called tubular nephrotoxins, e.g. aminoglycosides, radiocontrast media, heme pigments and others. The hallmark of ATN is structural damage to the tubular cell, which regenerates over a few weeks with recovery of renal function.

Other intrinsic renal causes of ARF include acute glomerulonephritis, rapidly progressive glomerulonephritis, acute vasculitides, hemolytic uremic syndrome, malignant hypertension, acute cortical necrosis, acute allergic interstitial nephritis, acute pyelonephritis, intratubular obstruction due to heavy crystalluria and paraproteinemias. Rarely acute bilateral occlusion of renal arteries or veins by thrombosis or embolism leads to ARF.

Postrenal ARF

About 5% of cases of ARF are due to urinary tract obstruction. Obstruction at the bladder neck is the most common site. Ureteric obstruction causes ARF either when it is bilateral or it is a solitary functioning kidney. It is important to recognize obstruction since early correction leads to complete recovery.

Further discussion in this chapter will be confined to ATN which comprises more than 2/3 of all cases of ARF.

ARF used to be classified depending on the etiological setting from which renal failure develops. However this approach has been abandoned because of the advantages of the other classification systems.

Pathogenesis

The traditional views have given place to modern concepts

Pathogenetic mechanisms in ATN	
Traditional view	
Hemodynamic factors:	
Renal vasoconstriction mediated by humoral and neural mechanisms	
Tubular factors:	
Tubular obstruction	
Back leak of tubular fluid	
Modern concept	
Cellular mechanisms play the major role	

The following mechanisms have been postulated to explain the pathogenesis of renal failure in ATN.

1. *Tubular obstruction*: Intraluminal debris, cast formation or interstitial edema arising out of tubular necrosis results in renal tubular obstruction. Tubular obstruction, in turn, raises the intraluminal pressure which leads to reduction of GFR in ATN.
2. *The back leak theory*: Due to the disruption of the integrity of the renal tubular epithelium, the glomerular filtrate leaks back into the interstitium, leading to retention of fluid and waste products.
3. *Hemodynamic theories*: Hypovolemia, whether absolute or relative and sustained renal vasoconstriction results in a reduction of GFR. Cardiovascular baroreceptors and the sympathetic nervous system are activated. The vasopressor mechanisms such as renin-angiotensin-aldosterone system, vasopressin, and other vasopressors including endothelin are stimulated. All these factors act together to sustain the blood pressure, the cardiac output and cerebral perfusion. But in the kidney, intrarenal hemodynamics is deranged by the overplay of the vasopressors. This results in afferent arteriolar constriction, efferent arteriolar dilatation and decreased permeability of the glomerular membrane, all leading to reduction in GFR.
4. *Cellular mechanisms*: Several cellular and subcellular mechanisms have been identified in the renal tubular cells. Cytoskeletal injury, loss of cell polarity, impaired cell-cell and cell-matrix interactions, necrosis and apoptosis lead to the development of ATN. In addition to ischemia, reperfusion injury results in free radical induced oxidative stress, release of pro-inflammatory cytokines and reduction in nitric oxide, further perpetuating the injury.

Recovery and repair mechanisms are also mediated by growth factors which are released locally.

Clinical Features

- **Prerenal failure.** The most important symptom which draws the attention of the clinician to renal failure is oliguria. Patients commonly present with symptoms related to hypovolemia, including thirst, dizziness, and orthostatic hypotension. Evidence of excessive fluid loss through gastrointestinal tract, hemorrhage, sweating or renal losses may be present. Patients with advanced cardiac failure and renal hypoperfusion may present with signs of cardiac failure.
- **Intrinsic renal failure.** ATN should be suspected in any patient presenting after a period of hypotension secondary to hemorrhage, sepsis, drug overdose, or surgery. About 30% of patients with ATN may remain non-oliguric, especially those with nephrotoxic injury caused by drugs or radiocontrast agents. A careful

search for exposure to nephrotoxins should include a detailed history of all current medications and any recent radiocontrast administration. Allergic interstitial nephritis should be suspected with recent drug ingestion, fevers, rash, and arthralgias. Nephritic syndrome of hematuria, edema and hypertension point to glomerular etiology of ARF.

- **Postrenal failure.** Postrenal failure usually occurs in older men with prostatic obstruction, main symptoms being urgency, frequency hesitancy and obstruction to flow of urine. In women, the common causes include gynecologic conditions like prolapse, carcinoma cervix or irradiation of pelvic structures. Renal calculi and papillary necrosis present with flank pain and hematuria.

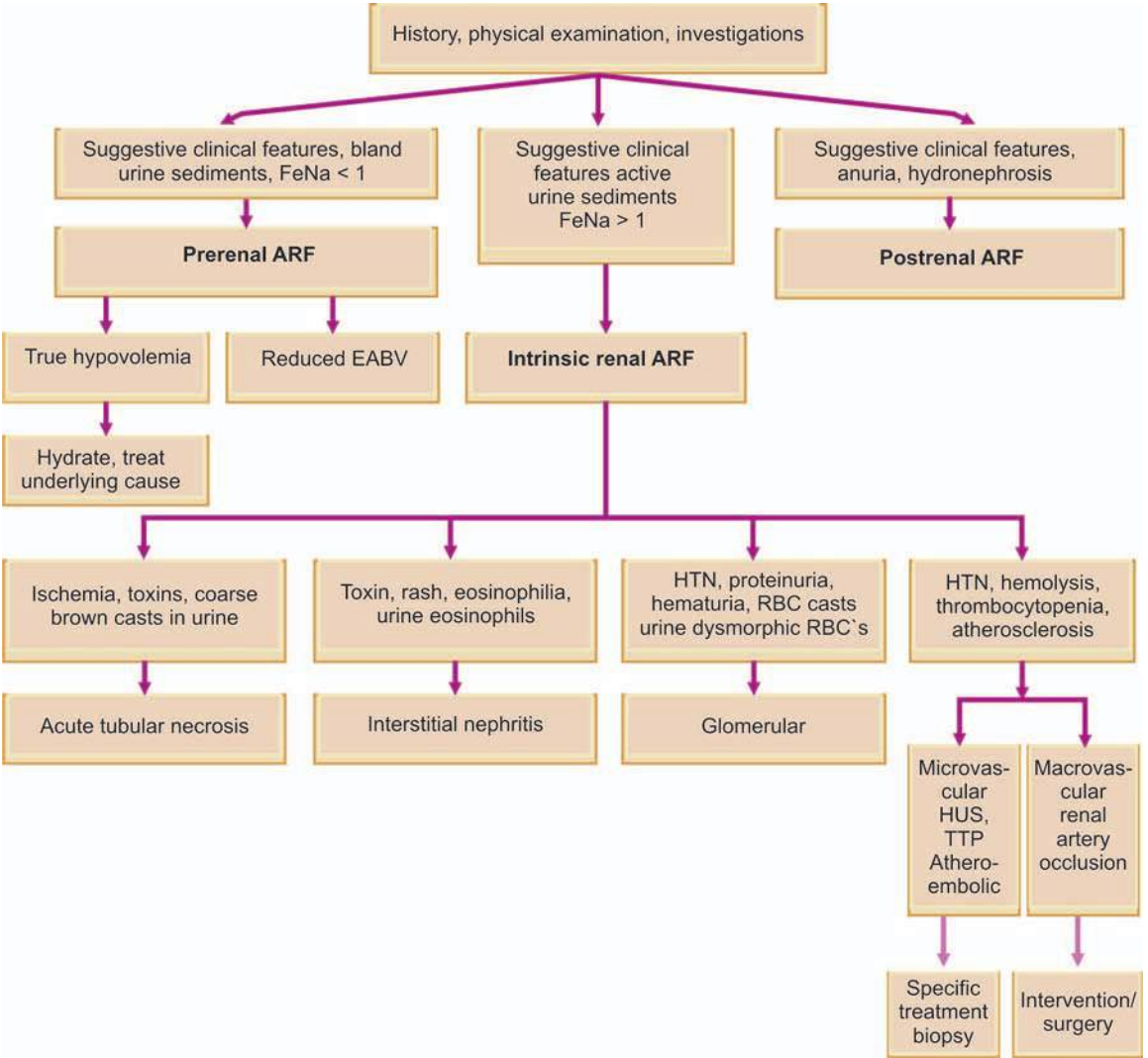
The most important part of the physical examination is the assessment of cardiovascular status and the state of hydration. Regular recording blood pressure helps to

identify hypovolemia early. Postural hypotension is the earliest sign of hypovolemia. Severe congestive cardiac failure (CHF) may cause hypotension without hypovolemia (Flow chart 178.1).

Investigations

- **Urinalysis:** Urinalysis is important in the initial evaluation of ARF. The daily urine output is usually low in about 2/3rd of the patients whereas in the remaining third, it may be normal or even increased. Reddish brown or cola-colored urine is present in patients with acute glomerulonephritis or in the presence of myoglobin or hemoglobin in the plasma. Presence of RBCs and RBC casts are very suggestive of acute glomerulonephritis. The presence of WBCs or WBC casts may denote pyelonephritis or acute interstitial nephritis. Presence of eosinophils in urine

Flow chart 178.1: Diagnosis of acute renal failure



suggests arterial embolic disease, or drug-induced interstitial nephritis. Presence of granular muddy-brown casts is suggestive of tubular necrosis.

- Complete blood cell counts and peripheral smear. These tests may be useful, and the peripheral smear may show schistocytes in conditions such as hemolytic uremic syndrome or thrombotic thrombocytopenic purpura.
- *Blood urea and serum creatinine:* Increase in the levels of blood urea and creatinine is the hallmarks of renal failure, the rate of rise of urea and creatinine is more important for confirming the diagnosis and follow-up. In prerenal failure, the rate of rise of urea is higher than that of creatinine. The proportion of urea to creatinine is usually 20 :1.
- *Urinary electrolytes:* The fractional excretion of sodium (FENa) is commonly used as an indicator of tubular integrity. The formula for calculating the FENa is given below:

$$\text{FENa} = (\text{U}_{\text{Na}}/\text{P}_{\text{Na}}) / (\text{U}_{\text{Cr}}/\text{P}_{\text{Cr}}) \times 100$$
 where, U and P represent Urine and Plasma, Na = sodium and Cr = creatinine.
 The FENa helps to differentiate oliguria caused by prerenal failure from that caused by established acute tubular necrosis. In prerenal failure the FENa is usually less than 1% whereas in ATN, it is greater than 1%. Exceptions to this rule are ATN caused by radiocontrast nephropathy, severe burns or ATN following diuretic use.
- *Ultrasound examination:* Renal ultrasonography is useful for detecting intrinsic renal disease and ruling out chronic renal failure and obstructive uropathy. Doppler studies can detect thromboembolic or renovascular disease.
- *Serologic tests:* These tests are very informative if ordered judiciously even though they are expensive. Tests such as antinuclear antibody, ANCA, cryoglobulins, and hepatitis serology markers are helpful when ARF is suspected to be due to systemic vasculitis.

Renal biopsy: This is the diagnostic investigation when other tests are inconclusive. It is particularly useful in conditions like RPGN and for distinguishing between acute glomerulonephritis and interstitial nephritis.

Management of ARF

Principles of management of ARF

1. Treatment of the underlying cause
2. Maintenance of fluid and electrolyte balance
3. Maintenance of nutritional status.
4. Monitor for life-threatening complications
5. Renal replacement therapy when indicated

Treatment of the Underlying Cause

The cornerstone in the management of ARF is the treatment of the underlying cause. The most important factor determining the outcome is the severity of the underlying disease. For example ARF complicating sepsis in the ICU setting has a mortality of up to 70%. On the other hand, ARF following snake envenomation and leptospirosis have a mortality of only around 30-40% even though they are severe and they need dialysis support.

Prerenal ARF improves with restoration of renal perfusion, by appropriate fluid therapy. The use of vasodilators and ionotropes help to restore renal perfusion in congestive heart failure.

In postrenal ARF, relief of obstruction is the crucial factor influencing recovery of renal function. Specific therapy of the underlying cause of obstruction such as prostatic enlargement ensures recovery.

Maintenance of Fluid and Electrolyte Balance

Hypovolemia potentiates and exacerbates all forms of ARF. In many forms of ARF, correction of hypovolemia may be the only treatment required. Fluid replacement should be undertaken carefully to avoid fluid overload and pulmonary edema. Therefore accurate determination of a patient's fluid volume status is essential. Loss of skin turgor, dryness of the mucous membranes and postural fall in blood pressure are reliable clinical parameters of volume depletion. Fluid intake-output chart and daily weight monitoring are essential to detect changes in the fluid volume status promptly. Monitoring of central venous pressure is indicated especially when there is severe volume depletion, clinical signs are equivocal and the patient is oliguric or anuric. In established ARF diuretics do not influence the final outcome. They are used to convert oliguric to nonoliguric ARF in order to facilitate easier fluid management.

Hyperkalemia and acidosis are the most serious and life-threatening disturbances in the acute setting. The treatment depends on the degree of hyperkalemia and the changes seen on the electrocardiogram. Calcium gluconate 10 mL of a 10 percent solution given slowly IV is cardioprotective and temporarily reverses the neuromuscular effects of hyperkalemia. Potassium can be temporarily shifted into the intracellular compartment by intravenous administration of 10 units of soluble insulin and 25g of glucose. Inhalation of beta agonists such as salbutamol or IV administration of sodium bicarbonate achieves the same purpose. Elimination of potassium is achieved by using ion-exchange resins like sodium polystyrene sulfonate and diuretics. Sodium polystyrene sulfonate is given orally (25 to 50 g mixed with 100 mL of 20 percent sorbitol) or as an enema (50 g in 50 mL of 70 percent

sorbitol and 150 mL of tap water). If these measures do not control the potassium level, dialysis should be initiated. Acidosis is corrected by giving IV or oral sodium bicarbonate if the serum bicarbonate level is less than 15 mEq per L or the pH is less than 7.2. Intractable acidosis requires dialysis for correction.

Maintenance of Nutritional Status

Acute renal failure is a catabolic state and therefore, patients need nutritional support. The total daily caloric intake should be 30 to 45 kilocalories/kg bw. Most of this should be derived from a combination of carbohydrates and fats. In patients who are not on dialysis, protein intake should be restricted to 0.6 g/kg per day. Patients on dialysis need a daily protein intake of 1 to 1.5 g/kg body weight. Fluid administration is based on the urine output, body temperature and ambient temperature in all forms of ARF. Fluid restriction is crucial in the management of oliguric renal failure. In non-oliguric renal failure, the fluid administration can be more liberal. Since the levels of potassium and phosphorus may go down in non-oliguric renal failure, they have to be monitored and supplemented.

Life-threatening Complications

Several life threatening complications may develop which require prompt management including renal replacement therapy. These complications are:

- Volume overload
- Hyperkalemia ($K^+ > 6.5$ mmol/L or it is rising)
- Acid-base imbalance, mainly metabolic acidosis
- Symptomatic uremia (pericarditis, encephalopathy, bleeding diathesis, nausea, vomiting, pruritus)
- Severe azotemia (If BUN > 100 mg/dL or creatinine > 5 mg/dL).

Renal Replacement Therapy

The principal methods of renal replacement therapy (RRT) are intermittent hemodialysis (IHD), continuous veno-venous hemofiltration (CVVH), and peritoneal dialysis (PD). Each has advantages and limitations.

IHD is widely available and is the most efficient way to remove solutes and fluids. Dialysis-associated hypotension is an adverse factor, particularly in patients who are critically ill.

CVVH is the technique of choice in patients who are hemodynamically unstable. In this hypotension does not occur. It is more expensive and it is available only in a few centers. CVVH achieves patients on better control of uremia and clearance of solutes. Since the procedure is continuous, patients on CVVH are able to remove larger fluid volumes. This is an added advantage for patients on parenteral nutrition and multiple infusions.

Peritoneal dialysis is relatively inexpensive and widely available. It does not lead to hypotension. It has been widely used in managing ARF, with good results.

179

Chronic Kidney Disease

Ramdas Pisharody

16

Chapter Summary

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Chronic kidney disease (CKD) is an important public health problem affecting more than 10% of the general population. CKD is an important risk factor progressing to end stage renal disease (ESRD), cardiovascular disease and premature mortality. Management of ESRD is expensive and beyond the reach of many sections of the population in developing countries. CKD is a silent disease and if not detected and treated early, may progress

to ESRD. Hence, it is important to identify CKD early and institute measures to retard its progression.

Definition and Staging

Chronic kidney disease is defined as either kidney damage or GFR <60mL/min/1.73m² for ≥3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

CKD is characterized by kidney damage characterized by structural, functional or pathological abnormalities in the kidney associated with abnormalities in the composition of urine and/or blood of more than 3 months duration. Anomalies in the imaging tests and decrease in the GFR may be demonstrable. If the GFR is less than 60 mL/min/1.73 m² body surface, persisting for more than 3 months, this by itself can constitute CKD.

Stages of Chronic Kidney Disease

Stage	Description	GFR (mL/min/1.73m ²)
1.	Kidney damage with normal or increased GFR	≥ 90
2.	Kidney damage with mild decrease in GFR	60-89
3.	Moderate decrease in GFR	30-59
4.	Severe decrease in GFR	15-29
5.	Kidney failure	< 15 or dialysis

The present concept of CKD was put forth by the K-DOQI (Kidney Disease Outcomes Quality Initiative) in 2002. Over the years, there has been a shift in nomenclature from *chronic renal failure* to *chronic kidney disease*. Chronic renal failure is defined as a condition where there is a permanent and irreversible impairment of renal function persisting over a period of three months or more. Kidney damage is defined as structural or functional abnormalities of the kidney. The markers of kidney damage include persistent abnormalities in urine tests such as proteinuria, microalbuminuria or microscopic hematuria or abnormalities in the blood such as rise in urea or creatinine. Presence of abnormalities in imaging tests like ultrasound, IVP or CT scan, such as small echogenic kidneys, hydronephrosis or polycystic kidneys even without reduction of GFR in early stages constitutes CKD. The GFR may decrease eventually.

Staging

Stage 1 CKD represents kidney damage when GFR is normal or high. This includes patients with albuminuria or those with abnormal imaging studies.

In stage 2 CKD, there is evidence of kidney damage with mild decrease in GFR (60- 89 mL/min/1.73 m²). In the absence of kidney damage, this level of GFR *per se*, does not constitute CKD.

Stage 3 CKD includes patients with moderate decline in GFR (59-30 mL/ min/ 1.73 m²). All patients with GFR of less than 60 mL/min/1.73 m² are classified as having CKD irrespective of whether kidney damage is present or not. This is the stage where serum creatinine starts to rise. Majority of patients still remain asymptomatic. Nocturia and polyuria are early symptoms that may appear at this stage.

In stage 4 CKD, the fall in GFR is severe (29-15 mL/ min/1.73 m²). Overt uremic symptoms like loss of appetite, nausea, anemia and recurrent infections occur during this stage.

Stage 5 CKD is the stage when GFR is less than 15 mL/ min/ 1.73 m². At this stage the patient usually requires dialysis or other forms of renal replacement therapy.

GFR is the best measure of overall kidney function in health and disease. GFR can be affected by chronic kidney disease which reduces the number of nephrons. Hemodynamic factors affect single nephron GFR and they result in fall in the GFR. The normal GFR of a young adult is around 120-130 mL/min/1.73 m². Normal values in women are 8% lower from those of men at all ages. Above the age of 30 years, GFR declines at the rate of approximately 1 mL/min/1.73 m² per year.

Normal range and variability of GFR

Age (sex)	Mean GFR ± SD (mL/min/1.73 m ²)
1 week (males and females)	40.6 ± 14.8
2-8 weeks (males and females)	65.8 ± 24.8
>8 weeks (males and females)	95.7 ± 21.7
2-12 years (males and females)	133.0 ± 27.0
13-21 years (males)	140.0 ± 30.0
13-21 years (females)	126.0 ± 22.0

Etiology

The causes of CKD are broadly classified as given below.

Glomerular Diseases

Primary—Focal segmental glomerulosclerosis (FSGS), IgA nephropathy, membranoproliferative glomerulonephritis (MPGN).

Secondary—Diabetes, systemic lupus erythematosus (SLE).

Tubulointerstitial diseases—Reflux nephropathy, obstructive uropathy.

TABLE 179.1

Distribution of CKD in different geographical regions in India and the USA

	Chandigarh	Chennai	Indian CKD registry	USA
Diabetes	24	30	27.5	33
Hypertension	13	11	15.5	21
Chronic glomerular disease	37	21	19.3	19
Chronic tubulointerstitial disease	14	31	8.6	4
Cystic (ADPKD) disease	3.5	2.3	2.0	6

Vascular diseases—Hypertensive nephrosclerosis, ischemic nephropathy.

Cystic diseases—Autosomal dominant and recessive polycystic kidney disease (ADPKD and ARPKD).

Heredofamilial—Alport’s syndrome.

Diseases in the transplant -Chronic allograft nephropathy.

Age, ethnicity and distribution of renal diseases may be different in various geographical regions. Diabetes and hypertension are the two most important causes of CKD world wide. In the developing countries chronic glomerulonephritis and chronic interstitial nephritis are relatively more common than in the developed countries (Table 179.1).

FSGS, IgA nephropathy, reflux nephropathy and congenital anomalies of the urinary tract lead to CRF usually before the age of 40 years. Diabetes, hypertensive nephrosclerosis, ischemic nephropathy, multiple myeloma, analgesic nephropathy and systemic vasculitis are more common above the age of 55 years.

NATURAL HISTORY AND PROGRESSION OF CKD

Many diseases can initiate kidney injury and lead to progression. Reduction in the number of functioning nephrons lead to hypertrophy and increased glomerular filtration by the surviving nephrons. Glomerular hyperfiltration initially maintains GFR but later, the overworked nephrons succumb to the increased workload and lead to proteinuria, which causes further damage to the glomeruli and the tubulo-interstitium. The extent of tubulo-interstitial damage is an important factor determining disease progression. Hypertension which is present in over 90% of cases of advanced CKD leads to further progression of the disease, if not controlled. Hyperglycemia also causes structural and functional changes in the glomeruli leading to progressive renal

failure. Progressive destruction of nephrons leads to several adaptive mechanisms which enable the remaining nephrons to maintain body homeostasis. Though these adaptive changes are beneficial, later, they lead to maladaptive consequences. For example, early in the course of renal failure, loss of nephrons result in reduction of phosphate excretion and lead to hyperphosphatemia. This causes a fall in serum calcium due to its binding to the excess phosphorus. Hypocalcemia stimulates PTH which results in reduction of tubular reabsorption of phosphate and increased phosphorus excretion. This helps to normalize serum phosphate levels. With progressive loss of nephrons, higher and more sustained levels PTH develop leading to secondary hyperparathyroidism with all its adverse consequences. The nature of the primary kidney disease and its activity also dictates the progression. The rate of progression of glomerular diseases is faster than that of tubulo-interstitial diseases (Table 179.2).

CLINICAL MANIFESTATIONS OF CKD

Renal impairment is associated with a variety of signs and symptoms that are collectively referred to as the uremic state. The symptomatology may involve any system of the body. However, there is no correlation between the development of symptoms and the severity of renal disease. The early stages of CKD are usually asymptomatic and are detected only on investigations.

Edema

Most of the glomerular diseases are associated with edema. In chronic glomerular disorders, development of intermittent edema and hematuria indicates disease activity. In disorders that are not primarily due to glomerular disorders, as in most tubulointerstitial diseases, edema appears late.

Hypertension

Hypertension is the most common manifestation and it may appear early during the course of renal disease (90% in glomerular and 30% in tubulointerstitial diseases). If untreated, it leads to further damage. Rarely, uncontrolled hypertension can lead to precipitous and irreversible reduction in GFR. Hypertension is also an independent risk factor for cardiovascular morbidity.

Cardiovascular Manifestations

Cardiovascular manifestations include left ventricular hypertrophy (LVH) due to hypertension and anemia, ischemic heart disease, congestive cardiac failure due to fluid overload and myocardial dysfunction due to uremia (uremic cardiomyopathy). Electrolyte disturbances,

TABLE 179.2

Factor affecting the onset, progress and course of CKD	
Increased susceptibility to kidney damage Older age Family h/o CKD Reduced kidney mass Low birth weight Racial factors	Directly initiate kidney damage Diabetes mellitus Hypertension Autoimmune diseases Systemic infections Urinary tract infections Urinary stones Lower urinary tract obstruction Drug toxicity
Progression factors These cause worsening of kidney damage and faster decline in kidney function after initiation of kidney damage Higher level of proteinuria Uncontrolled hypertension Poor glycemic control in diabetics Smoking Non-compliance with treatment	End stage factors increase morbidity and mortality in kidney failure Late referral Lower dialysis dose Temporary vascular access Anemia Low serum albumin level

particularly hyperkalemia can lead to bradycardia, syncope and cardiac arrhythmias. Other manifestations include premature atherosclerosis, vascular calcification due to secondary hyperparathyroidism and pericarditis. Pericarditis presents with chest pain. Loud pericardial friction rub is audible on auscultation. Sometimes, fibrinous pericarditis may lead to pericardial effusion and cardiac tamponade. CKD is a major risk factor for cardiovascular disease and even mild impairment of renal function can lead to cardiovascular morbidity and mortality. Conversely, compromise in cardiac function worsens renal function too.

Gastrointestinal Manifestations

The GI manifestations like anorexia, nausea, vomiting, dyspeptic symptoms, constipation or diarrhea usually appear in Stage 4 CKD (GFR between 15 and 30 mL/min). The symptoms are mainly due to gastrointestinal mucosal ulcerations. Uremic stomatitis with dry mucous membranes, multiple small oral ulcers and parotitis are seen in advanced uremia. Rarely, gastrointestinal hemorrhage may occur. ‘**Uremic fetor**’ describes the ammoniacal odor occurring in patients with advanced renal failure and it is due to the hydrolysis of urea in saliva by bacterial urease. Intractable hiccoughs may occur in advanced uremia. Severe abdominal pain and paralytic ileus may occur as a result of hypokalemia. Ascites may occur in advanced renal failure.

Neuropsychiatric Manifestations

Paresthesias, sensory or motor peripheral neuropathy, pruritus, restless legs syndrome and bladder dysfunction are the neurologic manifestations. Subtle to gross behavioral abnormalities such as anxiety, depression, personality changes and disturbances of sleep are the psychiatric manifestations. Flapping tremor (asterixis) and myoclonic jerks are features of uncontrolled uremia. Rarely, convulsions and coma may occur. When a patient is initiated on dialysis, abrupt and rapid removal of urea from the blood may lead to higher concentration of urea in the brain since it does not cross the blood-brain barrier rapidly. This leads to cerebral edema and transient neuropsychiatric manifestations, collectively called ‘**dialysis disequilibrium syndrome**’. This can be prevented by adjusting the initial few sessions of dialysis so as to achieve very gradual fall in blood urea. Patients on long term dialysis may develop features of dementia and this is attributed to aluminum intoxication which may occur due to intake of aluminum containing antacids or through the water used for dialysis. This is no longer a major problem at present because of water treatment which involves removal of contaminants like aluminium in dialysis water and withdrawal of use of aluminum hydroxide as a phosphate binder.

Cutaneous Manifestations

The characteristic sallow complexion in renal failure is due to pallor and the deposition of yellowish brown

urochrome pigment. Recurrent skin infections, dry scaly skin with severe itching, rashes, erythema, vesicles and ulcerations are common. Cutaneous calcification in association with secondary hyperparathyroidism contributes to the severe itching. Pruritic hyperkeratotic papular eruptions or **Kyrle's disease** occurs in diabetics. In stage V CKD, precipitation of urea on the surface of the skin gives rise to '**uremic frost**'. Bleeding into the skin and mucosa may occur as a result of platelet dysfunction. Nail changes include pitting, burrowing and '**half and half**' nails. In half and half nail, the distal half of the nail is pink or brown and the proximal half is white or pale. The conjunctival deposition of calcium leads to redness and gritty feeling in the eye also called the '**uremic red eye**' while deposition of calcium as a band in the lamina propria of the cornea leads to '**band keratopathy**.'

Hematological Manifestations

Anemia is common in chronic kidney disease. It appears when the GFR is below 50 mL/min (Stage 3 CKD) and progressively worsens as GFR declines further. Symptoms appear much later, (stage 4 CKD). Usually the anemia is normocytic normochromic. The most important cause is decreased secretion of erythropoietin (EPO). Other factors, apart from EPO deficiency which contribute to renal anemia include the following.

1. Circulating uremic toxins - bone marrow resistance to the effect of EPO.
2. Reduced RBC survival (120 days to 80 days) probably due to mild hemolysis.
3. Platelet dysfunction - Bleeding, including occult gastrointestinal blood loss.
4. Iron deficiency.
5. Hyperparathyroidism – bone marrow suppression or fibrosis.
6. Folic acid deficiency.
7. Chronic inflammation.
8. Aluminum toxicity (rare).

Prolonged anemia can lead to worsening of renal function and lead to left ventricular hypertrophy and increased myocardial oxygen demand. Disturbances in the coagulation system and platelet dysfunction are common in advanced uremia. Platelet dysfunction occurs due to factors like retention of uremic toxins, nitric oxide and hyperparathyroidism.

Skeletal Abnormalities - Renal Osteodystrophy

As renal failure progresses, hyperphosphatemia, hypokalemia and secondary hyperparathyroidism develop leading to skeletal abnormalities. Renal tubular defects

and altered vitamin D metabolism also contributes to skeletal changes of renal osteodystrophy. Stunting of growth, bone deformities and rickets occur due to end organ resistance to hormones as a result of circulating uremic toxins. Adults with advanced CKD manifest with high turnover bone disease (due to hyperparathyroidism), low turnover bone disease (due to vitamin D deficiency or aluminum toxicity) or adynamic bone disease (due to excessive suppression of PTH). Skeletal deformities are more pronounced especially in children. These manifest even before there is significant reduction of GFR. This is called **non-uremic renal osteodystrophy**. This is caused by renal tubular acidosis and disturbances in Vitamin D metabolism. With advancing renal failure, bone disease and growth retardation become more evident. Short stature is an important feature of chronic kidney disease of childhood. Uremic toxins and end-organ resistance to growth hormone/insulin like growth factor have been implicated. Prolonged use of corticosteroids may also contribute to growth retardation. Children with advanced chronic renal failure caused by chronic tubulointerstitial and glomerular diseases also develop severe rickets with deformities (**Uremic renal osteodystrophy**). In adults, the most common skeletal disturbance is hyperparathyroid bone disease (osteitis fibrosa) characterized by increased osteoclastic bone resorption. This is known as high turnover bone disease. Typical radiographic features include subperiosteal resorption in the phalanges, 'salt and pepper' pattern in the skull, vascular calcifications in peripheral arteries like radial and femoral arteries and osteosclerosis (**rugger jersey spine**). Large osteoclastic tumours may be seen (**brown tumours**) in the skeleton around weight bearing areas. A rare and unusual syndrome in patients with severe osteitis is **calciophylaxis**. This is due to extra-osseous calcium deposition in soft tissues. It manifests as painful violaceous mottling of the skin followed by progressive gangrenous ulcerations at the fingers, toes and ankles. **Osteomalacia** is the second pattern of bone disease seen in chronic kidney disease. Vitamin D deficiency and/or aluminum intoxication occurring in those receiving long-term hemodialysis aggravate this condition. It is characterized by severe bone pain, recurring fractures and proximal myopathy. In some cases, a mixed pattern of hyperparathyroidism and osteomalacia may be found. In addition, adynamic bone disease is being increasingly recognized. It is a histological diagnosis showing lack of bone formation and resorption. It is probably due to excessive suppression of PTH by calcium supplements and Vitamin D therapy.

Respiratory Manifestations

Patients with advanced kidney disease may develop dyspnea due to pulmonary edema, pleural effusion or severe metabolic acidosis. Flash pulmonary edema occurs

in patients with renovascular diseases due to accelerated hypertension. **‘Uremic lung’** may be seen radiologically as a butterfly shadow in the area of the hilum and this is due to noncardiogenic pulmonary edema associated with increased pulmonary capillary permeability and exudation of proteinaceous fluid into the alveoli. Uremic serositis may present as pleurisy with associated pleural friction rub or underlying hemorrhagic pleural effusion.

Other Manifestations

In early CKD due to chronic tubulointerstitial diseases, hyperchloremic metabolic acidosis with a normal anion gap is common. As the renal failure advances, high anion gap metabolic acidosis supervenes. Chronic metabolic acidosis has deleterious effect on the bone and several organ functions. Chronic malnutrition is common and it is caused by anorexia, nausea, poor dietary intake and vomiting. **Sexual dysfunction** is also common in both sexes. In males, it manifests as decreased libido, erectile dysfunction and azoospermia. In females, reduction of libido and menstrual irregularities are common. Patients with CKD are more prone to develop infections due to immunocompromised state. Infection tends to persist longer.

Diagnosis

Often CKD may go unnoticed until renal failure is advanced. Strong clinical suspicion and appropriate investigations are essential for early diagnosis. The diagnosis is established by demonstrating decreased GFR or markers of kidney damage. Estimation of serum creatinine and a creatinine clearance are usually used for this purpose. Though several formulas are available for calculating creatinine clearance, (CrCl) the most widely used one is Cockcroft-Gault formula:

$$\text{CrCl for males} = \frac{(140 - \text{age}) (\text{weight in kg})}{72 \times \text{serum creatinine (mg/dL)}}$$

Note: For females multiply the figure by 0.85

Markers of kidney damage include proteinuria, hematuria or abnormalities of urinary sediment. Since elevation of serum creatinine occurs only when GFR is below 50% of normal, early detection of CKD depends on the other markers.

Detection of more than 5 erythrocytes per high power field in a freshly voided specimen of urine indicates significant microscopic hematuria if present on repeated examinations. Presence of dysmorphic RBCs and acanthocytes in urine usually indicates pathology in the glomerulus. Coexistence of proteinuria and cellular casts points to renal parenchymal disease. Urinary specific

gravity and osmolality may be relatively fixed at around 1010 and 290 respectively, signifying the inability of the kidneys to concentrate or dilute urine.

Low serum calcium, high serum phosphorus with high serum alkaline phosphatase is often seen in advanced kidney disease. Serum bicarbonate is often reduced as a result of metabolic acidosis. High anion gap is due to decreased ammonium ion production and decreased excretion of hydrogen ions. Serum levels of sodium are usually normal until renal failure is very advanced. The ability of the kidney to maintain serum potassium homeostasis is preserved till the patient is in stage IV CKD. Hyperkalemia may set in early in patients consuming excessive potassium in diet and those taking potassium sparing diuretics, ACE inhibitors or angiotensin receptor blockers (ARBs).

X-ray of the skeleton may show features of renal rickets in children or osteomalacia, osteitis fibrosa or osteosclerosis in adults.

Presence of smaller kidneys detected by ultrasound imaging suggests long standing kidney disease. The exceptions to this rule include diabetes mellitus, multiple myeloma, polycystic kidney disease and obstructive uropathy. Demonstration of scarring of the kidneys may be the earliest indicator of parenchymal damage in diseases like reflux nephropathy. Asymmetry of the kidneys on ultrasound examination may be an indicator of underlying renovascular disease. Calcification and stone disease may be demonstrated by plain X-ray KUB or by ultrasound. Doppler imaging of the kidneys and renal blood vessels helps to detect renovascular disease early.

MANAGEMENT OF CHRONIC KIDNEY DISEASE

All patients require conservative management in the early stages. When the patient approaches Stage V CKD, renal replacement therapy has to be introduced.

The general management consists of:

- 1. Treatment of reversible causes.
- 2. Preventing or slowing the progression of the renal disease.
- 3. Treatment of the complications of renal dysfunction.
- 4. Identification and adequate preparation for renal replacement therapy.

Reversible Causes of Renal Dysfunction include the Following

- a. Exacerbation of original renal disease,
- b. Decrease in renal perfusion,
- c. Hypotension,
- d. Infections,
- e. Use of drugs which reduce GFR,
- f. Nephrotoxic agents,

- g. Urinary tract obstruction,
- h. Accelerated hypertension,
- i. Malnutrition, hypoalbuminemia, anemia,
- j. Congestive cardiac failure, hepatic failure and
- k. Persistent metabolic abnormalities such as hyperuricemia, hypercalcemia and hypokalemia

Preventing or Slowing the Progression of the Renal Disease

Hypertension, hyperfiltration, hypertrophy, proteinuria and dyslipidemia contribute to glomerulosclerosis and tubulo-interstitial damage.

The blood pressure should be maintained below 130/80 mm Hg by appropriate drug therapy. Administration of angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) slows the progression of chronic renal failure, particularly in those with proteinuria. This therapy is most effective if it is initiated early, before the serum creatinine level exceeds 1.5 to 2 mg/dL (132 to 176 μ mol/L).

ACE inhibitors and ARBs should be used with caution since they can cause decline in renal function and hyperkalemia. Strict glycemic control is mandatory for slowing the rate of progression. Other general measures include weight reduction, cessation of smoking, alcohol misuse and avoidance potentially nephrotoxic drugs or agents.

The progression of CKD can be slowed down by instituting measures for:

1. **Control of hypertension:** Antihypertensives should be used to achieve blood pressure less than 130/80 in patients with CKD and to < 125/75 in those with proteinuria of 1 g/day.
2. **Control of diabetes.**
3. **Diet modification:** Protein intake should be restricted to < 0.8 g /kg/day to reduce the nitrogenous load on the kidney. Salt intake should be restricted to < 5 g/day. The fluid intake should be adjusted to avoid edema. Phosphorus restriction to < 800 mg/day is recommended to reduce hyperparathyroidism.
4. **Control of hyperlipidemia:** In addition to diet control, statins should be used in doses of 10-20 mg/daily to maintain serum cholesterol below 200 mg%.
5. **Reduction of proteinuria:** ACEI and ARB's prevent progression of renal disease both by reduction of blood pressure, proteinuria and by their anti-inflammatory actions. These agents should be used early in the course of the disease, before the serum creatinine goes above 1.5 mg/dL. In some patients with renovascular disease, the renal functions may deteriorate and should be monitored.
6. **Control of hyperuricemia, hyperphosphatemia and metabolic acidosis.**

7. **Life style modification:** This consists of dietary measures, exercise programmes, control of obesity, cessation of smoking and alcohol.

Treatment of the Complications of Renal Dysfunction

The complications include disorders of fluid and electrolyte balance, hyperkalemia, metabolic acidosis, hyperphosphatemia, anorexia, nausea, vomiting, fatigue, hypertension, anemia, malnutrition, hyperlipidemia, bone disease and pericarditis.

Fluid and salt balance — Even though sodium and intravascular volume are usually maintained till the GFR falls below 15 mL/min they are unable to cope up with rapid fluctuations in fluid and electrolytes. Treatment is by restriction of dietary sodium and fluids combined with administration of a loop diuretic. Salt intake is restricted to 2-4 g per day. Single large doses of frusemide (200 - 500 mg) or torsemide (30-100mg) daily are necessary. Those with CKD and salt wasting state require additional salt intake.

Treatment of Hyperkalemia

Hyperkalemia develops in patients with CKD who are oliguric or those with increased dietary potassium intake. Use of potassium sparing diuretics, ACEI, ARB's, NSAIDs or beta blockers tend to increase serum potassium. Patients with hyporeninemic hypoaldosteronism (especially diabetics) develop hyperkalemia early in the course of their disease. Hyperkalemia can be controlled by avoidance of the offending drugs, salt and K⁺ restriction, use of diuretics and potassium binding resins. Hyperkalemia above 6 mmol/L is an emergency warranting aggressive treatment.

Treatment of Metabolic Acidosis

Metabolic acidosis is common in stages 4 and 5 CKD. This is treated by administering sodium bicarbonate in doses of 0.5-1 mmol/kg/day so as to maintain serum HCO₃ above 22 mmol/L. As an alternative, Shohl's solution which contains a buffered pair of sodium citrate and citric acid can be used. One mL of Shohl's solution provides 1 mmol of bicarbonate. Severe metabolic acidosis is however, difficult to correct without dialysis.

Treatment of Renal Osteodystrophy

Along with dietary phosphate restriction to < 800 mg/day, oral phosphate binders like calcium acetate or non-calcium based phosphate binders like sevelamer are used. These help to reduce phosphate absorption from the gut. In patients who have increased serum

parathormone levels and/or hypokalemia in spite of correction of hyperphosphatemia, 1,25, dihydroxy vitamin D supplementation is indicated.

Treatment of Anemia

The main causes of anemia in CKD include a combination of poor dietary intake of iron, blood loss and erythropoietin deficiency. The initial step is detailed work-up to diagnose the cause. This includes screening of body iron stores and for sources of blood loss. Patients with iron deficiency should be given preferably, parenteral iron preparation to correct iron deficiency. Parenteral iron is usually administered IV or IM as iron dextran or iron sucrose complex. Once the iron levels are corrected, most patients with advanced CKD require erythropoietin in doses of 50-200 iu/kg/ week. The hematocrit has to be maintained at 36% (Hb 11 to 12 g/dL) by adjusting the dose. Correction of anemia improves the quality of life and improves functions of vital organs.

Treatment of Dyslipidemia

Hyperlipidemia causes progression of renal disease and therefore it should be managed aggressively. Early and judicious use of statins such as atorvastatin or simvastatin in doses 10-20 mg oral at bed time is necessary to maintain

serum LDL levels <100 mg/dL. Patients with elevated triglyceride levels need gemfibrozil in addition.

Treatment of Malnutrition

Patients with CKD are usually malnourished. This is due to poor intake of food, hypercatabolic state and the pro-inflammatory effects of uremia. In addition, protein restriction contributes to muscle wasting. The calorie intake should be 30-35 Calories/kg bw/day. The serum albumin levels should be maintained >3.5 g/dL.

Treatment of Uremic Bleeding

Platelet dysfunction is the usual cause of bleeding in CKD. Usually this is asymptomatic and no specific therapy is needed. In patients with overt manifestations or those undergoing invasive procedures, the administration of desmopressin (dDAVP), cryoprecipitate and or dialysis is recommended to correct the bleeding manifestations.

Renal Replacement Therapy (RRT)

RRT (dialysis or renal transplant) is needed in patients with stage V CKD (GFR < 15 mL/mt) or in those with severe uremic manifestations like diuretic resistant fluid overload, severe hyperkalemia, resistant metabolic acidosis, pericarditis or uremic encephalopathy.

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Renal Replacement Therapy

Ramdas Pisharody, M. Sreelatha

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Chapter Summary

- Hemodialysis 1169
- Peritoneal Dialysis 1170
- Continuous Ambulatory Peritoneal Dialysis 1171
- Newer Forms of Dialysis 1171
- Kidney Transplantation 1171

When the kidneys fail and life cannot be sustained any more, therapies tailored to replace all or most of the functions of the kidney are essential. They constitute renal

replacement therapy (RRT). In chronic kidney disease, a sustained reduction in GFR below 5%, is termed as end stage renal disease (ESRD). This warrants treatment with maintenance dialysis or kidney transplantation. In acute renal failure, life is supported by any one of the forms of dialysis till kidney function recovers.

Dialysis

There are broadly two forms of dialysis namely: (1) peritoneal dialysis and (2) hemodialysis. Either of them can be used as a short-term measure in ARF patients (acute



Fig. 180.1: Hemodialysis machine

Note: Blood tubings connected to the patient circulating blood through the artificial kidney and returning to the patient. The 2 cans in the base of the unit contain acetate and bicarbonate concentrate

dialysis) or as a long term option in ESRD (chronic dialysis).

HEMODIALYSIS

Principles

Hemodialysis is the modality of extracorporeal purification of blood using an artificial filter. At its simplest, blood and dialysate are pumped into a dialyser using a dialysis machine. The dialysate is a solution of specially treated water, sodium, potassium, magnesium, calcium, chloride and dextrose with bicarbonate as buffer. Its constitution is akin to plasma water except that potassium levels are usually kept low. A semipermeable membrane separates the blood from the dialysate. During the passage through the dialyser, diffusion occurs across the membrane depending on the concentration gradient. Diffusion is maximised by maintaining high flow rates of blood and dialysate in a countercurrent manner Fluid can be removed from the blood compartment by exerting a transmembrane pressure. The modern dialysis machines are equipped with electronic devices to monitor blood flow, dialysate flow, temperature and conductivity of dialysate, ultrafiltration rate and to detect blood leak into the dialysate or air in the blood circuit (Fig. 180.1).

Blood is drawn into the extracorporeal circuit and returned to the patient through a vascular access. Arteriovenous shunt or cannulation of major veins (femoral , internal jugular or subclavian) are used for

TABLE 180.1		
Definite indications for dialysis in ARF		
Clinical indications include, anuria of >48 hours, fluid overload, pulmonary edema, metabolic encephalopathy, uremic bleeding or pericarditis. The biochemical indications are		
Blood urea	≥	150 mg/dL
Daily rise of urea	>	50 mg/dL
S creatinine	≥	7 mg/dL
Daily rise of S creatinine	>	1 mg/dL
S sodium	<	125 mmol/L
Daily fall of sodium	>	8 mmol/L
S potassium	>	5.5 mmol/L
Daily rise of potassium	>	1.0 mmol/L
S bicarbonate	<	15 mmol/L
Daily fall of bicarbonate	>	5 mmol/L.

temporary vascular access. For permanant access, an arteriovenous fistula or graft is created.

Indications for Dialysis in ARF

In acute renal failure, the objective of dialysis is to prevent complications such as fluid overload, encephalopathy, hyperkalemia, hypokalemia, metabolic acidosis and other life-threatening complications. This serves to gain time for the recovery of kidney functions. Dialysis is usually initiated early in the course of the illness. Definite indications for dialysis in ARF are shown in Table 180.1.

The duration and frequency of dialysis is determined by the catabolic state of the individual which is reflected by the rate of change of the biochemical parameters, hemodynamic status of the individual and general well being. Short daily dialysis and slow low efficiency extended dialysis (SLEED) are some of the modifications of conventional hemodialysis in ARF.

Hemodialysis in ESRD

Chronic maintenance hemodialysis (MHD) in ESRD should be carefully planned in advance. The patient and the family should be appraised of the eventual need for dialysis sufficiently early. Other forms of dialysis and transplantation should also be discussed. If the patient opts for MHD and is clinically suitable, a permanent vascular access (A-V fistula) is created and allowed to mature. An AV fistula is usually created between the radial artery and cephalic vein at the wrist (Fig. 180.2) or occasionally between brachial artery and cephalic vein in the cubital fossa. Dialysis should be initiated when GFR falls below 15 mL/min or if the patient is symptomatic. The duration and frequency of dialysis is prescribed taking into account

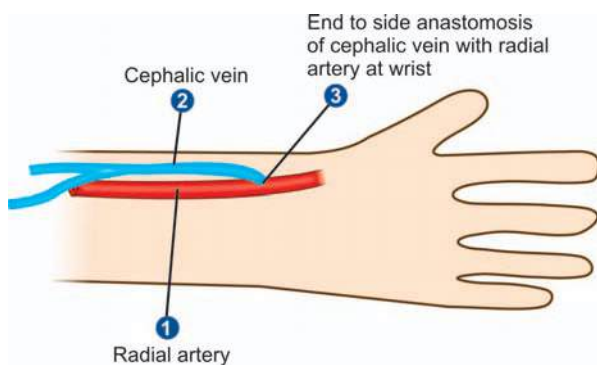


Fig. 180.2: AV fistula at wrist

the body mass index of the individual, nutritional status, occupation and comorbidities such as cardiac and vascular disease. Ideally 4 hours dialysis should be done thrice weekly in adults. The patient should be periodically evaluated for adequacy of dialysis, general well-being, bone disease, calcium-phosphorus balance, nutritional status and anemia. Most patients on dialysis require treatment with antihypertensive medication. Other supportive measures include erythropoietin with parenteral iron for correction of anemia, water soluble vitamin supplements, phosphate binders and active form of vitamin D₃ for treating bone disease.

The 10 years survival in young patients exceeds 80% if they are initiated into maintenance dialysis early. In those above 55 years, the 5 years survival is below 20%. In India, financial constraints seriously impair the long term results.

Factors Determining Dialysis Efficacy

The important factors that determine the efficacy of dialysis are:

- Blood flow rate
- Dialysate flow rate
- Membrane permeability and surface area and
- Length of a dialysis session and frequency of dialysis.

In conventional dialysis, blood flow is usually kept at 200-400 mL and dialysate flow at 500-800 mL per minute. Different types of dialysers are available, the most widely used are the hollow fibre dialysers. The membranes used in the dialysers are made of processed cellulose or synthetic polymers such as polysulphone (PS), polyacrylonitrile (PAN) or poly methyl-methacrylate (PMMA). Generally the synthetic membranes have higher permeability. The surface area of the membranes varies between 0.8 to 1.6 m². Dialyser efficiency is usually measured by its ability to clear urea (urea clearance), remove water (ultrafiltration rate {UFR}) and clear larger molecules like vitamin B₁₂ (B₁₂ clearance). Conventional dialysers have urea clearance of 300 to 500 mL / minute and UFR of 5-10 ml/mm of Hg of transmembrane pressure. High efficiency and high flow dialysers can

achieve urea clearances of > 700 mL/minute. They have higher UFRs and they also clear larger molecular weight solutes. However, when using high flux dialysers the machines need to be more sophisticated.

Dialysis Adequacy

Adequacy of dialysis is assessed by the clinical improvement and objectively determined by biochemical indices. The most widely used index is the Kt/V where K is the efficiency to clear a substance, it is the duration of dialysis and V is volume of distribution of the substance in the body. The recommended Kt/V urea per dialysis session is 1.3. A four hour session of dialysis using a conventional dialyser and blood and dialysate flow rates of 200 and 500 mL per minute respectively often achieves this Kt/V in an average adult patient. Other measures of dialysis adequacy are urea reduction ratios (1- post dialysis serum urea/pre dialysis serum urea). Time averaged concentration of urea calculates the average urea between the beginning of two successive dialysis sessions. Assessment of the quality of life (QOL) measured by specific questionnaire is also an important measure of adequacy.

Complications of Maintenance Hemodialysis

Hypotension, pyrogen reactions, first use syndrome and dialysis disequilibrium are the common acute complications. Rapid removal of urea during the initial dialysis sessions may cause symptoms due to brain edema as a result of concentration gradient of urea between brain and blood. This is referred to as **disequilibrium syndrome**. This can be prevented by deliberately giving shorter and less efficient dialysis sessions initially. First use syndrome develops in some patients when a new artificial kidney membrane is used. It does not occur during reuse. Vomiting, headache, muscle cramps, hemolysis and bleeding are less frequent adverse effects. Patients with cardiovascular disease may develop hemodynamic instability, angina, acute coronary events, arrhythmias and sudden death.

Long-term complications of MHD include metabolic bone disease, neuropathy, dialysis dementia, chronic subdural hematoma and amyloidosis.

PERITONEAL DIALYSIS

Peritoneal dialysis (PD) was first done in 1936 for a patient of acute renal failure. The peritoneal membrane with its underlying capillary bed acts as the semipermeable membrane across which exchange occurs by diffusion between blood and dialysate. The peritoneal dialysate is a sterile solution of water with its solute concentration similar to that of plasma water. The buffer used is lactate

and dextrose is used as an osmotic agent to facilitate ultrafiltration.

Acute intermittent PD is performed by introducing a rigid or soft cannula into the peritoneal cavity using a trocar. Fluid exchanges of 500 mL to 2L are given at a time. The fluid is allowed to dwell in the peritoneal cavity for 30-45 minutes and drained off under strict sterile precautions. This process is repeated. Each exchange takes about 1 hour. 20 such exchanges constitutes one session of acute PD and is particularly effective in children where the ratio of peritoneal surface area to body surface is greater. PD is advantageous in hemodynamically unstable patients and in those with multiple organ failure.

Complications include infection, bleeding, perforation of hollow viscera, and blockage of the cannula. Disequilibrium is uncommon in PD, as the solute exchange is slow. PD may be inadequate in hypercatabolic patients.

CONTINUOUS AMBULATORY PERITONEAL DIALYSIS (CAPD)

Introduced in the 1980's CAPD has become a viable option for about 10% of ESRD patients world wide. The principles of CAPD are the same as that of IPD, except that the fluid is permitted to dwell for 3-4 hours during each exchange. A permanent silicon catheter (Tenckhoff catheter) with 2 cuffs is placed in the peritoneum surgically through a subcutaneous tunnel. One of the cuffs is positioned just before the entry of the perforated end of the catheter into the peritoneum. The other cuff is positioned in the subcutaneous tissue just deeper to the skin exit site of the catheter. The exit site is fashioned suitably below and lateral to the umbilicus. The composition of PD fluid is similar to that for IPD except that the containers (bags) are made of non-leachable plastic material. Single or double bags with appropriate connecting and transfer sets are used. A titanium adapter is usually used to connect the catheter to the transfer set in order to minimise infection. Sufficient training of the patient or a bystander to the techniques is essential to avoid infection which is the most serious complication. .

CAPD involves 3-4 exchanges per day for an average adult. Individual prescriptions vary depending upon the clinical condition of the patient, the transport characteristics of the peritoneal membrane and the type and concentration of PD fluid. Dialysis is taken to be adequate if the Kt/V is 2 for adults.

Indications of CAPD

CAPD is a suitable option for patients with cardiovascular disease, poor vascular access, those living away from centres of hemodialysis facility, and those who prefer home-dialysis. It is the preferred option for small children and elderly patients. The advantage of CAPD is the relative freedom of mobility, better rehabilitation and

quality of life, preservation of renal function and lesser need for EPO to manage anemia. Disadvantages include cost, need for clean and adequate space, self reliance and likelihood of progressive ultrafiltration failure due to change in peritoneal permeability. Complications of CAPD include peritonitis, blockage of catheter, hernias, and metabolic complications such as worsening of hyperglycemia, dyslipidemia, hypocalcemia, bone disease and obesity. Other rare but dreaded complications include loculation of PD fluid and sclerosing peritonitis. Life expectancy with CAPD is similar to that of MHD patients.

NEWER FORMS OF DIALYSIS

In order to meet the demands of acutely ill patients in the ICU setting with ARF, newer forms of dialysis have come into vogue. They are collectively called as **continuous renal replacement therapy** (CRRT). Using the principles of ultrafiltration and convective transport through highly permeable and low resistance dialysers, solute removal and fluid removal are achieved in a more physiological way, continuously (as in the kidney) to suit the hemodynamically unstable, hypercatabolic patients in the ICU. Vascular access is through a double lumen venous cannula in a central vein. Various modes used include hemofiltration, slow continuous hemodialysis and hemodiafiltration. Advantages include hemodynamic stability, removal of large volumes of fluid, thereby facilitating good nutritional supplementation and ease of performance at the bed side. Disadvantages include continuous anticoagulation and its problems, manpower for close monitoring and increased cost.

Kidney Transplantation

This is currently the best and finite option for patients with ESRD. The kidney can be procured from live donor or brain dead vegetative subjects (cadaver donor). The first successful kidney transplantation was performed in 1955 by Joseph Murray at the Peter Bent Brigham Hospital, Boston, Ma, USA, using an identical twin as a kidney donor and the recipient survived for 38 years with a functioning graft.

The most important barrier to transplantation of human organs is the immune response mounted by the recipient against the donor organ. Life long immunosuppression is required. The median survival in live related donor kidney transplantation with matched donors is 24 years and in unmatched live donors it is 18 years. In cadaver transplant the median survival is 14 years in ideal situations.

Any healthy adult can be a renal donor. Donor and recipient have to be ABO compatible and it is desirable that they are also matched to the best possible extent for

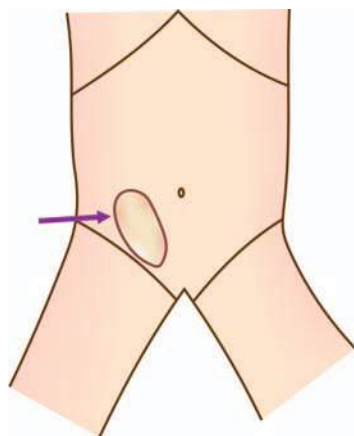


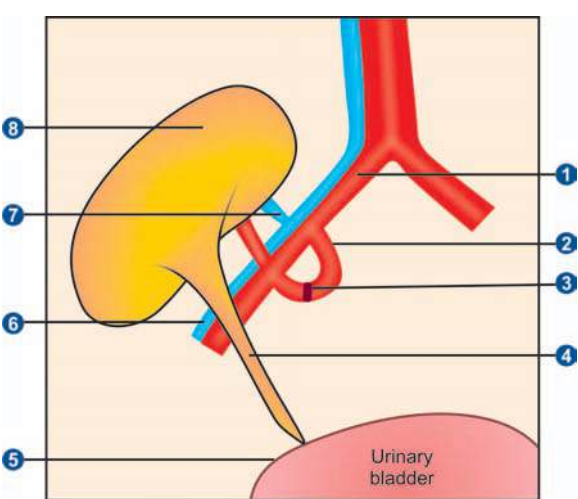
Fig. 180.3A: Renal transplantation: Position of the transplanted kidney (arrow) in the iliac fossa extraperitoneally (right or left side)

the HLA antigens. The recipient serum should not cross react with donor lymphocytes. (Lymphocytotoxic antibodies). The donor renal artery is anastomosed with internal iliac artery of recipient's (end to end), donor renal vein to external iliac vein of recipient, and donor ureter into the recipient's urinary bladder (Figs 180.3A and B). Donor selection and recipient preparation goes a long way for success in transplantation.

The donor kidney along with a portion of the ureter and the vascular pedicle is removed surgically and transplanted into the iliac fossa of the recipient. The vascular anastomosis is done after the kidney is perfused with cold isotonic solutions and the ureter is implanted into the native bladder. The native kidneys of the recipient are not removed unless there are specific indications. Usually brisk diuresis occurs after transplantation. Rarely graft function can be delayed due to acute tubular necrosis. This is more common with cadaver donors.

Complications of Renal Transplantation

Graft rejection: There are essentially three types of rejection: Hyperacute rejection resulting from performed lymphocytotoxic antibodies, acute rejection due to sensitization to donor HLA antigens and chronic rejection



- 1. External iliac artery
- 2. Internal iliac artery
- 3. Arterial anastomosis (internal iliac artery to renal artery end to end)
- 4. Ureter
- 5. Anti-reflux anastomosis of ureter into bladder
- 6. External iliac vein
- 7. Venous anastomosis (renal vein to external iliac vein-end to side)
- 8. Transplanted kidney

Fig. 180.3B: Vascular anastomosis in renal transplantation and implantation of the ureter

due to low grade humoral and cell mediated immune response against the graft. Acute rejections are reversible with treatment, but hyperacute rejection is irreversible resulting in graft loss immediately after transplantation. Chronic rejection can be retarded with treatment. Current therapy minimises acute rejection episodes and targets at decreasing chronic graft loss.

Surgical complications include *artery and vein thrombosis, ureteric obstruction or leaks, wound dehiscence, lymphoceles and urinomas*. Current refined surgical techniques have minimised these complications to a large extent.

Other complications after renal transplantation include opportunistic bacterial, viral and fungal infections, malignancy, adverse effects of drugs, diabetes mellitus, metabolic bone disease and cardiovascular morbidity.

In countries with high incidence of infective complications, and economic constraints, the survival after successful transplantation is lower compared to developed economics with subsidised health care delivery.

Chapter Summary

Vulnerability of Kidneys 1173
 Mechanisms of Drug Induced Renal Damage 1173
 Common Drugs Implicated in Renal Damage 1174
 Adjustment of the Dosage of Drugs in Renal Failure 1175
 Drugs and Dialysis 1176

Since the kidneys are involved in the excretion of several drugs or their metabolites, avoidance of certain drugs or modification of dosage may be needed in renal disease. In addition, as more and more drugs are introduced for various disorders, the risk of drug induced kidney disease will increase. It is important to know why the kidneys are affected by some drugs, the mechanisms of injury and principles of modification of dosage in renal dysfunction.

Vulnerability of Kidneys

The kidneys are highly vulnerable to the effect of drugs and toxins. The blood flow to the kidneys is nearly 20% of the cardiac output. Since the kidneys weigh about 300 g, the blood flow per gram of renal tissue is 3.5-4.0 mL/min/g. Thus, the kidneys are among the most vascular organs in the body. This results in drugs and toxins attaining high levels in the kidney. This load is exaggerated in the renal cortex, which gets 90% of renal blood flow. Substances that are filtered by the glomeruli reach the tubules and their concentration increases in the tubules because of selective water reabsorption. Some drugs such as gentamicin, which are reabsorbed by the proximal tubule reach the tubular cell in very high concentrations. Urinary concentration by countercurrent mechanism, high metabolic activity of the tubular cells, tubular secretion and precipitation of drugs in tubules depending on the concentration and pH are the other

important reasons for the high vulnerability of the kidneys.

Mechanisms of Drug Induced Renal Damage

Drug induced damage accounts for 5-20% of acute renal failure and above 20% of chronic renal disease. In many instances it may go off unrecognized. A high index of suspicion is necessary for early identification of drug induced renal damage. The various mechanisms of cell injury due to drugs are:

1. Direct interaction of drug with tubular cell membrane.
2. Insertion into the lipid components of the cell membrane.
3. Transportation into the cells and
4. Blockade of cytoplasmic metabolic events.

Renal damage due to drugs may be broadly classified as follows:

1. Prerenal:
 Volume depletion, e.g. diuretics.
 Increased catabolism, e.g. steroids.
 Vascular occlusion, e.g. oral contraceptives.
 Loss of renal autoregulation—non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin converting enzyme inhibitors (ACEIs).
2. Immune mediated damage:
 Acute interstitial nephritis, e.g. rifampicin, penicillin, allopurinol.
 Allergic vasculitis, e.g. thiazides, penicillamine
 Glomerular damage, e.g. NSAIDs, gold salts and penicillamine.
3. Direct toxicity:
 Acute tubular necrosis.
 Papillary necrosis.
4. Obstructive uropathy:
 Retroperitoneal fibrosis, e.g. practolol, methyldopa, methisergide, hydralazine.
 Urinary tract obstruction.

Papillary necrosis, e.g. NSAIDs, acetaminophen.
Tubular blockade due to crystalluria, e.g. sulphonamides, acyclovir.

COMMON DRUGS IMPLICATED IN RENAL DAMAGE

The most common drugs extensively used clinically causing nephrotoxicity include NSAIDs, ACEI, angiotensin receptor blockers (ARBs) and radiocontrast agents. This combination is referred to as “**internist’s nephrotoxic quartet**”.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs produce renal damage in different ways.

- a. **Hemodynamically mediated renal failure:** This is the most common mechanism. All NSAIDs including selective Cox II inhibitors lead to the inhibition of protective vasodilatory intrarenal prostaglandins. Therefore under conditions of reduced renal perfusion loss of renal autoregulation occurs which may lead to renal failure. Patient groups at risk are the elderly, those with dehydration, underlying renal disease, decreased effective circulatory volume and use of other nephrotoxic drugs. Patients with hemodynamically mediated renal failure present with oliguria, bland urine sediment and raised serum creatinine. Recovery usually occurs following timely withdrawal of the drug.
- b. **Nephrotic syndrome:** Nephrotic presentation may occur after several weeks to months of therapy particularly in elderly women. Renal biopsy reveals foot process fusion under electron microscopy along with interstitial edema and patchy infiltration with T lymphocytes. This may suggest a delayed hypersensitivity reaction to the drug. Recovery often occurs following withdrawal of the drug.
- c. **Hyperkalemia:** This is secondary to hyporeninemic hypoaldosteronism and is seen usually when NSAIDs are used along with ACEI, potassium sparing diuretics or potassium supplements.
- d. **Papillary necrosis:** It follows the intake of large quantities of NSAIDs over a short period. Ingestion of 1-3 kg of paracetamol over a period of 3 years or the total ingestion of 2-8 kg of phenacetin over 8-10 years along with other analgesics can induce analgesic nephropathy. Papillary damage is due to the very high concentration of the drug established at the papillary tip.
- e. **Salt and water retention:** Edema occurs as a result of salt and water retention. This worsens pre-existing hypertension and congestive cardiac failure and this can lead to resistance to the action of diuretics.

Aminoglycoside induced renal failure is commonly seen in clinical practice. The important risk factors for aminoglycoside nephrotoxicity include extremes of age, volume depletion, concurrent use of other nephrotoxic agents, hypokalemia, hypomagnesemia, sepsis and liver disease. The dose, duration and frequency of administration of the drug determine the pattern and severity of damage. Patients usually present with non-oliguric renal failure 7-10 days after the initiation of therapy. Sometimes the manifestations of renal failure appear only after the completion of the course of antibiotic.

Aminoglycosides produce renal damage by acting as a direct tubulotoxins. They are freely filtered at the glomerulus and reabsorbed at the proximal convoluted tubule. The drug accumulates in the proximal tubule and can be seen under the electron microscope as ‘*myeloid bodies*’. These cells undergo necrosis, and clinically manifests as tubular dysfunction and renal failure. Aminoglycoside toxicity is often dose related.

In all groups of patients, especially in those at higher risk of developing nephrotoxicity, the baseline renal function should be checked and serum creatinine monitored every three days during and after drug administration. In the elderly and in those with preexisting renal dysfunction, the dose should be adjusted to the creatinine clearance as discussed below. At the earliest evidence of renal dysfunction the drug should be discontinued. In most cases, recovery occurs following drug withdrawal, but in those with established renal failure, dialysis support will be required.

ACE Inhibitors

ACEI are increasingly used now in the treatment of hypertension, congestive cardiac failure and in the prevention of progression of diabetic nephropathy. ACEI can produce hemodynamically mediated acute renal failure in a selected group of patients, e.g. bilateral renal artery stenosis, renal artery stenosis in a solitary kidney, moderate to severe congestive cardiac failure, volume depletion and pre-existing renal insufficiency. The efferent arteriolar tone, intraglomerular pressure and glomerular filtration rate (GFR) are modulated by angiotensin II. Administration of ACEI under these circumstances leads to relaxation of the efferent arterioles and a subsequent drop in the intraglomerular pressure and GFR. Although in most instances the renal failure is reversible, ACEI can produce irreversible renal failure, especially when there is underlying renal parenchymal disease. ACEI can also produce hyperkalemia when used in conjunction with potassium sparing diuretics, beta-blockers or potassium supplements. Captopril can produce nephrotic syndrome (membranous nephropathy). Careful use of these drugs with monitoring of renal function and serum potassium levels and avoiding the use of these drugs in the high-risk group can prevent renal toxicity to a large extent.

Radiocontrast Agents

Renal failure associated with radio contrast agents is reported as the third most common cause of in-hospital renal failure. Conventional contrast agents are hyper-osmolar, a property contributing to their toxicity. Ionic contrast agents are especially toxic. Maximum reduction in renal function is usually noticed 48 hours after injection of the contrast. Patients can present with transient renal dysfunction or severe renal failure requiring dialysis. A persistent nephrogram 24 hours after contrast administration is another finding in radio-contrast related renal failure. Risk factors precipitating radio-contrast nephropathy are pre-existing renal insufficiency, dehydration, elderly age, severe congestive heart failure, multiple myeloma. Concurrent use of other nephrotoxic agents, repeated exposure to radiocontrast agents and high dose of ionic contrast agents. Although uncomplicated diabetes as such is not a risk factor, those with diabetes and renal involvement are affected more.

Exact mechanism of contrast mediated renal damage is not clear. The two proposed mechanisms are renal hypoperfusion and direct tubular toxicity. Urine osmolarity tends to be high with a low fractional excretion of sodium suggesting prerenal failure. This may be due to intense intrarenal vasoconstriction mediated by renin, angiotensin II, intracellular smooth muscle calcium, adenosine and endothelin.

There is no specific treatment. In most cases it is reversible. The risk can be reduced by using minimum dose of non-ionic contrast agent, avoiding multiple radiocontrast injections and avoiding dehydration prior to, and during the procedure. Administration of half normal saline starting 12 hours before and up to 12 hours after the dye injection is probably the most effective measure to reduce radiocontrast nephrotoxicity. N Acetyl cysteine given in a dose of 600mg twice daily before and after contrast has been shown to be useful in some cases. The urine output must be maintained at around 100 mL per hour before and after the procedure.

Adjustment of the Dosage of Drugs in Renal Failure

Renal disease can affect the absorption, bioavailability, distribution, metabolism and excretion of some drugs. Pharmacologically active metabolites of drugs may accumulate in renal failure causing adverse reactions, e.g. nitrofurantoin when administered in renal failure can cause peripheral neuropathy and anesthetic agents like morphine can cause respiratory depression. Drug excretion by the kidneys depends on glomerular filtration, tubular secretion and tubular reabsorption. These may be altered in renal failure. Thus, dose modification may be necessary in renal disease. The necessity and degree of dose reduction depends on the class of drug. The goal of drug

modification would be to maintain efficacy while avoiding drug accumulation and adverse reactions. This is achieved by the following methods:

1. **Using dosage nomograms:** This is based on knowledge of the creatinine clearance. This may either be estimated using 24 hours urine collection or calculated from serum creatinine using the Cockcroft and Gault formula. For patients with acute renal failure and/or end stage renal disease, the creatinine clearance must be assumed to be < 10 mL/mt.

The dose for the level of creatinine clearance for individual drugs can be read from the nomogram. Although the method is simple, the disadvantage is that different people behave differently and the nomogram may not be applicable to all individuals alike.

2. **Adjusting the loading dose and altering the maintenance dose:** If ECF volume is normal, the loading dose in renal failure is usually the same as that for a normal person, except in the case of digoxin where only 50-75% of the normal loading dose is required. For aminoglycosides 75-80% of the normal loading dose may be sufficient. In those with edema or ascites, a higher loading dose may be required. The maintenance dose is adjusted either by decreasing the individual dose or by increasing the dosage interval. In the case of gentamicin, the daily maintenance dose can be roughly calculated by the formula:

$(5 \text{ mg/kg body wt.} \div \text{serum creatinine}),$

or

By the 'rule of 8'—i.e. – frequency of administration may be 8-hourly if serum creatinine is 1 mg%, 16-hourly if serum creatinine is 2 mg, and 24-hourly if serum creatinine is 3 mg and so on.

It is prudent to monitor drug levels to ensure therapeutic levels while avoiding toxicity.

(Table 181.1 for dose modification of commonly used drugs in renal failure).

Special Group of Drugs and Dose Modification in Renal Failure

1. **NSAIDs:** Due to their inhibitory effects on vasodilatory prostaglandins, their use could result in a further fall in GFR and hyperkalemia. Of the NSAIDs sulindac has less chances of renal failure.
2. **Diuretics:** As most of the diuretics have to reach the lumen of the tubule for their action, efficacy may be affected in renal failure. Thiazide diuretics are generally ineffective when the creatinine clearance is less than 25 mL/mt. Loop diuretics are mainly secreted into the lumen in the proximal tubule through the organic anion transporter. In renal failure, high doses are required to overcome the competing action by other organic anions. So, high

TABLE 181.1

Drug dose adjustment in renal failure				
Drug	Normal dose	In mild renal failure (SCr.2-4 mg%)	Moderate renal failure (4-8 mg%)	Severe renal failure (>8 mg%)
Gentamicin	1.5 mg/kg q8h	1.5 mg/kg q12h	1 mg/kg q12h	1 mg/kg q24h
Amikacin	7.5 mg/kg q12h	7.5 mg/kg q24h	5 mg/kg q24h	5 mg/kg q24.4h
Cefazolin	1 g q6h	1 g q12h	1 g q24h	500 mg q24h
Cefotaxime	1-2 g q6h	1 g q8h	1 g q12h	500 mg-1 g q24h
Ceftazidime	1-2 g q6h	1 g q12h	1 g q24h	500 mg-1 g q24h
Crystalline penicillin	10-20 L q6h	10-20 L q6h	10-20 L q6h	10-20 L q8 h
Ampicillin	500 mg q6h	500 mg q6h	500 mg q6h	500 mg q12h
Ciprofloxacin	200 mg q12h	200 mg q12h	200 mg q12h	200 mg q24h
Vancomycin	500 mg q6h	500 mg once in 3 days	500 mg once in 5 days	500 mg once in 7 days
INH	300 mg OD	300 mg OD	200 mg OD	200 mg OD
Ethambutol	10 mg/kg OD	10 mg/kg OD	5 mg/kg OD	5 mg/kg OD
Rifampicin	450-600 mg OD	450-600 mg OD	450 mg OD	450 mg OD
Methyldopa	250-600 mg O8h	250-500 mg O8h	250-500 mg O12h	250-500 mg OD 12 h
Enalapril	2.5-10 mg OD	2.5-10 mg OD	2.5-10 mg OD	2.5-10 mg OD
Digoxin	0.25 mg OD	0.125 mg in 36 h	0.125 mg in 48 h	0.125 mg in 48 h

doses of oral loop diuretics are used. When parenteral administration is needed, high dose of frusemide IV or continuous infusion is more effective.

3. **ACE inhibitors:** Generally, it is better to be cautious in using ACEI in those with serum creatinine of > 3.5 mg%. If ACEI are used, periodic monitoring of renal functions and serum potassium are needed. Withdrawal of the drug may be necessary if serum creatinine or potassium increases steadily.
4. **Beta blockers:** Dose reduction may be needed in advanced renal failure. They should be used cautiously as they can produce hyperkalemia particularly when used with ACEI and or potassium sparing diuretics.
5. **Antibiotics:** Aminoglycosides require significant dose reduction with renal failure as well as increased dose interval. Most of the cephalosporins also require dose reduction and/or increase in interval. Vancomycin has prolonged blood levels in renal failure and this needs to be given only once in five days for moderate renal failure and once a week in severe renal failure.
6. **Antituberculous drugs:** Most of the antituberculous drugs with the exception of rifampicin require dose reduction. Dose of ethambutol is reduced to 5 mg/kg in severe renal failure and INH to 200 mg daily. Pyrazinamide is preferably avoided in severe renal failure. As rifampicin is metabolized by the liver, dose reduction is not usually required.

Thus, knowledge of drug modification in renal failure is vital to the proper management of a patient with renal disease. At the same time, it is important to periodically monitor renal functions when drugs with

potential deleterious effects are used in patients with renal disease.

Drugs and Dialysis

The dialyzability (dialytic clearance) of the drugs depends on its volume of distribution, molecular size and protein binding. Generally, protein bound drugs are less dialyzable, e.g. secobarbitone, amylobarbitone and other short acting barbiturates. The non-protein bound drugs such as, e.g. phenobarbitone and other long acting barbiturates are dialyzable. Drugs with lower molecular size and less protein binding are more dialyzable. Such drugs (barbiturates, certain antibiotics) should preferably be administered in the post-dialysis period to ensure therapeutic levels. In the case of poisoning/overdose by non-dialyzable drugs, their removal from the body is possible by charcoal hemoperfusion.

Some antibiotics are dialyzable and hence a booster dose at the end of each dialysis will be required to achieve therapeutic blood levels, e.g. aminoglycosides. In patients who are on long-term dialysis it is preferable to administer most drugs after dialysis. The property of dialyzability of drugs can be exploited in the management of poisoning/overdose with these drugs. Hemodialysis is more effective than peritoneal dialysis in drug elimination for most dialyzable drugs.

Since the kidneys are highly vulnerable and drugs can adversely affect the kidney function the clinician must try to understand the basic pharmacology and pharmacokinetics of these drugs and use appropriate drugs with conventional or modified dose, depending on the level of renal function. This may help to reduce the incidence of drug induced renal disease to a large extent.

Neurology

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Nervous System: General Considerations

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Chapter Summary

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General Considerations

The central nervous system is a highly differentiated organ in the body. Compared to its relative size in other animals, human brain is relatively the largest, most of the matter being the highly expanded frontal cortex. Neurons constitute only less than 5% of the total number of cells in the cerebral grey matter. The rest of the cells are astrocytes and other glial cells that support the neurons. The function of any portion of the brain depends upon three factors 1. where the input comes from 2. where its output goes and 3. what kind of processing is performed on the information received by the circuitry in the particular area.

The nervous system is composed of two parts: (1) The central nervous system (CNS) and (2) the peripheral nervous system (PNS). The CNS consists of the brain and the spinal cord. The PNS includes the cranial and spinal nerves. The autonomic nervous system (ANS) although functionally a separate system, is central and peripheral.

The adult human brain weighs 1250-1400 g and the spinal cord about 30 g in health. The brain develops from ectoderm. Parts of the central nervous system develop in the first twelve weeks of intrauterine life. Infections in the mother or toxic damage during this period may lead to congenital damage to the central nervous system. The cranial end of the neural tube develops into the brain and the caudal portion develops into the spinal cord. The brain and spinal cord are effectively protected by the skull and vertebral canal respectively. Within the bony structures, the dura mater, and the arachnoid mater invest the brain

and spinal cord. The dura mater is attached to the bony structures at the the entry or exit of blood vessels and nerves.

The space between the arachnoid mater and the pia mater investing the brain is called subarachnoid space and it contains the **cerebrospinal fluid** (CSF) which is secreted by the choroid plexuses in the lateral, third, and fourth ventricles. The CSF thus formed in the ventricles escapes into the subarachnoid space through the apertures on the roof of the fourth ventricle (*foramina of Magendie and Luschka*) to circulate around the brain and spinal cord. It is returned into the dural venous sinuses through the arachnoid villi. More than three times the volume of the total CSF is produced daily for circulation. When suspended in the cerebrospinal fluid, the weight of the brain is only 50g. The total quantity of CSF is 130-150 ml in an adult. It provides a cushioning effect and a proper chemical milieu for nerve cells. The normal pressure of CSF in the lumbar subarachnoid space is 50-150 mm of water when the individual lies quiet on his side. Maneuvers such as straining, coughing, sneezing, and compression of the jugular veins lead to obstruction of venous return from the head and neck and rapid rise in CSF tension.

The pia mater which is thin and transparent is closely applied to the surface of the brain and spinal cord. The blood vessels which run on the surface penetrate this membrane and reach the inner structures. A sheath of pia is carried down along with these vessels and this constitutes the *Virchow Robin space*.

The brain receives its blood supply from the internal carotid and vertebral arteries. These two systems effectively communicate between them at the circle of Willis named after Thomas Willis (1621-1675), who was trained under William Harvey.

This arrangement ensures optimal distribution of blood to the different areas of supply and also provides for collateral circulation in the event of obstruction to any of the major arteries. More than 17% of the cardiac output goes to the brain to meet its intense metabolic demand. The blood flow is autoregulated to 45-50 ml/mt/100 g of brain tissue at a mean blood pressure range of

60-130 mm Hg. The brain utilizes mainly glucose for its metabolism. Hence impairment of cerebral blood flow and hypoglycemia lead to the rapid development of neurological dysfunction. About 20% of total oxygen consumption in the body is by the brain. The arteries that supply the brain are, in a sense end-arteries. This is true of the perforating branches which arise from the main arterial trunks to supply the deeper parts of the nervous tissue. The vascular territories of the major arterial branches show considerable overlap. Congenital variations are not infrequent. Moreover, anastomosis between the external carotid and internal carotid systems can also develop. On account of these factors, the extent of infarct and the anatomical blood supply to the brain may not always correlate. The cerebral blood flow is subject to dynamic variations depending upon the cardiac output, state of tone of cerebral vessels, presence of vasodilator substances such as carbon dioxide, level of intracranial tension, and the presence of external influences such as accelerating or gravitational forces. Venous blood from the interior of the brain is drained through the cerebral veins into the straight sinus.

The cerebrum consists of the external gray matter which contains the neurons and the internal white matter which is mainly made up of myelinated nerve fibres. This arrangement is seen in the cerebellum as well. But in the spinal cord, the white matter is external and the gray matter which is arranged as the anterior and the posterior horns is internal. Masses of nuclei such as the corpus striatum are seen as islands of gray matter deep inside the cerebrum. On either side, the cerebral hemisphere is divided into the frontal lobe, parietal lobe, temporal lobe, and occipital lobe. Functions of all parts of the cerebral cortex have been accurately mapped and these functional areas have been numbered. The nuclear masses of gray matter contained within the **cerebellum** are the nucleus dentatus, globosus, emboliformis and fastigial nucleus.

Functional Organization of the Central Nervous System

Voluntary activity is initiated in the cerebral motor cortex. It is executed through various descending nerve tracts. It is influenced by the activity of the cerebellum and extrapyramidal system.

Motor System

Voluntary movement results from coordinated contraction and relaxation of groups of muscles. The prime movers or agonist muscles contract while reciprocal antagonist muscles relax. Synergists are those muscles which stabilize to make the movement most effective. Voluntary activity is initiated by the corticospinal tracts (also called pyramidal tracts or the upper motor neurons) which

originate from pyramidal neurons of the motor cortex of the precentral area. The rate, range, rhythm, direction and amplitude of motor activity are controlled by the cerebellum which modifies the action of the agonist, antagonist and synergist groups of muscles.

The maintenance of posture is mediated largely through the extrapyramidal system and the vestibular and spinal reflexes. Information processing for programming the movement occurs in the extrapyramidal system. The influences from the pyramidal system, extrapyramidal system and cerebellum act upon the anterior horn cells of the spinal cord or the motor nuclei of the brainstem (the lower motor neurons) which have connections with the various muscles in the body.

Upper Motor Neuron (UMN)

Motor neurons in the cerebral cortex, basal ganglia and the brainstem are called the “upper motor neurons”. These upper motor neurons that influence voluntary motor activity, give rise to corticospinal tracts, reticulospinal tracts, tectospinal tracts, rubrospinal tracts, vestibulospinal tracts, and the olivospinal tracts.

In the motor cortex, which represents the opposite side of the body, parts are represented from above downwards on the lateral surface in the order of thigh, trunk, arm, forearm, hand, face, and tongue. The perineum, leg and foot are represented on the medial surface of the cerebral hemispheres. This representation of the body is called the homunculus. The extent of the area of motor representation is proportional to the functional importance of the part, so that the hand, face, and foot receive a wider representation than the other parts.

The corticospinal tracts are concerned with voluntary, discrete, skilled and rapid movements especially of the distal part of the limbs. The fibres of the tracts arise mainly from pyramidal cells in the precentral gyrus (areas 4 and 6) and to a smaller extent from the postcentral gyrus also (areas 3, 1 and 2). From the cortex the fibres pass down through the subcortical region. These fibres descend in the corona radiata and then pass through the internal capsule, the brainstem and the spinal cord. In the internal capsule they form a compact bundle and occupy a small area in the genu and anterior part of the posterior limb. Here the fibres for the head and neck are anterior and those for the lower limbs are posterior. Still further behind in the posterior limb of the internal capsule are the sensory fibres, visual fibres, and auditory fibres. From the internal capsule the motor fibres pass through the midbrain, the pons and the medulla. In the pons the UMN fibres are criss-crossed by pontine nuclei (Fig. 182.1).

At the anterior surface of the medulla 80% of the corticospinal fibres become grouped together to form the visible swellings known as the pyramids. Only these corticospinal fibres that form the pyramid in the medulla

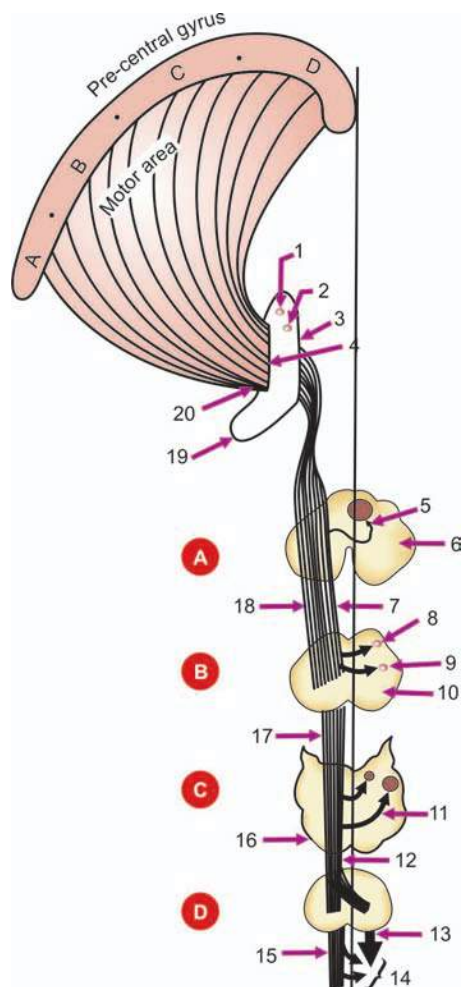


Fig. 182.1: The motor pathways

- (A) Midbrain
- (B) Pons
- (C) Medulla
- (D) Spinal cord
- A. Cortical area representing head
- B. Cortical area representing upper limb
- C. Cortical area representing trunk
- D. Cortical area representing lower limb
- 1. Visual fibres
- 2. Sensory fibres
- 3. Posterior limb of internal capsule
- 4. Fibres for lower limb in internal capsule
- 5. Fibres to opposite midbrain nuclei
- 6. Cerebral peduncle (crus cerebri)
- 7. Fibres to opposite pontine nuclei
- 8. 6th nerve nucleus
- 9. 7th nerve nucleus
- 10. Ventral aspect of pons
- 11. Fibres to opposite medullary nuclei
- 12. Decussation of pyramidal tract
- 13. Lateral (crossed, indirect) corticospinal tract
- 14. Corticospinal fibres of direct tract crossing to supply opposite spinal nuclei
- 15. Anterior (direct) corticospinal tract
- 16. Medullary pyramid
- 17. Corticospinal (Pyramidal) tract
- 18. Fibres for lower limb in pons
- 19. Anterior limb of internal capsule
- 20. Fibres for head in internal capsule

are generally referred to as the pyramidal tract. At the lower border of the medulla they cross to the opposite side and form the crossed corticospinal tract. The supra-nuclear pathways upto the cranial nerve nuclei in the brain stem and the anterior horn cells of the spinal cord constitute the upper motor neuron (UMN).

In the brainstem corticospinal fibres cross to the opposite side to provide UMN innervation to the cranial nerve nuclei of the opposite side. In the midbrain corticospinal fibres are in close relation with the third cranial nerve nucleus, in the pons close to the 7th cranial nerve nucleus, and in the medulla close to the 12th cranial nerve nucleus. Therefore, lesions at these levels usually produce ipsilateral LMN paralysis of these cranial nerves and contralateral hemiplegia. Except for that part of the 7th cranial nerve nucleus that supplies the muscles of the lower part of the face and the part of the 12th cranial nerve supplying the genioglossus muscle, all the cranial nerve nuclei receive bilateral UMN connection.

The uncrossed fibres descend on the same side as the anterior corticospinal tract. At different levels they also cross to the opposite side to synapse with the anterior horn cells up to mid thoracic level. The corticonuclear and corticospinal fibres end by synapsing with the cranial nerve nuclei or anterior horn cells either directly or indirectly though internuncial neurons, also known as interneurons or connection neurons.

The *reticulospinal tracts* facilitate or inhibit voluntary and reflex motor activity. The *tectospinal tracts* are responsible for reflex postural movements in response to visual stimuli. The *rubrospinal tracts* facilitate the motor activity of flexor muscles and inhibit the activity of extensor muscles. The *vestibulospinal tracts* are concerned with postural activity associated with balance and equilibration. The *olivospinal tracts* also regulate motor activity.

Lesions of the corticospinal tract result in loss of voluntary motor activity. Since the UMN normally carries fibres which inhibit the stretch reflexes mediated by the LMN, lesions of the UMN result in exaggeration of these stretch reflexes. The superficial reflexes which are also known as cutaneous protective reflexes also show characteristic changes.

Signs of Upper Motor Neuron Lesions

1. **Loss of Voluntary Movements—Paralysis**
2. **Increase in Motor Tone—Spasticity**

Spasticity: This term refers to the velocity-dependent increase in resistance to passive stretch felt by the examiner as a sudden catch which will also give way suddenly leading to the clasp-knife phenomenon. When spasticity is severe it can be appreciated in all limbs in all groups of movements. In early and mild cases the

spasticity may be appreciated in the pronators and supinators of the forearm and adductors of the thigh. For eliciting spasticity the limb has to be moved passively. To elicit spasticity better, the movement has to be rapid.

3. **Exaggerated stretch reflexes—Hyper-reflexia** When the stretch reflexes are exaggerated, they are increased in amplitude and also sustained. Simple increase in amplitude may occur even without neurological disorders, e.g. anxiety. Exaggerated reflexes are abnormal if they are:
 - i. Asymmetrical
 - ii. Associated with changes in power or tone and
 - iii. Associated with changes in superficial reflexes

Inequality between corresponding reflexes on either side is of great diagnostic value. In bilateral UMN lesions above the level of the pons, the jaw jerk is also exaggerated. When the UMN lesion is well established, clonus may develop. In clinical practice patellar clonus and ankle clonus in the lower limbs and wrist clonus in the upper limbs are the ones commonly looked for.

4. **Alteration in superficial reflexes:** The abdominal and cremasteric reflexes are lost. The plantar reflex or response becomes extensor. This is referred to as Babinski's sign. Joseph Babinski, a French neurologist described the Babinski's sign in 1896. Normally on stroking the lateral aspect of the foot from the heel to the ball of the big toe with a sharp object a set of responses occurs. The big toe flexes, the lateral four toes also flex and crowd together. Minimal contraction of the tensor fascia lata, the adductors of the thigh and sartorius also occurs. This whole response is referred to as the 'flexor' plantar response. Flexion movement of the foot and toes are more powerful than extension since stronger flexion is needed for locomotion. Therefore the normal plantar response is flexor. Even in normal persons stroking the medial margin of the foot may elicit an extensor response. Therefore plantar response is not elicited on the medial side.

In UMN lesion the big toe extends (dorsiflexes), and the other toes fan out and dorsiflex when a nociceptive stimulus is applied to the lateral aspect of the foot, with stronger stimuli the ankle dorsiflexes with flexion at the hip and knee. If the UMN lesion is small, this abnormal response is elicitable only from the lateral margin of the sole of the foot. As the lesion extends, the response can be elicited by applying the stimulus over a wider area such as the medial aspect of the foot and the leg. These pathological reflexes are known by different eponyms.

Oppenheim's sign: Extensor plantar responses elicited by stroking down on the shin of the leg.

Schäfer's sign: Squeezing the tendo-Achilles to elicit the extensor plantar response.

Gordon's sign: Squeezing calf muscles elicits extensor plantar response.

Chaddock's sign: Light stroke applied to the lateral aspect of the dorsum of the foot elicits the extensor response.

It is important to elicit the plantar response carefully since it is of great value in deciding upon the presence or absence of an UMN lesion. Fibres, from the area 6 are concerned with extensor plantar response. The plantar response is normally extensor in babies till the age of one year by which time the corticospinal tract becomes myelinated. When the baby learns to walk the plantar response becomes flexor. The plantar response is bilaterally extensor in deep sleep and coma.

5. **Absence of muscle atrophy:** Unlike as in LMN lesion, UMN lesion does not lead to marked wasting of muscles. This is because the lower motor unit is intact, so that reflex activity and trophic influences are preserved. However, prolonged disuse of muscles in UMN lesions, gives rise to slight disuse atrophy.

6. **Electrical reaction of the affected muscles are not altered.**

Localization of the Level of Lesion of the UMN

Since the UMN extends from the cerebral cortex and passes through several structures of the central nervous system finally to ramify on the anterior horn cells in the spinal cord it is necessary to determine the level at which this tract is affected. Lesions at different levels give rise to distinct groups of clinical abnormalities.

Cortical lesions: These are characterized by restricted paralysis of either of the face or a limb on the contralateral side. Since the motor area of the cerebral cortex is extensive, only large lesions result in total hemiplegia. Presence of other cortical dysfunctions such as aphasia and convulsions is also suggestive of a cortical lesion. In the cortex a lesion in middle cerebral distribution produces hemiplegia where arm is weaker than leg. Aphasia occurs if the lesion is on the dominant side. In lesions in the anterior cerebral distribution leg is weaker than the arm and there is no aphasia.

Internal capsule lesions: Since all the corticospinal fibres are held together within a small area in this structure, small lesions at this level result in extensive paralysis of the opposite side leading to hemiplegia in which the face, upper and lower limbs and the trunk are paralyzed. Extension of the lesion more posteriorly results in hemianesthesia and hemianopia as well. Weakness of arms and legs is equal.

Brainstem lesions: Lesions in the midbrain, pons and medulla lead to lower motor neuron paralysis of the corresponding cranial nerves on the side of the lesion and paralysis of the limbs on the opposite side (crossed hemiplegia).

Midbrain lesions: Ipsilateral 3rd cranial nerve palsy and hemiplegia of the opposite side.

Pontine lesions: Ipsilateral 7th cranial nerve palsy and hemiplegia of the opposite side.

Medullary lesions: Ipsilateral 12th cranial nerve palsy and hemiplegia of the opposite side.

Spinal cord lesions: Since the major portion of the corticospinal tract has crossed at the lower margin of the medulla, lesions of the pyramidal tract below this level in the spinal cord produce ipsilateral UMN palsy. In many cases however the lesion usually affects the corticospinal tract in both sides. In pure corticospinal tract lesions, the upper level is determined by the loss of voluntary motor power and abnormalities in superficial and stretch reflexes.

If the lesion in the spinal cord is above the fifth cervical segment the stretch reflexes of the upper and lower limbs are exaggerated. Other signs of UMN lesion such as *Hoffman's sign* may appear. Lesions at C5 or C6 levels give rise to the phenomenon of *inversion of the supinator reflex*. This consists of absence of elbow flexion and exaggeration of finger flexion when the radial styloid is tapped.

If the lesion is below T1 spinal segment, but above second lumbar segment (L2) both the knee and ankle reflexes are exaggerated and clonus may develop.

If the lesion is between L2 and L5 segments, both the ankle jerks will be exaggerated.

Lower Motor Neuron (LMN)

The motor neurons of the cranial nerve nuclei in the brainstem and the anterior horn of the spinal cord form the lower motor neurons. The axons from these cells form cranial and peripheral nerves respectively and reach the motor end plates of corresponding muscles. The motor cranial nuclei or the anterior horn cell, its axon, and all the muscle fibres it innervates comprise a lower motor unit. Each muscle is composed of several such motor units. The lower motor neuron is an integral part of the spinal reflex arc. It is the final common path for all motor activity (both voluntary and reflex) of all muscles. The lower motor neurons are influenced by impulses from the UMN, extrapyramidal tracts, cerebellum and sensory afferents from the sensory nerve roots. Integrity of the lower motor neuron is essential for maintaining the normal nutrition and size of the muscle fibres and when the lower motor neuron is damaged the corresponding muscles undergo atrophy. LMN is the final common path for eliciting contraction of the muscles it innervates. Whereas the LMN controls contraction of individual muscles, the UMN controls movements as a whole.

Signs of Lower Motor Neuron Lesion

1. *Loss of all movements*—Voluntary and reflex.
2. *Loss of motor tone*—Flaccidity.
3. *Loss of stretch and superficial reflexes*—Hyporeflexia.
4. *Atrophy of affected muscles* appears within 2-3 weeks of the lesion.
5. *Denervated muscle fibres contract spontaneously*. This is not visible, but can be detected by electromyography. Spontaneous contraction of individual motor units causes fasciculation.
6. *Electrical activity of the muscle fibres is altered* and this can be detected by electromyography. The pattern of altered electrical activity depends on the site of damage in the lower motor neuron unit.

Lesions of anterior horn cells produce selective wasting and weakness of motor units, which will be patchy, whereas lesions of the anterior roots produce fairly uniform involvement of all muscles supplied by that root. Lesions in the peripheral nerve give rise to paralysis of the muscles supplied by that nerve. Often peripheral nerve lesions are associated with sensory disturbances.

Extrapyramidal System (EPS)

This consists of a complex neuronal network extending from the cortex through the brain stem to the spinal cord. The descending pathways emerging from this system influence the lower motor neuron in the brainstem and the spinal cord.

Components of the Extrapyramidal System

These are cortical, subcortical and spinal.

1. Areas in the cerebral cortex, which are diffuse, and nondefinable and are arising from cells other than pyramidal cells. These constitute the cortical component.
2. Basal ganglia composed of : (a) the caudate nucleus, (b) the lentiform nucleus which can be functionally divided into the globus pallidus and the putamen, (c) the substantia nigra, and (d) the nuclei of the thalamus and subthalamic nuclei. These constitute the subcortical component.
3. The tegmental nuclear system: (a) red nucleus, (b) reticular nuclei, and (c) vestibular nuclei. These constitute the spinal component.

The main descending pathways are the rubrospinal, olivospinal, vestibulospinal, and tectospinal tracts. Their fibres synapse with the lower motor neuron. The extrapyramidal system assists the pyramidal system to perform motor activity smoothly. In addition, it controls functions such as maintenance of tone and posture and associated movements on walking.

The extrapyramidal system intimately connects the cerebral cortex with the cerebellum and the lower motor

neurons on the opposite side. The neurotransmitters of the EPS are dopamine and acetylcholine. When the balance between dopamine and acetylcholine is maintained the system functions normally. This balance is disturbed in disorders of the EPS.

Signs of Extrapyrarnidal Disorders

1. *Alterations in tone*, e.g. rigidity of either cog-wheel type or lead pipe type in parkinsonism and flaccidity in chorea.
2. *Involuntary movements*, e.g. tremors, chorea, athetosis, myoclonus.
3. *Bradykinesia and paucity of spontaneous movements*, e.g. parkinsonism.
4. *Disturbances in posture*, e.g. parkinsonism and dystonia.
5. *Several other subtle abnormalities* in fine motor activities, sensory perception and cognitive functions are being recognized. These account for considerable functional disability in advanced stage of some of these disorders.

Cerebellar System

Main function of the cerebellum is to coordinate synergistic and smooth action of muscles during voluntary and automatic movements. It is also involved in the maintenance of posture, and muscle tone. Afferent impulses reach the cerebellum from the proprioceptive end organs, skin, and vestibular nuclei. Fibres from the opposite cerebral cortex and basal ganglia also reach the cerebellum. Efferent fibres from cerebellar cortex via the cerebellar nuclei reach the reticular formation in the brainstem, red nucleus, and vestibular nuclei of the opposite side from where distinct tracts descend in the spinal cord, cross to the opposite side and reach the anterior horn cells at various levels. Due to this double crossing, the cerebellum controls activities of the same side of the body. Fibres from the cerebellum also pass up to the contralateral thalamus and thence to the cerebral cortex. There is evidence that the cerebellum plays an important part in modulating memory, intelligence and behaviour.

Signs of Cerebellar Disease

Clinical abnormalities are very prominent when the lesion appears acutely. As time passes compensatory mechanisms develop, and therefore, the disability becomes milder. Clinical effects are seen on the same side as the cerebellar lesion. These are:

1. **Alteration in motor tone:** Generalized hypotonia.
2. **Disorders of posture and gait:** The patient tends to sway towards the side of lesion on walking. The head may be turned to the same side. The gait is reeling

and can be compared to that of a drunken man. Truncal ataxia results from midline vermis lesions whereas cerebellar hemispherical lesions affect ipsilateral extremities and eye and speech.

3. **Disorders of movement** occur as a result of hypotonia. Incoordination and abnormalities of rate, range, rhythm, direction and amplitude lead to ataxia which can be elicited in several ways.
 - i. **Dysmetria:** When the patient is asked to touch an object with a finger repeatedly, it can be noticed that the force and amplitude of movement are not accurately adjusted to locate the object. The finger either falls short of the object or overshoots it. Past-pointing is the phenomenon which is elicited when the patient is asked to touch an object with a finger with the eyes open. The finger overshoots the target on the side of cerebellar lesion.
 - ii. **Dyssynergia:** When movements involving several joints are attempted, the movements are broken up into their component parts and they appear jerky.
 - iii. **Intention tremor:** When the patient is asked to touch an object with a finger, coarse irregular tremor appears and increases as the finger approaches the target. This phenomenon is the result of a combination of dyssynergia and dysmetria. Similarly, the muscles which maintain posture of the trunk may be affected giving rise to truncal ataxia.
 - iv. **Dysdiadochokinesis (adiadochokinesis):** Performance of alternating movements rapidly, i.e. to stop one movement and start the opposite one in quick succession, requires proper coordination of the muscles and synergy. In cerebellar lesions rapid alternating movements become impossible, or are performed in a clumsy and jerky manner.
 - v. **Rebound phenomenon:** In a normal person when the resistance to contraction of a muscle is suddenly withdrawn, the contraction can be arrested without the limb overshooting. In cerebellar disease, the limb shoots beyond the normal range.
4. **Alteration in stretch reflexes:** As a result of hypotonia, the stretch reflexes are either diminished or pendular. The pendular knee reflex is elicited with the patient sitting and legs hanging. The legs are seen to oscillate more than three times. This phenomenon is the result of muscular hypotonia.
5. **Disturbances of speech:** Articulation and phonation become incoordinated (dysarthria). As a result, speech becomes irregular, slurred and explosive (*staccato*). The volume of sound is poorly controlled. The syllables in a word tend to be separated and this is called *scanning speech*.
6. **Nystagmus:** Jerky nystagmus develops usually in the horizontal plane as a result of defect in postural

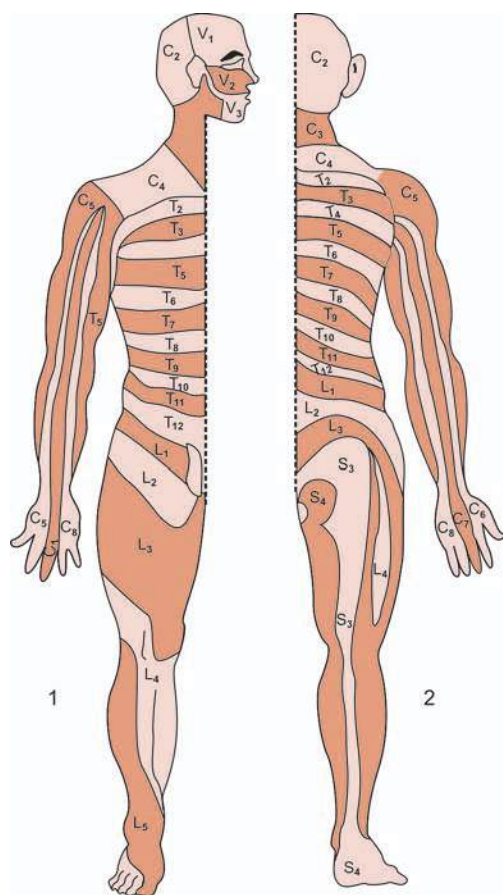


Fig. 182.2: Dermatomes—segmental innervation
(1) Front (2) Back

fixation of conjugate gaze. In unilateral lesions the nystagmus increases in amplitude and slows down in rate when the eyes are turned towards the side of lesion.

Sensory System

The sensory representation over the body is arranged depending on the distribution of the sensory roots arising from the brainstem and spinal cord. The sensory areas subscribed by these sensory fibres are called dermatomes (Fig. 182.2).

The sensations can be broadly divided into: (1) *superficial sensations* (touch, pain and temperature); (2) *deep sensations* (deep pain, pressure, sense of position, sense of movement, joint sensation and vibration); and (3) *cortical sensations* (tactile localisation, tactile discrimination and stereognosis). At the periphery, there are receptors to appreciate different sensory modalities.

- Touch** : Free nerve endings, nerve endings in the hair follicles, Meissner’s corpuscles, Merkel’s discs.
- Pain** : Free nerve endings

- Temperature** : Free nerve endings, Krause’s corpuscles, Ruffini’s corpuscles.
- Pressure** : Pacinian corpuscles
- Proprioception** : Muscle spindles Golgi tendon organs.

The sensations of itching (pruritus) and pain are transmitted through C fibres of polymodal nociceptors, by distinct subgroups of neurons. There are no identifiable receptors for pruritus in the skin. Centrally situated opioid receptors may also modulate the sensation of itching.

Pain receptors are not strictly specific to any kind of stimuli. Even though specific stimuli such as pin prick are appreciated as pain, any stimulus beyond threshold levels is appreciated initially as pain. After the delay of a few seconds the true nature is appreciated. This phenomenon is known as ‘*Lewis’ double response.*’

Sub-threshold sensations are perceived as itch (pruritus), through a special group of C-fibres which ascend up to the thalamus where it is appreciated. These fibres may be specifically involved in multiple sclerosis.

When the receptors are stimulated, afferent impulses pass in the dendrites of the first sensory neuron into the spinal cord through the posterior root ganglion. The axons of the cells from the ganglion pass through the posterior root into the spinal cord and ascend up as the sensory tracts. Fibres subserving different sensations take different paths.

Fibres subserving proprioception, vibration, and a portion of touch ascend up on the same side as the posterior column (*column of Goll and Burdach*) in the spinal cord to reach the lower part of the medulla, where they synapse with the cells in the *gracile* and *cuneate nuclei*. Medial fibres carry sensation from the lower limbs. After synapse the second order neurons cross the midline in the medulla and pass up in the medial lemniscus to reach the main sensory nucleus of the thalamus.

Fibres subserving the remaining part of touch, pain, heat and cold synapse with the cells in the posterior horn of the spinal cord soon after their entry. The second order neurons arising from these cross to the opposite side at different levels. Pain and temperature fibres cross more or less horizontally whereas touch fibres cross more obliquely one or two segments above and pass up on the other side as the *anterior spinothalamic tract* (touch) and *lateral spinothalamic tract* (pain and temperature). In the lateral spinothalamic tract fibres from the lower limbs are placed laterally and fibres from the upper limbs are medial. Some fibres do not cross and they pass up as the ipsilateral spinothalamic tracts. In the brainstem the spinothalamic tracts pass up lateral to the medial lemniscus to reach the thalamus. Third order neurons arise from the thalamus and their fibres which maintain their functional specificity pass up through the internal capsule to be relayed to the sensory area of the cortex in the postcentral gyrus (Fig. 182.3).

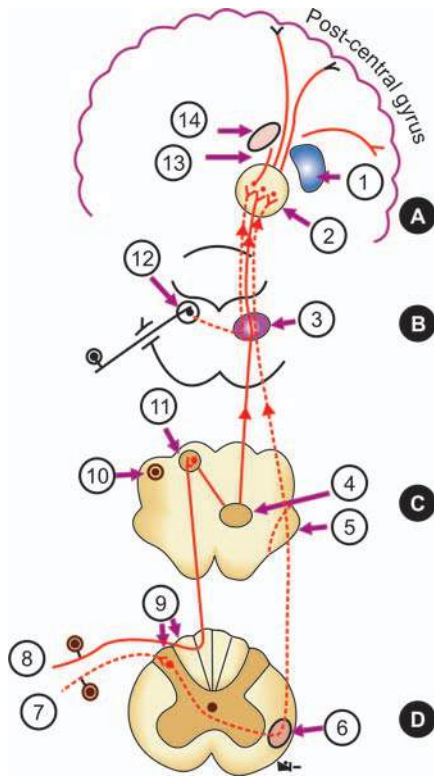


Fig. 182.3: Sensory pathways

(A) Cerebral cortex	(C) Medulla
(B) Pons	(D) Spinal cord
1. Lentiform nucleus	9. Posterior column
2. Thalamus	10. Nucleus cuneatus
3. Medial lemniscus and spinothalamic tract	11. Nucleus gracilis
4. Medial lemniscus	12. Fifth nerve nucleus
5. Spinothalamic tract in medulla	13. Internal capsule
6. Spinothalamic tract in spinal cord	14. Caudate nucleus.
7. Posterior nerve roots forming the spinothalamic tract	
8. Posterior nerve roots forming the posterior column	

In the sensory cortex the body image is arranged similar to that in the motor area from above downwards. From the postcentral gyrus fibres project to other cortical areas. In the parietal lobe the sensory information derived from superficial and deep sensations is integrated to give the impression of size, shape, texture, weight and pattern of the objects (*stereognosis*). The mental picture of the body (*body image*) is obtained by integration of the sensory information with information obtained from the special senses. This function of “body image” is mainly carried

out by the nondominant parietal lobe. The corresponding portion of the dominant hemisphere carries out the function of receptive and interpretative components of speech. This part of the parietal lobe has connection with the ipsilateral motor cortex. This arrangement helps to produce patterns of movements in the lips, tongue, fingers, and respiratory muscles which form motor symbols to represent speech—*gestural language*. It is now known that the dominant cerebral hemisphere contains the major centres for speech. The nondominant hemisphere is responsible for several other higher functions including emotions, feelings and the like.

Developing cells of the nervous system produce signals which give them identity, help to make the topographic map for migration and make the right synapses. Defects in the signalling causes mis- identity, defective migration and defective synaptogenesis.

Occasionally the organisation of neurons in the grey matter may be disorderly due to defects of migration of these cells during brain development. Such disorders are called ‘**neuronal migration disorders.**’ They may lead to several defects such as seizures, mental retardation and cognitive disturbances and tumours.

The thalamus appreciates crude (*protopathic*) sensation and pain. The fine sensations (*epicritic*) are appreciated in the cortex. Among the myriad afferent impulses reaching the CNS, many do not reach consciousness.

Some subserve spinal reflexes. These afferent fibres make contact either directly or through interneurons with the spinal motor nuclei. Other fibres which carry muscle and joint sensations end in the base of the posterior horn of the spinal cord and in the Clarke’s column. The second order of neurons. These neurons form tracts which ascend up as the anterior and posterior spinocerebellar tracts to reach the cerebellar cortex of the same side. Most of the fibres ascend on the same side but some fibres of this tract cross to the opposite side to ascend as the anterior spinocerebellar tracts.

These tracts carry proprioceptive impulses which enable the cerebellum to coordinate activity.

Some other sensory fibres which do not bring sensation to consciousness are collateral branches of the main spinothalamic pathways and of the special sensory paths which join the upper part of the reticular formation in the midbrain. In the reticular formation there is an inter-communicating system of short neurons which also receive fibres from most parts of the cerebral cortex. This system is important for maintaining consciousness.

Neurological Examination and Investigations

S.R. Chandra, P.K. Mohan

Chapter Summary

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Clinical Examination

HISTORY

Pathological lesions in the nervous system may give rise to either positive or negative symptoms. Convulsions, pain and paresthesia are examples of positive symptoms whereas loss of motor strength and loss of sensations indicate negative symptoms. Generally positive symptoms are due to irritative lesions and negative symptoms arise from destructive lesions. At times, positive symptoms may occur in destructive lesions as well, due to release of some structures from inhibition, e.g. spasticity.

In neurological diagnosis, a properly taken history is one of the most important helpful tools for the physician. Broadly, neurological disorders may be divided into the following pathological classes—congenital, developmental derangements, vascular disorders, inflammations, infections, neoplasia and space occupying lesions, degenerations and traumatic injuries. Vascular accidents such as embolism, thrombosis, and hemorrhage come on abruptly, often within minutes to hours. Inflammatory or infective lesions (e.g. meningitis, encephalitis, and brain abscess) start acutely or subacutely and evolve over a

period of days to weeks. In addition to the neurological features, they are usually accompanied by signs of infection such as fever and toxemia.

Generally, space occupying lesions have subacute onset and course progressing to the full-fledged stage over a period of weeks to months. The progress may be steady or punctuated by periodic exacerbations caused by complications such as vascular thrombosis, hemorrhage or edema in the tumour. It should be borne in mind that in conditions such as intracranial bleeding and cerebral edema, the progress of the disease may be rapid and steady.

Degenerative lesions (e.g. presenile dementia, spinocerebellar degeneration) have a very insidious onset and progressive course extending over several years.

HIGHER FUNCTIONS

These include the level of consciousness, intelligence, memory, emotional state and speech. These are all cortical functions. These are deranged in cortical lesions.

SPEECH

This is a highly evolved function of the cerebral cortex and is defined as that human faculty by which thought processes are symbolically expressed.

In neurological parlance, speech has many more facets to it than what is understood by the lay public. *Speech* and *language* are the main modes of expression and communication available to humans. In addition to spoken speech, gestures, signs, signals and graphic symbols of written language all can serve the same purpose. All these modes of expression of thoughts and ideas to others and comprehension of others' thoughts and ideas constitute language. Language is defined as symbolization of ideas (i.e.) ability to convert thoughts into comprehensible words. Language consists of five parameters. These include **speaking, writing, repeating and comprehending through visual stimuli and auditory stimuli**.

Speech is the mechanical function of one's ability to communicate in oral language and this includes articulation and phonation.

The subcortical structures concerned with language are well-delineated. They include the claustrum, lentiform and caudate nuclei, thalamus and the internal capsule, which are contained in the **Marie's quadrilateral space**.

Communication through signs, signals, gestures and vocalisations, mainly to convey one's emotions is called **emotional language**. Communication through the medium of symbols or words is called **symbolic language** (*spoken and written speech*). Infants and, to some degree, animals, communicate through emotional language. As opposed to this, the symbolic language which is unique to man is dependent on fully mature, intact cerebral functions. Synthesis of spoken and written language is a function of the brain. This function is lateralised in the left cerebral hemisphere in 99% of right handed and 75% of left handed individuals and it is the dominant hemisphere for speech and language.

Four distinct areas concerned with speech and language are identified in the brain which constitute the cortical areas for speech. Two of these are anterior to the central sulcus and the other two are posterior to it. All the four are located in the perisylvian region which is called the central zone of language. Just as the cortex anterior to the central sulcus is motor and that posterior to it is sensory in function, the two anterior speech areas are responsible for motor aspects of speech, one for *spoken speech* and the other for *writing*. The two posterior areas are concerned with the sensory aspects of speech, one for comprehension of spoken speech and the other for comprehension of visual speech, i.e., *reading*. The motor area for spoken speech is situated in the posterior part of the left inferior frontal gyrus and it is called *Broca's area*. Pierre Paul Broca, a French surgeon described the Broca's areas in 1865.

The motor centre for writing is thought to be just anterior and superior to the *Broca's area*, very close to that part of the motor cortex that controls the hand muscles *Exner's centre*. The auditory comprehension of spoken speech takes place in the posterior end of the left superior temporal gyrus (*Wernicke's area*). Karl Wernicke, a German neurologist identified the Wernicke's area and later described the conducting pathways between the Broca's and Wernicke's areas. The Broca's and Wernicke's areas are connected by arcuate fasciculus. These three structures are situated around the sylvian fissure, and hence called the peri-sylvian area. The area of the cerebral cortex surrounding this zone is called the para sylvian area. Structures in the subcortical region within an area called Marie's quadrilateral space constitute the subcortical language areas. These include the caudate nucleus, thalamus, lentiform nucleus, claustrum and the internal capsule (Figs 183.1 and 183.2).

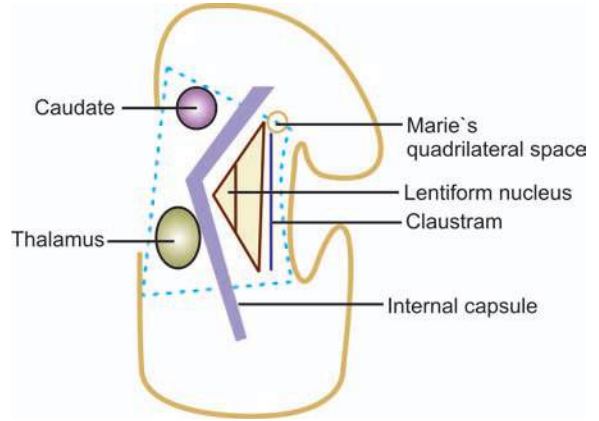


Fig. 183.1: Marie's quadrilateral space

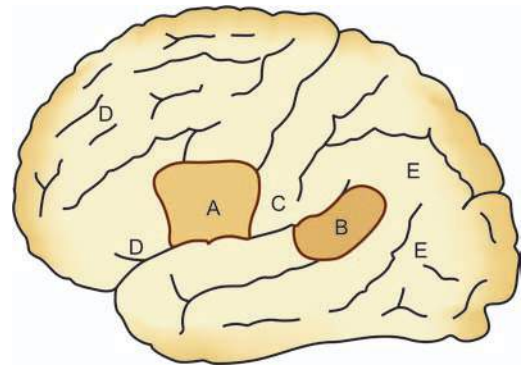


Fig. 183.2: Left cerebral hemisphere—cortical areas of speech

A. Broca's area	D. Transcortical motor area
B. Wernicke's area	E. Transcortical sensory area
C. Conduction area	

The centre for reading is thought to be in the medial aspect of the left occipital lobe and the splenium of the corpus callosum. All these speech areas are connected with each other and the rest of the brain by the neural pathways in the underlying white matter.

The conversion of the intended ideas into words and syllables requires synchronized delicate movements involving structures in the larynx, palate, tongue and lips which are supplied by motor cranial nerves. This neuromuscular apparatus constitutes the peripheral mechanism of *motor speech*, i.e., *articulation*. Cerebellum coordinates these movements and sounds to produce proper prosodic speech. Defects occurring in specific areas in the central pathways produce characteristic abnormalities. By analysis of the abnormality, the central defect can be inferred. Research to understand the interrelationship between speech abnormalities and the lesion in the

central mechanisms of speech is continuing and new information has emerged in the recent past. For instance the possible roles of the subcortical grey matter such as the thalamus and caudate nucleus of the left side and also the right cerebral hemisphere are beginning to unfold.

When a question is asked, it is received by the aWernicke's area and comprehended, then by interacting with various areas in the brain, the answer is formed. This is transmitted through the arcuate fasciculus to the Broca's area for execution. The unique function of the perisylvian area is to receive the information and transmit it to the Broca's area. If the perisylvian area is disconnected from the rest of the brain the only function that will be retained is repetition of the examiners words- also known as *parrot's speech*. The parasylvian zone conveys message from the rest of the brain to perisylvian speech area. The subcortical zones are mainly concerned with the motor scheme of language.

Loss of the language due to a dysfunction of the central mechanism in the brain is called **aphasia**, and a minor disturbance is called *dysphasia*. Loss of ability to read, is called **alexia**. Loss of ability to write is called **agraphia**. Dysfunction of the peripheral mechanism of speech leads to defective articulation which is called **dysarthria**.

Speech disturbance is due to defects in articulation (**dysarthria**), or disturbance of phonation (**aphonia**). Articulation is the process of production of syllables by the coordinated action of facial, lingual and palatal muscles controlled by the cerebellum.

Precise rate, range and strength of movements of these muscles are necessary for normal speech. Alteration in any of these aspects of motor speech resulting from a neurological disorder leads to dysarthria. Depending on the nature of the underlying neurological disorder, the pattern of dysarthria varies. Dysarthria may be spastic,

TABLE 183.1

Depending on the site of the lesion in the speech areas in the brain, the following types of aphasia may occur:

Aphasia type	Site of lesion
1. Broca's aphasia Syn: Expressive aphasia Nonfluent aphasia Motor aphasia Anterior aphasia	Posterior end of left inferior frontal gyrus
2. Wernicke's aphasia Syn: Receptive aphasia Fluent aphasia Sensory aphasia Posterior aphasia	Posterior end of left superior temporal gyrus
3. Global aphasia	In both the above sites (1 and 2)
4. Conduction aphasia	Between the above two sites (1 and 2)
5. Transcortical aphasia a. Motor b. Sensory c. Mixed transcortical	Anterior and/or superior to Broca's area Posterior and inferior to Wernicke's area.
6. Subcortical	

flaccid, ataxic, hypokinetic, hyperkinetic or mixed in type (Tables 183.1 to 183.4).

Dysarthria: There are three main types of dysarthria.

In cerebellar disease the speech is slow, deliberate and scanning or staccato. This is called **ataxic dysarthria**.

In bilateral corticospinal lesions occurring above the level of the brainstem the speech is spastic, e.g. pseudo-bulbar palsy-which may be vascular or degenerative. Such patients show evidence of upper motor neuron lesion of the cranial nerves supplying the muscles of the face, larynx, tongue, and respiration. Other associated features such as dysphagia are present because of spasticity of the muscles of deglutition. Lower motor neuron lesions of the muscles supplied by the brainstem nuclei give rise to

TABLE 183.2

Representation of various components of speech in anatomical areas of the cerebral cortex

Components of speech	Anatomical areas of cerebral cortex
1. Ability to read and comprehend written speech	1. Visual cortex and its association areas
2. Ability to hear and comprehend	2. Heschl's gyrus (transverse temporal gyrus) and the superior temporal gyrus
3. Ability to comprehend symbols	3. Superior temporal gyrus and parieto-occipital areas
4. Ability to identify and name objects	4. Supra-marginal and angular gyrus
5. Genesis of motor engram of speech	5. Broca's area (posterior part of inferior frontal gyrus)
6. Genesis of motor engram for writing	6. Exner's area in the middle frontal gyrus
7. Execution of the expressive part through the motor system coordinated by the pyramidal, extrapyramidal and the cerebellar connections along with the emotional component executed by the prefrontal lobe and connections.	
8. The main white fibre tracts connecting the Broca's and Wernicke's areas constitute the arcuate fasciculus.	

TABLE 183.3

Lesions in different regions of the brain affect language modalities differently	
Site of lesion	Results
1. Left temporal lobe	Disturbance of verbal comprehension, repetition and writing
2. Left frontal lobe	Articulation and fluency of verbal expression are mainly affected
3. Left parieto-occipital region	Impairment of reading (visual language function)
4. Left parietal lobe	Writing is particularly impaired

flaccid dysarthria. The speech is slurred, e.g. bulbar palsy. The muscles of the tongue and lips are mainly affected. This manifests as difficulty in pronunciation of labials (P and B) and linguals (L).

Dyskinetic dysarthria may be hypo- or hyperkinetic. Hypokinetic dysarthria is slow monotonous speech with steady decline of the level of voice. This occurs in Parkinsonism. Hyperkinetic dysarthria occurs in chorea and dystonias affecting the tongue muscles. The speech in chorea is characterized by sudden unwarranted punctuations when chorea occurs. Action dystonia of the tongue (aphthogonia) is a special action-induced movement disorder caused by lesions in the corpus striatum. The patient goes into a twisting spasm and the speech stops abruptly.

Aphonia: *Phonation* is the process by which voice is produced by the vocal cords. Inability to produce sounds while still able to make syllables and gestures is termed

aphonia. This may be organic as a result of bulbar or pseudobulbar palsy or it may be a hysterical phenomenon.

Anterior Aphasia (Broca’s aphasia)

In Broca’s aphasia there is difficulty in repeating spoken words and also difficulty in grammar, but the matter is conveyed – This is called **telegraphic speech**. The same phenomenon occurs in writing also. Reading loud is not possible, but he can read and obey; since comprehension is preserved.

In parietal lobe lesions occurring with defects in the central mechanisms of speech, sometimes an element of apraxia may alter language function giving it a dysarthric character in addition to the language defect (dysphasia).

In anterior aphasia (Broca’s) the patient is unable to express properly, but when the first syllable is prompted he catches the correct word. In severe degree of Broca’s aphasia he can not respond to prompting, but he can select the correct word when multiple choice is given.

In lesions of the left posterior temporal region, speech is made up only of asyllabic neologisms without producing any normal sense. This is called **jargon aphasia or empty speech**. There is considerable impairment of comprehension of spoken speech in posterior aphasias (Wernicke’s aphasia). *Patients with Wernicke’s aphasia cannot repeat spoken words. They cannot also read loud or read for comprehension. They cannot respond to prompting by the examiner nor can they choose the correct word from multiple choice.*

Conduction Aphasia

This occurs due to lesions of the arcuate fasciculus with the Broca’s and Wernicke’s areas remaining intact. This

TABLE 183.4

Showing the features of different types of dysarthria							
Dysarthria type	Phonation	Prosody	Nasality	Pitch	Loudness	Rate	Disease
Spastic	Strained/voice tremor	Excess or insufficient	Hyper or hypo	Low or monotonous	Harsh or monotonous	Slow	Pseudobulbar palsy
Flaccid	Impaired	Insufficient	Hyper	Low	Reduced	Slow	Bulbar palsy
Spastic and Flaccid	Strained	Excess/insufficient	Hyper	Low	Hoarse	Slow	Amyotrophic lateral sclerosis
Ataxic	Strained	Excess	Normal	Irregular	Irregular	Slow	Cerebellar disease
Extra-pyramidal	Impaired	Insufficient	Normal	Reduced monotonous	Reduced monotonous	Slow	Parkinsonism
Dyskinetic	Variable	Variable	Variable	Unpredictable	Speech arrest	Slow	Chorea
Dystonia	Do	Do	Do	Variable	Unwanted	Variable punctuation	Dystonia

Features of Perisylvian Aphasia		
Broca's aphasia	Wernicke's aphasia	Arcuate (conduction aphasia)
Repetition not possible	Not possible	Not possible
Non-fluent	Fluent	Moderately fluent
Effortful	Effortless	Moderately effortful
Emotional	No significant emotion	Moderate depression
Telegraphic speech (meaning not affected)	Neologism (no meaning)	Moderate paraphasia
No paraphasia	Paraphasia: (letters and words substituted)	Moderate affection of meaning
Grammar affected	Not affected	Occasional paraphasia
Comprehension normal	Affected	Occasional mistakes
Writing similarly affected (telegraphic)	Writing meaningless	Mild affection
Reading loud-defective	Not possible	Mild mixture of both elements
Reading for comprehension normal	Not possible	Mild disability
		Mild disability—moderate alteration of all faculties, but, with severe affection of repetition

is a unique situation where the patient has only minor difficulty in motor and sensory language function, but severe impairment of the capacity to repeat even single words spoken by the examiner.

Global aphasia is a combination of all the above three resulting in inability to comprehend, express and repeat.

Gestural language is unaffected in verbal language disorders, since it is a function of the non-dominant hemisphere.

Parasyylvian disorders include transcortical motor, transcortical sensory, and mixed transcortical aphasia. Parasyylvian disorders resemble the perisylvian aphasia except that repetition is retained. Broca's aphasia with retained repetition is **transcortical motor aphasia**. Wernicke's aphasia with retained repetition is **transcortical sensory aphasia**. Global aphasia with retained repetition is **mixed transcortical aphasia**.

Subcortical disorders include striatal, thalamic and capsular aphasia.

Subcortical Aphasia

Subcortical aphasia are characterized by loss of speech followed by rapid recovery. There is severe naming defect and a dysarthric element.

Apart from the common features, defect of each structure produces specific characteristics which help to identify the lesion precisely.

Blood Supply of the Language Areas

Middle cerebral artery supplies the perisylvian area. Its upper division supplies the Broca's area, lower division

supplies the Wernicke's area.

Parasyylvian area is the watershed area which receives its blood supply by perfusion from middle cerebral and anterior cerebral arteries. When these arteries are affected infarction occur in these areas due to hypoperfusion. Subcortical structures receive their blood supply from the carotid and basilar systems.

Special Language Disorders

These include **visual agnosia, auditory agnosia and tactile agnosia**. In these disorders the patient has difficulty for comprehension and expression through a particular sensory mode only, while the same object can be correctly comprehended and expressed when presented through another sensory mode.

Apraxia: The inability to perform learned complex motor acts in the absence of motor or sensory paralysis is known as apraxia. Apraxic subjects may be able to perform the components of such acts but are unable to complete them. Apraxic subjects cannot make use of objects, though their use will be recognized by them. For example the patient may know the use of a pencil, but when asked to write he may not be able to do so. Apraxia results from damage to left parietal cortex, parietal white matter of left or both hemispheres or the interhemispherical fibres passing through the corpus callosum.

CRANIAL NERVES

The next step is to examine the cranial nerves. This is described along with the individual cranial nerves, in Chapter 184.

OPHTHALMOSCOPY

Optic nerve head and retina can be inspected using an ophthalmoscope. Both direct and indirect ophthalmoscopy are available. In direct ophthalmoscopy the image of the retina is upright. In indirect ophthalmoscopy it is inverted.

Direct ophthalmoscopy (funduscopy): The direct ophthalmoscope gives a direct view of the fundus and other structures of the eye. Opacities in the media and lesions of optic nerve and retina are seen with great accuracy and under a magnification of 15. Lesions of retina in front of the equator are not detected with this technique. When the media are hazy fundus details may be indistinct. These two defects are remedied to a great extent in indirect ophthalmoscopy.

Method: The direct ophthalmoscope is used with a positive 12 lens. Corneal and lenticular opacities are outlined against the red reflex of the fundus. The power of the lens in the ophthalmoscope is then reduced until the retina is in focus. The power of lens in the ophthalmoscope required to focus upon the optic disc corresponds approximately to the patient's refraction.

The examiner should systematically examine the media of the eyes, optic disc, blood vessels and all portions of the retina.

Abnormalities that can be detected by ophthalmoscopy are:

1. Opacities in the media,
2. Abnormalities of optic disc,
3. Vascular abnormalities,
4. Hemorrhages,
5. Exudates,
6. Degenerative changes,
7. New growths,
8. Retinal detachment, and
9. Several others.

Appearances of Normal Fundus

Optic Disc

When the patient looks straight ahead, the optic disc comes into view as the most prominent structure. It is pink in colour and oval or circular in shape. The margins are sharp and there is a small depression in the centre — the *physiological cup*. The central retinal vein and artery are seen to course over to the retina. These divide into the superior and inferior trunks at or near the surface of the disc. Each trunk divides further into temporal and nasal branches. The vessels should be followed in all the four quadrants as far as the equator, with the patient looking in all the four directions.

The arteries are bright red and narrower than veins, which are purplish. The normal A-V ratio is 2 : 3. After examining the disc and the vessels, the macula is

examined. A mydriatic may be instilled into the eye to facilitate proper examination, since light falling on the macula leads to pupillary constriction.

Major abnormalities of the optic disc include papilledema, optic atrophy, papillitis and glaucomatous cupping. Medullated nerve fibres may appear as bright streaks fanning out from the margin of the optic disc into the retina. These are congenital variations, which are not pathological and which should not be mistaken for pathological lesions.

Blood Vessels

Arteries: Normally arterial blood column is seen through the transparent arterial wall and gives the appearance of the normal streak. Thickening of arterial wall leads to reflection of light. The streak becomes wider and appears as burnished copper—*copper wire arteries*. When the arteries are seen as white lines they are called ghost vessels.

Sheathing: When the arteries are bordered by white lines this is referred to as sheathing.

Generalized narrowing of arteries occurs in hypertension, arteriosclerosis, vasculitis from various causes, central retinal artery occlusion, toxic amblyopias, migraine and conditions that cause retinal degeneration.

Irregular narrowing appears as irregularity in size of the arteries. Constricted segments alternate with normal or dilated segments. These changes occur mainly due to endothelial proliferation of the intima.

Pulsation: Normally pulsations of arteries are not visible. Arterial pulsation at the disc is always pathological. This is seen in aortic regurgitation, aneurysms and exophthalmic goitre. Capillary pulsation can occur in aortic regurgitation and this is seen as alternating hyperemia and pallor of the disc corresponding to systole and diastole. Veins normally pulsate due to transmission of the pulsations of the brain.

Veins: Congestion of retinal veins occurs in systemic diseases such as cardiac failure, polycythemia, respiratory failure, coarctation of aorta, thyrotoxicosis, chronic myeloid leukemia, acute leukemias and hyperviscosity states. All these conditions may predispose to venous occlusion. Marked congestion, tortuosity and dilation of veins occur in papilledema.

Arteriovenous changes: Normally the veins can be seen through the transparent arteries. In sclerosis, loss of transparency of the artery obscures the vein. A thickened artery may press the vein at crossings and therefore the vein appears to be interrupted proximally and distended distally. This is called nipping. Sometimes the vein may be pushed aside at crossings. New vessels develop in long-

standing venous occlusion and diabetes. This is called neovascularisation.

Hemorrhages: Retinal hemorrhages are always pathological. When the hemorrhage is superficial it occupies the nerve fibre layer and appears as striate or flame shaped bright red patches. When deeply placed, they appear as rounded irregular patches which are darker in colour. When hemorrhage occurs between retina and the vitreous, i.e. pre-retinal or subhyaloid hemorrhage, usually the macular area shows it up as a large spherical reddish patch. It becomes hemispherical slowly due to settling down of erythrocytes.

Exudates: Soft exudates are spherical cottonwool-like patches in the retina. These are caused by microinfarcts and are seen in vasculitis and hypertension associated with renal disease. Hard exudates are irregular yellowish white patches or plaques usually seen around the macula. They are due to neuronal degeneration and lipid infiltration of the retina. They are seen in diabetes and arteriosclerosis.

Motor System

The muscle groups have to be examined with a view to elicit the following points:

- 1. Bulk,
- 2. Tone,
- 3. Strength,
- 4. Fasciculations,
- 5. Presence of involuntary movements,
- 6. Stretch reflexes and superficial reflexes
- 7. Coordination, and
- 8. Gait.

In assessing these parameters it is important to have an idea of the normal bulk and strength and tone of the different muscles in relation to the general body build and age of the individual.

Muscle strength: This is to be graded as follows:

- Grade 0 Complete paralysis with no movement.
- Grade 1 Only a flicker of contraction is present.
- Grade 2 Patient can move the limb when gravity is eliminated by suitable positioning.
- Grade 3 Limb can be moved against gravity, but not against further resistance.
- Grade 4 There is some degree of muscle contraction ranging from poor, fair or moderate strength, against mild to moderate resistance.
- Grade 5 Normal power is present. Movement against full resistance is possible.

Neurological motor disability may take several patterns.

Hemiplegia: Paralysis of the limbs of one side of the body with paralysis of the face in most cases; this results from contralateral lesions of corticospinal tract above the brainstem.

Crossed: Lower motor neuron paralysis of cranial nerves on one side hemiplegia on the opposite side; this results from lesions in the brainstem ipsilateral to cranial nerve palsy.

Paraplegia: Paralysis of both lower limbs.

Monoplegia: Paralysis of only one limb.

Quadriplegia: Paralysis of all four limbs.

Double hemiplegia: Hemiplegia occurring on both sides.

Stretch reflexes: The stretch reflexes are monosynaptic reflexes. Sudden tap on a lightly stretched muscle tendon evokes a sharp contraction. Elicitation of these reflexes gives valuable clues about the integrity of the afferent and efferent reflex pathways and excitability of the reflex centre. Several reflexes are elicited in clinical examination. The reflex pathways of stretch reflexes are located in different levels in the spinal cord and brainstem. Their elicitation helps to determine the level of neurological lesion.

From above downwards, these reflexes are:

Stretch reflexes	Centre
Jaw reflex	Trigeminal nuclei in the pons
Biceps reflex	C5, C6 spinal segments
Triceps reflex	C6, C7 spinal segments
Supinator reflex	C5, C6 spinal segments
Knee reflex	L2, 3 and 4 spinal segments
Ankle reflex	S1 and 2 spinal segments

Stretch reflexes may be absent, normal or exaggerated (very brisk). Exaggerated stretch reflexed may be accompanied by clonus.

Superficial reflexes: These are polysynaptic reflexes elicited by stimulating the skin or mucous membrane. Several superficial reflexes can be elicited by appropriate stimuli. These are also altered in upper and lower motor neuron lesions. These also help to establish the location of neurological lesion.

Superficial reflexes	Centre
Abdominal reflexes	T7 to T12 spinal segments
Cremasteric reflex	L1 and 2 spinal segments
Anal reflex	S3, 4 and 5 spinal segments
Bulbocavernous reflex	S3 and 4 spinal segments
Plantar reflex	L5, S1 and 2 spinal segments

Co-ordination: This term implies the smooth recruitment, interaction and cooperation of agonists the prime movers, antagonists which oppose them and synergists which are supportive, which result in a smooth and definite motor act. Coordination is effected by several factors such as afferent proprioceptive impulses from muscle spindles and joint receptors, cerebellar function and muscle tone. Incoordination results in imperfect performance of the motor act and leads to ataxia. Ataxia may be due to loss of proprioceptive sensations (sensory ataxia) or diseases of the cerebellum (cerebellar ataxia). In the case of sensory ataxia (e.g., tabes dorsalis), visual clues can compensate to maintain posture and movement so that with eyes open the patient is able to maintain posture, but with the eyes closed, ataxia manifests. Ataxia occurring in cerebellar disease is not influenced by visual impulses.

Gait: The term gait refers to the manner in which a person walks. Normal gait involves both central mechanisms and peripheral mechanisms to execute the act of walking. These include:

- a. Antigravity stretch
- b. Stepping
- c. Propulsion, and
- d. Equilibration.

The peripheral mechanisms include muscles, tendons and joints. Components of the gait are **stance, pace, turns stamp**.

Stance is the distance between the two feet, necessary for stable standing. Normally it is equal to the length of one's own foot.

Pace is the distance covered between two feet during stable walking.

Turns: Sudden turning from one direction to another needs fine adjustments of motor skills to maintain balance. So, subtle problems in balancing will be manifest only during sudden turning.

Stamp is the force with which the feet are brought down to the ground on walking. It is determined by the height to which the toe is raised before the foot is brought down.

Disorders of gait can be due to disorders of:

1. Antigravity stretch, e.g. apraxic gait
2. Stepping, e.g. shuffling and hopping gait
3. Propulsion, e.g. dragging gait
4. Equilibration, e.g. swaying and reeling.

Defects due to peripheral mechanisms lead to limping and waddling. Analysis of the gait gives valuable neurological information. Well-defined neurological disorders give rise to characteristic types of gait.

Spastic gait

Indicates corticospinal tract lesions such as spastic paraplegia or hemiplegia.

Stamping gait

This occurs in sensory ataxia in which the patient stamps his foot on the ground with the heel touching first. This gait is seen in posterior column lesions.

Cerebellar gait

This is described as the reeling or drunken gait.

Festinant gait

It is seen in florid Parkinsonism.

Waddling gait

It resembles the gait of a duck. This results from defects in maintaining posture due to weakness of the truncal and gluteal muscles. This is seen in proximal myopathies. A similar gait may occur in bilateral disease of the hip joints as well.

High stepping gait

The patient lifts up his feet high to avoid tripping from the toes catching the ground. This type of gait is seen in patients with foot drop. e.g. peripheral neuropathy.

Apraxic gait :

The patient appears to be glued to the ground without moving forward. He tries to move the trunk instead of the feet. This is seen in frontal lobe disease.

Shuffling gait:

In this, the pace is short so the speed is grossly reduced. This is seen in frontal lobe disease.

Sensory System

Reliable results of sensory examination are obtained only when the patient is alert and cooperative. Considerable skill is required to elicit the sensations properly without unduly tiring out the patient. When testing the sensation it is better to proceed from the abnormal to the normal area.

The primary modalities that are tested include:

1. *Tactile sensitivity*, including light touch, pressure, tactile localization and discrimination;
2. *Pain (superficial and deep)*;
3. *Temperature (heat and cold)*;
4. *Position sense and appreciation of passive movement*;
5. *Vibration*; and
6. *Stereognosis* — Recognition of size, shape, weight, texture and form of objects.

RECORDING OF NEUROLOGICAL FINDINGS

The findings elicited on clinical examination should be systematically recorded. Many neurological disorders progress or resolve within short periods. Therefore, the examination may have to be repeated at regular intervals depending on the type of the disorder. This is all the more important in conditions such as transient ischemic attacks (TIAs), head injury, and meningitis.

Investigations

LUMBAR PUNCTURE (LP)

This can be safely performed in the absence of raised intracranial tension. The LP needle is introduced between the third and fourth lumbar vertebrae. The cerebrospinal fluid (CSF) is collected in four bottles for: (1) cytology, (2) biochemical examination, (3) microbiological studies and (4) for special tests like oligoclonal bands, immunoglobulins, lactate, pyruvate and others.

Manometry during LP is performed to measure the CSF tension. Compression of the jugular vein leads to rapid rise in lumbar CSF tension and release of the compression results in its rapid fall. This phenomenon is abolished in spinal block. **Queckenstedt's test** is done to detect block in the spinal subarachnoid space as occurring in spinal tumours or arachnoiditis. In the Queckenstedt's test the jugular vein is compressed on one side and then on the other side while doing spinal manometry. In lateral sinus thrombosis pressure on the ipsilateral jugular vein fails to raise the intracranial and spinal CSF pressure. Compression on the unaffected side leads to rise in CSF tension and the spinal subarachnoid fluid pressure.

In the **Tobey Ayer test** the jugular veins on either side of the neck are compressed in succession (not together).

Normally rise in intracranial CSF pressure is transmitted to spinal subarachnoid space and the lumbar CSF pressure rises. Failure to raise the spinal subarachnoid CSF pressure by jugular compression done on both sides, is indicative of spinal subarachnoid block.

Normal CSF is colourless, clear, and watery. Xanthochromia (yellow colour) occurs following subarachnoid hemorrhage and in Froin's syndrome. Turbidity results from increase in cells. Normally the cells number below 5/cmm and all of them are lymphocytes. Rise in cells is called pleocytosis. Lymphocytic pleocytosis occurs in viral, tuberculous and syphilitic meningitis. Neutrophil pleocytosis occurs in pyogenic meningitis, e.g. meningococci, pneumococci. Mixed pleocytosis (both lymphocytes and neutrophils) occurs in leptospirosis, tuberculosis or following subarachnoid hemorrhage. In neuroleukemia immature white cells may be seen in the CSF. Malignant lesions involving the meninges or extending to the surface of the brain or ventricles may give rise to presence of malignant cells in the CSF which can be detected by appropriate staining or millipore filtration (Table 183.5).

Biochemical composition of normal CSF		
Proteins	30-40 mg/dL	Much lower than serum level
Sugar	60-80 mg/dL	≥ 50% of serum level
Chlorides	720 mg/dL	same as serum level

The CSF cytology, biochemical characteristics, and serology alter in disease (Table 183.5).

The CSF should be examined with Gram stain for pyogenic organisms, Ziehl-Neelsen stain for mycobacteria and India ink preparation for cryptococci. In meningitis

Alterations in CSF in health and CNS infections					
	Tension	Colour	Cells	Protein	Sugar
Normal	50-150 mm water	Clear	0-5 lymph/cm	30-40 mg/dL	60-80 mg/dl
Pyogenic meningitis	Raised	Turbid	>1000, mostly neutrophils	Increased considerably	Very low
Tuberculous meningitis	Raised	Cloudy (cob-web)	Up to 300-500, mostly lymphocytes	200-300 mg/dL or more	Very low
Viral meningitis	Raised	Clear	10-100, mostly lymphocytes	50-100 mg/dL	Normal
Syphilitic meningitis	Raised	Clear	Up to 20-500, mostly lymphocytes	100-200 mg/dL	Normal
General paralysis of the insane	Normal	Clear	up to 100, mostly lymphocytes	40-100 mg/dL	Normal
Tabes dorsalis	Normal	Clear	Up to 100, mostly lymphocytes	30-60 mg/dL	Normal
Encephalitis	Raised	Clear	Up to 100, mostly lymphocytes	Normal or marginally raised	Normal or raised

this is an excellent method for early etiological diagnosis. The specimen for microbiological examination should be cultured without delay to get positive cultures. In tuberculous meningitis a fine coagulum (*cob-web*) forms when the CSF is left at room temperature for 12-24 hr. This is due to coagulated fibrin and it may show acid fast organisms on staining.

The rise of proteins in the CSF may be selective and this can be used for diagnosis. Selective rise in globulin fraction can be identified by suitable tests. Previously the colloidal gold test (*Lange's test*) used to be done for this purpose. A more modern and accurate method is to do immunoelectrophoresis. Determination of the immunoglobulins in the CSF and comparing them with the blood levels give diagnostic information. For example, in multiple sclerosis, CSF shows rise in oligoclonal IgG. Early identification of infective agents is made possible by molecular biological methods such as polymerase chain reaction.

The complications of lumbar puncture include sudden herniation of the cerebellar tonsils or uncus of temporal lobe, severe headache and introduction of infection into the meninges (iatrogenic meningitis).

Lumbar puncture is very risky in the presence of raised intracranial tension. Sudden release of CSF pressure by LP leads to herniation of the cerebellar tonsils into the foramen magnum or uncus of temporal lobe through the tentorium cerebelli resulting in fatal depression of respiration and other vital functions. Therefore, lumbar puncture is contraindicated in such situations unless a neurosurgical team is ready at hand. If available, CT scanning of the head which is a noninvasive but expensive procedure should be done to assess the intracranial pathology before undertaking a risky lumbar puncture. At least in some cases such as subdural hematoma or localized fluid collection, the LP can be shelved. **If meningitis or encephalitis is clinically suspected, lumbar puncture should be done with due precautions without delay, since early institution of specific antibiotic treatment is the most important factor leading to a successful outcome.**

Sometimes when an LP cannot be performed or the lumbar subarachnoid space is obliterated, CSF can be obtained by cisternal puncture. When the CSF tension is high a safe method to obtain CSF is ventricular puncture through a burr hole in the skull.

Electrophysiological Studies

ELECTROENCEPHALOGRAPHY (EEG)

EEG is a specialized neurological investigation which involves recording of the spontaneous electrical activity of the brain from the scalp. This is a safe, non-invasive, relatively inexpensive, painless, easily repeatable procedure to know the functional status as opposed to the CT and MRI scan which reveal the morphology

of the brain. Since the EEG findings in many of the cerebral disorders are non-specific, its diagnostic value is confined to a few conditions such as epilepsies, encephalitides, metabolic, toxic, anoxic and drug induced encephalopathies, brain death, and sleep disorders. EEG was introduced into clinical medicine by Hans Burger. The modern EEG machine has 8 to 16 channels to record the brain's electrical activity simultaneously from many areas of the scalp. Electrodes, which are usually silver—silver chloride discs are applied to the scalp, by means of an adhesive material which also provides good electrical contact between the electrode and the skin after the hair and the scalp are cleaned of oil and grease. The placement of these electrodes on the scalp is standardized internationally (10-20% system), and the tracing is recorded on a moving sheet of paper for about 30-60 minutes during the awake state, while the patient comfortably lies in a quiet room. The patient need not fast for this test nor miss his medication, including the anticonvulsants. In many laboratories, hyperventilation for three minutes, photic stimulation at different rates with a flickering light (strobe) and sleep are used as provoking procedures.

The EEG tracing is studied to note the frequency, amplitude, morphology and topography of the brain electrical activity. Four types of frequency bands of EEG are encountered. They are (i) delta (less than 4 Hz activity), (ii) theta (4-8 Hz), (iii) alpha (8-13 Hz), and (iv) beta (more than 13 Hz) bands.

The EEG of a normal adult in the awake and resting state with eyes closed consists of alpha rhythm of 30-60 microvolts over the posterior regions of the head. In children, the frequency is slower in the theta or delta range, depending on the age.

The abnormalities in the EEG may be in the form of asymmetrical activity, faster or slower frequency activity, low or high amplitude activity or abnormal wave forms like sharp waves, slow waves and/or spikes. Localised or focal abnormalities, though highly significant, cannot reliably distinguish the underlying pathological lesion such as tumour, abscess, hematoma or infarct.

EEG is of greatest value in seizure disorders not only to document the inter-ictal subclinical seizure activity but also to classify the epilepsy as partial or generalized, depending on whether the seizure activity is focal or generalized. Sporadic spikes, sharp waves, spike and slow wave complexes or 3 Hz spike and wave complexes in absence attacks are some of the EEG patterns seen in epilepsy. However, it should be mentioned here that a normal EEG does not exclude epilepsy because in only 50-60% of these patients EEG will be abnormal in the interictal period.

The characteristic periodic EEG complexes in subacute sclerosing panencephalitis and Jacob-Cruetzfeldt disease, the triphasic waves in hepatic coma and the electrocerebral silence in brain death are some of the other diagnostic EEG patterns.

Evoked Potentials

Evoked potentials are specific cortical, thalamic or brainstem responses to visual, auditory or somatosensory stimuli. They have several components beginning at a constant latency after application of the stimuli. They are maximal in the cortical areas appropriate to the modality and laterality of the stimulus. Since these electrical potentials are very low in amplitude (0.5-20 microvolts), computers are required to amplify them and distinguish them from background electrical activity of the brain. Three main evoked potential tests are in current use. These are: (1) *visual*, (2) *brainstem auditory*, and (3) *somatosensory*. They are found to be of great value in the diagnosis of several disorders, which may present problems in diagnosis, e.g. visual evoked potentials are useful in identifying demyelinating disease, multiple sclerosis, compressive lesions of the visual pathway, Friedreich's ataxia, Huntington's chorea, etc. It also helps in distinguishing factitious visual loss from genuine blindness. Auditory evoked potentials help to diagnose acoustic neuroma, multiple sclerosis, and central pontine myelinolysis. Somatosensory evoked potentials help in the diagnosis of sensory peripheral neuropathy, tabes dorsalis, subacute combined degeneration, progressive myoclonic epilepsy, etc.

Magnetoencephalography

Magnetoencephalography has been employed to record molar evoked potentials in humans. The magnetic fields generated by the neuronal and other activities of the brain are evaluated using an array of magnetic probes. This investigational tool may form an adjunct to the other available methods, especially in the investigation of disorders such as epilepsy demyelination and others.

Polysomnography records EEG, eye movements, EMG of chin muscles and tibialis anterior muscles, ECG, oral

and nasal airflow, respiratory movements of the chest and abdomen, and oxygen saturation. This is indicated for study of sleep disorders, sleep apnea syndrome, seizures, and other forms of brain disease. The study is done in special sleep-laboratories. It helps to distinguish between wakefulness and sleep and also to record the stages of sleep.

ELECTROMYOGRAPHY (EMG)

EMG is an investigation in which the electrical activity of muscle is picked up with a needle electrode inserted into the muscle and is displayed on a cathode ray oscilloscope and played over a loudspeaker for simultaneous visual and auditory analysis. Usually, this is performed by the neurologist and is associated with some amount of discomfort to the patient because of multiple needle insertions into the muscles. Interpretation of EMG is done taking into consideration the following parameters (Table 183.6):

- 1. Insertional activity.
- 2. Spontaneous activity.
- 3. Activity in minimal muscle contraction.
- 4. Activity in maximal muscle contraction.

Basically, it is carried out to know whether a muscle is normal or shows evidence of myopathy or neurogenic lesion, both of which can lead to muscle weakness and wasting. A normal muscle is electrically silent when it is at complete rest. When it is minimally contracted voluntarily, the action potentials of motor units that are activated appear on the oscilloscope which have a certain configuration, amplitude and duration. With more and more vigorous voluntary contraction, the number of these action potentials increases and during maximal contraction which recruits all the motor units for contraction, these potentials merge with each other to give full recruitment pattern. When the muscle contraction ceases, again the muscle becomes electrically silent.

TABLE 183.6

EMG abnormalities in different neurological disorders

EMG parameters	Myopathy	Neuropathy	Myotonia
Insertional activity	Normal	Increased	Increased
Spontaneous activity	Normal	Increased fibrillation, fasciculation	Normal
Minimal voluntary contraction	Low amplitude short duration with polyphasic complexes	Large amplitude Long duration polyphasic complexes	Discharges wax and wane in amplitude and frequency
Maximal voluntary contraction	Full recruitment	Incomplete recruitment	Not affected
Audio	Nil characteristic	Rain on roof top sound due to fibrillation	Dive bomber sound

When a muscle becomes weak due to a primary muscle disease like myopathy, its EMG pattern differs from that of a normal muscle. When the affected muscle is at rest, there will be spontaneous electrical activity in the form of fibrillation potentials. During minimal voluntary contraction, the generated action potentials will be of lower amplitude and shorter duration as compared to a normal muscle and during maximal contraction, the recruitment potentials will be full. As against this, a muscle which is weak due to a neurogenic lesion, i.e. its neural connection to the anterior horn cells of the spinal cord is affected, it shows spontaneous electrical activity at rest in the form of fibrillation and fasciculation potentials and during minimal voluntary contraction, the action potentials will be of larger amplitude and longer duration than normal and during maximal contraction, the recruiting potentials will be less than normal.

Thus, EMG helps to differentiate muscle weakness due to a primary muscle disease from that due to a nerve or anterior horn cell disease. But it does not indicate the causes of the disease for which other supplementary investigations are required. Many a time it is possible to distinguish primary myopathy from neuropathy clinically, but occasionally it is difficult. EMG is most valuable to distinguish such cases. Characteristic EMG pattern occurs in myotonic disorders (dive-bomber sound) and EMG also helps to differentiate true myotonia from pseudomyotonia and true weakness from hysterical weakness.

Muscle enzyme levels like creatine phosphokinase (CPK) and lactic dehydrogenase (LDH) in the serum may transiently increase, following an EMG investigation because of the needle trauma to muscles. Therefore, the blood samples for estimation of these enzymes should be collected before performing the EMG.

Nerve Conduction Studies

Nerve conduction study is employed to test the integrity of a peripheral nerve. The presence or absence of denervation, the site of nerve block if any, and nature of the lesion such as demyelination or axonal lesion can be detected easily even if the patient is not cooperative. Hence this test can be employed in infants, children and in comatose patients.

Nerve conduction velocity studies (NCV) are of two types:

1. Motor nerve conduction velocity study (MNCV), and
2. Sensory nerve conduction velocity study (SNCV).

NCV studies are valuable (i) to detect demyelination in the peripheral nerves where the NCV will be significantly slowed down, and (ii) to detect axonal lesion where the NCV may be within normal limits but the evoked muscle action potential will be of abnormally low amplitude and longer duration. NCV study also helps to localize the site of pathology in the peripheral nerves. NCV and EMG are complementary investigations and

should be done together. Prognosis for muscle recovery should take into account the results of both.

In demyelinating neuropathy the NCV is grossly delayed, but EMG is normal. Axonopathy shows normal NCV with abnormal EMG. This combination (i.e) **normal NCV with low amplitude EMG indicates a poor prognosis for recovery whereas abnormal NCV with normal EMG indicates good prognosis.**

Imaging Studies

Neuroradiology: This branch of radiology has expanded tremendously and several diagnostic techniques are available.

Plain X-ray of skull in the anteroposterior, lateral and special views, (e.g., Towne's view for the internal auditory meatus) help to detect rarefaction of the skull, fractures, bony erosions, calcification, enlargement of the sella turcica, and shift of midline structures such as a calcified pineal gland. Radiology of the cervical spine helps to visualize bony lesions, vascular calcification and abnormalities of the craniovertebral junction.

X-ray of the skull is a very useful investigation to detect congenital and other acquired abnormalities of the skull such as hydrocephalus, Paget's disease of bone, punched out lesions occurring in multiple myeloma, histiocytosis and malignant secondaries, hyperplasia of bone marrow as occurring in thalassemia, endocrine abnormalities such as hyperparathyroidism, fractures of the skull vault and base of the skull and several others. With the availability of CT scans and MRI, the preference is for them for the detection of intracranial lesions, particularly of the soft tissues and blood vessels.

Special radiological studies: Myelography demonstrates the spinal subarachnoid space. Direct myelography is an invasive procedure associated with the risk of reactive myelopathy. Hence, where MRI myelography using contrasts it is the procedure of choice.

Angiography: A very elegant method is *digital subtraction angiography* by which the background shadow of the skull and other structures are eliminated so that the vascular lesion stands out in prominence. Another great advantage of digital subtraction angiography is that the contrast medium can be given by a simple intravenous injection thereby avoiding arterial puncture.

COMPUTED TOMOGRAPHY

This is a non-invasive method which has obtained universal acceptance due to its safety and usefulness. Moreover, CT scan can be repeated without much inconvenience to the patient, and therefore, the progress of lesions can be followed. The principle of the method is as follows: A beam of X-ray is passed through the tissue to be investigated. Part of the X-ray is absorbed by the

tissue depending on its optical density, and the remainder comes out. Highly sensitive detectors pick up this emergent beam. The source of X-ray is rotated through 360° and then a transectional image is produced by feeding the emergent beam into a computer. The resultant picture gives details of the bony structures, brain, ventricles, and other soft tissues. It is easy to interpret the picture. Space-occupying lesions, infarcts, aneurysms, vascular malformations, subdural collections, etc. can all be diagnosed with precision. Refinements of techniques enable the coronal or sagittal reconstruction of the image. The vertebral canal and spinal cord can also be visualized by appropriate techniques.

Indications: CT scan of the head is indicated and essential for the diagnosis and management of the following conditions. A patient with:

1. Focal neurological deficit of relatively recent onset and of undetermined cause,
2. Features of definite or suspected raised intracranial pressure,
3. Altered sensorium or mental status of undetermined cause,
4. Focal seizures of recent onset,
5. Late onset seizures,
6. Subarachnoid hemorrhage,
7. Head trauma, and
8. Suspected intracranial mass lesion.

CT scan is also the procedure of choice in patients in whom MRI is contraindicated due to the presence of implanted cardiac pacemakers, mechanical heart valves or magnetizable intracranial aneurysmal metal clips.

Although a normal CT is sometimes reassuring to the patient as well as to the clinician, the practice of ordering CT scan indiscriminately should be discouraged. Under no circumstances, CT should be considered as a substitute to clinical examination except in dire emergencies.

Limitations: While CT imaging of the supratentorial structures in the brain is quite good, its use in the evaluation of the posterior fossa structures such as brainstem and the cerebellum is limited because of the beam hardening artifacts of adjacent bones. For the same reason, CT for the evaluation of spinal cord disease is less than satisfactory. The other limitations of CT are its inability to reveal very small lesions, isodense lesions (lesion density same as that of normal brain) and cerebral infarcts in the first 24 to 48 hours of their occurrence. Hence, a normal CT does not ensure that all possible structural pathologies have been excluded. In such situations MRI may reveal abnormalities. In a few cases of meningitis encephalitis and brain abscess CT may be normal in the early stages. In these situations MRI is more rewarding.

Modern machines such as the third generation CT scanners are much faster and technically more perfect than the older generation machines. Several procedures such as aspiration of brain abscess and hematoma and stereotaxic procedures can be undertaken with CT guidance. CT exposes the patient to ionizing X- rays

CT has advantage over MRI in conditions like sub-arachnoid and other intracranial bleeds, calcified lesions and bony lesions. However distinction between grey matter and white matter is poor. Very small lesions (< 1 cm) and lesions in tissues surrounded by bone (e.g. pituitary) can be missed by C T. In intracerebral vascular accidents infarction may be missed in the first 24 hours.

CT is indicated before LP in the following conditions:

1. Unknown unconscious patient
2. Raised intracranial tension
3. Intracranial bleed suspected, and
4. Acute posterior fossa lesions.

MAGNETIC RESONANCE IMAGING (MRI)

Magnetic resonance imaging offers better visualization of the anatomy of the brain and the spinal cord because of its high resolution. This is also a safe, rapid and non-invasive procedure like CT. MRI distinguishes white matter and grey matter of the brain better. For MRI scan, the patient is placed in a powerful magnetic field which makes the atoms of the tissues to align themselves in the orientation of the external magnetic field. A brief radio-frequency pulse is introduced into the magnetic field which excites the atoms (protons) and changes their alignment. When the pulse excitation ends, the protons return to their previous orientation in the magnetic field and radiofrequency energy is emitted from the tissues. By computer analysis of this emitted energy, a series of images of the tissue is created, in horizontal, coronal and sagittal planes. Differences in proton characteristics of tissues are imaged with T1 or T2 weighted sequences. T1 is the time required after excitation for longitudinal magnetization to return close to its pre-excitation state. T2 is the time required after excitation for transverse magnetization to return close to its pre-magnetization level. While T1 weighted images provide higher resolution and low contrast, the T2 weighted images are of lower resolution but of higher contrast. Intravenous administration of contrast agents such as gadolinium diethylene triamine penta-acetic acid improves the contrast if there is disruption in the blood brain barrier. The advantages of MRI over CT scan are:

1. It has better spatial and contrast resolution than CT,
2. It is free of exposure to radiation, and
3. It is free of bone artifacts.

Because of its higher resolution, it is also useful to detect smaller lesions in the cerebral hemispheres such

as lacunar infarcts, demyelinating plaques in multiple sclerosis, small granulomas such as tuberculomas and cysticercosis cysts, which may escape detection on CT. At present, because of its higher cost, it may be reserved for investigation of lesions in the posterior fossa and spinal cord, such as syringomyelia and other structural lesions.

Further developments in MRI imaging include MRI angiography which produces images of blood flow in brain without the need to inject contrast agent and MRI spectroscopy which helps in the chemical analysis of the tissues in the living brain.

Advances in ultrafast and echoplanar imaging has made MRI as fast as CT. Functional MRI is a method of imaging the functional state of brain, and assess cerebral blood flow and other metabolic parameters. For MRI scan, the patient has to be kept in a highly confined space which makes some patients claustrophobic. Open MRI machines which do not cause claustrophobia are available at present. MRI is contraindicated in patients with implanted cardiac pacemakers, mechanical heart valves, magnetizable intracranial aneurysm clips or any other implanted metallic prosthetic device.

Positron Emission Tomography (PET)

Whereas CT and MRI techniques provide information regarding the structural details of the brain and the spinal cord, PET provides information about their function also.

It is performed by administering intravenously or by inhalation, a positron-emitting radionuclide of very short half-life. This necessitates the availability of a cyclotron near the scanning site in order to provide the radio-isotopes. Because of this requirement, at present, its cost is very prohibitive and this investigation is available in only a few advanced centres in the world, mainly as a research tool rather than an investigative technique in clinical medicine. Processes such as cerebral blood volume can be studied noninvasively both in health and disease. The concentrations and locations of various neurotransmitters and their receptors can also be determined with PET. SPECT and PET are also useful in identifying regional cerebral blood flow, regional glucose metabolism and other cerebral metabolic activities. Their use in psychiatric and metabolic disorders has helped to identify the functional and metabolic basis of some of them, like schizophrenia.

Single Photon Emission Computed Tomography (SPECT)

Like PET, SPECT also provides information about the function of the brain. It also involves administration of gamma ray emitting radionuclides. However, these radionuclides are of longer half-life and hence do not need a costly cyclotron nearby. Therefore, SPECT can be described as a poor man's PET. It is now available only in some centres for clinical use, especially to study

cerebral blood flow, cerebral blood volume and cerebral neurotransmitter receptors.

Isotopic studies: Imaging and flow studies are available for the diagnosis of brain tumours, cerebrovascular disease, subdural hematomas and brain abscess. The commonly used radionuclide is ^{99m}Tc technetium pertechnetate.

Echoencephalography

This non-invasive ultrasound investigation, which was popular before the advent of CT scanner is still useful to detect the shift of the midline structures caused by supratentorial space occupying lesions, and to detect the size of the ventricles. Currently, an advanced real time ultrasound scanner capable of high resolution is available to diagnose intracranial hemorrhage in infants.

Transcranial Doppler Study

This is a noninvasive method employed to study the flow pattern in extracranial vascular tree and medium sized intracranial vessels. It also gives information on the nature of vessel wall stenosis, atheroma and luminal aperture.

During cardiac interventions and other surgical procedures on major vessels which are likely to release atheromatous emboli into the circulation and lead to residual cognitive defects, doppler study can be employed to monitor the procedural risk of embolism.

Histopathological Studies

Brain Biopsy

Brain biopsy as a diagnostic method, though available for many years, is sparingly undertaken at present due to availability of advanced neuroradiological and neurophysiological techniques.

In the majority of cases, this procedure is undertaken by neurosurgeons. With the availability of stereotaxic frames, stereotaxic brain biopsy of very localized and small lesions can be performed with precision and safety.

The indications for brain biopsy are:

1. Focal intracranial lesions, and
2. Chronic, progressive cerebral disorders of diffuse character accompanied by mental retardation or dementia, in whom all other possible diagnostic methods have already been done, but have failed to provide sufficient diagnostic information.

Brain biopsy should be undertaken only when laboratory facilities and staff experienced in the interpretation of the biopsy material are available.

Muscle and nerve biopsy: These biopsy procedures should be carried out by experienced persons because any damage to the tissue during biopsy will seriously hamper the correct interpretation by the pathologist.

Muscle biopsy is of value in the diagnosis of congenital myopathies, storage diseases of the muscle, vasculitis and polymyositis. It is also helpful in differentiating long-standing muscle weakness and wasting due to a primary muscle disease from neurogenic atrophy, when clinical and electrophysiological features are equivocal.

Nerve biopsy is useful to differentiate axonal from demyelinating neuropathies. Hereditary hypertrophic neuropathies, infective neuropathies like leprosy and infiltrative neuropathies such as sarcoidosis and amyloidosis and vasculitis, can also be identified by nerve biopsy.

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Cranial Nerves

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Olfactory Nerve

Syn: Cranial nerve I

The olfactory nerves which subserve the sense of smell have their cells of origin in the mucous membrane of the upper and posterior part of the nasal cavity. They are bipolar sensory cells, the distal portions of which consist of ciliated processes which penetrate the mucous membrane in the upper portion of the nasal cavity. The central processes of these nerves, approximately twenty on each side, pass through the cribriform plate of the ethmoid bone and synapse in the olfactory bulbs with specialised cells called mitral cells, the dendrites of which form brush-like terminals or olfactory glomeruli.

The axons of the mitral cells enter the olfactory tract, which course along the olfactory groove of the frontal bones to reach cerebrum. Posteriorly the olfactory tract divides into medial and lateral olfactory striae. The medial striae pass to the opposite side through the anterior commissure. Fibres in the lateral striae give off collaterals to the anterior perforated substance and terminate in the medial and cortical nuclei of the amygdaloid complex and prepyriform area. The latter represents the primary olfactory cortex.

Testing: Before evaluating olfactory sensations one must ascertain that the nasal passages are not blocked. Local lesions such as allergic rhinitis, polyps, and sinusitis which impair olfaction have to be excluded. The test substance should be nonirritant and volatile. Freshly ground coffee powder, asafoetida, eucalyptus oil or lemon oil are some of the common test substances used. Substances like chloroform which may stimulate gustatory end-organs or the peripheral endings of the trigeminal nerves in the nasal mucosa instead of stimulating the olfactory nerves, should be avoided. Each nostril should be tested separately with the other nostril kept occluded. The patient should be asked to inhale and identify the test substance. The perception of odour is more important than its identification.

Disorders of Olfaction

- Quantitative:** Loss (*anosmia*), reduction (*hyposmia*) or increased acuity (*hyperosmia*).
- Qualitative:** Distortion of smell (*dysosmia* or *parosmia*).
- Illusions and hallucinations of smell.**

Anosmia due to lesions in olfactory cortex occurs only if the disease is bilateral. Head injury, olfactory groove meningioma, frontal lobe tumours and aneurysms of anterior cerebral or anterior communicating artery are some of the causes of unilateral anosmia. Hyperosmia is usually a feature of neurotic patients, but can also occur in organic conditions such as cystic fibrosis and aura phase of migraine and epilepsy – It may occur during pregnancy in normal subjects. Dysosmia or parosmia may occur with local abnormalities in the nose. Olfactory hallucinations and delusions usually suggest psychiatric disorders. However, they may be associated with complex partial epilepsy (uncinate seizures) where there is brief olfactory experience

accompanied by alteration of consciousness and other epileptic phenomena.

Optic Nerve

Syn: Cranial nerve II

The optic nerve is not a peripheral nerve in the strict sense since it represents the fibre pathway that unites the retina with the brain. The receptors through which the visual impulses are perceived are the rods and cones which synapse with the inner nuclear or bipolar layer of the retina, the cells of which in turn synapse with those of the ganglion cell layer. The axons of the ganglion cells constitute the optic nerves. The *rods* react to dim light, peripheral vision and night vision. They are absent over the macula, where only the cones are present in abundance. The *cones* are concerned with vision in bright light and colour vision. The optic disc is devoid of *rods* and *cones* and hence in the visual field it projects as an area known as the *physiological blind spot*.

The optic nerve extends from the retina to the optic chiasma through the optic foramina, where the fibres from both the nasal sides cross. Fibres from the lateral (temporal) half of the retina are situated in the temporal

half of the nerve and they pass through the chiasma without crossing. Posterior to the chiasma the fibres constitute the *optic tract* which consists of the ipsilateral temporal fibres and contralateral nasal fibres. The optic tract fibres end in the lateral geniculate body by synapsing with neurons there. The axons of neurons from the lateral geniculate body pass posteriorly as the optic radiations which terminate on the striate or visual cortex (area 17) of the occipital cortex. The parastriate (area 18) and peristriate (area 19) areas in the occipital cortex function in a more complex way for visual perception and colour vision. The fibres subserving light reflex pass to the pretectal nucleus and the superior colliculus of the midbrain from the lateral geniculate body (Fig. 184.1).

Testing: Clinical examination of the optic nerve includes tests for visual acuity, visual fields and colour vision. Funduscopy should always be done as a routine. The visual acuity is ideally tested using a Snellen's chart. However, at the bedside one could examine grossly any defect in the near and distant vision (1) using flash light (2) finger counting and (3) Rosenthal chart. Visual fields are ideally tested by using a perimeter for peripheral fields and the Bjerrum's

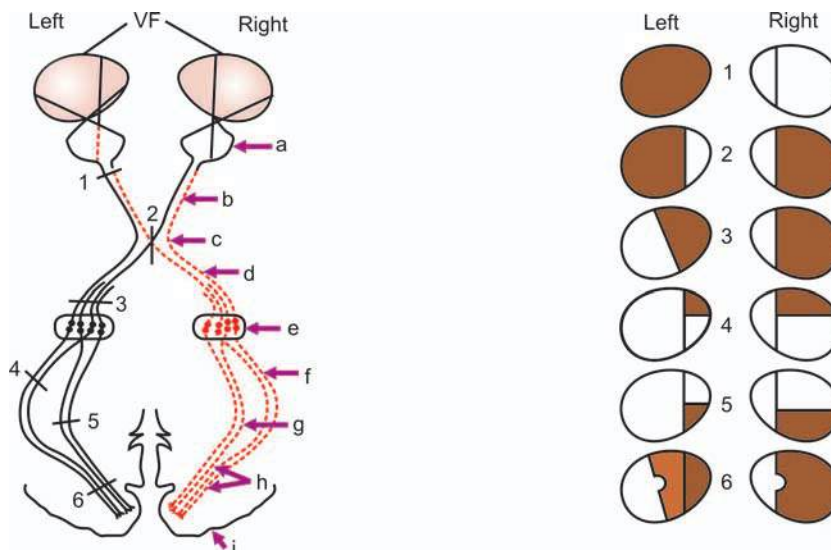


Fig. 184.1: Visual pathways and visual field defects produced by lesions at different levels

A. Visual pathways (a-i) and the common sites of lesions at different levels (1-6) a. Retina b. Optic nerve c. Optic chiasma d. Optic tract e. Lateral geniculate body f. Optic radiation, lower fibres in temporal lobe. g. Optic radiation, upper fibres in anterior parietal lobe h. Posterior parietal lobe, all fibres of optic radiation i. Occipital cortex	B. Visual field defects caused by lesions in the visual pathway at levels indicated 1-6: 1. Ipsilateral blindness 2. Bitemporal hemianopia 3. Right homonymous hemianopia 4. Right upper quadrantanopia 5. Right lower quadrantanopia 6. Right homonymous hemianopia with sparing of macula

screen for the central field. At the bedside it can be tested by the confrontation method. Here the field under investigation is compared with the examiner's visual field which is used as a standard. The examiner stands with one eye closed about one metre in front of the patient. The right eye of the patient is compared with the left eye of the examiner and vice versa. The patient is made to close one eye and instructed to fix the eye to be tested on the examiner's nose. Each eye is tested individually. Either a pin with a white or coloured head or even the examiner's finger is used as a test object. The test object, held midway between the patient and the examiner, is brought into the field of vision through various meridians of the visual field. The patient is asked to respond when he first notices the object. In this way the temporal, nasal, upper and lower visual fields can be compared with those of the examiner and field defects could be identified. During the same sitting visual inattention or extinction can be tested by simultaneously presenting objects in the upper or lower temporal quadrants of vision on both sides.

Colour vision is tested either by asking the patient to identify primary colours (red, green and blue) or by matching the colours of different objects in case he cannot name the colours—using Ishihara's chart and Holmgren's wools.

Disorders of vision: Amaurosis refers to blindness from any cause. Amblyopia refers to impairment or loss of vision which is not due to an error of refraction or to other diseases of the eye itself.

Visual impairment can be secondary to a disease process anywhere along the visual pathway from the cornea to visual cortex. Disorders affecting the media of the eye are included under ophthalmological disorders. Diseases of the retina may cause visual impairment owing to involvement of the peripheral neurons, the rods or cones. Conditions like retinitis, chorioretinitis, vascular diseases, retinal detachment and hemorrhages cause patchy or even complete loss of vision depending on the extent of lesion.

The optic nerve may be affected by demyelinating disorders, infections, neoplasms, toxins, trauma or vascular insufficiency. Such disorders begin as a central scotoma or a partial field defect and proceed to complete visual loss in that eye.

A lesion in the optic chiasma produces a characteristic field defect depending on whether the lesion begins at the centre of the chiasma or from the outer aspect. The former produces bitemporal hemianopia. The latter produces binasal hemianopia, usually due to extrinsic compression by a tumour.

Lesions in the optic tract produce contralateral hemianopia, with absent pupillary light reflex. However, if the

pupillary light reflex is preserved then the lesion is either at the lateral geniculate body or in the optic radiation. Involvement of the lower fibres of the optic radiation coursing in the temporal lobe causes contralateral superior quadrantic hemianopia, and affection of the upper fibres in the parietal lobe causes contralateral inferior quadrantic hemianopia. Lesions of one occipital lobe cause contralateral hemianopia. Involvement of the upper lip of the calcarine fissure causes inferior quadrantic hemianopia, and that of the lower lip causes superior quadrantic hemianopia. Lesions involving the optic radiation and the occipital cortex do not affect the pupillary light reflex. Incomplete lesions of the optic tract and radiation usually spare central (macular) vision. A lesion of the tip of one occipital lobe produces a central homonymous hemianopic scotoma since half the macular fibres from both eyes terminate there. Lesions of both occipital poles as in bilateral posterior cerebral artery embolization cause bilateral central scotoma, and bilateral lesions of the entire calcarine cortex cause cortical blindness.

Optic neuritis: This can be unilateral or bilateral, associated with marked loss of vision. It may be due to demyelination or toxic damage to the optic nerve. The condition is usually associated with pain behind the eyeball. When the underlying cause is removed or treated, the vision gradually recovers, but some cases may lead to inflammation of the optic disc (papillitis) and optic atrophy.

Causes: Toxic agents such as methyl alcohol, nicotine, lead, quinine, ethambutol or demyelinating diseases such as multiple sclerosis and neuromyelitis optica (a combination of optic neuritis and transverse myelitis).

Papilledema: This is swelling of the optic disc as seen through the ophthalmoscope. The margins of the disc are indistinct. The physiological cup is filled. The medial margin of the disc shows more marked changes. The veins are congested.

Papilledema leads to concentric diminution of the field of vision and enlargement of the blind spot. Compared to optic neuritis, visual loss due to papilledema is much less severe.

Causes: Increased intracranial pressure due to any cause, malignant hypertension, diseases of the retinal arteries such as giant cell arteritis, retinal vein thrombosis, cavernous sinus thrombosis, hematological disorders like acute leukemia and polycythemia vera, emphysema and pre-eclamptic toxemia.

Optic atrophy: The ophthalmoscopic appearance of optic atrophy consists of pallor of the optic disc, with a punched out appearance, prominence of the lamina

cribrosa and narrowing of the retinal arteries. Based on funduscopic appearance optic atrophy can be differentiated into primary and secondary. In primary optic atrophy the disc margins are clear and punched out and the lamina cribrosa is visible through the disc. Secondary optic atrophy follows papilledema. In this form, the disc margins as well as the lamina cribrosa are less distinct and venous congestion persists. The term “*consecutive optic atrophy*” is used when the optic atrophy results from retinal diseases. Optic atrophy may be unilateral or bilateral leading to progressive loss of vision.

Causes: All causes of optic neuritis may lead to optic atrophy as well. Other rarer causes include pressure on the optic nerve or optic chiasma, occlusion of the central retinal artery and injury to the optic nerve. Primary optic atrophy occurs in association with hereditary cerebellar ataxias and Leber’s optic atrophy.

Motor Nerves of the Eyes

These are the oculomotor, trochlear, and abducent nerves. Since they function together in the regulation of eye movements, they are examined together.

Oculomotor Nerve

Syn: Cranial nerve III

The oculomotor nuclei in the midbrain consist of several paired groups of nerve cells, adjacent to the midline, ventral to the aqueduct of Sylvius at the level of the superior colliculi. A centrally located group of nerve cells, the Edinger-Westphal nucleus, innervates the pupillary constrictor and ciliary muscles. It is situated more dorsally, and constitutes the parasympathetic portion of the oculomotor nerve. The nerve cells that mediate the action of the ocular muscles show a definite dorso-ventral topographic representation in the oculomotor nucleus. The nerve fibres from these neurons course anteriorly through the mesencephalon, medial to the red nucleus, the substantia nigra and the cerebral peduncle. The nerve emerges from the anterior aspect of the midbrain just above the pons, between the superior cerebellar and the posterior cerebral arteries. It penetrates the dura mater lateral and anterior to the posterior clinoid process and enters the lateral wall of cavernous sinus. From there it enters the orbit through the superior orbital fissure and supplies the levator palpebrae superioris, the inferior oblique, and the superior, medial and inferior recti muscles. The preganglionic para-sympathetic fibres from the Edinger-Westphal nucleus pass up to the ciliary ganglion in the orbit from where the postganglionic fibres supply the pupillary constrictors and the ciliary muscles which function in accommodation.

Trochlear Nerve

Syn: Cranial nerve IV

This is the shortest of all cranial nerves. Its nucleus is situated just anterior to the aqueduct in the midbrain immediately above pons. The axons of these neurons pass posteriorly around the aqueduct and decussate with those from the opposite side in the superior medullary velum on the dorsal surface of the midbrain. The nerve penetrates the dura mater posterolateral to the posterior clinoid process to enter the cavernous sinus where it is lateral and inferior to the 3rd cranial nerve. Through the superior orbital fissure, it enters the orbit to supply the superior oblique muscle.

Abducent Nerve

Syn: Abducens nerve, cranial nerve VI

This nerve arises from the lower part of the pons in the floor of the fourth ventricle. The nerve emerges from the brainstem at the pontomedullary junction. It has the longest intracranial course among all the cranial nerves and lies between the pons and the clivus. It pierces the dura mater at the dorsum sellae, between the posterior clinoid and apex of the petrous bone to enter the cavernous sinus, inferomedial to the 3rd cranial nerve. It enters the orbit through the superior orbital fissure to supply the external (lateral) rectus muscle.

The medial longitudinal fasciculus: This fibre tract unites the nuclei of 3rd, 4th, 5th, 6th, 7th, 8th, 11th, and the 12th cranial nerves and the motor nuclei of upper cervical nerves. Owing to this interconnection, both the eyes move in a coordinated manner simultaneously and isolated movements in one eye independent of the other do not occur usually. Visual, auditory, sensory, vestibular, and other stimuli produce conjugate deviation of the eyes and head.

Sympathetic innervation: The sympathetic fibres which control oculopupillary action arise from the eighth cervical and first thoracic spinal segments. The preganglionic fibres go to the inferior, middle, and superior sympathetic ganglia in the neck. The postganglionic fibres follow the course of the internal carotid artery and travel along the ophthalmic division of the fifth cranial nerve into the orbit. Through the long ciliary nerves they supply the pupillary dilators, the tarsal muscles, and the orbital muscle of Muller.

Cortical control: The posterior portion of the second and third frontal convolutions constitute the volitional cortical control of conjugate ocular movements. A pontine centre for lateral gaze has also been described in the vicinity of the abducens nerve—the *parapontine gaze centre*.

The light reflex: When light is focussed on one eye, there is constriction of both the homolateral (*direct light reflex*) and the contralateral pupil (*indirect or consensual light reflex*).

The accommodation reflex (near vision reflex): The phenomena which occur sequentially in this reflex are convergence of the eyes, pupillary constriction and increase in thickness of the lens due to relaxation of ciliary muscles. This is elicited by asking the patient to shift his gaze to some near object after he has relaxed his accommodation by gazing into the distance. The response to be noted is pupillary constriction and convergence of the eyes.

The afferent pathway for the light reflex passes along the optic nerve and chiasma to the superior colliculus and the pretectal region of the midbrain. From there the efferent fibres pass forward in two paths: (1) close to the aqueduct to enter the **Edinger-Westphal nucleus** of 3rd cranial nerve on the same side, and (2) through the posterior commissure to the opposite Edinger-Westphal nucleus. From the Edinger-Westphal nucleus fibres pass to the ciliary ganglion and through the short ciliary nerves, reach the constrictor pupillae muscles.

Pupillary dilatation is also under reflex control. Pinching the nape of the neck or other painful stimuli cause reflex dilatation of the pupils; the **cilio-spinal reflex**. Impulses arise from the posterior hypothalamus with activation of sympathetic fibres which pass down the brainstem and reach the orbit along the cervical sympathetic ganglia. The pupillary dilatation is facilitated by simultaneous inhibition of the Edinger-Westphal nuclei.

The cilio-spinal reflex is abolished in lesions of cervical sympathetic nerves, lesions of the cervical and upper thoracic segments of the spinal cord, medulla oblongata and T1 spinal roots.

Abnormal pupillary reflexes: Apart from sluggishness or loss of light and accommodation reflexes due to ocular or neurological diseases, qualitative abnormalities of pupillary reflexes may be seen. These include **Argyll Robertson pupil, Holmes-Adie pupil and the Marcus Gunn pupil**.

Argyll Robertson pupil: When the pupillary light reflex is abolished and the accommodation reflex is preserved it is called Argyll Robertson pupil. The pupils are constricted and irregular in the well-developed case. They react slowly, and do not react to mydriatics. Though the condition is usually bilateral, rarely it may be unilateral or asymmetric. The lesion is in the pretectal region of the midbrain affecting the light reflex fibres but not those for accommodation reflex. Classically seen in neurosyphilis (tabes dorsalis, and general paralysis of the insane), very rarely it may occur

in other midbrain lesions such as viral encephalitis, intracranial tumours, Wernicke's encephalopathy and demyelination. Argyll Robertson's pupils do not impair visual function.

Holmes-Adie pupil (Syn: Tonic pupillary reaction): In this the pupillary light reflex appears to be absent, or it may be present but delayed. Once the pupil constricts, the constriction may persist even after the source of light is removed. Once constricted, the pupils dilate only slowly in darkness as well as for distant vision. The pupils may therefore appear small or large on first examination and vary in size from time to time. The condition may be bilateral or unilateral and this results in inequality of the size of pupils (*anisocoria*). Absence of tendon reflexes especially ankle reflex, is noticed. The abnormal pupillary reaction may be due to partial parasympathetic denervation of the pupillary muscles. Adie's pupil has to be distinguished from Argyll Robertson pupil since the former is of only minor clinical significance, whereas the latter is not so. Adie pupil constricts in response to instillation of 2% methacholine drops into the eyes but the Argyll Robertson pupil does not, and this test distinguishes them.

Marcus Gunn pupil: This phenomenon is seen in partial afferent failure as occurring in optic neuritis or injury. Normally, when a bright light is swung from one eye to the other, both pupils constrict promptly as a result of direct and consensual light reflex. In partial lesions of the optic nerve such as optic neuritis or injury, the ipsilateral pupil which is partly constricted due to consensual light reflex, dilates when light falls on to it, since the abnormal optic nerve cannot transmit afferent impulses sufficient enough to produce full pupillary constriction.

Hippus: It is rhythmic alternating constriction and dilatation of the pupils. It may not be always abnormal but it is seen more often in retrobulbar neuritis and encephalitis.

Horner's syndrome: This is seen in paralysis of sympathetic innervation of the pupil. The affected pupil is smaller than its fellow (miosis), but it reacts normally to light and accommodation reflex. There is partial ptosis as a result of paralysis of the tarsal muscles of the eyelids (*Muller's muscles*). On the affected side a mild degree of *enophthalmos* (sunken eye) may also be noticeable.

The palpebral fissures: The patient is asked to look at a distance with the eyes in neutral position. Note the size of the palpebral fissure. Paralysis of the levator palpebrae superioris causes drooping of the upper eyelid (ptosis). Paralysis of upper tarsal muscles causes pseudoptosis, in which there is partial ptosis but the patient can voluntarily raise the eyelid. Partial ptosis is often compensated by the patient by the overaction



Fig. 184.2: 3rd nerve palsy—note ptosis right secondaries from abdominal tumour

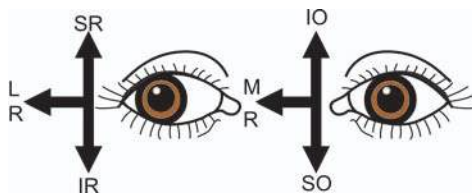


Fig. 184.3: Action of external ocular muscles



Fig. 184.4: Ophthalmoplegia due to orbital cellulitis—right; note ptosis

of the frontalis muscle of the forehead on that side. A narrow palpebral fissure indicates paralysis either of third cranial nerve or cervical sympathetic chain, whereas a wide palpebral fissure indicates seventh cranial nerve paralysis or cervical sympathetic overactivity.

The ocular movements: These are tested by having the patient move his eyeballs in the six cardinal directions—laterally, medially, upward and laterally, upward and medially, downward and laterally, and downward and medially. The lateral rectus moves the eye outwards and the medial rectus inwards. When the eye is turned outwards, the elevator is superior rectus and the depressor is inferior rectus. When the eye is turned inwards, the elevator and depressor are the inferior and superior oblique muscles respectively. In third cranial nerve palsy, there is ptosis, with inability to move the eyeball upward, downward and medially. On lifting the lid passively, the eye is found deviated outwards and slightly downward due to unopposed action of lateral rectus and superior oblique muscles. In addition, the pupil is dilated and non-reacting (*iridoplegia*). There is also paralysis of accommodation reflex (*cycloplegia*) due to parasympathetic involvement. In paralysis of the fourth cranial nerve, the eye is rotated outwards with weakness on downward movement, most marked when the eye is turned inwards. The patient often complains of special difficulty in reading or going down stairs and the head is tilted towards the opposite shoulder. In sixth cranial nerve lesion the eyeball is deviated inwards due to the unopposed action of the medial rectus (Figs 184.2 to 184.4).

Diplopia: When the visual axes of both the eyes are not in alignment the patient experiences double vision (*diplopia*). Study of the relative position of the images from the two eyes helps to determine the paretic muscle. The image arising from the normal eye is bright (*true image*) and that from the paralyzed eye is faint (*false image*). Patient is asked to follow visually the examiner's finger which is moved in all directions. He is then asked to indicate whether he sees double images and also the position of the finger where there is maximum separation of the two images. He is also asked to indicate when the double vision disappears. Diplopia is maximum when the eye is moved in the direction of action of the paretic muscle. Thus, in a right lateral rectus palsy, there is maximum separation of the images on looking to the right, while the diplopia disappears on looking to the left. By placing a red glass in front of one eye the source of the false image could be identified.

Disorders of ocular movements: Nuclear and infranuclear lesions of oculomotor nerves cause isolated paralysis of one or more extraocular muscles. Involvement of extraocular muscles sparing the pupillary sphincters is called **external ophthalmoplegia**. In total external ophthalmoplegia all the ocular muscles are paralyzed. Weakness of ocular muscles due to a nuclear lesion is identified by the associated brainstem signs like involvement of other cranial nerve nuclei and the long tracts. In midbrain

lesions paralysis of the third cranial nerve occurs along with contralateral hemiplegia (**Weber's syndrome**). The nuclei of the sixth and seventh cranial nerves are involved in pontine lesions with contralateral hemiplegia (**Millard-Gubler syndrome**). Infranuclear ocular palsy may or may not be solitary. The common causes include tumours at the base of the brain, injuries to the base of the skull, aneurysms of circle of Willis, infarction of the nerve as in diabetes and basal meningitis, especially due to tuberculosis and neuroleukemia. Less common causes include ophthalmoplegic migraine, herpes zoster, subdural hematoma, temporal arteritis and sarcoidosis. Myasthenia gravis has to be excluded in all cases of acute ocular palsy. Third, fourth and sixth cranial nerves may be affected together by lesions in the cavernous sinus and superior orbital fissure where these nerves along with ophthalmic division of fifth cranial nerve run in close proximity. Lesions in the cavernous sinus include thrombosis of the cavernous sinus, carotico-cavernous fistula and aneurysm of internal carotid artery. In the superior orbital fissure these nerves may be compressed by inflammatory masses, tumours, fractures or metastatic deposits (**Superior orbital fissure syndrome**). Rise in intracranial tension causes traction on the cranial nerves leading to cranial nerve palsies. Most commonly affected is the abducent nerve, but others may also be affected. The cranial palsy disappears when the cause is promptly corrected. Such cranial nerve palsies constitute false localizing signs. In about 20-30% of cases of ocular palsies the exact cause cannot be determined and usually such a palsy disappears in a few weeks (idiopathic ophthalmoplegia). In third cranial nerve lesions due to external compression by aneurysms, tumour or temporal lobe herniation, pupillary dilatation is an early sign since, the pupillary fibres are peripheral in the nerve trunk. In contrast, in cases of infarction of this nerve, that may occur in diabetes, the pupil is spared since infarction involves more of the central portion of the nerve.

Supranuclear and internuclear lesions: Cerebral lesions involving the frontal eye fields may be irritative as in seizures or paralytic as in an infarct or tumour. Irritative lesions produce conjugate deviation of both eyes to the opposite side. In paralytic lesions, there is paresis of conjugate deviation to the opposite side and hence the eyes will be pointing to the side of lesion. However, this is a transitory phenomenon. In contrast to this, in lesions of the brainstem involving the parapontine gaze centre, the eyes can move only to opposite side (i.e.) away from the side of lesion.

A lesion of the medial longitudinal fasciculus that interrupts the impulses from the centre for lateral gaze in

the lower pons to the third cranial nerve nucleus in the midbrain causes a dissociation of conjugate eye movements. This manifests as failure of adduction in the ipsilateral eye and nystagmus in the contralateral eye. This is called **internuclear ophthalmoplegia**. Usually presence of internuclear ophthalmoplegia indicates an intrinsic brainstem lesion like multiple sclerosis, glioma or infarct of the brainstem.

Nystagmus: This refers to involuntary rhythmic movements of the eyes. This may be jerky or pendular. Jerky nystagmus is characterized by alternate quick and slow movements. In pendular nystagmus, the oscillations are almost equal in speed in both directions.

While testing for nystagmus, the eyes should be examined first in the central position, then during upward, downward, and lateral movements. A complete description of nystagmus should include the type, direction, rate, amplitude, duration, intensity, and relationship of the response to movements of the eyes, head and body. Sometimes only a few irregular jerks without any sustained rhythmic movements may be observed. These are **nystagmoid movements** and they may not indicate any pathology. Also, while testing, extreme lateral gaze beyond the field of binocular vision should be avoided. Jerky nystagmus may be horizontal, vertical or rotary. The direction of nystagmus is named according to the direction of the fast component. In cerebellar lesions, the nystagmus (fast component) is in the direction of the gaze, irrespective of the side of lesion. In vestibular lesions, the nystagmus is only transient and may have a rotary component. In peripheral vestibular lesions of the labyrinth the nystagmus is horizontal and rotary with the slow component always towards the affected side.

In central vestibular lesions affecting the central connections, nystagmus can be purely up-beat or down-beat or rotary, if the nuclei are selectively affected. If the lesion is complete, the nystagmus resembles that of the peripheral lesions without any specific difference.

Downbeat nystagmus which is a subtype of vertical nystagmus is a characteristic feature in cervico-medullary junction lesions such as tonsillar herniation in Arnold-Chiari malformation.

Pendular nystagmus: This term refers to the type of nystagmus in which the eyes oscillate from side to side or other directions at the same speed and extent. This is the result of failure to develop postural mechanisms of the eyeballs, as occurring in congenital blindness or blindness developing in childhood. Pendular nystagmus may be an acquired phenomenon in subjects working for long periods under dark environment such as deep mines (miner's nystagmus).

Opsoclonus

This term refers to irregular, jerky conjugate movements of the eyes occurring in lesions of the brainstem such as multiple sclerosis, viral encephalitis and tumours, hyperosmolar nonketotic coma, as a paraneoplastic phenomenon and in poisonings. It consists of ocular saccades (brief rapid movements of eyeballs) occurring reflexly or voluntarily. These rapid eye movements are under control of several populations of neurones in the paramedian reticular formation. One group of neurones (*burst neurones*) are responsible for the production of saccades while another group (*pause neurones*) terminate them. Opsoclonus is the result of imbalance between these neuronal groups.

Trigeminal Nerve

Syn: Cranial nerve V

This is the largest cranial nerve and serves both sensory and motor functions. The cell bodies of the sensory part of the nerve lie in the *gasserian ganglion*. The sensory root arising proximally from this ganglion enters the pons and divides into ascending and descending branches. The ascending branch is concerned with touch and deep sensation, and ends in the mesencephalic nucleus. The descending branch forms spinal tract of the trigeminal nerve which is concerned with pain and temperature. This tract extends caudally down into the upper cervical cord. From the nucleus of the tract, second order fibres cross to the opposite side to the thalamus.

From the gasserian ganglion, peripherally three branches arise. The first (*ophthalmic*) passes through the superior orbital fissure, the second (*maxillary*) passes through the foramen rotundum, and the third (*mandibular*) through the foramen ovale. The motor part of the trigeminal nerve has its origin in the mid-pons, the fibres passing beneath the ganglia, to become incorporated into the mandibular nerve.

Trigeminal nerve has four nuclei—the main sensory nucleus, the spinal nucleus, the mesencephalic nucleus and the motor nucleus. The main sensory nucleus is situated in the posterior part of the pons and is continuous below with the spinal nucleus. The spinal nucleus extends from the pons down through the whole length of the medulla oblongata and into the spinal cord as far as the second cervical segment. The mesencephalic nucleus is situated in the lateral part of the gray matter around the cerebral aqueduct in the midbrain and extends inferiorly into the pons as far as the main sensory nucleus. The motor nucleus is situated in the pons, medial to the main sensory nucleus.

The motor nucleus of the trigeminal nerve supplies the muscles of mastication (temporalis, masseter, the medial and lateral pterygoid muscles, the tensor tympani, tensor veli palatini, mylohyoid and anterior belly of the

digastric) through its mandibular division. The motor nucleus receives corticonuclear fibres from both cerebral hemispheres, fibres from the reticular formation, the red nucleus, the tectum, medial longitudinal fasciculus and from the mesencephalic nucleus.

The ophthalmic division supplies the ipsilateral eye, eyelids, forehead, and the scalp up to the line joining the two ears. The maxillary division supplies ipsilateral upper jaw, paranasal sinuses, side of nose, palate and neighbouring structures. The mandibular division supplies ipsilateral lower jaw except the angle of the mandible, up to the upper part of the neck.

Some secondary trigeminal fibres, both crossed and uncrossed, establish reflex connections between the muscles of mastication, skin of the face and mucous membranes of the tongue, mouth and nasal cavities.

Testing

Motor: The patient is asked to clench the jaw, while the examiner palpates for the contraction of the masseter and temporal muscles on both sides. Next he is asked to open the mouth, and move the lower jaw from side to side. In paralysis of the trigeminal nerve the jaw will deviate to the paralyzed side due to the unopposed action of the lateral pterygoid muscle on the normal side. While moving the lower jaw from side to side weakness of the paralyzed lateral pterygoid can be appreciated as inability to push the jaw to the opposite side.

Corneal sensation is subserved by the ophthalmic division of the trigeminal nerve. The cornea has only free nerve endings. The corneal reflex is tested by touching the cornea lightly with a wisp of moist cotton wool. The patient should gaze in the opposite direction, and the cotton wool should be brought from the side to avoid the blink reflex. The response is closure of the ipsilateral eye (*direct cornea! reflex*) and the contralateral eye (*indirect corneal reflex*). The efferent is through the seventh cranial nerve.

Marcus Gunn phenomenon: The upper eyelid elevates and eyes open when the mouth is opened or mandible moved from side to side. It is caused by abnormal connections between the nerve supply of the pterygoids and levator palpebrae superioris.

If the eyes close on opening the mouth, it is called *inverse Marcus-Gunn phenomenon*. This is caused by aberrant facial reinnervation on recovery from facial nerve lesions.

Trigeminal Neuralgia Syn: *Tic douloureux*

This is the most common disorder of the trigeminal nerve. It occurs usually in middle and late ages and consists of sudden severe, brief paroxysms of excruciating stabbing or electric shock like pain in the distribution of the man-

dibular and maxillary divisions and rarely in the ophthalmic division. The attack seldom lasts more than a minute, but it is so severe that the patient winces. The attacks recur frequently for several weeks at a time and they are usually precipitated by stimuli applied to certain areas of the face, lips or tongue, or by movement of these parts in chewing, speech or yawning (*the trigger zones*). Usually there is no demonstrable cause—idiopathic. Sometimes trigeminal neuralgia may be a symptom of involvement of the trigeminal nerve in multiple sclerosis, dyscollagenoses, pressure effects from basilar artery aneurysm, tumour in the cerebellopontine angle, or congenital vascular anomaly.

A small proportion of patients have persistent trigeminal artery which is a branchial arch artery. Normally this artery gets obliterated in postnatal life. If it persists and becomes arteriosclerotic, it may press on the trigeminal nerve at its point of exit from the brain stem and cause neuralgia. Such cases can be relieved by resection of this artery and release of the nerve.

Chronic dental infection and metallic dental fillings may predispose to trigeminal neuralgia. Bilateral trigeminal neuralgia may occur in multiple sclerosis, hereditary sensori-motor neuropathy of Dejerene and Sotta and also stilbamidine toxicity. The symptomatic variety should be suspected in the presence of sensory and/or motor deficit which is not a feature of idiopathic trigeminal neuralgia.

Trigeminal neuralgia usually manifests in persons, who have no other neurological disorder, and therefore, the condition may be initially mistaken for other painful conditions such as migraine, dental pain or temporomandibular arthritis. In many cases there may be a psychological overlay such as anxiety or depression. The recurrent severely painful episodes occurring without warning instil fear to carry out even daily duties such as washing the face, brushing the teeth, shaving or eating. Even suicidal tendencies may develop. Untreated, the condition persists for weeks to years, with the same or increasing severity.

Diagnosis should be suspected when a person complains of excruciating facial pain occurring repeatedly with absence of any physical signs in between the attacks. To a large extent, diagnosis is clinical. Cranial CT scan help to rule out other conditions which involve the trigeminal nerve. In some cases there may be abnormalities at the trigeminal nerve root entry zone in the form of compression by an aberrant arterial loop. Cerebral or MRI angiography is required to demonstrate the aberrant arterial loop crossing the trigeminal root entry zone.

Management: Initial treatment is medical. The condition responds satisfactorily in many cases to drug therapy. Gabapentin in a dose of 100-300 mg bid or tid is the drug

of choice on account of its effectiveness and safety but it is considerably more expensive compared to carbamazepine (Rs. 17 vs 313 for 10 equipotent tablets). Carbamazepine in a total dose of 600-800 mg/day is consistently effective in the majority of cases at least initially. Toxic effects include hepatic damage, aplastic anemia, and syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and Stevens-Johnson's syndrome. Phenytoin sodium and baclofen can be given as alternative or adjuvant drugs to carbamazepine. Pregabalin given in doses of 75 mg b.d. is also useful.

If this fails, relief of pain can be obtained by injection of either alcohol or phenol at the foramen ovale or rotundum or in the vicinity of the gasserian ganglion. Percutaneous coagulation of the involved division of the nerve utilising radiofrequency waves has been very useful in intractable cases. The advantage of this procedure is that it selectively destroys the pain fibres without affecting other sensations over the face.

The major problem following surgery is severe dysaesthesia over the face, which may be very disturbing. This complication is less with selective radio frequency procedure. Modern treatment is to release the aberrant arterial loop compressing the nerve root by microvascular technique.

Facial Nerve

Syn: Cranial nerve VII

The *facial nerve* is a mixed nerve. It has 3 nuclei—the main motor nucleus, parasympathetic nucleus and sensory nucleus. The main motor nucleus is situated deep in the pons and receives UMN innervation from the cerebral cortex. That part of the nucleus which supplies the muscles of the lower part of the face receives corticonuclear fibres only from the contralateral cerebral hemisphere, whereas that part of the nucleus which supplies the muscles of the upper part of the face receives corticonuclear fibres from both cerebral hemispheres. This accounts for the fact that in unilateral upper motor neuron (UMN) type of facial palsy only the lower part of the face is affected on the opposite side. The superior salivary and lacrymal nuclei, which are parasympathetic, lie posterolateral to the motor nucleus. The sensory nucleus is the upper part of the nucleus to the tractus solitarius and lies close to the motor nucleus. Sensation of taste from the anterior 2/3 of the tongue travels through the chorda tympani to the sensory nucleus. The fibres from the facial nucleus wind round the abducent nucleus in the pons and emerge from the brainstem at the junction between the pons and the medulla. In lesions of the pons, these two nuclei are often affected together.

After its emergence from the brainstem the facial nerve travels through the middle cranial fossa and enters the petrous temporal bone through the internal auditory meatus. The nerve then passes through the facial canal in the temporal bone. Within this canal it gives off a branch to stapedius muscle and distal to that branch the chorda tympani leaves the facial nerve to join the lingual nerve. In the petrous temporal bone, the nerve makes a sharp bend (genu) where the geniculate ganglion is situated. In the facial canal it lies in close relationship to the medial wall of the middle ear. This relationship makes the nerve vulnerable to damage in lesions of the middle ear. The nerve leaves the temporal bone through the stylomastoid foramen and traverses through the parotid gland to divide into terminal branches that supply all the muscles of facial expression, auricular muscles, posterior belly of the digastric and stylohyoid muscle.

The sensory nucleus receives taste fibres from the anterior 2/3 of the tongue, the floor of the mouth and the soft palate. Facial nerve carries general sensations from the external auditory canal, tympanic membrane, lateral surface of pinna, a small area behind the ear and skin over the mastoid process. It also carries proprioceptive sensations from the muscles it supplies, and deep pain and pressure from the face. However, it does not carry any superficial sensation from the face.

The superior salivary nucleus supplies the submandibular and sublingual salivary glands and the lacrimal nucleus supplies the lacrimal gland.

Testing: Ask the patient to frown, wrinkle his forehead, raise his eyebrows, close his eyes tightly against resistance, retract the angle of his mouth, show his teeth, blow his cheeks and whistle. If there is difficulty in any of the above functions it could be compared with the healthy side. Also look for any asymmetry of palpebral fissure and the nasolabial fold in the resting position. The palpebral fissure will be wider on the paralyzed side. The nasolabial fold will be flatter and the angle of the mouth will be at a lower level than the normal side (Fig. 184.5).

The term **Bell's phenomenon** is given to denote the rolling up of the eyeball when the patient attempts to close the eye. This is due to the physiologic synkinesis between the orbicularis oculi and the superior rectus muscles. This is a normal phenomenon in both eyes. In Bell's palsy the rolling up on the affected side will be exaggerated. In UMN facial palsy there is no exaggeration of rolling up of the eyeball (Fig. 184.6).

The sensation of the anterior aspect of the external auditory canal is tested with cotton wool. Taste from the anterior two-thirds of the tongue is tested using sugar for sweetness, sodium chloride for salty taste, 1% acetic acid for sour taste and quinine for bitter taste. The tongue should be held protruding throughout the test and the patient should not be allowed to speak. The words—sweet, salt, sour and bitter are written on a paper, and the subject is asked to indicate the taste he perceives. For the posterior third of the tongue, the same materials



Fig. 184.5: Herpes zoster ophthalmicus left with facial palsy. Note the vesicles and deviation of angle of mouth to the right



Fig. 184.6: Bilateral facial palsy. Note inability to close the eyes and Bell's phenomenon

can be used for testing. As an alternative stimulus, galvanic current can be used. *Ageusiometer* is used since it is difficult to test the posterior third of the tongue by the conventional method. Loss of taste is called **ageusia**. Diminution of taste perception is called **hypogeusia**. Altered appreciation of taste is **parageusia**.

Facial Paralysis

Syn: Facial palsy

Paralysis of the facial nerve may be of the *upper motor neurone type (UMN)* or *lower motor neurone type (LMN)*. In the former the corticonuclear tract supplying the facial nerve nucleus is affected and the lesion is above the level of the pons. In LMN paralysis the lesion is at the facial nerve nucleus or in the course of the nerve.

Supranuclear Facial Palsy

Syn: *UMN facial palsy*

In this only the lower half of the face is affected, contralateral to the side of lesion.

Supranuclear palsy is of two types—volitional and emotional. In volitional palsy, the involvement is most marked on voluntary contraction. On automatic involuntary movements such as crying or smiling, there is preservation of function. Here the lesion is in the motor cortex or in the corticobulbar fibres as they go through the internal capsule, cerebral peduncle and pons to reach the facial nucleus. In emotional or *mimetic facial paresis*, there is no asymmetry of the facial muscles on voluntary movements. The patient can close his eye, retract his mouth or blow his cheeks without difficulty. However, the paresis becomes apparent during smiling or crying. Here the lesion is either in the frontal lobes anterior to the precentral cortex or deep seated in the thalamus or basal ganglia.

Nuclear or Infranuclear Facial Palsy

Syn: *LMN facial palsy*

As the lower motor neuron (facial nucleus) is the final common pathway, lesions at this site produce weakness of the entire half of the face on the ipsilateral side. The exact site of lesion is determined by the associated signs. In pontine lesions as in a tumour or vascular occlusion, the facial palsy is associated with ipsilateral sixth cranial nerve paralysis. In cerebellopontine angle lesion, such as acoustic neuroma facial palsy is associated with ipsilateral eighth and fifth nerve palsies, cerebellar signs, and contralateral pyramidal signs.

Within the facial canal the nerve can be affected in many ways. Inflammatory conditions such as herpes zoster can affect the geniculate ganglion to produce **Ramsay-Hunt syndrome**. Other infections like mumps, scarlet fever and malaria, metabolic conditions like diabetes, alcoholism and nutritional deficiency, metastatic neoplasms and neuroleukemia can affect the facial nerve within the facial canal. Owing to the proximity of the nerve to the middle ear facial paresis can be a complication of otitis media, suppuration of temporal bone or mastoiditis. Immediately outside the stylomastoid foramen, the nerve could be involved by tumours of the parotid gland, injuries and obstetrical trauma due to forceps delivery in the newborns. Involvement of the terminal branches of the nerve is a feature of leprosy. Involvement of the upper part of the face, sparing the lower part is not an uncommon manifestation of leprosy. Bilateral facial palsy is usually due to Guillain-Barré syndrome or sarcoidosis. Facial palsy can occur during the course of tick-borne relapsing fever and Lyme borreliosis.

This condition is named after Sir Charles Bell, a Scottish physiologist and surgeon (1774-1842). This is the most common cause of unilateral LMN facial palsy. It usually develops suddenly and spontaneously, often starting with a mild pain in the ear. Sometimes a history of exposure to cold or wind, or a mild systemic infection is obtained. The lesion may be either compression of the nerve by edema or periostitis at the facial canal, ischemia of the nerve or a viral infection. *Herpes simplex virus* type 1 (HSV-1) is found to be a common cause for Bell's palsy, as revealed by raised antibody levels. The onset is abrupt with the occurrence of weakness of pursing movements of the lips, inability to hold water in the mouth, deviation of the angle of the mouth to the normal side, incomplete closure of the eyes and watering from the eyes. While washing the mouth the water escapes through the paralysed side. Food materials collect in the vestibule on mastication. Severity of paralysis varies. As time passes the condition becomes stable and recovery starts within days to weeks. In the majority of patients sensory symptoms may be minimal or absent, but some complain of a numb feeling and heaviness of the affected side. In the majority of patients the facial palsy completely improves. In a few cases the paralysis may be irreversible. In those that recover, signs of recovery start within a week and recovery may be complete in a month. Complications include corneal ulceration and exposure keratitis, facial contracture and aberrant innervations on recovery.

Chronic facial palsy may lead to contracture of the ipsilateral paralysed muscles giving a picture which may be mistaken for paralysis of the contralateral (normal) side while at rest. On testing, the weakness of the paralysed muscles will become apparent. The affected side may develop hemifacial spasm due to faulty conduction of nerve impulses through the partially damaged nerve fibres.

Management: Facial palsy is a frightening event and so the patient has to be reassured about the condition and the generally benign nature of the malady. It is important to distinguish LMN facial palsy from the UMN types since the latter may be a part of more serious neurological disease such as stroke.

Aims of Treatment

1. To prevent damage to the eye due to exposure keratitis,
2. To avoid further damage to the paralyzed muscles resulting from unopposed action of the normal side, and
3. To hasten recovery.

Exposure keratitis can be avoided by wearing dark glasses. Distortion of the angle of the mouth can be prevented by appropriate splints. Prednisolone in a dose of 40-60 mg/day orally may be given for 5-7 days, by which time the response is well-manifest. Further

maintenance dose depends on the response. Since herpes virus is a common cause for Bell's palsy, a c y c l o v i r 800 mg five times a day for 7-10 days may be started early. However recent reports confirm the superiority of steroids over acyclovir. The drugs have to be continued for 7 days. Early institution of specific therapy, ideally within six hours to 48 hours is most beneficial.

Physiotherapy consists of massage over the face and electrical stimulation of the facial nerve at the stylomastoid foramen. Electrophysiological assessment with EMG and NCV done after one week will help to devise decompressive therapy and also to assess prognosis for recovery. Evidence for axonopathy with early denervation potentials indicates poor chances for recovery. If there is conduction block indicating entrapment, decompression at the stylomastoid foramen will be beneficial.

If at the end of six months deformity and paralysis persist, facial muscle reconstructive surgery should be considered.

In those cases which do not recover, plastic surgery procedures to reduce deformity and facial nerve anastomosis to glossopharyngeal nerve have been successfully employed.

Ramsay-Hunt syndrome: This consists of severe facial palsy associated with vesicles in the pharynx, external auditory canal, and sometimes over the mastoid. The 8th cranial nerve may also be involved in many. The lesion is due to herpes zoster affecting the geniculate ganglion.

Acoustic Nerve

Syn: Cranial nerve VIII, auditory nerve

The acoustic nerve has two components—the *cochlear nerve* or the nerve of hearing, and the *vestibular nerve* which subserves equilibration.

Cochlear system: The end-organs of the cochlear nerve are the hair cells in the organ of Corti, within the cochlea of the inner ear. The central fibres from the cell bodies, pass as the cochlear nerve. It traverses the internal auditory meatus, where it is inferolateral to the facial nerve and crosses the subarachnoid space at the cerebellopontine angle and enters the upper part of the medulla to terminate in the dorsal and ventral cochlear nuclei. Secondary acoustic fibres project via the trapezoid body and lateral lemniscus to the primary auditory receptive areas in the transverse temporal gyri of Heschl through the auditory radiations.

Vestibular system: The vestibular system consisting of the semicircular canals has the function of orienting the subject in space (all the 3 planes), and also maintaining the relative position between the head and the body. Changes in position set up electrical discharges in the neuroepithelium of the ampullae of the semicircular canals and the maculae of the utricle and saccule. Bipolar cells of the Scarpa's ganglion transmit these impulses to the vestibular nuclei of the

same and opposite sides in the upper part of the medulla. Vestibular nuclei are connected to the cerebellum through the inferior cerebellar peduncle, to the spinal centres through the vestibulospinal tracts and to the motor nuclei of the eye muscles, through the medial longitudinal fasciculus.

Disturbances of vestibular function lead to vertigo, inability to maintain posture, nystagmus and systemic disturbances such as nausea, vomiting, visual hallucination, feeling of rotation of the surroundings, sweating, tachycardia, and hypotension. Vertigo, an illusion of movement, is the cardinal symptom of vestibular dysfunction. Rotational vertigo may indicate dysfunction of the semicircular canals or their central connections. A feeling of tilting or linear displacement may occur in disorders affecting otolith organs or their projections. In vertigo there is a distinct sense of rotation. The objects may seem to revolve around the patient (*objective vertigo*) or the person may experience the sensation of spinning in the surroundings (*subjective vertigo*).

Testing of cochlear system: Hearing is evaluated by noting the patient's ability to perceive the sound made when the examiner rubs his thumb and index finger or better still by a ticking watch held in front of the external auditory meatus. The distance from the ear is noted, and the examiner compares the patient's acuity of hearing with his own. Better information can be obtained by using a tuning fork.

Rinne test: Here the patient's air conduction is compared with the bone conduction. The base of a vibrating tuning fork (512 Hz) is placed firmly against the mastoid and the patient is asked to indicate when the sound is no longer heard. It is then placed in front of the external auditory meatus and the time during which it is heard is noted. Normally, air conduction is better than bone conduction—*Rinne positive*. In conductive deafness due to middle ear disease bone conduction is better than air conduction (*Rinne negative*). In sensorineural deafness, both bone and air conduction are diminished, but they retain the normal relationship and the Rinne is positive.

Weber test: Here the base of the vibrating tuning fork is placed over the forehead and the patient is asked to point to the ear he hears better. Normally, it is heard equally well in both ears. In conductive deafness the sound is better heard by the involved ear, while in sensorineural deafness it is better heard by the uninvolved ear.

Disorders of acoustic function: Sensorineural deafness can be secondary to diseases of the cochlea, auditory nerve or brainstem. The cochlea may be congenitally aplastic, or it could be damaged by maternal rubella. Mumps or meningitis may cause nerve deafness from childhood. Herpes simplex virus 1 (HSV-1) DNA has been detected in the vestibular ganglia by

PCR in about 60%. Both vestibular and cochlear neuritis may be caused by HSV-1. Drugs like streptomycin, gentamicin, quinine, and salicylates could damage the cochlear hair cells and produce deafness. The auditory nerve could be involved by tumours of the cerebellopontine angle, or by basal meningitis. Deafness could also result by demyelinating lesions in the brainstem. Middle ear deafness is usually secondary to wax, chronic otitis media, otosclerosis, and fracture of temporal bone. Other rarer causes include glomus jugulare tumours, cholesteatomas and nasopharyngeal carcinomas.

Tests for vestibular system: Vestibular dysfunction usually presents with vertigo, especially if the lesion is acute.

Objective testing includes the elicitation of the vertigo in specific positions of the head and observation of the nystagmus. The caloric tests help to identify the lesions in the different parts of the membranous labyrinth and their connections. Other tests include the rotation test done in a Barany's chair, cupulometry and electronystagmography. These require special equipment.

Caloric tests: Each ear is syringed with warm water (44°C) and cold water (30°C) with the patient resting supine and head flexed to 30° till a jerky nystagmus sets in. The slow phase is due to local stimulation and the fast phase is mediated through cortical connections. Irrigation with cold water produces nystagmus with fast component to the opposite side, nausea, vomiting, tendency to fall to the same side and past-pointing to the opposite side. The nystagmus persists for 90-140 sec. Syringing with warm water produces nystagmus with the fast component to the same side. The time for onset of nystagmus and its duration are recorded. When there is perforation of the tympanic membrane water should not be used for the test, instead jets of air at different temperatures can be used.

Significance of caloric tests: The caloric tests depend upon the integrity of the vestibular apparatus, its connections and the higher cortical influences. This test is used in assessing the integrity of these structures. In addition, since the fast phase of the nystagmus is mediated through the cortical connections, in conditions with deepening coma, loss of the fast phase indicates progressive loss of cortical function.

Tinnitus: This is a sensation of noise caused by abnormal excitation of the acoustic pathway in the absence of any external stimuli. Tinnitus may take several forms such as tuning, roaring, whistling, buzzing, and the like. It is felt most during sleep when the environment is silent. It may interfere with normal hearing.

Common causes include lesions of the nose and middle ear such as eustachian catarrh, otitis media or occlusion of the external auditory meatus by wax. Several drugs like salicylates, quinine, and streptomycin may produce tinnitus. Neurological disorders like acoustic neuroma, meningitis, and vascular lesions of the lateral aspects of the pons may lead to tinnitus. High pitched tinnitus is produced by lesions of the cochlear nucleus or auditory nerve apparatus. Low pitched tinnitus occurs in middle ear disease. Pulsatile tinnitus is characteristic of vascular anomalies of the brain stem. Tinnitus associated with pain in the affected ear should suggest the possibility of Meniere's disease. Tinnitus may also occur as an aura of temporal lobe epilepsy.

Acute vestibular neuronitis could occur at any age and it is characterized clinically by either paroxysmal or usually a single attack of vertigo without tinnitus or deafness.

Ménière's Disease

Ménière's disease is a disorder of labyrinthine function characterised by recurrent attacks of vertigo associated with tinnitus and deafness. Prosper Ménière, a French physician described the disease. His name was given to the syndrome consisting of vertigo, tinnitus and deafness in 1870, ten years after his death. The diagnostic criteria include:

1. At least two episodes of vertigo of 20 minutes or longer duration
2. Hearing loss confirmed by audiometry at least on one occasion and
3. Tinnitus or aural fullness during the attacks.

It begins in the fifth decade. These attacks last for minutes to an hour. Nystagmus is present during the acute attack with a slow phase towards the affected ear. The attacks usually occur in clusters with progressive hearing loss. The pathologic change consists of dilatation of the endolymphatic system with destruction of the cochlear hair cells.

Treatment consists of salt restriction to 2.5 g salt / day and drugs.

These include:

1. Acetazolamide 500-750 mg daily is divided doses which will reduce endolymphatic hydrops,
2. Labyrinthine sedatives such as prochlorperazine or cyclizine. Paradoxically histamine analogues such as betahistine 8 mg given in repeated doses may also help.
3. Anxiolytics such as alprazolam 0.25 mg/tds help to allay fear and insecurity.

Surgical measure used to be done to interrupt labyrinthine afferent impulses. These are not commonly done now. External appliances which counteract the

tinnitus by neutralizing the frequencies from the labyrinth are helpful. These have to be made specifically for individual patients.

Labyrinthine adaptive exercises help to reduce the attacks.

Glossopharyngeal and Vagus Nerves

Syn: Cranial nerves IX and X

These two cranial nerves are intimately connected and hence they are described together.

Glossopharyngeal Nerve

This has sensory and motor components. The motor fibres arise from the *nucleus ambiguus* situated in the lateral part of the medulla. Along with the vagus and accessory nerves, this nerve leaves the skull through the jugular foramen and supplies the stylopharyngeus muscle whose function is to elevate the pharynx. Autonomic efferent fibres of the glossopharyngeal nerve arise from the inferior salivatory nucleus. The preganglionic fibres pass to the otic ganglion through the lesser superficial petrosal nerve, and postganglionic fibres pass through the auriculo-temporal branch of the fifth cranial nerve to reach the parotid gland. The nuclei of the sensory fibres of the glossopharyngeal nerve are situated in the petrous ganglion which lies within the petrous bone below the jugular foramen and also the superior ganglion, which is small. The sensory fibres supply the faucial tonsils, posterior wall of the pharynx, part of the soft palate and taste sensations from the posterior third of the tongue.

The Vagus

This is the longest among all the cranial nerves and serves both motor and sensory functions. The motor fibres arise from the nucleus ambiguus and supply all the muscles of the pharynx, soft palate and larynx, with the exception of tensor veli palati and stylopharyngeus. The parasympathetic fibres arise from the dorsal efferent nucleus and leave the medulla as preganglionic fibres of the craniosacral portion of the autonomic nervous system. These fibres terminate on ganglia close to the viscera which they supply by postganglionic fibres. They are parasympathetic in function. Thus vagal stimulation produces bradycardia, bronchial constriction, secretion of gastric and pancreatic juice and increased peristalsis. The sensory portion of the vagus has its nuclei in the *jugular ganglion* and *ganglion nodosum*. The vagus carries sensations from the posterior aspect of the external

auditory meatus and adjacent pinna and pain sensation from the dura mater lining the posterior cranial fossa.

Testing: It is better to test the 9th and 10th cranial nerve functions together as they are usually affected together leading to symptoms like dysphagia, dysarthria, nasal regurgitation of fluids, and hoarseness of voice.

The motor part is tested by examining the position of the median raphe in the midline above the uvula when the patient is made to open his mouth. In unilateral vagal paralysis the ipsilateral palatal arch will be flattened and lowered. On phonation, the median raphe deviates to the normal side.

The **gag reflex** or the pharyngeal reflex is elicited by applying a stimulus, such as a tongue blade or cotton swab stick to the posterior pharyngeal wall or tonsillar region. If the reflex is present, there will be elevation and contraction of the pharyngeal musculature accompanied by retraction of the tongue. The afferent arch of this reflex is subserved by the glossopharyngeal nerve while the efferent is through the vagus nerve. This reflex is lost in the lesions of either of these cranial nerves. General sensations over the posterior pharyngeal wall, soft plate and faucial tonsils, and taste over the posterior third of the tongue should also be tested. These are impaired in glossopharyngeal paralysis. Isolated involvement of either nerve is rare and usually they are involved together. Eleventh and twelfth cranial nerves may also be affected.

Testing laryngeal muscles: These are tested by asking the patient to speak. Loss of phonation (producing vocal sounds) is called aphonia. Common neurological cause for aphonia is uni- or bilateral vagal paralysis. In unilateral or bilateral adductor paralysis of vocal cords the tussive phase of cough will be abolished and this is described as bovine cough. Movements of the vocal cords can be visualized by direct or indirect laryngoscopy. Bilateral paralysis of the abductors of the vocal cords leads to laryngeal obstruction and this is fatal, unless emergency measures to restore the airway are undertaken. Persons with vocal cord paralysis cannot hold their breaths and they run the risk of drowning if they get into water.

Glossopharyngeal neuralgia is a rare condition which presents with lancinating pain or other types of severe pain felt episodically at the back of the throat. The pharyngeal phase of swallowing triggers the attack. This may prevent the patient from taking foods. Most of the cases are idiopathic. Rarely glossopharyngeal neuralgia may be the symptom of primary demyelinating lesions affecting the brain stem such as multiple sclerosis. At times vagal phenomena such as bradycardia may also occur. These are referred to as vago-glossopharyngeal neuralgia. As in the case of trigeminal neuralgia,

physical examination is usually normal. This condition also responds to carbamazepine and phenytoin. More effective drug is gabapentin in a total daily dose of 300-1200 mg given in divided doses.

The nuclei of IX and X cranial nerves may be involved together either unilaterally or bilaterally in diseases affecting the brainstem such as motor neuron disease, lateral medullary infarction, bulbar poliomyelitis and tumours. Posterior fossa tumours, basal meningitis and demyelinating diseases may involve these nerves outside the brainstem.

Accessory Nerve

Syn: Cranial nerve XI

This is purely a motor nerve. This has two roots—*cranial* and *spinal*. The spinal root arises from the anterior horn cells of the upper five cervical segments, and it enters the skull through the foramen magnum. These fibres are joined by the cranial root which arises from the caudal part of the *nucleus ambiguus* and together they leave the skull through the jugular foramen along with the vagus nerve. In the jugular foramen the cranial root fibres join the vagus nerve fibres to be distributed to the pharynx and larynx. This part of the nerve cannot be tested separately. The spinal part supplies the sternomastoid and upper part of the trapezius muscles. At the nuclear level the representation is the contralateral trapezius and ipsilateral sternomastoid muscles. On the other hand the accessory nerve innervates both the ipsilateral muscles. This phenomenon can be made use of to distinguish between intrinsic and extrinsic lesions of the brainstem (i.e.) whether the lesion affects the nucleus or the nerve.

Testing: This is limited to evaluation of the motor power of the sternomastoid and the trapezius. The sternomastoid is evaluated by inspection and palpation as the patient turns his head to one side against resistance. The paralysed muscle is flat and it does not prominently stand out on turning the head to the opposite side. Strength of the muscle can be tested by asking patient to turn his head to the opposite side while applying resistance at the chin.

The trapezius is tested by asking the patient to shrug the shoulders against resistance.

Hypoglossal Nerve

Syn: Cranial nerve XII

This is also a purely motor nerve which supplies the muscles of the tongue. It arises by a series of rootlets from the medulla between the pyramid and the inferior

part of the olive and emerges out of the skull through the hypoglossal foramen before supplying the tongue.

Testing: Ask the patient to open the mouth without protruding the tongue. In unilateral LMN paralysis, the tongue curves slightly to the healthy side. On protruding the tongue, it deviates to the paralyzed side. This phenomenon helps to distinguish an UMN paralysis from LMN paralysis. In UMN paralysis the tongue always deviates to the side opposite to the lesion irrespective of whether it is inside or outside the mouth. Strength of sideways movements of the tongue can be tested by asking the patient to push with his tongue the examiner's finger kept outside the cheek. Unilateral paralysis leads to loss of strength while pushing to the opposite side. Examine for fasciculations and wasting with the tongue lying in the floor of the mouth. Presence of these suggests LMN lesion. Wasting of the tongue leads to longitudinal furrows on it. In upper motor neuron lesions, the tongue is small and spastic.

Lower Cranial Nerve Palsies

LMN paralysis of the IX, X, XI and XII cranial nerves which arise from the medulla (bulb) occurring in various combinations, constitutes **bulbar palsy**. UMN lesion affecting these cranial nerves leads to supranuclear bulbar palsy, also known as **pseudobulbar palsy**. Clinically these two conditions have to be differentiated from each other. Dysphagia, dysphonia, dysarthria and nasal regurgitation of fluids occur in bulbar as well as pseudobulbar palsies. Emotional lability in the form of unprovoked and uncontrollable laughter or crying is an added feature in pseudobulbar palsy. Examination reveals marked wasting and fasciculations of the tongue and sternomastoid muscles in bulbar palsy, but not in pseudobulbar palsy. However in acute bulbar palsy as in diphtheria, poliomyelitis or Guillain-Barré syndrome, there is no time for these muscles to undergo atrophy. The jaw reflex is usually absent in cases of bulbar palsy while it is brisk and exaggerated in pseudobulbar palsy.

LMN Lesions of the Lower Cranial Nerves

i. Brainstem Lesions

Vascular occlusions, tumours, motor neuron disease, poliomyelitis, demyelinating diseases including multiple sclerosis and syringobulbia.

ii. Lesions Outside the Brainstem

Fractures of the base of the skull, primary or secondary neoplasms affecting the base of the skull, basal meningitis, tonsillar herniation, coning of the brainstem,

paralytic diphtheria, rabies, Guillain-Barré syndrome and others.

iii. Lesions Outside the Cranial Cavity

Left recurrent laryngeal nerve may be involved in upper thoracic lesions such as mediastinal tumours, or other causes of thoracic outlet syndrome.

UMN Lesions of the Lower Cranial Nerves

These are due to bilateral lesions of the cerebral cortex or corticospinal tracts above the level of the medulla. Common causes include bilateral cerebrovascular accidents, motor neuron diseases, metastatic tumours and degenerative and demyelinating diseases.

Distinction between bulbar and pseudobulbar palsy		
Clinical features	Bulbar palsy	Pseudobulbar palsy
Emotional lability	Nil	Present
Wasting of tongue and sternomastoid	+	Nil
Fasciculation of tongue and sternomastoid	++	Nil
Jaw reflex	Absent	Exaggerated
Type of lesion	LMN	UMN

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Coma and Brain Death

S.R. Chandra, P.K. Mohan

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General Considerations

Consciousness has two clinical aspects, namely, wakefulness and awareness. Disorders of the reticular system leads to coma in which the patient remains with eyes closed, he lacks both wakefulness and awareness, and is unresponsive to external stimuli. The essence of the vegetative state is wakefulness without awareness. Consciousness is a stage of normal awareness of the self and surroundings and the ability to respond to various types of stimuli, both endogenous and exogenous. During sleep the subject can be roused by appropriate stimuli to full consciousness. Coma is a state of unarousable unresponsiveness which implies defects in arousal, awareness of surroundings and ability to respond. In coma

generally the eyes are closed and the sleep-wake cycles are absent.

Coma is defined as deep unconsciousness from which the patient cannot be aroused even by painful stimuli. When a patient gradually sinks into coma, the following stages may be recognizable:

Confusional state: The patient is conscious, but may be disoriented in time, space and person. He shows misperception of the environment.

Stupor: In this state of disturbed consciousness, only vigorous external stimuli produce arousal. The spells of consciousness tend to be brief and the patient slips back into stupor soon.

Coma: The patient is unarousable by all external stimuli. In this stage all the protective reflexes (sneeze, cough, withdrawal to nociceptive stimuli, etc.) are absent.

Glasgow Coma Scale (EMV Scoring)

An objective method of evaluating the depth of coma is the Glasgow coma scale. Recording the progress of the patient by this method is extremely useful for initial assessment and follow-up in cases of coma due to head trauma and cardiorespiratory arrest.

Glasgow Coma Scale

Test		Scoring
1. Eye opening (E)	Spontaneous	4
	To sound	3
	To pain	2
	Nil	1
2. Motor movements (M)	Obeys command	6
	Localises pain	5
	Normal flexion withdrawal	4
	Abnormal flexion (decorticate rigidity)	3
	Extension (decerebrate rigidity)	2
	No response	1
3. Verbal response (V)	Well-oriented	5
	Disoriented and converses	4
	Confusedly	3
	Inappropriate words	2
	Incomprehensible sound	1

A conscious individual will have a score of 15.

The scores progressively diminish as the coma becomes deeper. The fallacy of Glasgow coma scale is that even a dead person will have a score of 3. This has not in any way reduced the importance of the Glasgow coma scale.

TABLE 185.1

Causes of coma

Neurological causes

1. Ischemia to the brain and brainstem. e.g. stroke, Stokes-Adams attacks, low cardiac output states, and cardiac arrest.
2. Infections, e.g. meningitis, encephalitis.
3. Rise in intracranial tension due to various causes.
4. Physical agents, e.g. craniocerebral injuries, hyperpyrexia, hypothermia.
5. Degenerative disease, e.g. Tay-Sachs disease, Creutzfeldt-Jakob's disease.
6. Demyelination — Postvaccinal, infective, and allergic causes.
7. Seizure disorders like status epilepticus.

Systemic diseases

1. *Metabolic causes*—Diabetic coma, uremia, hypoglycemia, acidosis, alkalosis, hyperosmolar states, respiratory failure, hepatic failure and endocrine disorders such as hypothyroidism, Addison's disease and hypopituitarism.
2. *Poisoning*—Alcohol, narcotics, and other poisons, cobra and krait bites.
3. *Infections*—Several infections affecting the brain or meninges directly as in meningitis and encephalitis lead to coma. Others give rise to toxic encephalopathy, e.g., septicemias, septic shock, salmonellosis.

Psychiatric disorders

Though these are not comatose states, their presentation may very closely resemble that of coma from which they have to be distinguished e.g., catatonic stupor and hysterical coma.

In the case of nontraumatic coma, extending for at least 5-6 hours, the common causes are:

1. Sedative drugs with or without alcohol 40%
2. Cerebral hypoxic and ischemic damage caused by cardiac arrest and anesthetic accidents 25%
3. Stroke and subarachnoid hemorrhage 20%
4. Infections and metabolic derangements 15%

Mechanism of coma: Coma may develop due to several mechanisms.

General mechanisms leading to coma are: (i) reduction in blood supply to the brain, (2) lesions affecting the reticular formation, (3) electrical disturbances as in seizure disorders, and (4) disturbance in metabolism leading to dysfunction of cellular processes in the neurons.

Common causes of coma are given in Table 185.1.

Examination of a Comatose Patient

CLINICAL FEATURES

The history given by immediate attendants and the circumstances of the illness give valuable clue to the diagnosis.

General examination should elicit the following features.

1. Evidence for trauma.
2. Bleeding from the nose or ears suggesting fracture of the base of the skull.
3. Pallor and shock indicating recent blood loss.
4. Smell of alcohol and evidence of poisoning.
5. Signs of repeated venepunctures seen in intravenous drug abusers.
6. Type of respiration—Acidotic breathing, Cheyne-Stokes respiration or respiratory depression.
7. Presence of systemic diseases such as diabetes, renal failure, hepatic failure, hypertension, cardiovascular lesions which may act as sources of emboli, etc.
8. Convulsions, e.g. epilepsy.
9. Signs of systemic or intracranial infection.
10. Pupils: Inequality of the pupils suggests transtentorial herniation. The dilated nonreacting pupil is the result of oculomotor paralysis, which may be due to an involvement of the nerve or its nuclei in the midbrain.

Any patient in deep irreversible coma due to neurological or systemic disease may have fixed dilated pupils as a terminal or preterminal phenomenon.

Bilateral pin-point pupils, non-reactive to light are seen in pontine and thalamic hemorrhage. Pin-point pupils may be seen as well in narcotic poisoning (e.g., morphine).

After ascertaining the general condition of the patient, and depth of coma, systematic neurological examination should be carried out.

Oculocephalic Reflex (reflex eye movements)

This is tested by turning the head of the patient firmly to either side by 70° and then passively flexing and extending the neck. The eyes move opposite to the movement of the head. These “dolls-eye movements” depend on the intactness of the third, fourth and sixth cranial nerves and their nuclei, the labyrinth, otoliths and their central connections in the brainstem including the vestibular nuclei and the medial longitudinal fasciculi.

Preservation of the “doll’s-eye movement” helps to exclude disease of the brainstem. Unilateral absence of doll’s eye movement suggests ipsilateral pontine lesion. The doll’s eye movements are totally abolished in extensive structural damage to the brainstem and deep metabolic coma. However, this test should not be performed when injury to the cervical spine is suspected.

Conjugate Deviation of the Eyes

This should be looked for. Lateral conjugate deviation occurs in cerebral or pontine lesions. Conjugate deviation is towards the side of the lesion in destructive disorders and to the contralateral side in irritative disorders in cortical lesions. The converse is true of pontine lesions. In tectal and thalamic lesions the eyeballs are depressed. In brainstem lesions spontaneous vertical nystagmus and skew deviation may occur. The eyeballs are deviated to the opposite side in cerebellar hemorrhage.

The caloric tests: These tests give information of the integrity of the vestibular apparatus, its connections in the brainstem and the connections with higher cortical centres. In deepening coma, when cortical function becomes progressively depressed, the fast phase of the nystagmus tends to disappear. Abnormal caloric tests indicate irreversible damage to the brainstem.

Posture

Decerebrate posture/rigidity: A patient in coma caused by structural lesions in the brain such as tumour, hemorrhage, infarct and others may assume this posture unilaterally or bilaterally either spontaneously or in response to painful stimuli. This is characterized by tonic extension and internal rotation of the upper extremity and tonic extension and plantar flexion of the lower extremity associated with jaw clenching and head retraction.

It is important to recognize this grave sign because it indicates dysfunction of upper brainstem between the superior colliculus of the midbrain and vestibular nuclei in the pons. In metabolic and drug induced coma, this posture does not develop. Decerebrate posture is caused by uninhibited vestibulospinal discharges.

Decorticate posture/rigidity: This posture is characterized by tonic flexion of the forearms at the elbow, adduction and flexion of the arm at the shoulder and flexion of the fingers, with tonic extension of the lower extremity, either on one or both sides. This is seen in lesions above the brainstem, affecting the cortex or the corticospinal tracts. Like decerebrate posture, this also occurs in coma and in chronic stages of hemiplegia. It indicates uninhibited rubrospinal discharges.

Funduscopy

This procedure should be performed in all cases to exclude papilledema and retinal abnormalities. It is mandatory to exclude raised intracranial tension before lumbar puncture is attempted.

DIAGNOSIS OF COMA

In neurological disorders, localizing signs pointing to damage to parts of the nervous system may be present such as hemiplegia, cranial nerve palsies or focal seizures. Meningitis and subarachnoid hemorrhage are associated with signs of meningeal irritation such as neck rigidity, Kernig’s sign and Brudzinski’s signs. In metabolic coma localizing signs may be absent. In poisoning, other effects of the poison may also be evident.

Investigations

1. Routine investigations to exclude systemic disorders include complete urinalysis, estimation of blood sugar, urea, electrolytes, blood gases and pH.
2. In suspected poisoning the gastric contents, blood, urine and other materials should be sent for chemical examination for the poison.
3. Cerebrospinal fluid should be examined when meningitis, encephalitis, subarachnoid hemorrhage, or meningeal leukemia are suspected.
4. Further tests are decided by the clinical examination and progress of the case. EEG, CT scanning, MRI and radio-isotopic scanning may be indicated in some cases.

Differential Diagnosis of Coma

- A. Coma with focal or lateralizing neurological signs, e.g. cerebral tumour, cerebral hemorrhage, infarction, abscess.
- B. Coma without focal neurological signs, but with signs of meningeal irritation, e.g. meningitis, encephalitis, subarachnoid hemorrhage.
- C. Coma without focal or lateralizing neurological signs or meningism, e.g. anoxic-ischemic lesions, metabolic disorders, intoxications, systemic infections, seizures, physical agents such as heat or cold.

Differential diagnosis of coma includes brain death, vegetative state, minimally conscious state, locked-in syndrome, catatonic stupor and hysterical behaviour (Table 185.2).

TABLE 185.2

The main differentiating features of the major conditions						
	Awareness	Wakefulness	Brainstem respiratory cycles	Motor reflexes	EEG	Evoked potential
Coma	–	–	±	±	Abnormal	Abnormal
Brain death	–	–	–	–	Silence	Absent
Vegetative state	–	Present, intact sleep wakefulness rhythm	+	±	Abnormal	Abnormal
Minimally conscious state	Intact but poor response	+	+	±	Non-specific	Abnormal
Locked in syndrome	Intact but communication poor	+	+	Quadruplegia, pseudobulbar normal palsy	Normal	Abnormal

key: + normal; – absent; ± variable

Locked-in Syndrome

The locked in syndrome is not a disorder of consciousness. This is a condition in which voluntary control of almost all body movements is abolished without abolition of arousal or awareness. Locked in syndrome is a state of profound paralysis with intact consciousness and cognition which may be mistaken for coma. In many cases it is due to a disorder of the pons caused by infarction or hemorrhage which de-afferents all supranuclear motor circuits except those of vertical eye movements.

Brain Death

The term “brain death” is used to denote irreversible loss of all brain functions. Most common cause is cardiac arrest persisting for over 3 mintues. Other causes include traumatic damage to the brainstem, extensive infarction and others.

Brain death has become an important issue since removal of organs for transplantation is done from comatose patients who are not likely to recover. Patients who are on supportive measures including artificial ventilation may pass into a stage where the cerebral and brainstem functions are irreversibly lost, still the patient may continue to have circulation on account of the supportive measures. Withdrawal of these supports will lead to physical death. The decision to withdraw these supports is a medicolegal one. Therefore, brain death has to be recognised clinically and supported by EEG wherever it is possible (Table 185.3).

TABLE 185.3

Criteria for brain death and vegetative states
1. Non-receptivity and non-responsivity to external stimuli, unawareness of self and surroundings
2. Absence of spontaneous movement and breathing and social intractions
3. Abnormality of brainstem reflexes such as pupillary reflexes, corneal reflex, caloric tests and cough and gag reflexes
4. Preservation of sleep-wakefulness rhythm
5. Preservation of autonomic and hypothalamic functions which enables them to survive with the provision of medical and nursing care.
6. Incontinence of micturition and defecation
7. Preservation of cranial nerve relfexes
8. Isoelectric EEG – i.e., flat EEG.

Deep coma without any movement or reflexes for over 24 hours, absence of brainstem reflexes such as oculoccephalic reflexes, light reflex, caloric tests and spontaneous respiration; and a flat EEG record indicate irreversible brain damage — i.e., brain death. These criteria are not valid if the coma is the result of overdose of poisons or hypothermia.

Persistent Vegetative State (PVS)

This denotes a state of wakefulness without awareness. Normal functioning of the cerebral cortex and midline structures of the upper pons, midbrain and thalamus are crucial to the maintenance of wakefulness. When these are disrupted the normal higher functions are lost. PVS results from any injury or other destructive process which grossly damages the cerebral hemispheres or the upper brainstem

structures. Common causes include ischemic damage to the brain stem and other parts, trauma and end stages of degenerative neurological disorders such as Alzheimer's disease and parkinsonism. PVS is a state of mere physical life without any intellectual activity or social interaction. The body maintains life without appreciating any sensation and devoid of all higher functions. Some of the autonomic reflexes and vital functions are preserved. Some spontaneous limb movements may occur. All signs of conscious perception and deliberate action are abolished.

Prognosis for recovery is better in children, traumatic lesions and in PVS of shorter duration.

These criteria should persist when repeated 24 hours later. For legal purposes three physicians, none of them forming part of any organ transplant team should independently certify brain death, before removing organs for transplantation.

MANAGEMENT OF COMATOSE PATIENT

General management: Comatose patients are very susceptible to develop several complications as a result of loss of protective reflexes and these have to be prevented.

Maintenance of the airway is of utmost importance. The neck has to be kept extended to prevent "falling-back" of the tongue. If necessary a patent airway should be introduced. Secretions have to be removed by postural drainage and suction. In cases with respiratory depression assisted ventilation has to be instituted early. Tracheostomy may be required in some cases.

Maintenance of Nutrition, Fluid and Electrolyte Balance

Adequate nutrition (at least 2000 cal/day and 2L of fluid) in the form of milk, sugar, eggs, cereals, salt and water are given through a nasogastric tube. Oral feeding carries the risk of aspiration into the respiratory tract, and therefore, this should be avoided. Parenteral nutrition is started through the intravenous route to supplement nasogastric feeding. The intravenous needle should be maintained aseptically. In prolonged illness, the

position of the needle should be changed every 36-48 hours to avoid thrombophlebitis.

Care of the Skin

Bedsore develop due to continuous pressure on localised areas. This risk is avoided by turning the patient in bed every 2-4 h and keeping the skin clean and dry. Adequate intake of proteins helps to minimize the risk of bedsore. When coma is likely to be prolonged, special beds which are capable of turning the patients, and which help to avoid pressure over localized areas may be used with advantage.

Care of Bladder and Bowel

The unconscious patient voids his bladder and bowel automatically and this creates many problems in nursing. Institution of a closed drainage system for the bladder helps to avoid soiling of the clothes and prevents infection. Bowels are moved by small enemas or suppositories at regular intervals.

Positioning of the Limbs and Physiotherapy

The limbs should be maintained in optimal position to avoid fixed deformities. Regular passive movements of the limbs help to prevent venous thrombosis and subsequent pulmonary embolism.

Specific Therapy

This depends upon the cause of the coma. Anticonvulsant medication is indicated if seizures occur. Intercurrent infection (respiratory, urinary or cutaneous) has to be treated with antibiotics.

Note: With the wide spread use of organs for transplantation and the international network for donor recipient matching and transplation procedures the importance of brain dead persons as donors has increased considerably. Since the chance for recovery is almost nil, supportive care which sustains life is withdrawn after strictly following legal procedures including the consent of relatives, independent certification of brain death and other formalities.

Chapter Summary

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General Considerations

Headache is one of the most common, and yet the most difficult clinical problem encountered by the physician. Though the term 'headache' can mean pain anywhere in the head, it is usually confined to pain arising in the region of the cranial vault. Most often headache is a symptomatic expression of some minor ailment, mental tension or fatigue, and in the vast majority of cases the cause is non-neurological. Occasionally, it is of sinister significance, indicative of serious intracranial disease.

Pain in the head may arise from different structures, which include:

1. The cranial vault consisting of skin, subcutaneous tissue, muscles, arteries, and periosteum of skull;
2. Intracranial venous sinuses and their tributaries;
3. Intracranial arteries before they penetrate brain parenchyma;
4. Meninges at the base of the brain;
5. Trigeminal, glossopharyngeal, vagal, and the first three cervical nerves; and
6. Structures of eye, ear, and nasal cavity.

Classification

Headache may be broadly classified into:

1. Referred headache.
2. Neuralgic headache.
3. Headache due to meningeal irritation.
4. Vascular headache.
5. Headache due to traction on intracranial structures, and
6. Psychogenic headache.

Headache is one of the most common nonspecific symptom occurring in several systemic illnesses such as

infections, fever, digestive disturbances, fatigue and others. It is also a very common adverse side effect of several drugs.

Referred headache: This includes pain arising from the eyes, ears, nose, air sinuses, teeth, cervical spine, and other structures which may be referred as headache. Iridocyclitis and glaucoma produce headache which is referred to the frontal region. Nasal and paranasal sinus diseases may cause pain over the frontal or malar region. Cervical spondylosis may cause severe occipital headache. In some people a cold stimulus in the soft palate may produce referred headache which is spoken of as an "ice-cream headache."

Neuralgic headache: Trigeminal neuralgia is a typical example of cranial neuralgia. The pain is episodic and lancinating in character. This occurs within the distribution of the fifth cranial nerve. In post-herpetic neuralgia pain is continuous and burning in character. In glossopharyngeal neuralgia a pain of stabbing character is felt in the pharynx and deep in the ear. Loss of teeth or ill-fitting dentures cause malalignment of the bite and secondary to this, changes occur in the temporomandibular joint resulting in temporomandibular neuralgia. Here the pain varies from dull ache to intense agonizing stabbing pain. The pain may radiate from the region of the affected joint to temporal and frontal areas and to the cheek or neck.

Meningeal irritation: Headache is almost always a symptom of meningitis and encephalitis. This results from meningeal inflammation which lowers the threshold of pain-sensitive structures at the base of the brain and hence minimal mechanical stimuli produce headache. This headache may be generalized or sometimes more severe in the occipital region. It is aggravated even by minimal movements of the head. The diagnosis is suggested by the associated fever, photophobia and neck stiffness.

Head ache of subarachnoid hemorrhage is often abrupt in onset, sometimes precipitated by exertion and felt at particular regions depending on the vessel involved. The patient is afebrile. Many become unconscious. At times incontinence may develop. It is important to recognize the

extremely severe headache of subarachnoid hemorrhage which demands immediate, referral to a centre where neurosurgical intervention can be undertaken.

Tension headaches which may be either episodic or chronic are the most common headaches and include muscle contraction headache, stress headache and psychogenic headache. The sensation is often described as the pressure exerted by a tight hat. The pain is mild to moderate, bilateral and does not worsen with normal physical activity. This group can be further subdivided into two: (1) those with abnormalities of the pericranial muscles, detected by palpation or demonstrating overactivity by electromyographic studies, and (2) those without such abnormalities. Muscle contraction headaches may also be secondary to localized disease of the head, temporomandibular joint dysfunction, cervical spondylosis, eye muscle disorders and sinus diseases. Treatment of such headaches consists of attention to any removable underlying cause, use of sedatives, altering the lifestyle and relaxing techniques such as biofeedback, meditation and leisure activities.

Vascular headache: This type of headache is the result of dilatation of intracranial or extracranial vessels. The pain is throbbing in nature and it tends to aggravate with head movement.

Migraine

The most common form of vascular headache is migraine (megrim means hemicranial). Migraine is characterized by episodic, throbbing hemicranial headache, beginning in childhood, adolescence or early adult life with a tendency to decrease in intensity and frequency as age advances. It is estimated that 5% of the population suffers from migraine. Women are slightly more affected. In many cases a positive family history is elicitable.

Mechanism of migraine: Though the exact mechanism is unknown, it is the consensus that an attack of migraine consists of a neurovascular disorder of the intracranial as well as the extracranial vessels. Sequential studies of cerebral blood flow show an initial reduction which may be localized or generalized followed by increase in blood flow (35-50%) later. The basic cause of this circulatory disturbance is not known. It is found that the blood levels of histamine, serotonin, and norepinephrine increase during the attacks. There is also increase in platelet aggregability. This may account for strokes which sometimes complicate migraine. The headache has been attributed to excessive pulsation of extracranial arteries, and possibly intracranial ones also.

Migraine with aura or classic migraine: Here the episode begins with prominent neurologic symptoms (*auras*) such

as visual disturbances like dazzling zig-zag lines, spreading scotoma, homonymous hemianopia, field defects or rarely total blindness, sensory disturbances affecting one-half of the body, disturbances of speech or hemiparesis. These neurologic symptoms last for 15-30 minutes and usually merge into a hemicranial or generalized throbbing headache with nausea and vomiting, all of which may last even for 1 to 2 days. In the majority of cases the duration is much shorter. Many complain of photophobia and phonophobia during the attacks.

Migraine without aura or common migraine: Here there is no preceding neurological symptoms, but there is unheralded onset of headache, nausea and vomiting following the same sequence.

Diagnosis of both classic and common types of migraine is made mainly from history. Long duration of illness, onset during childhood, positive family history and relief with ergot derivatives are in favour of migraine. Migraine has to be differentiated from other organic disorders such as raised intracranial tension, subarachnoid hemorrhage and arteriovenous malformations.

Course and prognosis: In the majority of patients migraine tends to be chronic with periods of exacerbation and remission. With increasing age the attacks tend to come down. Complications may occur rarely in some cases. These include cerebrovascular accidents, ocular and other cranial nerve palsies.

TREATMENT OF MIGRAINE

The physician should give full explanation of the nature and phenomena of migraine to the patient and this often relieves the patient's anxiety and helps to restore his morale. All known precipitating factors such as emotional tension, exposure to cold, foods such as cheese, and chocolates should be avoided. Hypoglycemia is a common precipitating factor and this should be avoided by proper timing of meals.

Many cases are made symptom-free by simple analgesics such as *aspirin in a dose of 900 mg or paracetamol 0.5-1 g given at suitable intervals. NSAIDs such as ibuprofen, naproxen and mefenamic acid are good alternatives.* If nausea and vomiting are troublesome metoclopramide 10 mg or domperidone 30 mg may be helpful. These drugs often help to abort an attack if given early. The specific drug which helps to abort an attack if taken at the earliest symptom is **ergotamine** which is a nonselective 5-hydroxy tryptamine agonist, in a dose of 1 mg. Available preparations include sublingual tablets of 1 mg, chewable tablets, subcutaneous injection (0.25 mg) or aerosols. If the drug is taken after the headache has set in, higher doses and repeated medication may be needed. In any case the weekly dose should not exceed 12 mg. Ergotamine preparations are contraindicated during pregnancy and in patients with ischemic heart disease, hypertension and peripheral occlusive vascular disease.

Adverse side effects include nausea, muscle cramps and peripheral vasoconstriction. Other drugs which can terminate an attack are metoclopramide 10 mg IV and prochlorperazine 10 mg IV.

Selective Serotonin Receptor Modifying Drugs in Migraine

The serotonin receptors 5HT₁, 5HT₂ and 5HT₃ are relevant to migraine. 5HT₁ inhibitory receptors produce vasoconstriction. 5HT₂ receptors are excitatory. Drugs such as cyproheptadine, propranolol and methysergide are 5HT₂ antagonists.

5HT₁ receptors are subclassified into 5HT_{1A}, 1B, 1D and 1F. Most of the triptan drugs which act in acute migraine act as agonists on 5HT_{1B} or 5HT_{1D}. **Sumatriptan** was the first drug of this class introduced to stop acute migraine attacks.

It is effective in the treatment of acute attacks of migraine, complicated migraine and cluster headache. The dose is 50-100 mg to be taken soon after the onset of migraine. For the same attack a second dose should not be given. If migraine attacks recur, doses upto 300 mg can be given in 24 hours.

A parenteral preparation of sumatriptan is available for subcutaneous injection in a dose of 6 mg as soon as possible after the onset. Peak plasma levels are reached in 20 minutes. For the same attack of migraine the drug should not be repeated. A second dose can be given for subsequent attacks upto a total dose of 12 mg in 24 hours.

Side effects include tingling, feeling of tightness of the different parts of the body, flushing, transient rise in blood pressure, hypotension, brady- or tachycardia and seizures.

Newer analogues are available for treatment of acute attacks of migraine. These include **zolmitriptan, naratriptan, rizatriptan, almotriptan and others**. Side effects, especially cardiac side effects are less for the newer analogues. Rizatriptan is available in India-It is given in a dose of 5-10 mg at the onset of the attack.

Drug prophylaxis: This is employed to prevent migraine attacks and allay their severity. The commonly used drugs include:

Propranolol 10-40 mg/day bid or tid

Cyproheptadine 4 mg HS

Calcium channel blockers: Nimodipine 30 mg bid, verapamil 40-60 mg bid. Flunarazine 5-10 mg HS.

These drugs have to be continued at first for six months after which the case has to be reviewed for continuation of therapy. In asthmatic subjects, propranolol may have to be replaced by more selective beta adrenergic blockers.

General measures such as regulated life, physical exercise, avoidance of smoking and leisure activities are important to prevent relapse.

CHRONIC DAILY HEADACHE

This term denotes the presence of headache for more than 15 days in a month for longer than three months. The term *transformed migraine* is used to denote the condition where classic migraine is altered, to assume the character of chronic daily headache, often due to overuse of drugs. The term *medication overuse headache* is given to conditions where headache is present at least for 15 days a month, associated with worsening of the headache during medication overuse, and reversion to previous episodic pattern (< 15 days per month) within 2 months after withdrawal of the medication.

Transformed migraine is an iatrogenic condition in which head pain occurs daily or almost daily (> 15 days per month), each attack lasting for 4 hours or more and worsening over the previous three months. At some point of time features of episodic migraine, meeting the International Headache Society (IHS) criteria, may be elicitable. The reason for this transformation is not clear. The IHS criteria for migraine without aura include the following:

1. At least five attacks that last for 4-72 hours—untreated or successfully treated.
2. Headache must have at least two of the characteristics given below;
Unilateral location, pulsating quality, and moderate or severe pain intensity, avoidance of usual physical activities such as walking or climbing stairs.
3. These attacks, themselves should be accompanied by at least one of the features such as nausea, vomiting, phonophobia not accountable by other conditions. Most patients with transformed migraine and medication overuse headache are women and they have a history of episodic migraine from adolescence or early adulthood.

The transformation from *migraine* to *transformed migraine* occurs over a period of months or years and the clinical picture is a mixture of tension type headache and migraine.

The over use of acute-headache medications such as aspirin, acetaminophen, caffeine, ergot, opioids or triptans by patients with frequent headache gives rise to **medication—overuse headache** which occurs almost daily (at least > 15 days a month) and maintained by the same medications used to relieve pain. Withdrawal of medication relieves the headache dramatically. Once the drugs are withdrawn, the headache reverts to the original pre-treatment pattern within months.

Management of Transformed Migraine and Medication Overuse Headache

1. Withdrawal of the offending medications,
2. Lifestyle changes including regular exercise, leisure activities,
3. Yoga and meditation,
4. Reintroduction of drugs should be based on trial and observations. In addition to regulated use of the common analgesics, drugs like amitriptyline 10 mg HS, corticosteroids (prednisolone 20-40 mg/day for 5 days) and nonsteroidal anti-inflammatory drugs have been used with benefit. Physical measures such as injections of botulinum toxin into specific points over the forehead and neck 25-75 units once in 4-6 weeks allays the frequency and severity of the headache in many cases.

Cluster Headache

Syn: histamine headache,
Horton's syndrome

This is a migrainous variant. The name 'cluster headache' refers to its occurrence in bouts. Men are more affected than women in the ratio of 4 : 1. The headache starts within 3 hours of falling asleep, it is non-throbbing, unilateral, and orbital in location. Along with pain there may be lacrimation, nasal obstruction, rhinorrhea, and sometimes miosis, ptosis, and flushing, and edema of cheek—all lasting approximately for an hour or two. It tends to occur every night for weeks or months followed by complete freedom for years. Such clusters of headache may recur over the years. Periods of headache are brought on by stress, prolonged strain, overwork and emotional disturbances. Alcohol, nitroglycerine or tyramine-containing foods may precipitate the headache. The Hypothalamus is probably at fault. Diagnosis is clinical.

Treatment of cluster headache: This may respond to antihistamine drugs. In resistant cases, drugs used in migraine may be necessary. Acute attacks respond to oxygen inhalation at the rate of 7 L/minute. Sumatriptan is given in doses of 6 mg by SC injection. It controls 75% of attacks. Ergot preparations given oral or by aerosol inhalation (1-2 mg) are effective. Nasal instillation of 1% lidocaine solution on the side of headache helps to arrest the attack.

Prevention of recurrence: Verapamil in doses of 240-320 mg or lithium in doses of 600-1500 mg a day is effective. In intractable cases surgical treatment on the gasserian ganglion of the trigeminal nerve and deep brain stimulation have been employed.

CHRONIC PAROXYSMAL HEMICRANIA

This term refers to brief spells of headache recurring frequently and following a chronic unremitting course,

unless modified by drugs. It differs from cluster headaches in the brevity of attacks. Response to indomethacin is dramatic.

OTHER VASCULAR HEADACHES

Headache following an alcoholic bout (*"hangover" headache*) is thought to be due to vascular mechanisms. Vascular dilatation and headache may be a feature of hypercapnia in patients with respiratory failure. Severe arterial hypertension may cause headache. In the elderly, localized temporal headache may be due to cranial arteritis (temporal arteritis).

Headache due to Traction on Intracranial Structures

An intracranial lesion such as a growing tumour or subdural hematoma may press upon pain sensitive structures situated intracranially and produce headache. This may occur even if there is no generalised rise in intracranial pressure.

Rise in intracranial pressure almost invariably produces headache which is often diffuse and aggravated by maneuvers which increase intracranial pressure further, such as straining at stools, stooping forward or coughing. Headache of raised intracranial pressure tends to be troublesome on waking up in the morning and when the patient is lying flat. When he assumes the erect posture, there is a slight fall in pressure and this relieves the headache to some extent in early cases. Headache is an important symptom in benign intracranial hypertension.

Post-lumbar puncture headache: Following lumbar puncture, if there is excessive leak of CSF through the puncture site the CSF pressure falls and this leads to traction on intracranial structures. This produces post-lumbar puncture headache. Other mechanisms also operate to perpetuate this symptom.

This can be avoided by doing LP with a small-bore needle, withdrawing only small quantities of CSF (< 2 mL) and administering drugs like caffeine (50-100 mg) and theophylline 100 mg orally. Creation of an epidural blood patch may be necessary if the headache is persistent.

Psychogenic headache and other cranial pains occurring in psychiatric diseases:

Headache is a common symptom in psychiatric disorders. Such headache involves the whole head or may be confined to the front or vertex. Though the sensation is usually described as pain, further scrutiny reveals it as a sort of pressure or tightness felt by the patients. Tension headache tends to occur following emotional excitement or other stresses. Constant tension developing in the muscles of the forehead and upper part of the face leads to this symptom. This type of headache may persist continuously for days or weeks. Common analgesics like salicylates and

paracetamol are ineffective. Patients with tension headache reveal prominent symptoms of depression, anxiety, and hypochondriasis. Majority of patients with anxiety neurosis, hysteria, obsessive compulsive neurosis and schizophrenia with prominent anxiety, exhibit this type of headache. Miscellaneous headaches not associated with structural lesions are characterized by severe stabbing pains lasting for very brief periods (probably only seconds) commonly felt in the distribution of the first division of the trigeminal nerve. They respond to reassurance. Indomethacin is very effective in some cases.

Coital headache occurs at the time of sexual intercourse and may cause severe anxiety. This is a benign condition in the vast majority of cases, but if it is of recent onset, subarachnoid hemorrhage has to be excluded by suitable investigations before reassuring the patient. Exercise induced headache also comes under the same category.

Diagnosis

Majority of headaches encountered in clinical practice are nonrecurrent and occur as manifestations of systemic illnesses. Recurrent headaches present a common diagnostic problem since one has to differentiate conditions like migraine and tension headache from more serious causes like intracranial structural lesions. Presence of accompanying signs like neurological deficits simplifies the problem, but usually history is the only

clinical guide for diagnosis and further management. Some general points help to assess the severity of the disorder.

Headache described as throbbing or burning is more significant than tension headaches. Localised headaches are often indicative of serious underlying disease than diffuse pain. Headache situated over the occipital or frontal region is more important than that situated over the vertex. Headaches which disturb sleep usually arise from organic lesions. Headache of recent onset is more sinister than that of long standing. Presence of phenomena like double vision or epilepsy indicates the presence of an intracranial lesion. **Late onset headache and recent change in pattern in chronic headaches are indications for brain imaging studies.**

Management

The investigation and treatment depend upon the clinical setting. Detailed history serves to sort out the cause in the majority of cases. Investigative procedures such as X-ray chest, EEG and computerized tomography of the brain are done before embarking upon more advanced procedures like MRI and angiography. In those cases in whom no serious underlying lesion is detected, reassurance and periodic follow-up is all that is required. It is important to avoid unnecessary medication and life-long invalidism.

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Nutritional Disorders of the Nervous System

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- Thiamine Deficiency 1225
- Wernicke-Korsakoff Syndrome 1226
- Other Nutritional Deficiencies 1226

Vitamins and minerals are required in optimal quantities for proper maturation and functioning of central and peripheral nervous system. Though more than 40 nutrients

are recognized today, neurological disorders usually manifest only from deficiency of B vitamins (thiamine, pyridoxine, nicotinic acid, B₁₂ and folic acid) and vitamin E. Deficiency of thiamine and vitamin B₁₂ are the commonest nutritional disorders in India which present with neurological dysfunction. Vitamin deficiency can affect various parts of the nervous system and hence the presentation may be varied (Table 187.1). Less commonly, vitamin excess may also impair neurological functions and manifest as neurological disorders (Table 187.2).

TABLE 187.1

Neurological syndromes associated with nutrient deficiency	
Dementia/encephalopathy	Vitamin B ₁₂ , nicotinic acid, thiamine, folate
Seizures	Pyridoxine, biotin
Extrapyramidal syndrome	Nicotinic acid
Cerebellar ataxia	Vitamin E, vitamin B ₁₂ ,
Myelopathy	Vitamin B ₁₂ , folate, vitamin E
Optic neuropathy	Vitamin B ₁₂ , folate, vitamin E
Polyneuropathy	Thiamine, vitamin B ₁₂ , folate, pyridoxine, vitamin E, nicotinic acid
Myopathy	Vitamin B ₁₂ , folate, vitamin E

TABLE 187.2

Neurological syndromes associated with vitamin excess	
Vitamin A	Idiopathic intracranial hypertension
Pyridoxine	Peripheral neuropathy

VITAMIN B₁₂ DEFICIENCY

Vitamin B₁₂ deficiency is a common cause for nutritional disorder of the nervous system. It is estimated that 10 - 25% of people over 80 years of age have vitamin B₁₂ deficiency. There are several causes of B₁₂ deficiency. A strict vegetarian diet excluding even dairy products may predispose to vitamin B₁₂ deficiency because animal-based foods such as red meat, dairy products, fish, poultry and eggs are the only rich source of dietary B₁₂. However, vegetarians rarely develop clinically evident vitamin B₁₂ deficiency as the daily requirement is only 0.5 µg and small amounts may be obtained from legumes and buttermilk and curd. Impaired absorption from the gut and utilization may predispose to deficiency. Causes include malabsorption syndromes and prolonged use of H₂ receptor antagonists or proton pump inhibitors, autoimmune diseases such as pernicious anemia, pancreatic disease, ileal resection, Crohn's disease, HIV infection, chronic gastritis and gastric or small intestine surgery.

Only 15% of patients with megaloblastic anemia develop neurological dysfunction. Neurological dysfunction arises due to impaired DNA synthesis and myelin formation.

Pathological findings include demyelination and axonal degeneration in the posterior and lateral columns of the cervical and thoracic cord, called as *subacute combined degeneration of the spinal cord*. Similar findings may be found in the peripheral nerves. It commonly presents as myeloneuropathy with tingling paraesthesias and reduced pain and touch sensation in a

stocking-glove distribution along with loss of vibration and joint/position sense, rombergism, sensory ataxia, pyramidal weakness in lower limbs and lower limb areflexia. Patients may also manifest with cognitive/psychiatric symptoms and visual impairment due to optic atrophy and centrocecal scotoma. In India, vitamin B₁₂ deficiency most commonly presents as peripheral neuropathy.

Diagnosis is essentially clinical and patients may have other markers of B₁₂ deficiency such as anemia, glossitis and hyperpigmentation over the knuckles. Diagnosis is supported by direct and indirect laboratory evidence of B₁₂ deficiency such as presence of macrocytic anemia, hypersegmented neutrophils in the peripheral smear and megaloblasts in bone marrow. Low serum B₁₂ levels below 100 pg/mL, increased excretion of methyl malonic acid in urine and elevated levels of serum homocysteine levels confirm the diagnosis. Magnetic resonance imaging may show lesions in the posterior and lateral columns of spinal cord and deep white matter of brain. MRI is required only to exclude other causes of myeloneuropathy in a doubtful case.

Treatment

As the most common cause for deficiency is malabsorption and impaired utilization the role of oral supplementation is limited. Parenteral vitamin B₁₂ gives gratifying results and treatment should begin with intramuscular injections of 1000 µg of cobalamin for 7 days, followed by weekly injections for a month. Patients may require to be continued on monthly injections, depending on the etiology. Cases of pure nutritional deficiency should have supplementation of cobalamin 1-2 µg in the diet. Correction of the dietary and gastrointestinal disease should receive attention.

THIAMINE DEFICIENCY

Thiamine deficiency occurs in the setting of poor nutritional status either due to poor intake, malabsorption or increased requirement. In India it occurs most commonly in nutritionally deprived chronic alcoholics and in individuals consuming polished rice. However it can be precipitated in individuals with borderline nutritional status in the setting of raised metabolic requirements for thiamine such as pregnancy, strenuous exercise, systemic infection and malignancy. In fact, acute presentation of Wernicke encephalopathy may occur when large doses of carbohydrates, especially parenteral glucose therapy, are administered without concurrent thiamine administration. The spectrum of thiamine deficiency involves the cardiovascular system (wet beriberi) and the nervous system (*dry beriberi* and *Wernicke-Korsakoff syndrome*). Consumption of a low thiamine, low carbohydrate diet

with relative physical inactivity favours the development of dry beriberi. Diagnosis of thiamine deficiency is essentially clinical and may be supported by reduced blood transketolase activity and elevated pyruvate levels.

Beriberi

Polyneuropathy due to thiamine deficiency is called dry beriberi. Classical wet and dry forms of beriberi refer to the presence or absence of edema. It manifests as a stocking-glove (length dependent) symmetric sensorimotor polyneuropathy affecting predominantly the lower limbs. Clinical features include tingling paraesthesias, pain and muscle cramps and tenderness, distal muscle weakness and loss of deep tendon reflexes. Rarely, optic neuropathy and laryngeal palsy have been described. Associated pedal edema occurs due to cardiac involvement. Signs of cardiac failure may be prominent. Unless promptly detected and treated death may occur due to cardiac failure.

Wernicke-Korsakoff Syndrome

The spectrum of central nervous system involvement due to thiamine deficiency ranges from acute Wernicke's encephalopathy to chronic Korsakoff's psychosis. The two conditions represent different stages of the same disease process. Pathological changes consist of hemorrhagic lesions in the peri-aqueductal grey matter and mamillary bodies. MRI may show lesions in the mamillary body, medial thalamus and peri-aqueductal grey matter. Wernicke's encephalopathy consists of acute or subacute onset of the clinical triad of *confusion*, *ophthalmoplegia* and *truncal ataxia*. Oculomotor abnormalities consist of nystagmus, lateral rectus palsy and conjugate gaze palsy. In addition, hypothermia and postural hypotension may occur. Treatment consists of parenteral thiamine 50-100 mg given IM or IV in 5% glucose solution slowly. Effects are dramatic and ocular signs may resolve within hours. Apathy and lethargy improve over days and gait disturbance resolves slowly. If the condition is not detected in time and promptly treated, it may be fatal. In some patients, as global confusion state recedes, selective impairment of learning and memory become prominent, characteristic of Korsakoff's psychosis.

The amnesic syndrome of Korsakoff's psychosis is characterized by impairment of memory out of proportion to other cognitive domains. Patients have anterograde and retrograde amnesia, with preservation of immediate and remote memory, disorientation to time and place and confabulation to fill up the gaps in the memory. The syndrome may improve with thiamine, but, only partially.

Abstinence from alcohol, avoidance of smoking and nutritional improvement serve to prevent relapse.

Other Nutritional Deficiencies

1. **Pyridoxine (vit. B₆).** Its deficiency produces polyneuropathy. It is commonly seen as a complication of therapy with isonicotinic acid hydrazide (INH) in marginally nourished individuals.
2. **Burning feet syndrome Syn. Gopalan's syndrome**
This syndrome is named after C Gopalan the eminent nutrition scientist from India. Patients experience burning pain in the feet, especially during night, interrupting sleep. Examination may reveal pallor, cyanosis, excessive sweating and areas of capillary dilation over both feet.

A third of these patients may show loss of sensation over these areas. More often, hyperalgesia may occur. Deficiencies of vitamin B factors and proteins and possibly toxic factors in old polished rice are considered as potential etiologic factors. Most of the patients respond dramatically to injections of pantothenic acid suggesting that this deficiency plays a major role in the pathogenesis of this syndrome.

3. **Strachan syndrome** was first described amongst sugarcane workers in Jamaica and consists of painful peripheral neuropathy, ataxia, optic neuropathy and stomatitis. Patients may also develop sensorineural deafness, spasticity, dizziness and confusion. It is most commonly seen in the setting of poor nutrition associated with famines or incarceration as prisoners of war. More recently, an outbreak resembling Strachan's syndrome occurred in Cuba following loss of food and fuel imports. The exact cause is not known, though postulates put forward include vitamin B deficiency and cyanide toxicity. Most patients respond to supplementation of B-complex vitamins.
4. **Protein energy malnutrition:** The human brain shows developmental spurt from 13th week of gestation and growth continues for about 3 to 4 years after birth. The major events during this critical period include proliferation of neurons and glial cells and myelination of nerves. These processes are mainly dependent upon proper nutrition of the mother and infant among other factors. Severe malnutrition (protein and energy) occurring during fetal life and in the early part of infancy may leave behind damage which may not be correctable with subsequent therapy. Children manifest with apathy, irritability, delayed acquisition of mental and fine motor skills, clumsiness, generalized muscle wasting, hypotonia and hyporeflexia. Neuropsychological changes are more profound in Kwashiorkor. Twenty five per cent of children with protein energy malnutrition may show

subtle cerebral atrophy. During the first few weeks of starting protein re-feeding, some children with Kwashiorkor may develop encephalopathy ranging from mild drowsiness to rigidity, myoclonus, coarse tremors and rarely coma, known as **nutritional recovery syndrome**. As the problem of infant malnutrition is closely linked with socioeconomic and geographic factors, it is of utmost public health importance to ensure proper nutrition during pregnancy and infancy

Nutritional Amblyopia

Visual disturbances may develop due to deficiency of multiple nutrients, including vitamin B factors. This sets in insidiously with dimness of vision, photophobia, and retrobulbar discomfort on moving the eyes. Visual acuity is reduced. Central or paracentral scotomas develop, but the peripheral fields of vision may remain intact.

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Infections of the Central Nervous System

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Nervous system is commonly affected by infections. The nervous system may be the primary target of infection, e.g. Herpes simplex encephalitis, rabies or purulent meningitis. On the other hand, it may be affected secondary to systemic infections, in which case the neurological lesions develop as part of the systemic manifestation of disease, e.g. encephalopathy complicating enteric fever.

The clinical presentations of various infections are distinct and identification of the pattern of clinical presentation helps in diagnosis and management (Table 188.1). Meningitis affects the leptomeninges and presents with the classical triad of fever, headache, vomiting. Depending on duration of symptoms, meningitis may be acute or chronic. Encephalopathy, characterized by altered level of sensorium and seizures, is characteristic of encephalitis where there is direct involvement of brain parenchyma. Infections causing focal structural brain parenchymal damage present with focal neurological deficits such as hemiplegia or aphasia. Infections affecting the spinal cord present with myelopathy. Rarely, CNS infections can present with chronic behavioral disturbances and dementia when the parenchyma and/or the vasculature is affected.

Bacterial Meningitis

Bacterial meningitis is the condition characterized by inflammatory response to bacterial infection of the leptomeninges. Likelihood of infection with a specific pathogen depends upon the age, immune status and any focus of sepsis in the patient. *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Neisseria meningitidis* account for 80% of cases of acute purulent meningitis. In pre-term and neonate babies group B streptococcus is most common. Next in frequency are coliform bacilli especially those possessing K₁ antigen. Other organisms include Klebsiella, Enterobacter, Salmonella, Listeria and others. Tuberculosis, cryptococcosis other fungal infections account for the majority of chronic meningitis.

TABLE 188.1

Classification of infections of the CNS based on clinical presentation

ACUTE MENINGITIS
Bacteriae <i>Streptococcus pneumoniae</i> , <i>Neisseria meningitidis</i> , <i>Haemophilus influenzae</i> , <i>Staphylococcus aureus</i> , <i>Listeria monocytogenes</i> , gram-negative bacilli, <i>Leptospira interrogans</i> , <i>Mycoplasma pneumoniae</i>
Viruses Coxsackie virus, echovirus, mumps, arbovirus, herpes, HIV
CHRONIC MENINGITIS
Bacteria Partially treated bacterial meningitis, <i>Mycobacterium tuberculosis</i> , <i>Treponema pallidum</i>
Fungus <i>Cryptococcus neoformans</i> , aspergillus, candida
Parasite Cysticercosis, toxoplasma, amebae
FOCAL NEUROLOGICAL DEFICIT
Abscess Brain abscess, subdural empyema, epidural abscess
Granulomas Tuberculoma, cysticercosis, fungal infections
Toxoplasma
Echinococcosis
Complication of meningitis: Arteritis, infarction
Focal encephalitis
ACUTE ENCEPHALOPATHY
Herpes simplex Arboviruses: Japanese B, West Nile, Kyasanur forest disease Enteroviruses, Varicella zoster Mumps Rabies Dengue
MYELOPATHY
Viruses Varicella zoster, Herpes simplex, rabies, cytomegalovirus, Japanese B
Bacteria Pyogenic abscess
Granuloma Tuberculoma, cysticercosis
Dementia Subacute sclerosing panencephalitis (SSPE) Prion diseases - kuru, Creutzfeldt-Jakob disease, variant BSE Neurosyphilis HIV associated dementia

The details of the organism, pathogenesis and clinical features are described in Section 6 Chapter 37.

Lumbar puncture is the investigation of choice and CSF pressure will be elevated (200-500 mm H₂O), protein content will be elevated (100-500 mg/dl or more), glucose will be reduced (< 40% of the serum glucose) and CSF will show marked pleocytosis (100-10000 leukocytes with 60% or more being neutrophil leukocytes). CSF Gram staining is positive in 60% and the organisms can be isolated in cultures in approximately 75%, if the CSF is collected and sent for culture ideally prior administration of antibiotics reduces the yield of CSF Gram staining and culture by 5-40%. Latex agglutination tests can detect antigens of the various pathogens.

Diagnostic workup includes evaluation for the source of bacterial infection such as otitis media, pneumonia, or any extracranial communications of CSF as in CSF rhinorrhea and otorrhea secondary to bone defects. Differential diagnoses include viral and tuberculous meningitis and febrile encephalopathies due to systemic infections. Antibiotic use is guided by the clinical setting (Table 188.2).

Dexamethasone should be started early along with the appropriate antibiotics.

Neurosyphilis

(See also Chapter 47).
Involvement of the nervous system in syphilis used to be common before 1950s, but now it is distinctly uncommon to see fresh cases. Neurological involvement occurs in 4% of untreated cases of syphilis. Men are affected 4-5 times more commonly than women. Along with the AIDS pandemic, syphilis has assumed greater importance since it predisposes to AIDS infection and the two diseases influence each other to causes greater severity. Neurological lesions are caused by direct invasion of the tissues by *Treponema pallidum*. Meningovascular involvement is more common in India, constituting 60-70% of cases (Table 188.3).

MENINGOVASCULAR DISEASE

Cerebral Involvement

Leptomeningitis is the common lesion, affecting the pia and arachnoid mater. It develops 2-7 years after primary infection, most often between the ages 18-40 years. Meningitis is most often seen at the base of the brain and over the cerebral hemispheres. Basal meningitis may involve the lower cranial nerves, leading to multiple cranial nerve palsies, and occlude the fourth ventricle outlet foramina, leading to obstructive hydrocephalus. Vascular lesion is endarteritis obliterans, characterized by vascular intimal thickening and infiltration of the arterial

TABLE 188.2

Antibiotic recommendations for specific pathogens

Clinical setting	Empirical therapy	Organism	Specific therapy
Age < 3 months	Ampicillin + gentamicin or Ampicillin + 3rd generation cephalosporin*	Group B <i>Streptococcus</i> <i>Enterobacteriaceae</i> <i>L. monocytogenes</i>	Ampicillin + gentamicin 3rd generation cephalosporin + aminoglycosides Ampicillin + gentamicin
3 months - 18 years	3rd generation cephalosporin	<i>N. meningitidis</i> <i>S. pneumoniae</i> <i>H. influenzae</i>	Benzyl penicillin Benzyl penicillin or 3rd generation cephalosporin 3rd generation cephalosporin or ampicillin + chloramphenicol
18 years – 50 years	3rd generation cephalosporin	<i>S. pneumoniae</i>	Benzyl penicillin or 3rd generation cephalosporin Alternatives –vancomycin + 3rd generation cephalosporin Rifampicin may be added to vancomycin
> 50 years	Ampicillin+ 3rd generation cephalosporin	<i>S. pneumoniae</i> <i>L. monocytogenes</i> Gram-negative bacilli	As above
Head trauma / neurosurgical procedure	Vancomycin + ceftazidime	<i>Staph. aureus</i> <i>Staph. epidermidis</i> Gram-negative bacilli including pseudomonas <i>S. pneumoniae</i>	Vancomycin + oxacillin Ceftazidime + aminoglycoside As above
Immunocom- promised state	Ampicillin+ ceftazidime	<i>L. monocytogenes</i> Gram-negative bacilli <i>S. pneumoniae</i> <i>Staph. aureus</i>	As above
Setting of sinusitis, otitis	Vancomycin + ceftazidime + metronidazole	<i>S. pneumoniae</i> <i>H. influenzae</i> Gram-negative bacilli Anaerobes	As above

*3rd generation cephalosporins includes ceftriaxone and cefotaxime

TABLE 188.3

Involvement of the nervous system in syphilis

- I. Secondary syphilis—meningitis
- II. Asymptomatic stage
- III. Tertiary syphilis
 - a. **Meningovascular disease**
Cerebral involvement: Basal meningitis, pachymeningitis, vascular thrombosis, optic atrophy, gumma
Spinal cord involvement: Meningomyelitis, Erb's spastic paraplegia, cervical pachymeningitis, syphilitic amyotrophy, radiculitis, gumma
 - b. **Parenchymal disease**
Cerebral involvement: General paralysis of the insane (GPI)
Spinal involvement: Tabes dorsalis
Optic nerve involvement: Optic atrophy
- IV. Congenital syphilis—Meningovascular disease, optic atrophy, deafness, general paralysis of the insane, tabes dorsalis

Granulomatous changes are also seen in the vessel wall. Less commonly, the dura mater over the cerebral hemispheres may be involved by the granulomatous process, leading to its thickening, called as *cerebral pachymeningitis*.

Syphilitic basal meningitis leads to subacute or chronic meningitis characterized by headache, cranial nerve palsies, raised intracranial tension and signs of meningeal irritation. CSF shows elevated proteins and lymphocytic pleocytosis. CSF sugar and chloride levels are normal. CSF serology for syphilis is positive.

Cranial pachymeningitis causes headache, seizures and focal neurological deficits such as aphasia or hemiparesis.

Syphilitic endarteritis used to be one of the common causes for occlusive stroke in the young. Patients present as cerebral thrombosis with hemiplegia. Lower motor neuron facial palsy and even trigeminal neuralgia may occur. The prognosis for recovery is good if the condition is diagnosed and treated early.

wall by lymphocytes and plasma cells. Thrombosis supervenes and this occludes the arterial lumen.

Spinal Involvement

Meningomyelitis: This gives rise to the picture of acute transverse myelitis or varying degrees of cord compression with root pains. In Erb's syphilitic paraplegia, spastic paraplegia develops with bladder dysfunction; sensory symptoms are rare.

Hypertrophic cervical pachymeningitis: Compression of the cervical roots leads to root pain, weakness and wasting of the upper limb and shoulder girdle muscles or quadriparesis.

Such a picture is also referred to as *syphilitic amyotrophy*.

The cauda equina may also be involved leading to root pain, areflexia, weakness and wasting affecting the thighs and legs.

PARENCHYMAL DISEASE

Cerebral Involvement

General Paralysis of the Insane (GPI)
Syn Dementia paralytica

GPI develops 15-20 years after the primary infection. Men above 40 years are more affected. The frontal and temporal lobes of the brain show cortical atrophy with gliosis. The meninges show thickening and lymphocytic infiltration. Ventricles show dilation and ependymitis. In about 50% of cases the organism (*T. pallidum*) can be demonstrated in brain biopsy.

Clinical features are characteristic. Higher mental faculties deteriorate gradually, leading to reduction in intellectual capacity, loss of memory and personality changes. Patients lack judgment and insight. Euphoria, loss of inhibition, as revealed by abnormal social behaviour, depression or mania may develop. Less commonly, grandiose delusions may be the prominent features. Around 50% of cases show *Argyll Robertson pupil* characterized by small irregular pupils with loss of light reflex, but preservation of the accommodation reflex. Optic atrophy occurs in 5-10% of cases and seizures develop in 50%. Limbs, lips and tongue may be tremulous and the to and fro movements of the tongue are described as "*trombone tremor*" since it bears similarity to the movements of the musical instrument trombone.

Vascular episodes occur from time-to-time. These manifest as focal neurological deficits such as hemiparesis, dysphasia or hemianopia. These recover spontaneously. The course of the disease is one of gradual progression with fluctuations, finally proceeding to incapacitation.

SPINAL INVOLVEMENT

Tabes Dorsalis

This form of parenchymal neurosyphilis is less common than GPI. It develops 25-30 years after the primary infection. Males are affected five times more frequently than females. Primary damage is in the dorsal root ganglia and is characterized by inflammation. Later, the posterior roots and posterior columns of spinal cord undergo atrophy.

Initial symptoms are pain and paresthesia of the limbs. As the condition progresses, sensory ataxia sets in. Clinical features include loss of joint and position sense and vibration perception. Gait is stamping in quality. Lower limb areflexia is common and the ankle reflex is abolished before knee reflex. Limbs are hypotonic. Romberg's sign is positive. Argyll Robertson pupil may be present. Optic atrophy occurs in a few cases. There is loss of deep pain sensation. This is elicited by squeezing the tendo-Achilles which normally causes pain, but in tabes dorsalis it does not elicit pain (*Abadie's sign*). Testicular sensation is also lost. Some patients reveal loss of touch and delay in the appreciation of pin-prick over the central parts of the face, ulnar border of the hands, distal parts of the legs, perianal region and over the chest.

Autonomic disturbances are characteristic. Bladder sensation is lost early and atonic distension of the urinary bladder and urinary incontinence may develop. Impotence occurs early. Partial ptosis develops due to sympathetic dysfunction and paralysis of Muller's muscle of eyelid. Many patients overcome the disability caused by partial ptosis by tilting the head backwards and wrinkling the forehead. This appearance is described as **tabetic facies**. Due to loss of trophic influences, the major joints develop painless swelling and undergo degenerative changes, called **Charcot's joints**. Painless trophic ulcers develop on the feet and other areas of pressure.

The course of the disease is often disturbed by the occurrence of **lightning pains**, which are unique for tabes dorsalis. These are lancinating pains occurring in transverse directions in the limbs, chest and face. Lightning pains differ from neuralgic pains in that the former do not follow the direction of nerve roots. Visceral crises develop frequently. Gastric crisis is characterized by severe epigastric pain and vomiting. Rectal crises give rise to tenesmus. Stridor develops as a result of laryngeal crisis.

OPTIC ATROPHY

Optic nerve involvement may result from meningo-vascular or parenchymal involvement. Former leads to arachnoiditis, optic neuritis or retrobulbar neuritis. Changes occur early during the tertiary stage of syphilis. At this stage, specific treatment may help to reverse the

condition. Optic atrophy due to parenchymal involvement occurs during the late stages.

CONGENITAL NEUROSYPHILIS

Stigmata of congenital infection with *T. pallidum* may be present at birth and include hydrocephalus, mental retardation, seizures, chorioretinitis, optic atrophy and sensorineural deafness. These may be associated with other evidence of congenital syphilis. Neurological involvement developing later in congenital syphilis may take the form of meningovascular lesions, optic atrophy, tabes dorsalis or GPI. Parenchymal lesions occur at a younger age (juvenile GPI, juvenile tabes dorsalis).

GUMMA OF THE CENTRAL NERVOUS SYSTEM

Gumma occur in tertiary syphilis. Pathologically the gumma consists of collagen deposition forming an amorphous matrix with lymphocytes and plasma cells at the periphery and multinucleated giant cells in the center. Later the lesions undergo fibrosis *T. pallidum* is not demonstrable in these lesions. Gumma may be seen in the cranium, dura, leptomeninges, cerebrum and spinal cord where they behave as space occupying lesions. Response to treatment is poor.

Syphilitic Deafness

Deafness may result from several mechanisms in the different stages of syphilis. It may result from affection of the cochlea, acoustic nerve, basal meninges or damage to the middle ear.

DIAGNOSIS

Neurosyphilis should be considered in the differential diagnosis of many neurological disorders. GPI should be differentiated from cerebrovascular disease, primary dementias, intracranial space occupying lesions and progressive degenerative disorders. Tabes dorsalis should be considered in the differential diagnosis of diabetic, toxic and nutritional neuropathies, hereditary ataxias and syringomyelia. Presence of **Argyll Robertson pupil** is a strong point to support the diagnosis of neurosyphilis.

Laboratory diagnosis: Blood serology is positive in 60-70% of cases. CSF analysis shows lymphocytic pleocytosis and elevated protein content. Neurosyphilis is confirmed by a positive CSF VDRL along with a positive serum FTA ABS or *T. pallidum* immobilization test. Clinical features should also be supportive. CSF abnormalities are positive especially in the early stages of meningovascular disease. Previous therapy with penicillin may mask the CSF changes.

PROGNOSIS

Meningovascular disease has the best outcome. Early cases of GPI may also show improvement. However,

results are poor in established cases of tabes dorsalis and optic atrophy.

TREATMENT

This is described in Chapter 47 As benzyl penicillin penetrates into the CSF, it is the drug of choice for neurosyphilis. Repeated courses of penicillin may be required and this has to be decided depending upon blood and CSF serology. Tabetic pains may respond to analgesics and carbamazepine. Visceral crises are treated by sedation and supportive measures.

Follow-up lumbar punctures are required to assess response to therapy.

Brain Abscess

Focal suppuration followed by loculation of pus within the brain parenchyma is called brain abscess. Despite advances in neurodiagnostic techniques, neurologic practice and antimicrobial therapy, diagnosis and management of brain abscess remains a challenge to the physician and surgeon even today.

Pathogenesis

The healthy brain resists the development of an infective focus within its substance even if bacteria gain entry into it. For suppuration to happen within the brain parenchyma, there should be:

1. An area of pre-existing brain damage.
2. Entry of infective organisms into that region.

Several conditions lead to such brain damage. These include:

1. Cortical thrombophlebitis resulting from the spread of infection from contiguous suppurative lesions such as otitis media, sinusitis or cranial osteomyelitis.
2. Septic or even sterile emboli.
3. Hypoxic or ischemic brain damage.

Infection supervening on such damaged neural tissue leads to abscess formation. Typically, the evolution of brain abscess passes through four stages:

1. The first stage is focal cerebritis of the white matter and edema around it.
2. In the second stage the focal cerebritis enlarges with central necrosis and early formation of a peripheral capsule.
3. The third stage is one of further developments of the capsule.
4. The fourth stage is one of capsular maturation. Depending on the virulence of the causative organism and immune status of the host, it may take three weeks or even longer for the brain abscess to mature.

Predisposing Conditions

1. Extension of infection from suppurative foci such as otitis media and mastoiditis (otogenic brain abscess) or sinusitis (rhinogenic brain abscess).

- 2. Spread of infection from a distant focus in the body such as lung abscess, empyema, infective endocarditis, dental sepsis, pelvic sepsis and congenital cyanotic heart disease (hematogenous brain abscess).
- 3. Introduction of infection from outside as in the case of head trauma (post-traumatic brain abscess) or during a surgical procedure in and around the head (iatrogenic brain abscess).

However, in a quarter of patients no predisposing factor may be evident (cryptogenic brain abscess).

There is generally a relationship between the primary site of infection, location of abscess in the brain and the causative organism:

Type of brain abscess	Location in brain	Causative organism
Otogenic	Temporal lobe Cerebellar hemisphere	<i>Streptococcus</i> <i>Bacteroides</i> Enterobacteriaceae <i>Staph. aureus</i>
Rhinogenic	Frontal lobe Temporal lobe	Same as above
Hematogenous	Gray and white matter junction	<i>Staphylococcus</i> <i>Str. viridans</i> Anaerobes <i>H. influenzae</i> Other gram-negative bacteria in case of cyanotic congenital heart disease
Post-traumatic Post-surgical	Near site of entry	<i>Staph. aureus</i> Enterobacteriaceae

In immunocompromised individuals, opportunistic infections due to low virulence bacteria may cause abscess formation. Apart from pyogenic bacteria, nocardia, toxoplasma and mycobacteria may rarely be the etiological agents. In over 75% of cases, only one pathogen may be present whereas in about 25% the microbial flora may be mixed.

Clinical Features

Typically, patient with brain abscess has a combination of:

- 1. Signs of infection.
- 2. Focal neurological signs which depend on the site and size of the abscess.
- 3. Raised intracranial pressure.

However, this classic picture is seen in only about 50% of patients. Absence of fever and acute phase reactants should not exclude brain abscess from the differential diagnosis of patients presenting with an intracranial space occupying lesion. Seizures, which may be focal or secondarily generalized, occur in majority of patients. Brain abscess may frequently present as a



Fig. 188.1: Contrast enhanced CT scan brain showing left cerebellar abscess—arrow

neurological emergency because of complications such as brain herniation.

INVESTIGATIONS

Whenever brain abscess is suspected, investigations are prioritized to confirm the diagnosis, identify the organism and detect any possible source for infection. Diagnosis can be established in almost all cases by CT scan, which should be done at the earliest and repeated if needed for follow-up. Mature brain abscess has a ring like appearance in contrast enhanced CT, due to capsule formation (Fig. 188.1). However in the earlier stages of infection, only a non-enhancing, hypodense area may be seen with surrounding brain edema. MRI is more sensitive than CT in identifying early stages of cerebritis. Attempts to isolate the infecting organism and establish its drug sensitivity should be undertaken depending on the individual case.

The organism can be identified and drug sensitivity ascertained by culturing specimens obtained from the primary focus of infection, blood or direct aspiration of pus from the abscess through a burr hole under CT scan guidance.

Lumbar puncture should not be routinely carried out when brain abscess is suspected or confirmed on CT or MRI because of the risk of brain herniation leading to deterioration of the neurological status or death. Moreover, CSF may not show diagnostic changes unless brain abscess is associated with ventriculitis or meningitis.

Complications

Rupture of the brain abscess into the cerebral ventricles may lead to ventriculitis and meningitis. Brain herniation due to raised intracranial pressure may occur leading to cardiovascular and respiratory compromise. Seizures may occur during the course of the disease or may develop much later as a result of scar formation. Brain abscess is fatal unless treated promptly. With early diagnosis and prompt treatment, full recovery is the rule in most cases.

Management

Specific Therapy

Early institution of antibiotics is the most important factor that predicts good outcome. Antibiotics are the mainstay of management , especially if abscesses are multiple and deep. The choice of antibiotics is initially empirical. A combination of penicillin 24 million units per day and chloramphenicol 0.5 g I.V. 6 h or penicillin/ 3rd generation cephalosporin and metronidazole 0.5 g I.V. 6 h has broad spectrum coverage and is sufficient as empirical therapy. Modifications should be made based upon the culture and sensitivity report. Antibiotic therapy should be continued for at least six weeks or even longer. Clinical improvement should be correlated with microbiological tests and repeat CT scans.

Anticerebral Edema Measures

Infusion of 200 ml of 20% mannitol rapidly over a period of 15 minutes helps to bring down the intracranial tension temporarily. Dexamethasone given in a dose of 4-8 mg I.V. 6h intravenously after instituting antibiotic therapy effectively lowers intracranial tension and cerebral edema.

Antiepileptic Drugs

Phenytoin and phenobarbitone are the usual medications and should be given after a loading dose. The drugs have to be given parenterally in the acute stage and later may be given orally. Prophylactic use of anti-epileptic drugs is however controversial.

Surgery

Surgical procedures include:

- 1. Aspiration of the pus with antibiotic instillation locally.
- 2. Excision of the abscess.

Decision regarding surgical intervention depends on the individual case. Indications for surgery can be diagnostic or therapeutic. Surgical procedures are prefer-

red in cases of post-traumatic, gas containing, multilobulated or fungal abscesses or if neurological status is deteriorating. Medical management is preferred:

- 1. In patients with multiple deep abscesses,
- 2. Location at important areas of the brain such as motor cortex or language areas,
- 3. Size less than 3cm and abscesses that shrink after antibiotics,
- 4. During the stage of early cerebritis, and
- 5. In cases of simultaneous meningitis or ependymitis.

In the case of rhinogenic or otogenic abscesses, the primary source should also receive proper attention in order to hasten recovery and prevent recurrence.

Prevention

Prompt treatment of infections such as mastoiditis, otitis media, sinusitis, dental sepsis and lung abscess helps to prevent the development of brain abscess. In subjects with congenital cyanotic heart disease, incidence and mortality due to brain abscess is high. Neurological manifestations in such patients may also be atypical. A high index of suspicion is required for early diagnosis in such patients.

Tuberculosis (TB) of the CNS

Tuberculosis (TB) of the CNS constitutes 10-15% of all cases of extrapulmonary TB. A general account of TB is given in Section: 6 Chapter: 49. Manifestation of tuberculosis in the nervous system includes:

- 1. Tuberculous meningitis.
- 2. Tuberculous arachnoiditis: optochiasmatic, basal, spinal.
- 3. Tuberculoma: Cerebral, spinal.
- 4. Tuberculous abscess.
- 5. Tuberculous encephalopathy.

Tuberculous meningitis (TBM) accounts for 70-80% of all the cases of CNS tuberculosis and is the commonest cause for chronic meningitis in India. It presents as subacute onset fever, headache and vomiting with signs of meningeal irritation of 2-6 weeks duration.

Table 188.4 gives the potential complications due to tuberculous meningitis.

TABLE 188.4
Complications of tuberculous meningitis
Raised intracranial tension
Cranial nerve palsies: 6th, 3rd or other cranial nerves
Hydrocephalus: Communicating and noncommunicating
Arteritis
Tuberculoma/tuberculous abscess
Spinal block
Syndrome of inappropriate antidiuretic hormone (SIADH)

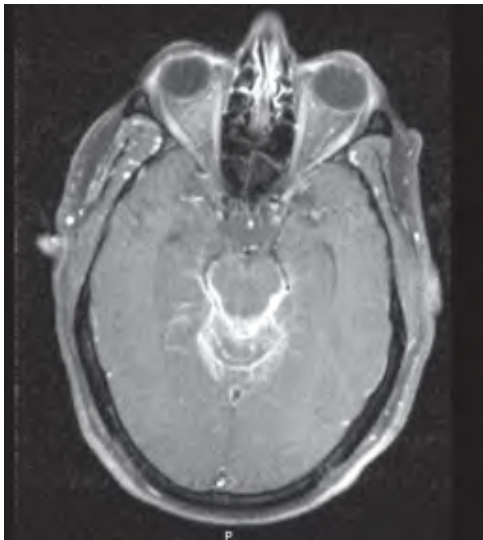


Fig. 188.2: Contrast enhanced MRI scan of a patient with TBM showing enhancement in the basal cisterns, suggestive of exudates

Diagnosis

The clinical diagnosis of TBM should be confirmed by CSF examination. X-ray chest may show evidence of concomitant pulmonary tuberculosis in 25-50% of adults and 50-90% of children. CT or MRI scan can demonstrate direct or indirect evidence for tuberculous meningitis such as contrast enhancement in the cisterns due to exudates. Figure 188.2 hydrocephalus, arteritis and tuberculomas.

CSF analysis is essential for diagnosis. Demonstrating acid-fast bacilli by microscopy and/or isolation by culture from CSF is the gold standard in the diagnosis of TBM. However, as TBM is a paucibacillary state, demonstration of *Mycobacterium tuberculosis* is often a challenge and hence several techniques have been developed to facilitate the diagnosis of TBM. Table 188.5 gives the CSF changes

TABLE 188.5

CSF findings in TBM

<i>Appearance:</i> Hazy or xanthochromic, presence of cob web formation
<i>Routine analysis:</i> Elevated protein, reduced sugar and lymphocytic pleocytosis
<i>Microbiological techniques:</i> Demonstration of acid-fast bacilli in CSF smears, isolation in solid media such as Lowenstein–Jensen medium
<i>Molecular technique:</i> Polymerase chain reaction (PCR) technique
<i>Immunological techniques:</i> Detection of mycobacterial antibodies, antigens, immune complexes
<i>Radiometric technique:</i> BACTEC technique
<i>Biochemical techniques:</i> Adenosine deaminase, detection of tuberculostearic acid by HPLC

and possible investigations in a suspected case of TBM.

Treatment involves using 3-4 first line antituberculosis medications for 9-18 months. Drug penetration into the CSF is maximal for INH, pyrazinamide, streptomycin and ethambutol. Corticosteroids play an important role by reducing inflammation, edema and fibrous tissue formation.

Viral Encephalitis

Encephalitis is most commonly due to viral etiology. Present epidemiological studies suggest that in India, herpes simplex and Japanese encephalitis are commonest, though other viruses such as rabies, mumps, West Nile, enterovirus, Kyasanur forest disease and Chandipura viruses are also responsible.

Herpes Simplex Encephalitis

HSV-1 encephalitis is the commonest cause for sporadic fatal encephalitis. HSV-1 is acquired by respiratory droplets or salivary contact. However in majority of cases, encephalitis is a consequence of reactivation and centripetal spread of latent virus in the trigeminal ganglion. Patients present with fever and headache along with behavioral changes, memory impairment, aphasia and focal neurological deficits. Subsequently, recurrent tonic clonic and complex partial seizures and altered sensorium dominate the picture. Diagnosis is established by CSF study that demonstrates lymphocytic pleocytosis, red blood cells, elevated protein content, normal or reduced glucose and detection of HSV DNA by PCR (sensitivity 95%, specificity 100% in first 2 weeks) or antibodies to HSV-1. EEG shows focal slowing or periodic lateralised epileptiform discharges (PLEDs). MRI

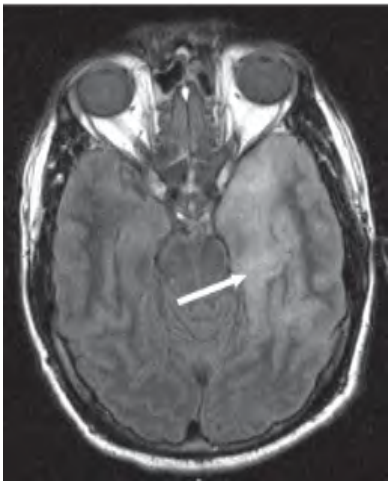


Fig. 188.3: MRI scan showing lesions in left temporal lobe in a patient with herpes simplex encephalitis—arrow

shows changes in mesial temporal lobe, insula and cingulate gyrus (Fig. 188.3).

Herpes simplex virus is the only viral encephalitis amenable to treatment and early treatment with acyclovir 10 mg/kg intravenously every 8 hours for 14 days reduces mortality from 70% to 20%. Vidarabine can also be given especially in cases of relapse (See Chapter 53).

Japanese Encephalitis (JE)

JE is the leading cause for epidemic encephalitis. Children are generally affected. Incubation period is 1-6 days after mosquito bite. Patients present with fever, headache, altered sensorium and recurrent seizures. Parkinsonism, dystonia or dyskinesias may develop during the illness or as sequelae. CSF shows lymphocytic pleocytosis, elevated protein content and IgM antibodies against JE virus. No specific therapy is available. MRI may show bilateral thalamic and basal ganglia changes. Eradication of vector and initiation of vaccination programmes can control the spread of JE. Ref: Section:6 for further details (See also Chapter 60).

Slow Virus Infections

Slow infections are persistent infections of the central nervous system where the infecting agent is capable of remaining dormant for long periods of time producing inflammatory or degenerative damage over several years. These are characterized by:

- a. Long period of latency lasting for several months to even years.
- b. Protracted course, usually ending in severe illness or death, and
- c. Limitation of the infection to a single host species and anatomical lesions in only a single organ system.

The following two groups are distinguishable according to the infecting agent:

1. **Slow infections by conventional viruses:** This group is caused by conventional viruses and is characterized by progressive encephalopathy following covert or overt infection by these viruses. These include subacute sclerosing panencephalitis (SSPE) caused by modified measles virus, progressive rubella panencephalitis (PRP) caused by rubella virus and progressive multifocal leukoencephalopathy caused by JC virus.
2. **Slow virus infections by unconventional viruses:** The second group, is caused by unconventional infective agents called prions, many of which may exhibit only a protein moiety of virus without the nucleic acid part.

TABLE 188.6	
Modified Jabbour's clinical staging of SSPE	
Stage 1	Cognitive deterioration, behavioural changes
Stage 2	Stereotyped, repetitive slow myoclonic jerks, choreathetosis, ataxia, seizures
Stage 3	Decerebration, decortication, autonomic instability
Stage 4	Bedridden, mute

SUBACUTE SCLEROSING PAN-ENCEPHALITIS (SSPE)

SSPE is a slowly progressive inflammatory disease caused by the modified measles virus. SSPE develops as sequelae to early measles infection, usually within the first two years of life, though the history of measles infection may be obtained in only one-half to two-thirds of SSPE patients. Occurrence of measles below one year of age is associated with higher risk of developing SSPE. Usual incubation period is 6-8 years following on overt clinical measles infection. Most frequent age group affected is 5-15 years. Clinical features are grouped into four stages (Table 188.6).

Patients may develop papilledema, optic atrophy and choreoretinitis. Progression of illness is subacute in 80% of patients and is fatal within 1-3 years. In 10%, the disease is fulminant and fatal within 3 months while in another 10%, it slowly evolves over 4-8 years. Diagnosis is essentially clinical and EEG shows typical periodic complexes characterized by repetitive discharges of high amplitude slow waves followed by spells of relatively flat patterns. CSF shows elevated protein concentration with normal sugar and cells. Raised anti-measles antibody titers by ELISA of 1:4 or greater in CSF is considered diagnostic. Treatment is generally unsatisfactory though isoprinosine and interferon have been tried. Implementation of universal measles vaccination will minimize the incidence of SSPE (See also Chapter 53).

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

PML is a subacute multifocal demyelinating disease caused by an opportunistic virus, J.C. virus or rarely SV40. Incidence is rising because of the HIV/AIDS pandemic. It may occur in association with any disorder that impairs cellular immunity such as lymphoproliferative disorders, sarcoidosis, prolonged immunosuppression and inherited immunodeficiency states. It is characterized by cortical blindness, cerebellar ataxia, motor weakness, confusion, amnesia, speech abnormalities and later dementia. Headache and seizures are rare. MRI establishes the diagnosis and shows multifocal confluent asymmetric

lesions of the parieto-occipital cerebellar and brainstem white matter without mass effect or contrast enhancement. The virus typically affects the oligodendroglial cells and pathologically there are multifocal areas of demyelination in the subcortical white matter. Routine CSF studies are normal but JC virus DNA may be detected using PCR technique. In patients of HIV/AIDS, lesions of PML improve with commencement of HAART. Cytarabine and Interferon- α have been tried.

SLOW INFECTION BY PRIONS

Transmissible spongiform encephalopathies refer to subacute, fatal, transmissible neurodegenerative disorders characterized by spongiform encephalopathy due to accumulation of abnormal proteins in the CNS. Stanley Prusiner (Nobel Prize laureate for medicine, 1997) proposed that the infective agent consisted only of a protein moiety without DNA or RNA and named it “prion” or proteinaceous infectious particle. Prion protein is a normally found protease sensitive cellular protein of unknown function encoded by the PRNP gene on chromosome 20. In prion disease, the normal cellular protein (PrP^C) is converted to an abnormal protease resistant isoform (PrP^{SC}) by a change in physical conformation. PrP^{SC} has a tendency to aggregate, leading to neuronal death. Four cardinal features of prions are:

- 1. At present prions are the only known infectious agents devoid of nucleic acid. All other known pathogens contain genomes containing either RNA or DNA which direct the synthesis of their progeny.
- 2. Prion disease may manifest as infections, genetic or sporadic disorders. This wide spectrum of pathogenesis is not possessed by other pathogens.
- 3. Prion diseases result from the accumulation of PrP^{SC} which has a substantially different conformation than PrP^C.
- 4. PrP^{SC} can have different conformations and depending upon this, the pathogenesis varies.

It is not known how a particular conformation of PrP^{SC} is produced, nor the factors which determine the localization in the CNS where PrP^{SC} gets deposited.

Prions are resistant to alcohol, formalin, ionizing radiations, proteases and nucleases which inactivate ordinary viruses. Prions are inactivated by methods which disrupt proteins such as autoclaving, exposure to detergents or extremes of pH changes.

Prions are resistant to the usual antiviral drugs. They do not evoke antibody response. The lesions caused by them are not inflammatory in nature.

For example, Kuru, Creutzfeldt-Jakob disease and others.

Though commonly presenting as a sporadic disease, prion diseases may manifest as a familial disease due to

TABLE 188.7

Prion diseases in humans
Creutzfeldt-Jakob Disease (CJD)
Kuru
Fatal familial insomnia (rare)
Gerstmann-Straussler-Scheinker disease (rare)

TABLE 188.8

Modes of transmission of CJD
Sporadic (90%)
Familial (10%): PRNP gene mutations
Iatrogenic: Neurosurgical procedures, dura mater grafts, cadaveric pituitary hormone extracts, corneal transplant
New variant CJD

various genetic mutations. Pathology is characterized by neuronal loss, gliosis and striking vacuolation or spongy state of affected areas (hence termed spongiform encephalopathy) with sparse inflammatory response. Table 188.7 gives the spectrum of human prion diseases.

Creutzfeldt-Jakob Disease (CJD)

Commonest of human prion diseases, it is a rare cause for dementia. Modes of transmission are enlisted in Table 188.8.

CJD presents with deficits in concentration, memory, problem solving abilities, inappropriate behaviour and visual hallucinations. Ultimately, patient progresses to global dementia. Initial neurological deficits include cerebellar ataxia and cortical blindness and with time, patients develop classical myoclonic jerks, extrapyramidal deficits, choreoathetosis and distal wasting and areflexia. Rarely, cerebellar ataxia (Brownell-Oppenheimer variant) or cortical blindness (Heidenhain variant) may precede cognitive and behavioral changes and may be the most prominent features. Diagnosis is facilitated by EEG, which shows periodic generalized sharp wave complexes and triphasic waves. CSF is usually normal, though protein concentration may be elevated. Immunoassay that detects a class of 14-3-3 proteinase inhibitor proteins released from damaged neurons into the CSF has sensitivity and specificity exceeding 90% and is available only at reference laboratories. MRI may show cerebral atrophy and symmetric lesions in bilateral basal ganglia. No specific treatment is known. Average time for survival is 4-6 months.

New Variant CJD (vCJD)

Recently, a CJD like illness has been reported in young individuals (mean age 28 years) characterized by psychiatric or sensory symptoms from Britain and other European countries. The illness progresses slowly and EEG changes are nonspecific. It has been associated with consumption of beef from cattle afflicted with bovine spongiform encephalopathy (mad cow disease). The source of infection of cattle in the UK is believed to be animal feeds produced from imported bones and animal carcasses from several countries. It is likely that the animal products would have been contaminated by human tissues as well. The diagnosis may be established by tonsillar biopsy. MRI shows thalamic lesions especially in the pulvinar. The epidemic has been controlled by removing infected cattle in large numbers and avoiding the consumption of beef from possibly infected

sources. Since the incubation period of vCJD may go up to several years it is likely that more cases may show up in future also.

Kuru

This disease was first described in the local tribal women and children of the island of Papua New Guinea. It is thought to be transmitted by ritualistic cannibalism practiced there and is clinically characterized by dysarthria, tremors, cerebellar ataxia, behavioural changes and dementia which ends fatally within 3 to 9 months. Pathologically, there is marked hypertrophy and proliferation of astroglial cells and status spongiosus (vacuolation of neurons) particularly affecting the cerebellum. There is no inflammatory reaction and no demonstrable antibody response.

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Dementias and Metabolic Encephalopathy

A.S. Girija, P.K. Mohan

Chapter Summary

- General Considerations 1237
- Alzheimer's Disease 1238
- Frontotemporal Dementia 1239
- Multi-infarct Dementia 1239
- Metabolic Encephalopathy 1239

General Considerations

Dementia is an acquired loss of cognitive (intellectual) functions due to an abnormal brain condition that leads to functional decline significantly interfering with work or usual normal activities. Three or more of the spheres of mental activity—namely, memory, language, visuo-spatial perception, praxis, calculation, semantic knowledge, executive function, personality and emotional expression are impaired. Failing memory and loss of other cognitive functions can result from multiple causes. In some the cognitive decline is progressive while in the others it is non-progressive. Dementia may be reversible or irreversible depending on its cause. Dementia may be the most prominent manifestation of many neurological diseases and it is rare to be the sole manifestation. Sometimes, depressed individuals appear to have cognitive impairment and slowed motor activity, but they

do not have true dementia. The term *pseudodementia* is used to denote such a condition. Patients with pseudodementia may not have symptoms of overt depression, but they have a flat affect and they tend to give up easily or fail to perform a task when their mental functions are being examined. They may exhibit changing patterns of mental deficits when subjected to repeated tests. This helps to differentiate pseudodementia from true dementia.

Delirium or acute confusional state has to be differentiated from dementia. Delirium can be distinguished from dementia by the following features:

1. Sudden onset
2. Altered consciousness
3. Disproportionately impaired attention and concentration
4. Fluctuations in cognitive function with lucid intervals
5. Psychomotor and autonomic overactivity, and
6. Hallucinations.

The Folstein's Mini Mental Status Examination (MMSE) is commonly used to screen for dementia and to grade the severity of dementia.

Causes of Dementia

1. Diseases where dementia is the only abnormality
 - a. Alzheimer's disease

- b. Pick's disease.
2. Diseases where dementia is associated with other neurological signs
 - a. Huntington's chorea
 - b. Leukodystrophy
 - c. Lipid storage diseases
 - d. Progressive myoclonic encephalopathy
 - e. Creutzfeldt-Jakob disease
 - f. Multiple cerebral infarctions (multi-infarct dementia) including cerebral vasculitis
 - g. Brain tumours
 - h. Subdural hematoma
 - i. Normal pressure hydrocephalus
 - j. Parkinsonism.
3. Diseases where dementia is a part of other systemic disorders
 - a. Hypothyroidism
 - b. Cushing's syndrome
 - c. Vitamin deficiencies (B_{12} , B_1 and B_6), Wernicke-Korsakoff's syndrome, pellagra and pernicious anemia
 - d. Neurosyphilis, neurotuberculosis, neurocysticercosis
 - e. Wilson's disease
 - f. AIDS
 - g. Chronic metabolic conditions—Chronic liver failure, renal failure, hyponatremia, hypercalcemia
 - h. Toxins—Lead, organic mercury and others.

A generalized reduction in the size of the brain occurs in old age and this may lead to mild senile dementia, which is known as *mild cognitive impairment*. In contrast, development of severe cortical atrophy in elderly age group (> 60 years) with progressive dementia is termed. Alzheimer's disease. Localized atrophy of the cerebral cortex with dementia, which may occur in the presenile age group (< 60 years) is known as frontotemporal dementia. Previously it was known as Pick's disease. Nearly 50% of dementias in the elderly is constituted by *Alzheimer's disease* and Frontotemporal dementia.

Alzheimer's Disease

This is one of the more common causes of dementia in adults. This usually occurs in the elderly. The onset of mental symptoms is so insidious that neither the family nor the patient can date its beginning. Day-to-day activities are forgotten and appointments not kept. The speech becomes discontinuous due to failure to recall the needed word. Simple calculations cannot be done. Visual-spatial disorientation soon sets in. The patient gets lost even along familiar routes. He forgets the use of common objects and tools. Later, social behaviour becomes changed. Stable marriages may be disrupted by sexual indiscretion. Difficulty in walking, with features of parkinsonism and

cerebellar ataxia appear. The legs may finally curl into paraplegia in flexion. Death occurs within a period of five or more years from the start.

Pathology

At autopsy the brain is atrophied. The atrophy is most prominent in the frontal and temporal lobes. Microscopically there are deposits of amorphous material scattered throughout the cerebral cortex, best seen by silver staining methods (senile plaques). Presence of fibre like strands of silver staining material in the form of loops and coils within the nerve cell cytoplasm (Alzheimer neurofibrillary tangles) and granulovacuolar degeneration of the neurons are the other remarkable pathological features. Extracellular amyloid fibrils consisting of 4-KD peptide, designated as beta amyloid protein (A4 protein) accumulate in cerebral and meningeal microvasculature. Other proteins involved in the plaques are presenilin 1 and 2, alpha-1 antichymotrypsin, apolipoprotein E(ApoE), alpha 2 macroglobulin and ubiquitin. Hyperphosphorylated tau protein and ubiquitin are found in the neurofibrillary tangles.

A subgroup of Alzheimer's disease has a genetic basis. Three to five percent of Alzheimer's dementia cases show autosomal dominant inheritance. Familial Alzheimer's disease shows abnormality in chromosome 21 and the gene for beta amyloid protein is situated on this chromosome. The gene for ApoE is situated on chromosome 19. ApoE can be used as a marker for Alzheimer's disease since it is absent in other dementias. Abnormalities in chromosomes 1 and 14 are also incriminated in familial, early onset Alzheimer's disease. The genes for presenilin 1 and 2 are located on these chromosomes respectively. The exact pathogenesis of the disease is not clear. It is possible that deficiency of choline acetyl transferase could be an important factor.

Role of viral and vascular causes have been suggested but not confirmed. Another mechanism recently implicated in the pathogenesis of Alzheimer's disease is dysregulation of apoptosis either by genetically determined processes or by subsequent mutation. This may result in premature degeneration of neurons with consequent dementia.

Investigations

These are aimed at identifying remediable causes. These include estimation of blood glucose, electrolytes, tests for hepatic and renal failure, thyroid function tests, serum levels of vit B_{12} , folate, homocysteine, antinuclear antibodies (ANAs), hexosaminidase levels and cortisol. HIV infection and neurosyphilis have to be excluded. Imaging studies such as MRI and PET and Doppler studies

to assess the extra- and intracranial circulation are indicated in cases of doubt.

Management

Tacrine was the earliest drug introduced for the treatment of Alzheimer's disease. It is an active noncompetitive inhibitor of acetylcholine esterase. Positive benefit occurs in 40% of cases. The drug is expensive and toxic. Main adverse effect is hepatotoxicity.

The less toxic anticholinesterase drug donepezil is effective, when given orally in doses of 5 mg daily for six weeks and followed up with 5 mg bid thereafter. This drug does not produce hepatotoxicity.

Other drugs include rivastigmine which can be given in all stages of the disease. It is an inhibitor of choline esterase action. It gives good symptomatic control of Alzheimer's disease. Galamine hydrobromide (galantamine) which acts on acetyl choline and nicotine receptors is beneficial in early cases.

Memantine-N-methyl D-aspartate (NMDA) receptor blocking agent is of use, in later stages, when given along with rivastigmine. NMDA is an excitotoxin.

Several other drugs such as dihydroergotamine mesylate, nicergoline and piraridil have been tried with varying results.

On account of the apparent increase in incidence of dementia in the aging population there is worldwide interest in the study of this disease and its management. Non-governmental organisations such as Alzheimer's societies are active in many parts of the world, including many towns in India.

Frontotemporal Dementia

Syn. Pick's lobar atrophy

Here the atrophy is limited to the frontal and temporal lobes with involvement of both grey and white matter. In contrast to Alzheimer's disease where the atrophy is diffuse and mild, here there is severe and localised brain atrophy. Clinically it is difficult to distinguish from Alzheimer's disease. However, focal disturbances appear to be more prominent in the former. The course of the illness is usually 2-5 years before the fatal outcome and there is no treatment except nursing care. Rarely the disease may show an autosomal dominant pattern. The proteins involved include ubiquitin and tau.

OTHER DEMENTING DISEASES

While Alzheimer's disease and fronto temporal dementia represent degenerative disorders where treatment is still unsatisfactory, there are other situations where reversible dementia occurs as a symptom of known diseases. These include hypothyroidism, brain tumour, subdural

hematoma, cryptococcosis, neurosyphilis, pellagra, other nutritional deficiencies, and normal pressure hydrocephalus. Specific neurological investigations like skull X-ray, EEG, CSF examination, CT scan and MRI can help to determine the particular disease.

MULTI-INFARCT DEMENTIA

This refers to impairment of intellectual functions due to multiple cerebral infarcts. In such cases, history of one or more strokes can usually be elicited. Multiple lacunae produce a picture of pseudobulbar palsy, slurred speech, dysphagia, and emotional lability. *Binswanger's disease* is a form of progressive arteriosclerosis with multiple lacunar infarcts that tend to be localized in the cerebral white matter and associated with dementia.

METABOLIC ENCEPHALOPATHY

Altered sensorium unassociated with any focal neurological deficit and a normal CSF is usually secondary to a metabolic disturbance.

General features of metabolic encephalopathy include:

1. Progressive deterioration of level of consciousness
2. Myoclonus
3. Flapping tremours in some types, eg. hepatic encephalopathy; and
4. Absence of any localizing signs.

Hypoxic Encephalopathy

This usually results from conditions producing asphyxia such as drowning, strangulation, aspiration into the respiratory tract, carbon monoxide poisoning, respiratory paralysis secondary to Guillain-Barré syndrome or poliomyelitis and shock states following myocardial infarction or cardiac arrest.

Mild degree of hypoxia causes inattentiveness, errors in judgement and confusion which are transitory. Prolonged and severe hypoxia lasting for more than 3 to 5 minutes produces serious and permanent injury to the brain resulting in coma. In such conditions presence of pupillary reflexes, intact Doll's head-eye movement and other brainstem reflexes generally indicate a favourable prognosis.

Doll's head-eye movement (oculocephalic reflex) is elicited by turning the head to either side, when the eyes are seen to deviate to the opposite direction. This sign is absent in conscious individuals. It becomes positive in the initial stages of coma, but it is lost as the coma deepens. However, when brainstem reflexes are absent with absence of spontaneous respiration, loss of Doll's eye movement suggests brain death. Absence of electrical activity in the EEG (flat EEG) supports the diagnosis. In less severe hypoxic damage,

the patient may recover from coma with some permanent neurological sequelae like dementia, extrapyramidal disturbances, choreoathetosis, ataxia and myoclonus.

The diagnosis of hypoxic brain damage depends on the clinical setting for hypoxia and arterial oxygen tension below 50 mmHg. The emergency treatment includes provision of a clear airway, cardiopulmonary resuscitation and oxygenation. Intravenous dexamethasone helps to reduce brain edema.

Hypoglycemic Encephalopathy

Abnormal lowering of blood sugar leads to confusion, stupor, convulsions or coma depending on the degree of hypoglycemia. Generally, when the blood sugar is 30 mg/dl confusional state sets in and when it is 10 mg/dl the patient becomes comatose.

Causes

1. Accidental overdose of insulin or a long-acting oral antidiabetic drug.
2. Insulin secreting tumours of the pancreas.
3. Alcoholic bouts.
4. Extensive malignant disease like fibrosarcoma.
5. Cerebral malaria, quinine therapy.

The effects of hypoglycemia manifest more slowly than those of hypoxia. Transient episodic behavior disturbances such as topographic memory loss or motor phenomena such as weakness or paralysis of limbs recurring at the same time can occur in diabetes treated with oral hypoglycemic drugs. These may be mistaken for transient ischemic attacks (TIAs)

As the condition progresses the medullary phase sets in. This is characterised by deep coma, shallow breathing and dilated pupils. Administration of glucose before the onset of the medullary phase results in complete reversal of the neurological lesions. However, once the medullary phase sets in, recovery may be delayed for months or may even be incomplete.

Hyperglycemic Encephalopathy

This may be either due to hyperglycemia with ketoacidosis or due to hyperosmolar non-ketotic state. In both conditions the patient becomes confused, stuporous, and comatose.

Convulsions may develop in some with non-ketotic hyperglycemia, resembling *epilepsia partialis continua*.

Hepatic Coma

Hepatic failure can lead to coma. Ammonia and toxic metabolic products which are formed in the bowel are carried in the portal circulation. They bypass the liver, not being further metabolized by the failing liver cells, and reach the cerebral circulation. This gives rise to neurological dysfunction (see Chapter: 85)

The onset of coma may be precipitated by high protein intake, hematemesis or electrolyte imbalance. It starts with mental confusion, increased psychomotor activity and progressive deterioration of the sensorium to end-up in deep coma. During the initial stage, the patient exhibits flapping tremors (*asterexis*) and this can be brought out when the hands are outstretched. Other signs of hepatic failure may be evident. The EEG reveals characteristic triphasic waves. Treatment consists of management of the hepatic failure. L-dopa has been found to improve the level of alertness in some cases. With improvement in hepatic function, the neurological syndrome also improves.

Uremic Encephalopathy

Both acute and chronic renal failure can result in confusion and stupor. This is usually due to rising blood levels of toxic nitrogenous products. Muscular twitchings, irregular muscular jerks and occasionally, convulsions predominate the clinical picture. The diagnosis can be established by the biochemical tests which reveal renal failure. The nature of the renal disease determines the prognosis. In chronic irreversible renal disease the condition does not improve without dialysis or renal transplantation. If convulsions occur, anticonvulsants should be given in small doses.

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General Considerations

An epileptic seizure is electrophysiologically characterized by abnormal transient and excessive electrical discharge of cerebral neurons and clinically characterized by paroxysmal episodes of loss or excess of motor, sensory, autonomic or psychic functions with or without alteration in consciousness. The abnormal electrical discharges (epileptic or seizure discharges) may involve only a small part of the brain or a much wider area in both cerebral hemispheres. The clinical manifestations of epilepsy correspond to the activation of the brain area(s) affected by the electrical discharges. This explains the wide diversity of clinical forms that a seizure might take. The term epilepsy denotes the peripheral events resulting from the abnormal electrical discharges from the brain, recurring on two or more occasions.

In other words seizure is a symptom and epilepsy is a syndrome. Though epilepsy begins first with a seizure, not all first seizures lead to epilepsy. Seizures may often occur in acute systemic conditions such as metabolic disturbances (hypoglycemia), drug toxicity (chloroquine) and drug withdrawal (diazepam) but usually they do not constitute epilepsy.

Prevalence

One in 20 persons in the general population would have had seizures at some point in their lives. One in 200 among the general population have epilepsy at any one period of time. A house to house study done on 25000 persons in Central Travancore gave the prevalence rate as 5/1,000 of persons (Radhakrishnan et al, Epilepsia 1999, 40;179-185). The International League Against Epilepsy gives the incidence as 50-100/100,000 population. Epilepsy is one among the common neurological abnormalities seen in general practice. Although eminently treatable in the majority of cases, in a minority it leads to poor long-term outcome with loss of employment and productivity, adverse psychosocial effects and poor quality of life. The family physician whom an epileptic patient first contacts has to suspect the diagnosis, initiate the appropriate treatment and arrange for further specialist advice.

ETIOLOGY OF EPILEPSY

In about 70% of cases of epilepsy, no cause can be determined even after extensive investigations (primary or idiopathic epilepsy). In the remaining group the etiology varies and is multifactorial depending upon the age of onset and the type of epilepsy. The causes include a large variety of genetically determined, congenital and acquired conditions. Among the acquired causes CNS infections (encephalitis, meningitis and brain abscess), cerebrovascular diseases (cerebral arteriovenous malformation, cerebral hemorrhage and infarction), perinatal hypoxic ischaemic cerebral damage, head trauma and brain tumours predominate. Drug induced seizures are common.

Most of the centrally acting drugs cause generalised convulsions following parenteral administration at high doses. Likewise, withdrawal of drugs like phenobarbitone, benzodiazepines and also alcohol may precipitate generalised convulsions. The onset of epilepsy due to hereditary, metabolic or genetic disorders like hypocalcemia and aminoaciduria is in childhood. Sturge-Weber syndrome and tuberous sclerosis usually lead to epilepsy in early life. Seizures in the first few days after birth are most commonly due to birth anoxia or neonatal intracerebral hemorrhage. Seizures in the first few weeks of life are due to CNS infections, hypocalcemia or other metabolic disturbances. Onset of seizures after the second week of life usually indicates developmental abnormalities of the brain. Epilepsy due to birth trauma manifests in childhood but occasionally the first attack may occur in adult life. Cerebral tumours, head trauma, neurotuberculomas, neurocysticercosis, cerebrovascular disease (overt or salient) and presenile dementia are the common causes of late onset epilepsy.

Simple partial seizures starting in adult life should suggest a newly developed focal structural lesion in the brain (e.g. tumour, tuberculoma or cysticercosis). Complex partial seizures are most frequently due to unilateral temporal lobe damage such as mesial temporal sclerosis or hamartomas. Typical absence seizures and generalised tonic-clonic seizures without aura are almost exclusively manifestations of primary generalised epilepsy. Atypical absence and atonic, tonic or clonic seizures usually occur in children with mental retardation and brain damage due to a variety of causes. Myoclonic seizures can be a manifestation of primary generalised epilepsy as well as several other symptomatic epilepsies.

PATHOGENESIS

The cortical neurons become abnormally excitable due to differentiation. The cytoplasm and cell membrane of such cells have increased permeability rendering them susceptible to activation by hyperthermia, hypoxia, hypoglycemia, and hyponatremia. Deficiency of the inhibitory neurotransmitter gamma-amino butyric acid (GABA) and disturbance of local regulation of extracellular K^+ , Na^+ , Ca^{2+} or Mg^{2+} are probably responsible for the membrane instability which leads to abnormal electrical discharge. Transition from normal to epileptiform behaviour of the brain is caused by greater spread and neuronal recruitment secondary to a combination of enhanced connectivity, enhanced excitatory transmission, failure of inhibitory mechanisms and changes in intrinsic neuronal properties. Generalized epilepsies are due to electrical activity occurring throughout the cerebral cortex, because of lowering of seizure threshold. Often this is genetically determined. If unchecked, this electrical discharge spreads to the ipsilateral and contralateral hemisphere across intra and

interhemispheric pathways and also to the subcortical structures like basal ganglia and brain stem reticular nuclei, from where the excitatory activity is fed back to the rest of the cortex.

MOLECULAR GENETICS OF EPILEPSY

Epilepsies have both a simple and complex inheritance pattern. Most idiopathic epilepsy syndromes have a complex inheritance. In these cases, more than one gene with or without the influence of acquired factors leads to a particular epilepsy syndrome. A number of syndromes with simple inheritance are also known. To site examples, benign familial neonatal convulsions is linked to 20q, the abnormal gene being KCNQ2. That for autosomal dominant nocturnal frontal lobe epilepsy is linked to 20q, the abnormal gene being CHRNA4. Juvenile myoclonic epilepsy is linked to 6p and 15q. The readers can refer to monographs on epilepsy for details.

Classification of Epilepsies

The classification of epilepsy has undergone several changes from time to time and it is likely that further changes may follow. To standardize the classification, the International League Against Epilepsy has suggested the following two classifications:

1. **Classification of epileptic seizures:** This is largely based on the seizure type and to a lesser extent on EEG findings. In this classification, seizures are divided into two main categories depending upon the location of the initial epileptic discharge in the brain, i.e. localized to a small area (partial seizures) or larger areas in both hemispheres (generalised seizures).
2. **Classifications of epilepsies and epileptic syndromes:** This is based on clinical manifestations, age of onset, genetic predisposition, associated neurological and other abnormalities, response to specific anti-epileptic drugs and overall prognosis.

Classification of Epileptic Seizures

Partial Seizures

- A. Simple partial seizures
 1. with motor manifestations
 2. with somatosensory or special sensory manifestations
 3. with autonomic manifestations
 4. with psychic manifestations.
- B. Complex partial seizures
 1. with simple partial features at onset followed by impairment of consciousness
 2. with impairment of consciousness at onset.
- C. Partial seizures evolving to secondarily generalised seizures
 1. simple partial seizure – generalised seizure

2. complex partial seizure – generalised seizure
3. simple partial seizure – complex partial seizure – generalised seizure.

Generalised Seizures

- A. Absence seizures
- B. Myoclonic seizures
- C. Clonic seizures
- D. Tonic seizures
- E. Tonic-clonic seizures
- F. Atonic seizures

Unclassified Seizures

CLASSIFICATION OF EPILEPSIES AND EPILEPTIC SYNDROMES

1. Localization related (focal, local, partial) epilepsies and syndromes

- 1.1 Idiopathic with age related onset
 - Benign childhood epilepsy with centrottemporal spikes
 - Childhood epilepsy with occipital paroxysms
 - Primary reading epilepsy.
- 1.2 Symptomatic
 - Chronic progressive epilepsia partialis continua of childhood
 - Syndromes characterized by seizures with specific mode of precipitation
 - Temporal lobe epilepsies
 - Frontal lobe epilepsies
 - Parietal lobe epilepsies
 - Occipital lobe epilepsies
- 1.3 Cryptogenic.

2. Generalised epilepsies and syndromes

- 2.1 Idiopathic with age related onset
 - Benign neonatal familial convulsions
 - Benign myoclonic epilepsy of infancy
 - Childhood absence epilepsy (pyknolepsy)
 - Juvenile absence epilepsy
 - Juvenile myoclonic epilepsy (impulsive petit mal)
 - Epilepsy with grand mal seizures on awakening
 - Other generalised idiopathic epilepsies not defined above
 - Epilepsies with seizures precipitated by specific modes of activation.
- 2.2 Cryptogenic
 - West syndrome (infantile spasms, Salam seizures)
 - Lennox-Gastaut syndrome
 - Epilepsy with myoclonic/astatic seizures
 - Epilepsy with myoclonic absences.
- 2.3 Symptomatic
 - 2.3.1 Nonspecific etiology

Early myoclonic encephalopathy
 Early infantile epileptic encephalopathy with suppression burst
 Other symptomatic generalised epilepsies.

2.3.2 Specific syndromes
 Epilepsies, which form part of the clinical profile of certain neurological disorders.

3. Epilepsies and syndromes, undetermined whether focal or generalised

- 3.1 With both generalised and focal seizures
 - Neonatal seizures
 - Severe myoclonic epilepsy of infancy
 - Epilepsy with continuous spike and wave during slow wave sleep
 - Acquired epileptic aphasia
 - Other undetermined epilepsies not included above.

4. Special syndromes

- 4.1 Situation related seizures
 - Febrile convulsions
 - Isolated seizures or status epilepticus
 - Seizures occurring only when there is an acute metabolic or toxic event caused by factors such as alcohol, drugs, eclampsia and nonketotic hyperglycemia.

PARTIAL SEIZURES

Partial seizures or focal seizures are due to a small epileptic focus in the brain. They are divided into two main categories.

- a. simple partial seizure in which the seizure starts as a focal discharge and remains focal throughout without alteration of consciousness and
- b. complex partial seizure when a seizure starts as a focal discharge, but consciousness is also altered or lost.

Simple Partial Seizures

These seizures may have motor, sensory, autonomic or psychic manifestations.

Simple focal or partial motor seizures are due to a discharging epileptic focus in the opposite frontal lobe (motor cortex). These consist of clonic movements of the hand, foot or angle of mouth or turning of the head or eyes. These movements may constitute the entire motor component of the seizure or may be followed by generalised clonic movements and loss of consciousness. The term jacksonian motor seizures (Jacksonian epilepsy) is applied to the type where clonic contractions start in the fingers of one hand, one side of the face or the foot and slowly spread (march) to the other muscles on the same side of the body. This may or may not be followed

by involvement of the opposite side and loss of consciousness. The presence of the characteristic march distinguishes Jacksonian seizures from partial motor seizures. However, both have the same localizing significance.

Complex Partial Seizures (Psychomotor Epilepsy)

These are defined as focal or partial seizures in which consciousness is impaired or lost. They are frequently due to epileptic discharges in the temporal or frontal lobes. Less commonly they may arise from discharges in other parts of the brain. This forms the single most common type of seizure in adults. The seizure usually consists of complex hallucination of perceptual illusions, indicating its origin from the temporal lobe. The hallucinations are usually auditory and visual but sometimes they may be olfactory or gustatory. The subjects may show increased familiarity (*déjà vu*) or unfamiliarity (*jamais vu*) with the surroundings. In some cases these subjective experiences may constitute the entire seizure. Often this is followed by a period of unresponsiveness, during which the patient exhibits certain automatic behaviour like smacking of the lips or chewing movements (automatism). The patient may walk about or repeat a habitual act. However, when asked a question the unresponsiveness becomes evident. Sometimes unprovoked aggression or laughter may be the striking feature. The automatism usually lasts for a few minutes, but may sometimes be prolonged. The patient is totally amnesic for the whole period of automatism. The EEG recorded during sleep or hyperventilation may demonstrate the temporal lobe focus. Rarely, other areas of brain like the orbital surface of the frontal lobe or limbic system may be seat of epileptic discharge.

Partial Seizures Evolving to Secondarily Generalised Seizures

In many cases the generalised seizures are not generalised from their onset. They start as partial seizures, either simple or complex and then soon spread to become generalised, usually as tonic-clonic convulsions. These are called partial seizures becoming secondarily generalised. In such cases the initial manifestations of partial seizures are called “aura” or warning symptoms.

invariably impaired or lost at the onset of the attack. Generalised seizures are divided into several clinical types and some patients may suffer from more than one seizure type. Atypical seizure patterns may also occur, especially if the patient is on treatment.

Tonic Clonic Seizures

These are also called grand mal epilepsy.

The seizure attack occurs in different stages sequentially. The stages may be subdivided into the prodromal phase, tonic phase, clonic phase and the postictal phase. The prodromal phase may start several hours before the ictus (fit). It consists of several subjective phenomena like depressed or apathetic mood, irritability, vague abdominal cramps or other funny sensations, which are easily recognised by the patient. In many instances there is no aura and the patient gets the attack without any forewarning. Presence of aura suggests the nature of the seizure as of focal onset (i.e.) partial seizure.

The tonic phase consists of rolling up of the eyes associated with stiffening of the limbs followed by clenching of the jaws, often resulting in injury to the tongue. The attack may be heralded by an epileptic cry as the entire musculature goes into spasm forcing air through the closed vocal cords. The patient becomes cyanosed due to spasm of respiratory muscles. This phase lasts for about 10 to 30 seconds.

The tonic phase is followed by clonic phase characterised by alternate flexion-extension movements of all the four limbs (convulsions), strenuous breathing, sweating, frothing of the mouth and excess salivation. Urine and feces may be voided. The clonic phase usually lasts for 1-2 minutes. This is followed by a deep comatose state, which lasts for about 5 minutes. The pupils slowly begin to react and the patient then resumes speech, but still remains confused. If left undisturbed, he goes into sleep for several hours and often wakes up with severe headache and at times, vomiting. This is the post-ictal phase and the patient does not remember anything that had happened.

Electroencephalogram (EEG) taken during the attack or sometimes even during the intervals shows generalised seizure discharges. The EEG is often normal in the interictal period.

Absence Seizures (Petit Mal)

These are seen mostly in children. These are distinguished by brevity and absence of motor phenomena. The child does not fall. The attacks come on without any warning and consciousness is impaired only for a brief period often < 10 seconds. The child abruptly stops all ongoing motor activity and speech. There is a vacant stare. External

Primary Generalised Seizures

These are seizures in which there is no evidence of an epileptic focus, either clinically or on EEG, as opposed to secondary generalised seizures. The epileptic discharge involves both cerebral hemispheres simultaneously from the onset of the seizures. Hence, consciousness is almost

stimuli fail to evoke any response from the patient at that period. These attacks usually last for 2-10 sec after which the patient resumes the pre-seizure activity. At times there may be clonic movements of the eyelids or occasionally automatisms like smacking of lips or chewing movements. The attacks can be precipitated by hyperventilation. The attacks occur several times during the day, but they become less frequent or may even disappear in adolescence. Sometimes these may be replaced by tonic-clonic seizures.

The EEG abnormality in petit mal epilepsy is diagnostic. It shows classic “three per second” spike and wave generalised discharges.

Juvenile Myoclonic Epilepsy (Myoclonic Jerks)

This term refers to brisk, brief contractions of one or several muscle groups or a single muscle. The movements are jerky, generally abrupt and uncontrollable and render the patient momentarily helpless. The attacks may occur as a single jerk or may recur every few seconds. Recovery from the attacks is immediate and the subject does not lose consciousness.

Juvenile myoclonic epilepsy (JME) starts in early adolescence. Myoclonic jerks occur with or without generalized tonic-clonic seizures. Attacks occur early in the morning on waking up. A small proportion of childhood absence seizures may evolve into JME. Often the myoclonus may be missed or misinterpreted as seizure activity. It is important to make a proper diagnosis since anti-epilepsy drugs such as phenytoin and carbamazepine may worsen the myoclonus.

Myoclonic jerks are not always ‘epileptic in origin, and may occur in many other non-epileptic neurological conditions. The abnormal electrical discharges may arise from the cerebral cortex, brainstem or spinal cord. Myoclonus may be associated with other forms of epilepsy like absences or generalised tonic-clonic seizures. Myoclonus is seen in a variety of conditions. All types of metabolic encephalopathies like hepatic failure, renal failure, electrolyte disturbances and others may lead to myoclonus. It is an important feature of progressive myoclonic encephalopathy. At times it is precipitated by light, sound and touch stimuli.

Atonic Seizures

These are less common generalised seizures characterised by sudden loss of postural tone and consciousness without any other motor phenomena. This may lead to sudden “drop” of the individual to the floor without any warning. Atonic seizures have to be distinguished from cataplexy in which the drop attacks are not accompanied by loss of consciousness and syncope.

Common Epileptic Syndromes

INFANTILE SPASMS

Syn: Salaam spasm (hypsarrhythmia):

This condition is seen in infants below 1 year of age. This is characterized by brief sudden jerky flexion or less commonly extension movements of both arms, neck and torso. Usually these jerks or spasms occur in clusters, precipitated by sudden noise or tactile stimulus and may occur several times in a day. Usually there is evidence of other neurological disorders, secondary cerebral anoxia or birth injury. As the infant grows, the frequency of the spasms comes down but other forms of seizures may supervene. The characteristic EEG pattern is called hypsarrhythmia.

LENNOX-GASTAUT SYNDROME

This is an epileptic syndrome with onset between 1 and 6 years of age. It is characterised by mental retardation, and intractable seizures with mixture of tonic, atonic, tonic-clonic and atypical absence seizures. EEG shows diffuse slow and spike wave disturbances. The syndrome may occur without any definite cause or may be associated with a variety of neurodevelopmental or metabolic abnormalities in which case the prognosis is poor.

BENIGN ROLANDIC EPILEPSY

This is a common form of partial epilepsy in childhood with onset between 3 and 11 years. It is characterised by attacks of hemifacial twitches sometimes with involuntary vocalizations which may progress to a generalised or unilateral convulsion. These seizures usually or exclusively occur in sleep. The family history suggestive of autosomal dominant inheritance may be available. The EEG abnormality is highly characteristic showing frequent spike discharge in the rolandic area, especially during non-REM sleep. The prognosis is excellent as it is not associated with any other neurological, psychiatric or behavioural disorder and the seizures respond well to anticonvulsant drugs. In some they may remit spontaneously around puberty.

Febrile Convulsions

A febrile convulsion may be defined as a brief generalised convulsion occurring during fever in a child in the age group of 6 months to 5 years without pre-existing or concurrent neurological abnormalities or intracranial infection. About 70% of febrile convulsions occur in the age of 6 to 18 months. The convulsions usually last for a few seconds but may extend upto 15 min. At least 5% of children have one febrile fit before the age of 5 years and nearly 25-50% of them have recurrent attacks, but the risk

progressively diminishes with age. A strong family history of febrile fits is evident in many cases. The fits usually occur when the rectal temperature rises above 39°C.

Generally, the body temperature normalises after the fit. About 4 to 20% cases may develop convulsions even without noticeable fever. Though the risk of developing chronic epilepsy in such children is only about 2%, it is however higher than in the general population. The risk of developing epilepsy in later life is higher in the following groups:

1. When the first febrile convulsion is complicated, i.e. prolonged (> 30 minutes) or localised or is followed by multiple seizures in 24 hours.
2. Presence of neurological abnormalities before or after the onset of convulsion.

In general, the intellectual performance of children who had febrile convulsions does not differ from normals but prolonged or recurrent frequent febrile convulsions lead to brain damage and medial temporal sclerosis, which in later life, causes epilepsy.

Management: An acute attack can be controlled by diazepam in a dose of 0.08-0.3 mg/kg body weight given intravenously. Rectal administration is equally effective. Intramuscular administration should be avoided since absorption is erratic.

The temperature should be brought down by the administration of paracetamol in a dose of 30 mg/kg body weight and tepid sponging.

Further convulsions can be prevented by the administration of phenobarbitone in a dose of 15 mg/kg given intramuscularly or 30 mg orally repeated 6 hourly. In children below the age of 18 months, since fever and convulsions may be a presenting feature of meningitis, lumbar puncture is indicated, so also in children showing prolonged or lateralized seizures. Prophylactic administration of oral diazepam 0.25mg/kg/day or clobazam 5-10mg oral is useful in preventing fits. Clobazam is contraindicated in children below 3 years of age.

Prolonged prophylaxis is indicated for children who show:

1. Complicated and prolonged convulsions or focal seizures.
2. Frequent recurrence.
3. Abnormal birth history or neurodevelopmental abnormalities.
4. Onset before 6 months or after 4 years of age.
5. Presence of inter-ictal EEG abnormality.

Sodium valproate given in doses of 20 mg/kg/day oral is a good and safe prophylactic for prolonged use.

Progressive Myoclonic Epilepsies (PME)

These are rare, distinctive epileptic disorders with myoclonic seizures, tonic-clonic seizures and progressive

neurologic dysfunction, particularly ataxia and dementia. Myoclonic seizures are described as sudden, brief, lightning like jerks that may be generalised or limited to one or more muscle groups. They are not associated with loss of consciousness and are frequently precipitated by stimuli such as movement, bright light or stress. Physiological myoclonus may occur in many normal persons during sleep or in other disease states. This has to be distinguished from PME. A heterogeneous group of disorders may give rise to PME.

- a. **Biochemical disorders:** Unverricht-Lundborg disease, Lafora body disease, neuronal ceroid lipofuscinosis, sialidosis, mitochondrial encephalomyopathy, non-infantile neuronopathic Gaucher's disease, and others.
- b. **Clinically defined groups:** May give rise to seizures West's syndrome, Ramsay-Hunt syndrome (dyssynergia cerebellaris myoclonica), and others.

Diagnosis of these groups of disorders depends on the clinical patterns, characteristic fundal changes and biopsy studies of the skin, skeletal muscle, liver, rectal mucosa or brain. Study of these diseases is the realm of the specialist. Management consists of accurate diagnosis, genetic counselling and control of myoclonus by sodium valproate or clonazepam.

REFLEX EPILEPSY

Epilepsy precipitated by external stimuli has been designated as reflex epilepsy. The common stimuli which precipitate reflex epilepsy in susceptible people are hot water bath of the head, photic stimulation such as flickering light and TV watching, exposure to sunlight, reading, hearing music, startle and eating. Avoidance of precipitating factors and prophylactic anticonvulsants serve to prevent the attacks.

Epilepsy and Pregnancy

One-fourth to one-third of pregnant women with epilepsy get aggravation of seizure tendency during pregnancy. Status epilepticus may complicate 1-2% of epileptics who are in labor. Since drug levels of antiepileptic drugs are lower in many pregnant women, it is better to monitor free drug levels every month during pregnancy. Risks of AED during pregnancy include the following;

First trimester of pregnancy—congenital malformation in child—12.3%.

Status epilepticus: generalized convulsions during labour:

- Risk of hypoxia and acidosis for mother and fetus is high.
- Increased rate of neonatal hypoxia, low APGAR scores in the baby.

Pregnant women with epilepsy have higher risks of hyperemesis gravidarum, pre-eclampsia, abruptio placentae and premature labour. Serum AED levels rise after delivery and therefore monitoring is required.

Complication in the Offspring

These include fetal congenital malformations and developmental delay. Teratogenicity has been established for valproate, carbamazepine, phenytoin and phenobarbitone. Minor congenital malformations occur in 6-20% and major abnormalities occur in 4-6% of infants exposed to these drugs in utero, compared to 3% in babies of epileptic mothers not exposed to drugs.

Major malformations are particularly seen in babies exposed to phenytoin and phenobarbitone. These include cleft lip, cleft palate and congenital heart disease. Neural tube defects increase from a general rate of 0.2% to 1-2% in pregnancies exposed to valproate and carbamazepine. Administration of 5 mg folate daily early in pregnancy may reduce this risk. Perinatal death rates of the baby may rise from 1-3.9% in controls to 1.3-7.8% in the case of epileptic mothers. Low birth weight (7-10%) and prematurity (4-11%) may occur. Risk of epilepsy is higher in children of parents with epilepsy, especially so if the mother is epileptic. Mental retardation is more frequent in children of epileptic parents—8% if only mother is affected, 4% if only father is affected and 25% if both are affected.

Management of Women with Epilepsy

1. Pre-conception counselling.
2. Lamotrigine may be less teratogenic and hence it should be preferred.
3. Monitoring of serum alfa-fetoprotein (AFP) in the mother for neural tube defects.
4. USG examination with vaginal probe for demonstration of neural tube defects – Ultrasonography at 18 weeks should be able to detect most of the abnormalities. Serum level of anti-epileptic drugs (AED) may be monitored.
5. AEDs may impair the metabolism of vitamin K and lead to bleeding tendencies Oral supplementation of vitamin K 20 mg/day through out pregnancy reduces this risk. The baby should be given vitamin K 1-2 mg IM at birth.
6. Delivery: Elective lower segment cesarean delivery is done in those with risk of status epilepticus. If seizures occur lorazepam is the drug of choice. Pethidine should be avoided since it can exacerbate seizures.
7. Concurrent administration of oral contraceptives leads to lowering of serum levels of anti-epileptic drug and precipitate seizures.

Menopause: Usually the seizure tendency subsides, but hormone replacement therapy increases seizure tendency.

Diagnosis

Diagnosis of epilepsy is essentially clinical. History is most important in making the diagnosis. Careful interrogation of witnesses of an attack is essential to

determine the nature of the diagnosis. Epilepsy should be differentiated from simple faint and syncopal attacks. The epileptic attack can occur during day or night regardless of the position of the patient. Syncopal attacks usually do not occur in the recumbent posture. Also the occurrence of pallor at the onset, gradual loss of consciousness and prompt return of consciousness on adopting recumbent posture are diagnostic of syncope. In epilepsy loss of consciousness is abrupt and consciousness returns only slowly. Occurrence of post-ictal headache and vomiting should suggest the possibility of epilepsy. So also, occurrence of seizure during deep sleep is a strong point in favour of epilepsy. Occurrence of injuries such as biting the tongue or due to falls should suggest seizure disorder since these are practically absent in hysterical convulsions.

Hysterical attacks should be differentiated by the lack of aura, absence of injuries and incontinence, presence of peculiar grimacing or squirming movements and the retention of consciousness during a motor seizure, which involves both sides of the body. Moreover hysterical convulsions are bizarre and they continue for long periods, as long as the patient is being observed.

Diagnosis of the type of epilepsy depends upon the description of the attack and clinical examination. The epileptic focus and pattern of epilepsy are determined by investigations.

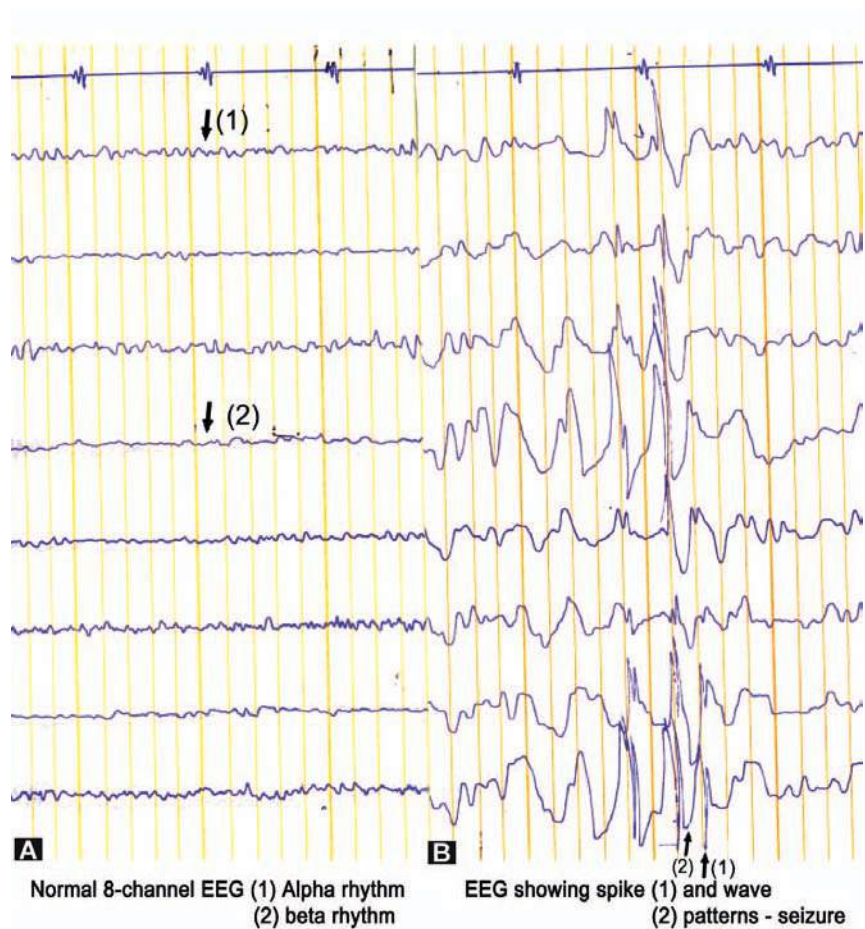
The electroencephalogram (EEG) is the most useful investigation to establish the diagnosis of epilepsy. The EEG gives positive records in 60-90% of cases, if the records are repeated during or after an attack and after 24 hours of sleep deprivation. Refinements in EEG procedure include the use of special electrodes such as sphenoidal, nasoethmoidal, nasopharyngeal and in selected cases, intracerebral electrodes. Photoc stimulation, sleep and hyperventilation are measures used to elicit abnormalities in the EEG (Figs 190.1A and B).

However, normal EEG does not exclude the diagnosis of epilepsy. Conversely, a small number of normal persons may show paroxysmal EEG abnormalities. Thus EEG can be used only as an additional evidence to the clinical diagnosis of epilepsy. So, also its role in predicting remission or selection of antiepileptic drugs is also limited. But in confirmed epileptics with EEG abnormalities, the decision to stop drug therapy can be based on the persistence of the abnormality.

In epilepsy occurring for the first time after 20 years of age, partial epilepsy, presence of focal neurological deficit and in those where the disease is resistant to conventional treatment, further investigations to exclude anatomical abnormalities and space occupying lesions in the brain are indicated. These include CT and MRI scans of brain.

PROGNOSIS

Over 60% of patients attain remission, which is defined as freedom from seizures for 2-5 years after stopping their



Figs 190.1A and B: Normal EEG and EEG in seizure

antiepileptic treatment. About a third do not achieve this state.

Chances for achieving remission are greater within the first few years after diagnosis and treatment. In those in whom remission does not occur within 1-2 years of starting therapy the chances of remission are low and these patients may require life- long anticonvulsant therapy. As a practical guide to long-term management, epileptics can be categorised into four groups.

- 17
1. Mild cases which may even be self-limiting or remit after short course of treatment—30%.
 2. Easily controlled with drugs and go into remission early—30%
 3. Chronic epilepsy which responds partially to drugs but relapses on withdrawal of the drugs—20%
 4. Response to drugs is unsatisfactory and remission is unusual (intractable)—20%

Factor which predict recurrence of seizures after the first attack

If risk factors are present, recurrence is more likely. In those with more than 2 risk factors the chance of recurrence is about 100%.

Risk Factors

1. Prior neurological insult
2. Partial seizure
3. abnormal EEG
4. Todd's paralysis, family history of epilepsy, seizure occurring during sleep and absence of precipitating factors.

Various rating systems are available to quantitate intractable seizures but as practical guide those that have one or more seizures per month despite regular, adequate and appropriate treatment may be considered as intractable seizures.

Epilepsy and its treatment can have deleterious cognitive and behavioral consequences. Affected individuals have a higher prevalence of neuropsychological dysfunction compared to the non-epileptic population. **Convulsive status is consistently associated with neuronal necrosis in vulnerable parts of the brain, especially the hippocampus, amygdala, cerebellar cortex, thalami and cerebral cortex.**

Sudden death in epilepsy is due to trauma, aspiration, continued status leading to hyperthermia, aspiration

pneumonia and cardiac asystole. Symptomatic epilepsy reduces life expectancy by 18 years.

MANAGEMENT OF EPILEPSY

This consists of (i) treatment of the acute convulsions, and (ii) prophylactic management of convulsive and non-convulsive seizures.

The latter consists of :

1. Removal of precipitating or causative factors.
2. Antiepileptic medication.
3. Social rehabilitation.

Management of an Acute Convulsion

Convulsion is a medical emergency especially if prolonged, which should be arrested without delay. The patient is put on a soft bed to avoid injuries, tight clothing is loosened and the airway is protected so as to avoid asphyxiation and aspiration. Dentures and foreign bodies in the mouth should be removed and a suitable mouth gag is applied in the position of the molar teeth, to keep the mouth open and prevent injury to the tongue. The patient should be kept with head low, so as to avoid aspiration of vomitus into the respiratory tract.

Most convulsions are self-limited and need no immediate treatment. However, prolonged or recurring convulsion should be controlled by slow intravenous injection of 5-10 mg or more of diazepam. An alternate anticonvulsant drug is lorazepam 4 mg IV given slowly over 5-10 minutes. Other drug that must be given parenterally is phenytoin sodium 100-200 mg IV. This helps to prevent recurrence as well.

The physician may encounter the patient with convulsions in the most embarrassing situations, and therefore, the first injection of anticonvulsant medication may have to be given IV in order to terminate the convulsion forthwith, fully realising the risk involved. Adverse drug effects include anaphylaxis, respiratory depression, hypotension and allergic manifestations.

Once the convulsions are controlled, further management has to be carefully planned.

Failure to arrest the convulsions leads to asphyxia, severe exhaustion, hyperpyrexia, electrolyte imbalance, further cerebral damage and death.

All cases of convulsions should be investigated for the presence of primary or secondary neurological conditions giving rise to symptomatic seizure. Conditions like meningitis, encephalitis, neurosyphilis, neurocysticercosis, fluid and electrolyte imbalance, hypocalcemia, abnormal glucose levels and intracranial space occupying lesions have to be excluded.

Prophylactic Management

Antiepileptic Drugs

Treatment of epilepsy is primarily medical and the mainstay is the use of anti-epileptic drugs (AEDs). Though AEDs are not curative in epilepsy, they help to control seizures and give symptomatic relief. In many instances prolonged administration results in abolition of the epileptic tendency. The response varies in the different types of seizures and hence it is necessary to administer the appropriate AED in optimum dosage. *The present consensus is to start with a single drug and add others later on, only when absolutely necessary. The first line AEDs are the time tested drugs such as phenytoin, phenobarbitone, primidone, carbamazepine, ethosuximide, sodium valproate, and clonazepam.* At present oxcarbazepine, topiramate and lamotrigine are also increasingly used as first line drugs (Table 190.1).

If the response to a single drug is not adequate, another drug should be added. In some the combination produces better effect. A stable drug regimen should not, however, be frequently changed. Sudden withdrawal of AED should be avoided since this is the most common cause for precipitation of status epilepticus.

Indications for starting antiepileptic therapy: When more than one unprovoked seizure has occurred in the preceding one to two years or when the risk of recurrent convulsion is high as in head injury or intracranial infections. AEDs should be started. Since the medication has to be prolonged and the drugs are potentially toxic and expensive, patients with single attack without demonstrable focal abnormalities either clinically or on investigations such as EEG, CT or MRI, the patient should be observed and therapy started only if seizures recur.

Guidelines for AED Therapy

1. Start with a single drug and adjust its dosage to achieve maximal clinical benefit without side effects.
2. If seizures occur even after achieving tolerable dose of the single drug a second drug should be introduced and the first one slowly withdrawn.
3. Different combinations of two drugs may be tried, each trial lasting for a maximum of six months, till the ideal combination is arrived at. There is no role for combining more than two drugs.
4. ***Therapy should continue till at least a 3-year seizure-free period*** is completed after which the drugs can be gradually withdrawn. Nearly 50% of the patients may not require any further treatment. The rest may relapse and this usually occurs within five years. Children who develop primary epilepsy in early life and who show prompt response to AED have greater chance for permanent remission.

TABLE 190.1

Details of the commonly used anticonvulsant-drugs				
Name of the drugs	Children dose	Adult dose	Toxic effects	Serum half-life in hours
Phenobarbitone (Luminal)	3-5 mg/kg	60-200 mg	Sedation, cognitive decline, ataxia	96 ± 12
Phenytoin (Dilantin)	4-7 mg/kg	300-400 mg	Gingival hypertrophy, ataxia, chorea, dyskinesia lymphadenopathy peripheral (Fig. 190.2) neuropathy, anemia hirsutism	24 ± 12
Carbamazepine (Tegretol)	20-30 mg/kg	600-1200 mg	Diplopia, giddiness, Stevens-Johnson syndrome hyponatremia, weight gain	12 ± 3
Oxcarbazepine	20-30 mg/kg	600-2400 mg	Oxcarbazepine is less toxic, toxicity similar	12 ± 3
Ethosuximide (zarontin)	20-30 mg/kg	750-1500 mg	Hepatotoxicity, blood dyscrasias, nephrotoxicity	30 ± 6
Valproic acid (sodium-valproate)	30-60 mg/kg	1000-3000 mg	Transient hair loss, tremors, obesity, thrombocytopenia	8 ± 2
Clonazepam	0.01-0.3 mg/kg	1.5-20 mg	Ataxia, sedation, lethargy	18-50



Fig. 190.2: Dilantin induced pseudolymphoma

5. Twenty-five percent of cases may develop chronic epilepsy and require life-long medication. Risk of chronicity is high in patients with neurological and psychological abnormalities and social handicaps. Partial seizures are more refractory to medical treatment in upto 20% of cases. These may require surgery. When confronted with intractable seizures, newer drugs should be considered. Before doing so it is wise to verify the following:
1. Is the diagnosis correct.
 2. Is the epilepsy secondary to other disease processes.
 3. Are the appropriate drugs taken regularly and in full doses.
 4. Are there any adverse psychosocial factors.

Newer Antiepileptic Drugs

Several newer antiepileptic drugs are on the anvil. Many of these are now freely available in India. At present, these newer drugs are recommended as add-on drugs along with conventional drugs, to treat intractable cases, although some of them are found effective as initial monotherapy.

Vigabatrin: Gamma vinyl GABA (GVG): This drug irreversibly inhibits GABA aminotransferase.

Dose: 50-100 mg/kg/day.

Indications: Complex partial seizures with secondary generalisation, infantile spasms. Adverse effects are mild. These include defects in the visual fields, sedation and behavioural disturbances.

Zonisamide: This is a benzisoxazole derivative.

Dose: 6-10 mg/kg/day. The initial dose is 100 mg/day.

Indications: Partial seizures with secondary generalisation, primary generalised tonic-clonic, atonic and myoclonic seizures. Adverse effects include feverishness, ataxia, leucopenia and urinary calculi.

Oxcarbazepine: This is chemically related to carbamazepine. Its action is similar to carbamazepine but this drug is better tolerated. Ataxia is the main adverse effect.

Dose: 1200-2400 mg/day.

Gabapentin(Neurontin): This is a GABA-related amino acid with broad spectrum anti-epileptic activity.

Dose: The initial daily dose is 300 mg increased to 600 to 1300 mg over a few days. Even doses as high as 3600 mg/day are safe. This drug is well tolerated and the full dose can be attained within 3-4 days. It can be safely

TABLE 190.2

Details of newer AEDS				
Drug	Indications	Daily dose mg	Benefits	Toxicity
Oxcarbamazepine	Partial and partial complex seizures	600-2400	Drug interactions	Ataxia, hyponatremia
Vigabatrin	do + secondary generalized	1000-2000	Broad spectrum	Psychosis, visual field defect weight gain, depression
Gabapentin	-do-	1800-3600	No drug interactions, rapid titration	Somnolence, fatigue, ataxia
Lamotrigine	-do-	100-500	Broad spectrum, wide experience, once or twice daily dosing	Skin rash, ataxia, tremor, gastrointestinal disturbances
Topiramate	-do-	100-500	Broad spectrum, wide experience, twice daily dosing	Ataxia, confusion, loss of weight, renal stones, word finding difficulty
Clobazam	Complex partial, secondary and primary generalized seizures	20-50	Less side effects and few drug interactions	Sedation, irritability, weight gain
Felbamate	-do- + Lennox-Gastaut syndrome	2400-3600	—	Aplastic anemia, hepatic failure
Tiagabine	Partial and secondary generalized	32-56	Only a few drug interactions	Gastrointestinal disturbances, confusion
Zonisamide	-do-	100-600	Broad spectrum, few drug interactions, once-daily dosing	Somnolence, renal calculi, ataxia
Leviteracetum	Broad spectrum, mainly partial epilepsies	1000-3000	Broad spectrum, few drug interactions, once-daily dosing	Somnolence, fatigue, ataxia, behavioral abnormalities

combined with any other antiepileptic drug. Gabapentin is an add-on drug for resistant partial and secondarily generalised seizures. Main adverse effects are somnolence, ataxia, fatigue, nystagmus, GI upset and weight gain.

Lamotrigine: This drug inhibits the release of the excitatory amino acid glutamate. The effective dose is 200-300 mg/day. The drug is started at 50 mg/day and gradually increased till the full dose is reached over 3-6 weeks. Further increase in dosage should be done only very cautiously, when combined with sodium valproate, it should be used in smaller doses. Lamotrigine is indicated in intractable partial seizures with secondary generalization, infantile status and Lennox-Gastaut syndrome. Adverse effects include dystonia, ataxia, severe hepatotoxicity, and skin rash.

Clobazam: Its antiepileptic activity is related to its binding to one or more specific GABA receptors increasing GABA mediated inhibition. It is effective in complex partial seizures and primary or secondarily generalised seizures. The adult daily dose is 20-50 mg. Sedation, irritability and weight gain are the main side effects.

Tiagabine: (30-60 mg), and

Topiramate (100-500 mg) are the other newer drugs found to be useful in partial seizures with secondary generalisation and primary generalised seizures.

Leviteracetum is an add-on drug for refractory partial seizures and for the generalised seizure in adults in a dose of 500 mg bd. It has the least drug interactions. It is useful in the presence of hepatic and renal insufficiency.

Felbamate: This drug raises the seizure threshold. Adult dose may vary from 1800-4800 mg/day. Daily dose for children is 15-45 mg/kg given in 3-4 doses.

Felbamate is used as add – on therapy for partial seizures with generalization resistant to other drugs and for Lennox-Gastaut syndrome.

When used as an add-on drug, the dosage of the original drug should be reduced progressively and withdrawn, when the full dose of felbamate is reached.

Side effects include insomnia, weight loss, nausea, anorexia and aplastic anemia. Due to serious toxic effects this drug is not licenced in many countries (Table 190.2).

TABLE 190.3

Interaction of AEDs		
	Serum drug levels	
	Phenytoin	Carbamazepine
Concurrent drug therapy		
Isoniazid	↑	↑
Rifampicin	↓	↓
Erythromycin	↑	↑
Lithium	—	↑
Antacids	↓	↓
Cimetidine	↑	—
Warfarin	↑	—
Pyridoxine	↓	↓
Oral contraception	↓	↓
↑ - serum levels increase, ↓ - serum levels decrease		

TABLE 190.4

Type of epilepsy and choice of AED	
Types of epilepsy	Drugs of choice
1. Generalised tonic-clonic seizures with partial onset	Phenytoin sodium Carbamazepine Phenobarbitone Sodium valproate
2. Simple partial seizures	Carbamazepine Phenytoin sodium Primidone Phenobarbitone Sodium valproate
3. Complex partial seizures	Carbamazepine Sodium valproate Primidone Phenytoin sodium Phenobarbitone
4. Absence seizures with 3/sec spike and waves on EEG	Sodium valproate Ethosuximide Clonazepam
5. Myoclonic seizures	Sodium valproate Nitrazepam Clonazepam Ethosuximide
6. Infantile spasms	ACTH/ Corticosteroids Nitrazepam Clonazepam
7. Neonatal seizures, Febrile seizures	Phenobarbitone Sodium valproate
8. Status epilepticus	Diazepam Phenytoin sodium Phenobarbitone Lorazepam

A serious problem on long-term AED therapy is the occurrence of drug interactions when other drugs are given concurrently. These may lead to rise or fall in blood levels of the AED, resulting in occurrence of toxic effects of the drug or the development of seizures (Tables 190.3 and 190.4).

Status Epilepticus

When recurrent seizures occur at a frequency which does not allow consciousness to be regained in the interval between seizures, it is called *status epilepticus*. Severe and permanent brain damage may result from status epilepticus persisting for more than an hour. Since prolonged or frequent seizures also lead to permanent damage to the brain (hippocampus, Purkinje cells of cerebellum and extrapyramidal system) it is the current consensus to consider any seizure (both clinical or electrical) lasting for more than 30 minutes, or more than one seizure within 30 minutes even if consciousness is not lost, as status epilepticus, for purposes of management. Status epilepticus may be convulsive or nonconvulsive. Convulsive status which may be partial or generalised may be tonic, clonic, or myoclonic types and secondary generalised forms. Nonconvulsive status (absence status) or complex partial status may vary from simple slowing of ideas to marked stupor from which the patient can be woken up only by painful stimuli. Nonconvulsive status can be diagnosed only by EEG recordings. Such patients are also prone to develop damage to the brain.

Lactic acidosis, hypoglycemia, autonomic dysfunction, hyperthermia and shock may follow if the status epilepticus continues for a long period. Longer the duration of the convulsive status epilepticus, the more difficult it is to control and higher is the incidence of morbidity and mortality. The mortality in uncontrolled convulsive status epilepticus may range from 5-50%.

Hypoglycemia and hypocalcemia which give rise to convulsions should be excluded by appropriate tests.

Management

Time is a critical factor in the management of status epilepticus. There are many therapeutic regimes but none of them is totally satisfactorily. Benzodiazepines such as **diazepam**, **lorazepam**, **midazolam** and **clonazepam** are all potent fast-acting antiepileptic drugs, preferred for terminating the attack immediately. Initially, when the patient is first seen, 10 mg diazepam (0.3-0.5 mg/kg bw) should be given slowly intravenously over a period of 2-5 minutes. Its action lasts for 20-30 minutes. Lorazepam in doses of 0.1 mg/kg at 2 mg/minute is preferable to IV Diazepam as it has longer duration of action (> 4 hrs) and lesser respiratory depression.

Acetazolamide which is a carbonic anhydrase inhibitor can be used as a second line drug along with other antiepileptic drugs to potentiate their action. Acetazolamide also reduces intracranial tension. Dose is 0.25-1 g in divided doses daily.

Simultaneously a loading dose of phenytoin, i.e. 0.5-1g (18 mg/kg) is given intravenously over 20 minutes at a rate of 50 mg/min in those who are not already on this drug. This dose serves to achieve optimum therapeutic blood level and maintains the antiseizure effect, for a longer period. The anticonvulsant action of **intravenous phenytoin** is manifest within 10-20 minutes. Phenytoin is not absorbed properly after IM injection, and therefore this route should not be relied upon. Large doses of IV phenytoin may lead to hypotension and cardiac arrhythmias, and therefore the patient should be closely monitored clinically and with ECG. In the absence of such a facility phenytoin should be given as IV bolus in doses of 200 mg. Phenytoin levels can be maintained by giving it as an IV drip containing 100 mg in 500 mL of normal saline or distilled water, run at the rate of 40 mL per hour, the infusion lasting for 12 hours. **Phenytoin is incompatible with glucose containing solutions and hence it should not be mixed with them.** If status epilepticus still persists, phenytoin is to be repeated at a dose of 5 mg/kg IV till a maximal total dose of 30 mg/kg is reached. Fosphenytoin is a water soluble prodrug of phenytoin which is similar in action and dosage, but with less of local irritant property. 150 mg fosphenytoin is equivalent to 100 mg phenytoin.

Phenobarbitone given intravenously in doses upto 0.8-1 g in 24 hours (20 mg/kg at 100 mg/min) is an effective anticonvulsant and this should be added if seizures are not controlled by diazepam and phenytoin. In intractable cases thiopental anesthesia is induced with IV injection of 0.3-0.6 g of the drug and this is very effective. Assisted ventilation is mandatory when phenobarb or thiopentone is given, especially after diazepam administration. Once the patient is seizure free, and is able to take oral medication, phenytoin or other antiepileptic drugs are introduced by the oral route.

Guidelines for the Management of Intractable Status Epilepticus

Time Interval Action

0-9 minutes	Assess cardiorespiratory function. Obtain history and perform neurologic and general physical examination. Draw venous blood sample for antiepileptic drug level (if the patient is already on them), glucose, blood urea and electrolyte tests. Establish an IV line with isotonic saline. Administer 25 g of glucose (50 mL of 50%) and 100 mg thiamine IV. Insert oral airway and administer oxygen if needed.
10-30 minutes	If convulsions recur after the IV line is established, administer diazepam (5 mg/min) or lorazepam (2 mg/min) until

seizures stop or the maximum diazepam dose of 20-30 mg or lorazepam dose of 1 mg/kg bw is administered. If convulsions have stopped, start phenytoin at the rate of 50 mg per minute IV to a total bolus dose of upto 18 mg/kg bw (100 mg) at a time and repeated 8 hourly.

31-70 minutes If seizures persist, intubate and ventilate the patient. Start phenobarbitone I.V. at the rate of 100 mg/min to a total dose of 20 mg/kg bw. At the end of 1 hour if seizures persist, continue phenobarbitone at the rate of 5 mg /kg loading dose and thereafter 1-3 mg/kg/hour so as to abolish the electrical seizure activity but without producing hypotension.

If the convulsions persist despite medications, the anesthetist's help is summoned. Patient is given ventilatory support and anesthesia is induced using medazolam or propofol. This controls the convulsions in almost all cases.

On many occasions status epilepticus may be encountered outside hospital settings. Management of such cases becomes more difficult due to problems of intravenous medication in a convulsing patient and the possibility of fatal toxicity of high doses of drugs. In such situations drugs such as **midazolam** in a dose of 0.07-0.08 mg / kg bw, given IM, may be effective. The seizure stops within 10 minutes.

Another safe, but less effective method is to administer any available parenteral preparation of **diazepam rectally** in a dose of 0.5 mg / kg bw to a maximum of 20 mg at a time. The seizure stops within 15 minutes.

IV sodium valproate in doses of 30 mg/kg in 100 mL saline given over 15 minutes has been found to be superior to phenytoin in status—epilepticus (Misra UK et al. Neurology 2006;67:340-42).

General supportive measures include

1. Maintenance of the airway and prevention of aspiration
2. Prevention of injuries
3. Proper oxygenation
4. Attention to fluid and electrolyte balance, and
5. Maintenance of nutrition.

Failure to control status epilepticus is due to one of the following causes:

1. Delay in starting treatment
2. Inadequate dosage of anticonvulsants
3. Improper route of administration of drugs
4. Inadequate supportive care, and
5. Gross involvement of the brain by disease processes such as encephalitis.

Ketogenic Diet

Induction of mild ketosis by instituting ketogenic diets has been found to reduce the frequency of seizure in children. Diet which contains 80% of energy by fat induces ketosis. This diet is not of much use in adults.

Surgical Management of Epilepsy

Cases not responding to medical treatment should be considered for surgery, especially if they have demonstrably abnormal focal brain lesions. When morphologically abnormal lesions are not demonstrable, the epileptogenic focus has to be demarcated by investigations such as intraoperative electrocorticography.

Removal of such an epileptogenic focus often improves neurological function as well. The surgical procedures include cortical excision, hemispherectomy and stereotaxic surgery. Several other procedures have also been developed. A common indication for surgical ablation is temporal lobe epilepsy. The surgical procedure is anterior temporal lobectomy.

Vagal stimulation is an accepted treatment modality for intractable epilepsy. It is advocated for patients above 12 years. This implanted programmable pacemaker like device is set to stimulate the left vagus nerve. Adverse effects include transient hoarseness of voice. In 30 percent of cases the seizure frequency is reduced by 50 percent or more.

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Involuntary Movements and Diseases of the Extrapyramidal System

Asha Kishore

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disease (e.g. tremor in patients with essential tremor, chorea in Sydenham's chorea), or part of the neurological manifestations of the disease, e.g. chorea occurring along with dementia and psychiatric problems in Huntington's disease and finally, delineating the probable etiology of the involuntary movements.

Classically, abnormal involuntary movements are classified into

- 1. **Hyperkinesia**, when there is excess movements and
- 2. **Hypokinesia**, when there is a relative paucity of movements that cannot be accounted for, by weakness or spasticity. The term dyskinesia denotes any involuntary movement but often, hyperkinesia.

Based on the clinical patterns, hyperkinetic movements are subcategorized into *chorea*, *ballism*, *dystonia*, *myoclonus*, *tremor* and *tics*. Identification of involuntary movements can be particularly difficult when a combination of movements coexist in the same individual.

Analysis of involuntary movements are based on the following characteristics: Distribution, velocity, amplitude, rhythmicity, suppressibility, relation to posture, activity and sleep, type of precipitating and relieving

Abnormal Involuntary Movements

GENERAL CONSIDERATIONS

Approach to a patient with involuntary movements involves identifying the type of involuntary movement, determining whether it is the sole manifestation of the

factors, diurnal variation if any and associated sensory and emotional components.

- 1. **Distribution:** Classic tardive dyskinesias in the orofacial region.
- 2. **Velocity:** Very fast in myoclonus, slow in dystonia, intermediate speed in chorea and tremor.
- 3. **Relation to posture:** Tremor at rest in rest tremor of Parkinson's disease, tremor in certain postures in essential tremor.
- 4. **Rhythm:** Regular, e.g. tremor and irregular, e.g. chorea, ballism.
- 5. **Relation to action:** Action tremor, action dystonia, action myoclonus.
- 6. **Relation to sleep:** Palatal tremor can persist in sleep. Most involuntary movements disappear in sleep.
- 7. **Suppressibility:** For example voluntary suppression of tics, sensory tricks such as touching a body part can suppress some forms of dystonia.
- 8. **Aggravating factors:** Stress and anxiety worsen almost all movement disorders.

HYPERKINESIAS

Chorea and Ballism: They resemble each other and often coexist. Chorea consists of rapid, jerky, irregular, movements that may be simple or complex and are usually distal and of low amplitude. The movements have a flowing character and migrate from one part of the body to the other. The movements are purposeless but patients may incorporate them into their voluntary movements as if to make them less conspicuous (quasi-purposive). At times, the movements can be very discreet and resemble fidgetiness, particularly in children.

Walking is interrupted by sudden stops and starts (dancing gait). The patient is unable to maintain smooth muscle contraction. The grip tightens and loosens alternately (milking sign). When the mouth is held open, the tongue is protruded and withdrawn alternately (Jack-in-pot sign). The tendon jerks are often pendular or sustained as a result of added muscular contractions (hung-up knee jerk). Main causes of chorea are Sydenham's chorea, chorea gravidarum, senile chorea, thyrotoxicosis, SLE, encephalitis and drugs like L. dopa and phenytoin.

Very large amplitude chorea with a violent flinging character and arising proximally in the limbs is termed **ballism**. Both chorea and ballism may be bilateral or unilateral; *hemichorea*, *hemiballism*. Hemichorea arises most often from dysfunction of the contralateral caudate nucleus, and ballism from vascular injury to the contralateral subthalamic region.

SYDENHAM'S CHOREA

Syn: Rheumatic chorea, **St. vitus dance**

This is one of the acute rheumatic manifestations. Pathological changes consist of edema and congestion of

different regions of the brain. Microscopy shows marked changes in the corpus striatum, subthalamic nuclei, substantia nigra, and cerebral cortex. The acute changes consist of vasodilatation and perivascular degeneration. Neuronal loss and perivascular glial proliferation have been described (See Chapter 37).

Adolescent girls are affected more often. The onset is abrupt with generalized chorea and emotional lability. Volitional activity and emotional excitement worsen the abnormal movements. Most of the cases recover fully even without treatment. Haloperidol and diazepam give symptomatic relief of the abnormal movements.

Causes of Chorea	
Hereditary-AD	Huntington's disease, benign hereditary chorea
Hereditary-AR	Wilson's disease, ataxia telengiectasia,
Hereditary-maternal inheritance	Mitochondrial encephalopathies
Immune mediated	Rheumatic chorea, SLE, chorea gravidarum
Vascular	Infarcts
Metabolic	Hypo or hypernatremia, hypocalcemia, hypo or hyperglycemia
	hyperthyroidism, hypoparathyroidism
Toxic agents	Carbon monoxide, mercury
Inflammatory drugs	Encephalitis, ADEM
	Neuroleptics, metoclopramide, L-dopa, phenytoin, steroids, oral contraceptives and several others
Key AD- autosomal dominant AR- autosomal recessive ADEM- acute disseminated encephalomyelitis	

TREMOR

Tremor consists of rhythmic involuntary oscillations of a body part produced by alternating or synchronous contractions of reciprocally innervated muscles. Tremor may be present solely at rest, on assuming a posture, during action or on reaching a target. Tremor may be fine or coarse. Tremor may be physiological when it is caused by subtetanic contractions of muscle fibres and is usually fine and detectable only with amplification systems. When this tremor becomes noticeable when the arms are held out against gravity or during action, it is called enhanced physiological tremor. Anxiety and fear are common situations which *enhance physiological tremor*. Thyrotoxicosis, hypoglycemia, alcohol withdrawal, drugs such as salbutamol and ephedrine, sodium valproate, lithium, amphetamines and caffeine can cause enhanced physiological tremor. These conditions should be excluded before diagnosing pathological tremor.

Essential tremor (ET): Tremor is the sole neurological sign. Tremor in ET is most often seen in the hands. It can also occur in the head, lips, chin, voice and rarely in the

legs. ET becomes manifest when the hands assume certain postures and may change with varying postures.

Parkinsonian tremor: Tremor at rest (RT) when the limb is in repose, is typical of Parkinson's disease and uncommon in other parkinsonian disorders. RT is coarse and slow with a frequency of 4-5 Hz, is often intermittent and begins in one of the hands. It is precipitated by anxiety and emotional excitement. It disappears during action or on assuming a posture and in sleep. Postural and action tremor can also occur in PD.

Intention tremor: Tremor of the limbs that exacerbate on reaching a target is called intention tremor (IT). It is coarse and the oscillations of the limb occur at right angles to the direction of movement of the limb. It indicates involvement of the cerebellum or its connections.

Wing-beating tremor: This tremor is typical of Wilson's disease and results in large amplitude of the outstretched limbs and is more proximal in its distribution. It results in the limbs being thrown up and down like flapping wings, particularly when the arms are kept abducted at the shoulder and flexed at the elbow with palms facing down.

Psychogenic tremor. The onset of tremor is usually abrupt and in the majority the maximum intensity is at onset and does not worsen with time. The tremors can occur at rest and persist during posture and action. With distraction, the tremor usually lessens in amplitude or changes frequency or may disappear. Even though other forms of organic tremor can be intermittent, complete cessation with distraction is not seen in organic tremors and it may even worsen during distracting actions demanding mental concentration. The arms are most commonly affected, followed by the head and then the legs.

DYSTONIA

The term dystonia was coined by Oppenheim in 1911 to describe a disorder causing variable muscle tone and recurrent muscle spasm. Dystonia is an abnormal involuntary movement characterized by sustained muscle contractions, frequently causing twisting and repetitive movements or abnormal postures. Dystonic movements are usually slow, but quick components may also coexist causing confusion with myoclonic jerks. They are arrhythmic and tend to aggravate with stress, fatigue and emotional upset but are relieved by sleep and rest. An interesting feature of dystonia is the patient's ability to suppress the movement by a sensory trick that is usually tactile or proprioceptive, e.g. dystonia of the neck may be suppressed by the patient by touching the chin or side of the face.

According to the site of involvement, dystonia is classified into (i) focal, e.g. dystonia of the neck (*spasmodic torticollis*) or eye lids (*blepharospasm*) or limb, (ii) segmental, when 2 or more contiguous parts are affected, e.g. *Meig's syndrome* which is a combination of blepharospasm with oromandibular dystonia, (iii) *multifocal*, when 2 or more noncontiguous parts are affected, (iv) *hemidystonia*, affecting hemibody and (v) *generalized* (leg with involvement of other parts). Dystonia is also classified based on etiology into primary or secondary dystonia. Many of the primary dystonias are due to known genetic defects and pathology is not clear. Secondary dystonias have a known cause, e.g. hemidystonia is often due to a pathology involving the opposite basal ganglia or its connections, e.g. infarct in the opposite putamen.

Secondary dystonias: These include:

1. Heredo-degenerative dystonias with known neuropathological features.
2. Drug-induced dystonia.
3. Dystonia caused by acquired structural lesions.

Athetosis

This term was used to denote a syndrome in which there is inability to maintain a single muscle or muscle groups in a fixed posture. The limbs, face, tongue or the whole body undergo a slow sinuous writhing involuntary movement which continuously goes on. The distal parts are affected more often. Athetosis may be unilateral at times. Choreoathetosis occurring at an early age is a sequel of hypoxic damage to the brain or kernicterus. Temporary athetosis may occur in hepatic encephalopathy or as a toxic reaction to phenothiazines and antipsychotic drugs. The term athetosis is seldom used now since the abnormalities merge under the common term dystonia.

Treatment

1. **Drugs:** Some dystonias are dopa-responsive. A trial of carbidopa-levodopa 25/100 mg tds is beneficial in 50% of cases. High dose anti-cholinergic drug treatment with trihexyphenidyl 6-80 mg/day or benzotropine 4-8 mg/day is partially effective in 40-50% of primary and secondary dystonias. Several other drugs including antiepileptic drugs have been tried.

Botulism toxin serotypes A and B inhibit the release of acetylcholine at the neuromuscular junctions, when injected into dystonic muscles. It reduces muscle spasm and dystonia in 70-90% of cases for varying periods.

2. **Surgery:** Selective peripheral denervation gives variable results. Deep brain stimulation of the globus

pallidus is being introduced for the treatment of medically refractory dystonia.

3. Physiotherapy

Muscle stretching and strengthening may be used to avoid contractures. Mechanical assisting devices reduce disability.

For additional on line information on dystonia the reader is referred to [www. dystonia-foundation. org](http://www.dystonia-foundation.org) and at [www. wemove. org](http://www.wemove.org).

MYOCLONUS

Myoclonus is a brief shock- like muscle jerk caused by neuronal discharges. A sudden interruption in ongoing muscular contractions can produce a postural lapse, called negative myoclonus, e.g. asterexis. Myoclonus can be spontaneous or triggered by an external stimulus (reflex myoclonus) or by voluntary muscle activation (action myoclonus). Myoclonus can be rhythmic or irregular. According to its distribution, myoclonus is classified as focal, segmental, multifocal or generalized. Based on its neurophysiological origin, myoclonus may be cortical, subcortical (brainstem) or spinal.

Classification of myoclonus

Clinical Presentation

- Spontaneous
- Reflex
- Action

Topography

- Focal
- Segmental
- Multifocal
- Generalized

Neurophysiological Origin

- Cortical
- Subcortical
- Spinal

Etiology

- Physiological
- Essential
- Symptomatic

Myoclonus can be associated with other involuntary movements in the same patient, e.g. myoclonus and dystonia in patients with hereditary essential myoclonus, chorea and myoclonus in patients with Huntington's disease. Myoclonus may be a major clinical manifestation of idiopathic epilepsy, e.g. juvenile myoclonic epilepsy. Myoclonus may be secondary to CNS dysfunction, e.g., post hypoxic myoclonus (**Lance-Adams syndrome**), myoclonus due to metabolic disturbances, drug-induced myoclonus, etc.

Sometimes myoclonus may occur in normal persons during sleep, without any evidence of disease.



Fig. 191.1: Facial hemispasm

Tics

Tics are recurrent, nonrhythmic, stereotyped movements (motor tics) or sounds (vocal tics). Motor tics can be simple such as eye blink, shoulder shrug, head jerk or complex movements such as jumping, kicking, touching etc. Vocal tics can be inarticulate sounds like throat clearing, sniffing or grunting and complex when they are words with meaning. These complex vocal tics could be repeating words of others (*echolalia*), repeating one's own words (*palilalia*), or obscene words (*coprolalia*). An irresistible urge precedes the tic. Tics can be suppressed temporarily but with a build-up of inner tension which is relieved only by execution of the tic (Fig. 191.1).

Extrapyramidal Disorders

Parkinsonism is the prototype of hypokinetic movement disorders and refers to a syndrome comprising of bradykinesia (slowness of movements), rigidity, tremor and postural instability. *Parkinson's disease* (PD) is the most common form of parkinsonism and the symptoms of parkinsonism constitute the predominant manifestation of PD. There is no biological marker for PD and the diagnosis is based entirely on the history and neurological examination. A few other conditions have in addition to parkinsonism, other distinctive neurological signs and are called *atypical parkinsonism*, e.g. progressive supranuclear palsy (PSP), multiple system atrophy (MSA), corticobasal degeneration (CBD) and dementia with Lewy bodies (DLB). In a third category of diseases called *secondary parkinsonism*, the causative factor is known, e.g. parkinsonism due to exposure to dopamine receptor blocking drugs like neuroleptics, dopamine depletors like

tetrabenazine and reserpine, infections, strokes, hydrocephalus and others. In one series, 20% of patients diagnosed as PD during life had some form of atypical parkinsonism at autopsy.

Parkinson's Disease

James Parkinson in 1817 wrote the original description of the disease in his monograph “An essay on Shaking Palsy” and the condition he described now bears his name. Interestingly, descriptions of similar symptoms can be found for the condition called “*Kampavatha*” in ‘*Charaka Samhitha*’ written in the Vedic times (1500 to 1000BC).

Epidemiology

PD is found world-wide and is one of the most common extrapyramidal disorders seen in clinical practice. PD occurs at a frequency of 1% in people older than 60 years and 0.3% of the general population, according to western statistics. Epidemiological studies have shown a relatively lesser incidence and crude prevalence of PD in countries like Africa, India and China when compared to Western populations except among the Parsis of India who have a high incidence of the disease. However, these observations are controversial because of the inadequate design of most studies. PD affects men and women with a slightly higher incidence among men. The mean age of onset of the disease is in the early 60s though it can occur at younger ages in 5-10% of cases. PD with age of onset less than 40-50 years is called “*young-onset PD*” and when less than 20 years, is called “*juvenile-onset PD*”.

Etiology and Pathology

The etiology of sporadic forms of PD is not known. Besides older age and positive family history, case – control studies seeking an association between environmental exposure and PD have suggested an increased risk associated with farming, rural residence, herbicide/pesticide exposure, employment in industries manufacturing chemicals, and mining and steel. There is

an inverse association between cigarette smoking and coffee drinking with PD and the exact mechanisms of these effects are unknown.

Pathologically, the disease is characterized by loss of pigmented neurons, most prominently but not solely, in the substantia pars compacta of the midbrain and in the locus coeruleus and the presence of ubiquitin-positive and alpha synuclein-positive inclusions called *Lewy bodies* in the degenerating neurons.

Genetics of Parkinson's Disease

About 10 to 15% of patients with PD have a first degree relative with the disease. In recent years, six genes (alpha synuclein, parkin, UCH-L1, DJ1, PINK1, LRRK2) and several more loci have confirmed the existence of genetic forms of PD, both autosomal recessive and dominant. Some of the defective genes cause disease by protein aggregation within cells and their discovery has enhanced the understanding of the potential mechanisms of neurodegeneration in both genetic and sporadic forms of PD.

CLINICAL FEATURES

- 1. **Hypokinesia or bradykinesia:** These terms refer to the poverty of automatic and voluntary movements due to defective motor planning. Voluntary movements are slow to initiate, reduced, and they lack precision. The associated movements on walking such as swinging of the arms and movements of the body are considerably reduced. Even though voluntary activity is difficult and slow, reflex activity remains normal for considerable periods. Though the voluntary movements are slow, the motor power is usually normal.
- 2. **Rigidity:** Increase in tone manifesting as rigidity of the limbs and trunk is characteristic of parkinsonism. This rigidity is present throughout the range of movement (‘lead pipe’ rigidity), unlike the spasticity of upper motor neuron lesion where the increase in tone is felt maximally at the commencement of the movement. When rigidity is associated with tremor,

Genetic forms of PD				
Name	Gene product	Mode	Difference from sporadic PD	Pathology
PARK 1	Alpha synuclein	AD	Early onset, less tremor	Lewy body +
PARK 2	Parkin	AR	Juvenile, dystonia, LIDS, slow	Lewy body –
PARK 3	Unknown	AD	Dementia, rapid progression	Lewy body +
PARK 4	Alpha synuclein	AD	Dementia, rapid progression	Lewy body +
PARK 5	UCH-L1	AD	Typical PD	Unknown
PARK 6	PINK-1	AR	Early onset, slow progression	Unknown
PARK 7	DJ-1	AR	Early onset, slow progression	Unknown
PARK 8	LRRK 2	AD	Typical PD	Lewy body –
PARK 9	Unknown	AR	Spasticity, gaze palsy, dementia	Unknown
PARK10	Unknown	Non	Typical PD	Unknown

it results in 'cogwheel' type of rigidity. Rigidity of the facial muscles gives rise to a 'mask-like facies' with no expression and also infrequent blinking.

3. **Tremor:** The characteristic tremor occurs at rest. Initially tremor is seen in the hands, but later this extends to the lower limbs. The thumb moves transversely across the tip of the flexed fingers rhythmically and this is aptly described as the 'pill rolling tremor'. Later the tremor becomes more extensive and in addition to the limbs, the face, lips and tongue also become tremulous.
4. **Alteration in posture:** The patient assumes an attitude of generalized flexion, which makes him stoop forward. He walks with short steps and as he walks he gains speed and tends to run forwards. This phenomenon is termed 'festination'. The terms 'propulsion' and 'retropulsion' are used to denote the phenomenon seen when the standing patient is gently pushed forwards or backwards. The patient continues to move forwards or backwards without control. Due to the rigidity in movement the patient finds it difficult to turn around while walking. He tends to trip and fall more often and postural adjustments become difficult. Speech becomes slow and monotonous. There is lack of initiative and the patient tends to restrict his activity progressively. The deep reflexes and sensations are generally unaffected.

Higher faculties such as intelligence and memory are usually preserved.

Resistant symptoms: In addition to the obvious classic symptoms, several others occur which are disabling and prove resistant to treatment. These include:

- a. Imbalance and postural instability,
- b. Paroxysmal akinesia,
- c. Vague body pains,
- d. Dystonias,
- e. Autonomic disturbances leading to difficulty in micturition, constipation, sexual problems, seborrhea, and excessive salivation,
- f. Speech difficulty, and
- g. Psychological abnormalities such as depression, melancholia and paranoid fears.

The clinical diagnosis of PD is made from history, clinical examination and response of symptoms and signs to the drug levodopa, which is the precursor of dopamine.

Presence of bradykinesia along with any of the 3 other cardinal signs of PD, i.e. rest tremor, rigidity and postural instability suggests PD. Bradykinesia or slowness of movement is the most disabling early symptom of PD. Patients often have micrographia, hypophonia and reduced armswing before the typical signs appear. It results in slowness of walking, difficulty in rising, doing fine motor tasks and other activities of daily living. Limb bradykinesia, rigidity and rest tremor of PD are typically

asymmetric at onset and the asymmetry often persists even after the disease becomes generalized. The rest tremor of PD is seen in the hands early, has a frequency of 3-5 Hz (resembles pill rolling) and is the first symptom in 70% cases of PD.

Muscle sounds in Parkinson's disease: A sound with a frequency of 40 Hz can be heard with a stethoscope over the muscles of the hand and forearm during tonic condition or movement in normal subjects. In parkinsonism this is replaced by slow activity sounds at 10 Hz. The sounds correlate with the piper-rhythm seen in EMG records of muscle activity.

The exclusion criteria to diagnose PD are causes of secondary parkinsonism,

These include

1. presence of signs that suggest atypical parkinsonism such as supranuclear gaze palsy (except mild upgaze restriction seen in old age),
 2. cerebellar signs,
 3. early and severe autonomic dysfunction such as orthostatic hypotension (unrelated to dopaminergic drugs), early urinary incontinence, early falls,
 4. cortical sensory loss, prominent pyramidal signs,
 5. early dementia, myoclonus,
 6. MRI evidence of subcortical white matter disease, focal atrophy, structural lesions or hydrocephalus.
- MRI is not required to make a diagnosis of PD but is necessary if there are atypical signs or symptoms.

The non-motor symptoms of Parkinson's disease include depression, anxiety, dementia late in the disease, psychosis, insomnia, rapid eye movement, sleep-disorder, autonomic dysfunction, urological, constipation and sexual disturbances, sensory symptoms, dysphagia and gastric dysfunction.

Natural History and Prognosis

Untreated, the progress of the disease is steady and relentless. The tremor is less disabling than rigidity and hypokinesia, since the tremor reduces or stops during voluntary activity. Rigidity and hypokinesia restrict motor activities considerably so that the patient is unable to get-up from bed and carry-out the activities of daily life. PD shortens life. Death is due to inanition, respiratory and other infections, falls and trauma. With treatment, the quality of life improves.

TREATMENT OF PD

At present there is no cure for PD. The concept of neuroprotection in PD is attractive and refers to therapeutic strategies that might modify the course of the disease by interfering with the underlying disease mechanisms. The first agent to be tested as a neuro-protective agent in PD was *selegiline*, which is an

irreversible inhibitor of the enzyme monoamine oxidase-B (MAO-B), which produces oxidative deamination of dopamine. A large multicentre trial (DATATOP study) which tested the neuroprotective roles of selegiline and vitamin E (antioxidant) showed that selegiline delayed the need for levodopa treatment. However, the latter effect could be attributed to the symptomatic benefits of selegiline on parkinsonism and hence its neuroprotective role remains unproven. *Coenzyme Q10 (COQ)* is an electron acceptor for complexes I and II in the mitochondrial electron transport chain and is also an antioxidant. Pilot studies have shown less disability in patients taking COQ. Larger studies are underway to test coenzyme Q 10 and the antibiotic minocycline for neuroprotective functions. There is preliminary data from functional imaging of the dopaminergic system suggesting that dopamine agonists may slow the progression of PD when compared with levodopa. However, the interpretations of these data have been debated and the issue of the neuroprotective role of dopamine agonists also remains unresolved. Even though the neurotrophic factor, *glial cell line derived neurotrophic factor (GDNF)*, was found effective when directly delivered to the putamen in PD in a small open labeled study of five patients, the observation remains to be replicated in large double blind studies. Based on the available information, there is no compound which can be considered to be unequivocally effective as a neuroprotective agent in the treatment of PD.

Symptomatic treatment of PD: In the general management, it is important to encourage the patient to continue in his job and daily activities, since restriction of activity leads to rapid deterioration.

The medical treatment of PD is challenging at every phase of the disease. The goal of therapy is to maximize the control of motor symptoms and minimize the complications of treatment which are also due to progression of the disease. Treatment is begun when patients experience functional or social disability because of their symptoms. The age of the patient, the most problematic symptom, severity of disability, presence of cognitive impairment, co-morbid medical conditions and cost of drugs influence the choice of drugs for early treatment. *The treatment options for early PD includes dopamine agonists (DA), anticholinergics, amantadine, MAO inhibitors (selegiline, rasagiline) and levodopa which should always be combined with peripheral decarboxylase inhibitor carbidopa or benserazide to prevent the peripheral metabolism of levodopa.*

Patients with young-onset PD develop motor response variations to levodopa treatment and levodopa-induced involuntary movements (chorea, ballism, dystonia) within 3-5 years of exposure to levodopa. For this reason, levodopa treatment is delayed in them till disease severity

or disability demands its use. Until then, early cases are best treated with dopamine agonists (DA). Dopamine agonists belong to two categories (i) ergot –derived (*bromocriptine, pergolide* and *cabergoline*) and (ii) the non-ergot- derived compounds (*ropinirole, pramipexole, apomorphine*). The long-term use of ergot-derived agonists is associated with the risk of retroperitoneal, pulmonary and cardiac-valve fibrosis. Therefore, non-ergot compounds are preferred. Apomorphine can be given subcutaneously or as an intravenous infusion, but is usually used in patients with advanced disease. Pergolide and apomorphine are not yet available in India. Many patients with early PD can be maintained on dopamine agonist monotherapy for the initial 2 years of the disease and L.dopa therapy can be instituted when dopamine agonist therapy becomes ineffective to control the symptoms. Motor response fluctuations and drug-induced dyskinesias are rarely seen during DA monotherapy. The common side effects of DA are nausea, hypotension, pedal edema, vivid dreams, nightmares, hallucinations and delusions, day time somnolence and sudden sleep attacks. Psychotoxic side effects of DA agonists are more in the elderly population (Table 191.1).

Young patients with prominent tremor may benefit from anticholinergic drugs like trihexyphenidyl and bztropine, even though these drugs are not superior to levodopa in controlling tremor.

Amantadine is a tricyclic amine and has multiple actions in the CNS. It has mild antiparkinsonian benefits similar to anticholinergic drugs. Patients may develop tolerance to its effects within a year of its use. In developing countries, *trihexyphenidyl* (up to 6mg daily) and *amantadine* (100mg 2-3 times /day) are often given to young patients who cannot afford dopamine agonist treatment.

Selegiline (MAO inhibitor) can also be tried in doses of 5 to 10 mg per day in early PD in the young. Its benefits are modest. Rasagiline, another MAO-B inhibitor and Zydus selegiline, a novel formulation of selegiline are under evaluation for use in early and late PD.

Levodopa (L. dopa)

Of all the available antiparkinsonian drugs, levodopa is most effective for relieving the signs and symptoms of PD. Tremor can be resistant to all drugs including levodopa. Treatment is begun in small doses of levodopa-carbidopa combination which contains 50-100 mg of levodopa and 5-10 mg once or twice a day for a week and increased gradually to a TID schedule. The lowest effective dose needed for improvement in activities of daily living should be maintained at all times. The average dose requirement is around 400 to 600 mg. Levodopa-carbidopa is also available as a sustained release formulation but it is still required in TID to QID doses. Monotherapy with the

TABLE 191.1

Details of the commonly used anti -Parkinsonism drugs			
Class of drug	Adverse events	Dosing	Dosage
Dopamine agonists <i>Bromocryptine</i>	Nausea, hallucinations, somnolence, orthostatic hypotension	TID	2.5 mg HS to start with later 2.5 mg to 5 mg bd or tid up to 40 mg/day
Anticholinergics <i>trihexyphenidyl</i>	Dry mouth, constipation, urinary retention, memory impairment, confusion, hallucinations	TID	Trihexyphenidyl 2 mg tid
Amantadine	Mental confusion, disorientation, leg edema	BID-TID	100 mg tid
Selegiline	Nausea, headache, insomnia, hallucinations	BID (no evening dosing)	5 mg bid with breakfast and lunch
Levodopa	Nausea, dizziness, somnolence hallucinations, on- off episodes	TID-QID	100-200 mg tid
COMT inhibitors (tolcapone, entocapone)	Somnolence, insomnia, hallucinations	Combine with each levodopa dose	

sustained released formulation has not been found to prevent the development of motor response fluctuations or levodopa-induced dyskinesias.

If the disease severity warrants levodopa treatment, it may be used as monotherapy in the minimum required doses to young-onset PD cases for whom quick and substantial relief of symptoms is needed. DA can be added later to this regimen if more dopaminergic treatment is required.

In view of the enhanced side effect profile of these non-levodopa classes of drugs in the elderly, treatment is begun initially with levodopa in older patients. Levodopa is contraindicated during pregnancy, lactation, severe psychosis, narrow angle glaucoma, children below 18 years and in the presence of allergy to the drug.

Complications of Levodopa Treatment

Long- term treatment with levodopa is associated with motor fluctuations. The exact mechanism of this phenomenon is not known but is related to the severity of the underlying disease as well as treatment related factors such as duration of treatment and dose of levodopa. It is believed to be caused by the short half life of levodopa (90-120mts). “Wearing off” is a type of motor fluctuation characterized by the perception of loss of mobility or dexterity, usually taking place over minutes up to an hour and usually has a close temporal relation to the timing of antiparkinsonian medications. “On –Off” fluctuations are unpredictable and cause sudden shifts between periods of good mobility (On) and immobility (Off) that are not related to the timing of antiparkinsonian medications. An increase in the interval between dose of medication and the patients experience of an “On” response (“delayed On”) and the absence of a response to an individual dose (“dose failure” or “no on”) may relate to delayed gastric emptying.

Treatment of fluctuations focuses on trying to improve gastric absorption, increasing the dosing frequency and prolonging the effect of individual doses by switching to sustained release formulation or addition of a new class of drugs called Catechol-O-methyl-transferse inhibitors (COMTI) e.g. *entacapone* or *tolcapone*, with each dose of L-dopa to prevent its metabolism by COMT. Combination of levodopa, carbidopa and entacapone are available. Tolcapone has been withdrawn from the US market because of reports of fatal hepatotoxicity with its use. Addition of DA can also reduce the duration of time spent by the patients in “off” state.

Levodopa-induced involuntary movements (levodopa-induced dyskinesias-LIDs) can take several patterns. Pulsatile stimulation of dopaminergic receptors by intermittent oral doses of levodopa is thought to be the underlying mechanism of development of LIDs. They are most common at peak dose and can be chorea, ballism or dystonia. Dyskinesias may appear only at the beginning or end of the effect of levodopa and are called diphasic dyskinesias. Patients can develop painful dystonia at the end of the levodopa dose cycle. Peak dose LIDs can be controlled by reducing the dose of levodopa but that can lead to worsening of the control of parkinsonism. Surgical treatment is recommended for patients with disabling motor fluctuations and dyskinesias that cannot be controlled by medical management.

Surgery for Advanced Parkinson’s Disease

In the pre-levodopa era, thalamotomy (chemical or electrical destruction of thalamic nucleus) was practiced for the control of tremor and pallidotomy (lesioning of globus pallidus) for parkinsonism, with variable results. Surgical treatment has been revived from the early 1990s to manage the problems of medically intractable motor

fluctuations. Currently newer imaging modalities such as MRI, intraoperative microelectrode recording for locating the target nucleus and macrostimulation with intra-operative neurological assessments for testing the safety and efficacy of the procedure in the target, are employed to make these procedures safer and more rewarding.

The two major targets for surgery are the globus pallidus interna (GPi) and the subthalamic nucleus (STN) which are the two nuclei in the basal ganglia motor circuit that become pathologically overactive as a consequence of dopamine deficiency. The currently used technique of pallidotomy involves a radiofrequency lesioning of the GPi. It relieves all contralateral parkinsonian signs for 2-3 years but more long-lasting and substantial benefit is seen in tremor and LIDs. Bilateral simultaneous pallidotomy carries the risk of cognitive side effects.

Deep brain stimulation (DBS) is the technique which involves implantation of electrodes into the GPi or STN and stimulating these nuclei at high frequency to reduce their neural activity, using an implantable pulse generator which is also programable. The stimulation is reversible and does not involve brain injury as in ablative procedures. Bilateral DBS provides substantial relief to all the motor symptoms of PD and long- term results of the procedure are awaited. Even though DBS has replaced pallidotomy in the West, the cost of the former procedure limits its wide spread use in developing countries. In India pallidotomy continues to be practiced in many centres.

Atypical Parkinsonian Disorders

The “atypical parkinsonian disorders” (previously known as “Parkinson-plus syndromes”) are characterized by a rapidly evolving parkinsonism that has a poor or transient

response to dopaminergic therapy and is often associated with one or more atypical features for PD. Some of these features include early presence of postural instability, early autonomic failure, vertical supranuclear gaze palsy, pyramidal or cerebellar signs, early dementia, loss of cortical sensations and apraxia. In clinical practice and research, it is important to differentiate atypical parkinsonism from PD as the former is associated with reduced life span, and diminished response to dopaminergic treatment. It is associated with more severe complications early in the disease. Such patients also need to be excluded from surgical treatment programmes.

The sporadic forms of atypical parkinsonism are progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), multiple system atrophy (MSA) and dementia with Lewy bodies (DLB). The familial atypical parkinsonian disorders include frontotemporal dementia with parkinsonism linked to chromosome17 (FTDP-17), spinocerebellar ataxia, rigid form of Huntington’s disease, Wilson’s disease, and pantothenate kinase associated neurodegeneration (PKAN, previously called Hallervoden-Spatz syndrome).

Secondary Parkinsonism

Causes: Parkinsonism may develop as a complication of several conditions—

- 1. Drugs—Neuroleptics, calcium channel blockers, some anti-emetics.
- 2. Heavy metals—Manganese, mercury.
- 3. Normal pressure hydrocephalus (NPH).
- 4. Infections—HIV, Creutzfeldt-Jakob disease.
- 5. Vascular injury—Infarcts in basal ganglia and subcortical white matter.
- 6. Hypoxia.

Differential diagnosis of atypical parkinsonian disorders				
	PSP	MSA	CBD	DLB
Progression	Rapid	Rapid	Rapid	Rapid
Postural instability/falls	Early	Early	Late	Early
Parkinsonism	Symmetrical axial more than limbs	Symmetric	Asymmetric	Symmetric
Vertical gaze palsy	++	-	Late	Rare
Dystonia	Neck, limbs	Neck	Asymmetric in limbs	Late
Myoclonus	Absent	++	++	++
Pyramidal signs	++	++	Asymmetric	Late
L-dopa response	+/-	1/3 may respond	No response	Variable response
Dementia	Early	Mild	Lateralized cortical dysfunction	Early, severe
PSP- progressive supranuclear palsy MSD- multiple system atrophy CBD- corticobasal degeneration DLB- dementia with lewy bodies				

7. Endocrine disorders—Hypoparathyroidism.
8. Toxins—Methyl phenyl tetra hydropyridine (MPTP) which is used for drug abuse.

Neurological Features of Wilson's Disease (WD)

See also Chapters 32 and 93.

In 1912, Kinnier Wilson described the clinical and pathological features of this condition in his doctoral thesis under the name of progressive hepatolenticular degeneration. Though case reports of similar cases were published by others before him, the disease bears his name for his accurate descriptions of its detailed characteristics which helped to define it as a distinct clinical syndrome. Wilson's disease was identified as a hereditary process in 1921 by Hall. In 1985 Frydman and colleagues suggested that WD gene (Wc1) was located on chromosome 13. In 1993 WD was discovered to be caused by a defect in the gene that encodes a copper transporting P-type adenosine triphosphatase (ATPase) that is expressed in the liver and kidney. WD is a disease of copper toxicity. The problem is not one of excessive absorption of copper but a consequence of faulty transportation and elimination of copper. Ceruloplasmin is a globulin that binds and transports copper molecules. Although ceruloplasmin is characteristically reduced in WD it is not merely a disease of ceruloplasmin deficiency. In fact 5-15% of cases with WD may have normal or only slightly reduced ceruloplasmin.

Clinical Features

Untreated WD will eventually develop symptoms and signs of neurological dysfunction and in 40% of patients, it may be the initial manifestation. The average age at which neurological symptoms manifest is later than the average age of onset of hepatic manifestations (18 years versus 11 years), although neurological symptoms can occur in childhood and in adults even beyond 50 years.

The most common neurological presenting symptom in WD is tremor which may be rest, postural or intention tremor, fine or coarse, proximal or distal in the limbs and is invariably asymmetric. The proximal coarse tremor of the upper limbs in WD has been called "wing beating" tremor. Dysarthria, drooling of saliva and a fixed grimace-like smile (risus sardonius) are common in WD. In addition to facial and pharyngeal dystonia which cause the latter symptoms, dystonia can frequently affect the limbs and trunk in WD. Wilson's disease can also have features of parkinsonism. Some cases of WD can give rise to a cerebellar syndrome with scanning or staccato speech, intention tremor and impaired coordination. This is called pseudosclerotic type of WD because of the superficial

resemblance to multiple sclerosis. Seizures can occur rarely. Pyramidal signs and lower motor neuron signs (wasting, areflexia) are not seen in WD.

A high index of suspicion is required to diagnose WD. It is important to examine for **Kayser Fleischer (KF) ring** which is formed by the deposition of copper in the Descemet's membrane of the cornea in children, adolescents and adults with dystonia, tremor, parkinsonism, psychiatric disturbances and cerebellar syndrome. The ring appears first at the periphery of the cornea in the upper pole, followed by lower pole and then spreads around and centrally. The colour of the ring can vary from golden brown to green and may be difficult to visualize in patients with brown or black eyes. It is therefore essential to get a slit lamp examination by an experienced ophthalmologist to see the KF ring. The diagnosis is confirmed by the demonstration of KF ring, 24-hour urinary copper which is high, serum ceruloplasmin which is low and estimation of hepatic copper by liver biopsy. MRI brain is more sensitive than CT scan to look for brain involvement in WD. The basal ganglia, brain stem and thalami are characteristically involved in WD and the MR changes appear as hyperintense (white) signals in these areas in T2-weighted MRI scans. Molecular genetic testing of WD is not yet commercially available. The treatment of WD consists of 4 approaches: Limiting dietary copper, drugs that chelate copper such as pencillamine, trientine (triethylene tetramine dihydrochloride), drugs that reduce intestinal copper absorption, e.g. zinc sulphate or zinc acetate and ammonium tetrathiomolybdate, and finally liver transplantation. For dosage details see section 10 Chapter 93.

Huntington's Disease

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease caused by mutation in the gene that encodes for the protein Huntington (IT15) which is expressed in normal neural and non-neural tissues. The genetic defect in chromosome 4 consists of an excessive number of trinucleotide CAG repeats that code for the polyglutamine stretch in the Huntingtin protein. HD occurs worldwide but the highest concentration is in Venezuela.

HD is characterized by choreiform movements, intellectual decline and behavioral disturbances and it runs a relentless course. The majority of patients develop the symptoms in the late 30s while 5-10% of cases occur before the age of 20 years (juvenile HD). Rigidity, dystonia and slowness of movements (bradykinesia) are the predominant features of juvenile HD (in whom paternal inheritance is more common) than in the typical adult-onset form. They also have longer CAG repeat lengths in their abnormal gene. Cognitive and psychiatric

features of HD are the most important indicators of functional decline. Around 30 to 50% of patients develop depression and the risk of suicide is high. Psychosis is seen in 10% of cases.

CT and MRI brain show atrophy of the caudate nuclei and volumetric MRI may show atrophy of putamen as well. The disease is confirmed by genetic testing. Pre-symptomatic testing of unaffected family members has ethical, psychological and social implications and should be done only after professional counselling in experienced centres. Treatment of HD is only symptomatic for chorea and behavioral problems. There is ongoing research on neuroprotective strategies in HD.

Tardive Dyskinesias

The term tardive dyskinesias (TD) applies only to the abnormal movements that result from chronic treatment with agents that block central dopamine receptors for at least 3 months in persons with no other identifiable cause for the movement disorder. Most often these are antipsychotic neuroleptic agents (NL). Antidepressants with dopamine receptor blockade (e.g. amoxapine), anti-nausea medications like metoclopramide and rarely calcium channel blockers (e.g. cinnarizine) can also cause TD. A variety of abnormal movements occur in TD. The most common movements are choreic or stereotypies which are regular repetitive movements in the same anatomic distribution. Any body area may be affected, but mouth is more often affected causing lip smacking, tongue protrusion or grimacing (classical TD). Dystonic movements (tardive dystonia) can occur in TD alone or in combination with chorea or stereotypies. Tardive akathisia is an unpleasant sensation of internal restlessness which is partially relieved by volitional movements, usually of the lower extremities. Tics, myoclonus and tremor can occur as part of TD.

TD has no universally effective therapy and therefore prevention is most important. Neuroleptics should be used

conservatively and only when necessary. The new class of atypical neuroleptics (e.g. clozapine, olanzapine and quetiapine) are less frequently associated with TD and should be preferred over the typical neuroleptics.

Essential Tremor

Essential Tremor (ET) is most likely the most common movement disorder in the population. The prevalence has been estimated to be around 1074 per 100,000 population in a western population and 1.59 in the Parsi community in India. The prevalence increases with advancing age and is more in men than women. Positive family history for ET varies from 17 to 70% and such cases are inherited in an AD manner. The genetic locus has been identified in some families but the abnormal gene has not been located.

ET can begin at any age and the course is variable. Tremor is the sole manifestation of ET and most frequently occurs in the hands. Minor abnormalities in tone or gait may be seen occasionally. Tremor is of the postural type best seen in the outstretched hands and sometimes manifesting only in specific postures. Voluntary goal directed action aggravates the tremors. Rest tremors may occur rarely. The frequency of the tremor may range from 4 to 12 cycles per second. The tremors may start unilaterally but later it involves both hands. The hand writing becomes tremulous and angular but there is no micrographia as in Parkinson's disease. Tremor of ET can affect the head, tongue and voice in isolation or combination with limb tremor. Alcohol may produce marked amelioration of ET. It is important to exclude anxiety, thyrotoxicosis and exposure to tremorogenic drugs before diagnosing ET. ET is often mistaken for PD because of the coarse tremor and the age related slowness in some individuals. Treatment involves the use of beta blockers such as propranolol and primidone. Severe disabling ET that does not respond to medical treatment can be ameliorated considerably by surgeries such as thalamotomy or deep brain stimulation in the ventral intermediate nucleus of thalamus.

Miscellaneous Extrapyrarnidal Syndromes

P.K. Mohan, K.V. Krishna Das

Chapter Summary

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 Stiff Man Syndrome 1265
 ISSAC Syndrome 1266
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Kernicterus

This is a sequel to severe neonatal jaundice occurring in Rh incompatibility or ABO hemolytic disease. The unconjugated bilirubin crosses the blood brain barrier and depresses oxidative metabolism of brain cells, especially the basal ganglia. Initial symptoms include convulsions, opisthotonus, rigidity, and coma. Late sequelae are athetoid movements, spasticity, nerve deafness, and mental deficiency, which manifest by the age of 6-7 months. The pathological changes include loss of neurons and gliosis in the subthalamic nuclei, thalamus, globus pallidus, and the nuclei of the oculomotor and cochlear nerves. Once established, the condition tends to be permanent. Early detection of neonatal jaundice and treatment by exchange transfusion are important prophylactic measures to avoid neurological damage.

Drug Induced Extrapyrarnidal Syndromes

Several drugs give rise to extrapyramidal dysfunction as troublesome side effects. Important among them are neuroleptics, such as phenothiazines, butyrophenones, thioxanthenes, reserpine, metoclopramide and the like. In many instances, development of these syndromes limit further use of the drug. The clinical presentations may be:

1. **Acute akathisia:** Akathisia means inability to sit down quietly for a while associated with a feeling of restlessness and anxiety.

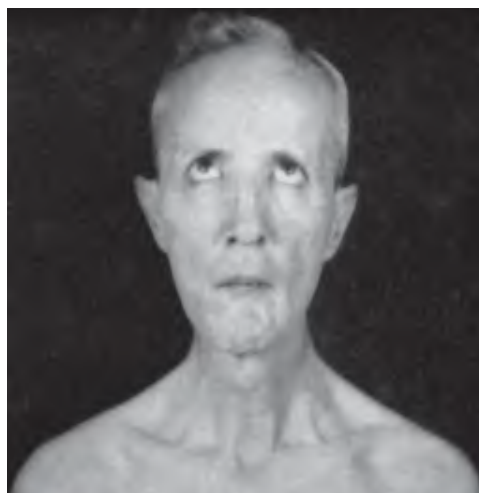


Fig. 192.1: Oculogyric crisis

2. **Acute dystonic reactions:** Adoption of grotesque postures.
3. **Oculogyric crisis:** Eyes are suddenly deviated to fixed postures lasting for minutes to hours (Fig. 192.1).
4. **Secondary Parkinsonism.**
5. **Tardive dyskinesia:** (tardive means late onset): This is a chorea like disorder in which facial grimaces are more prominent.
6. **Tardive dystonia:** It is a persistent dystonia often affecting the neck and upper limbs and stiff postures.
7. **Tardive akathisia:** In addition to the motor phenomena, they have subjective (psychological) symptoms which include feeling of tension, inability to remain still and urge to move.

Treatment consists of withdrawing the offending drug and parenteral administration of diazepam 5-7.5 mg, antihistamines like diphenhydramine 15 mg, or an anticholinergic like benztropine 2 mg.

Stiff Man Syndrome

Stiff man syndrome (Syn. Stiff-person syndrome, Meersch-Woltman syndrome, Anti-GAD antibody syndrome).

Patients with this rare disorder present with severe, symmetric stiffness of the axial and limb muscles that may wax and wane in intensity but progress steadily over several years. The stiffness is superimposed by muscle spasms which are triggered by volitional or passive movements, emotional stress, tactile stimulation or sudden noise. Typically, these symptoms disappear during sleep. The age of onset is usually between 30 and 50 years and women are more commonly affected than men.

The pathophysiology appears to be due to faulty modulation of spinal cord reflexes, mediated by GABA-ergic neurons in the spinal cord, which produce GABA at their synaptic nerve terminals. Glutamic acid decarboxylase, (GAD) is an enzyme required for the production of GABA at the motor nerve terminals. Autoantibodies against GAD are found in the serum of many patients with stiff man syndrome. This suggests that the disorder is of an autoimmune etiology. This is further supported by the presence of other autoantibodies, coexistence of other autoimmune diseases such as insulin dependent diabetes mellitus, thyroid disease and positive family history of autoimmune diseases.

EMG shows continuous normal motor unit potentials simultaneously in the agonist and antagonist muscles, even when they are apparently at rest. This motor activity disappears only with general anesthesia, spinal anesthesia, peripheral nerve blocks and therapy with diazepam, which is still the most effective drug to relieve muscle stiffness. Steroids, intravenous immunoglobulin and plasmapheresis are helpful in some patients.

ISSAC Syndrome

It is a syndrome of continuous muscle activity, pseudo-myotonia and neuromyotonia. Issac syndrome is a condition which is also characterised by progressive muscle stiffness, constant rippling movements of the muscles under the skin (myokymia), autonomic disturbances in the form of hyperhidrosis and tachycardia and grip or action myotonia, is referred to as *Issac syndrome*. Unlike in stiff man syndrome, the continuous muscle activity in Issac's syndrome persists even during sleep.

Phenytoin, carbamazepine and valproate, but not diazepam help to relieve muscle stiffness in Issac's syndrome. Antibodies against the potassium channels in the motor nerve terminals are thought to be responsible for the condition.

Writer's Cramp

Writer's cramp, the best known occupational (action-induced or task specific) dystonia is a form of action dystonia triggered only when the person attempts to write. It occurs usually between the ages of 30 and 50 years.

The symptoms usually begin as soon as the pen is picked up or only after writing a few words. The common symptoms are excessive gripping of the pen, flexion of the wrist, extension of one or more fingers, elevation of the elbow while writing and increase in muscle tone. Although cramps or aching of the hand is not invariable, many patients complain of discomfort in the fingers, wrists or forearms.

If the symptoms appear only during the act of writing the condition is referred to as *simple writer's cramp*. If dystonic symptoms appear also with other tasks such as eating with a spoon, shaving, using scissors or screw drivers, it is called *dystonic writer's cramp*. In either type, the course is variable. In the majority of patients, the severity will remain unchanged while some people may experience spontaneous improvement. The diagnosis of writer's cramp is essentially clinical. EMG can be employed to delineate the extent of the overactive muscles while writing.

Treatment of writer's cramp is unsatisfactory and it requires patience on the part of both the physician and the patient. Change of hand posture while writing, use of larger sized pens or pencils, and learning to write with the opposite hand are some of the strategies found to be useful. Anticholinergic drugs and botulinum toxin injections into selected muscles are helpful in treating severe dystonic spasms. Physical and occupational therapy, reassurance and relaxation techniques are beneficial.

Restless Legs Syndrome

The restless legs syndrome is characterized by unpleasant or uncomfortable feeling (aching, burning or crawling sensation) in the lower limbs and sometimes also in the arms and the trunk when the patient is supine. It is aggravated by nightfall and rest and is temporarily relieved by standing, walking or moving the legs, only to recur within a few seconds. The symptoms last from a few minutes to several hours and can disturb sleep. The neurological examination is normal. The cause is unknown. Genetic factors have been suspected. The course is protracted, although gradual improvement is sometimes observed. Restless legs syndrome is different from nocturnal leg and hand cramps, in which the affected person awakes from sleep with calf pain and muscle spasms.

Medication with L.dopa, bromocriptine, pergolide, benzodiazepines such as clonazepam, nitrazepam and diazepam, opioids such as propoxyphene and codeine administered at bed time are all reported to be beneficial in relieving symptoms. Recently, drugs like gabapentin, clonidine, baclofen, propranolol carbamazepine and pramipexole in a dose of 1.5 mg/day are also used.

Periodic Limb Movements Syndrome

Many individuals with restless leg syndrome also experience periodic limb movements (nocturnal myoclonus) only during sleep. These movements typically involve unilateral or bilateral flexion of the big toes, rapid ankle flexion and partial flexion of the knees and hips. Occasionally the arms may be affected. These movements last for less than five seconds but recur regularly every 20-40 seconds throughout the night during sleep.

However, most patients are unaware that these movements occur in their sleep but they usually complain of insomnia or excessive day time sleepiness, fatigue or asthenia. Periodic limb movement disorder is difficult to treat. The same drugs used for the treatment of restless legs syndrome may be tried with variable results.

Restlessness and movements of the upper limbs may be associated with local discomfort such as itching, burning and others. Pramipexole in a dose of 1.5 mg/day daily may be successful.

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Cerebrovascular Diseases

S.R. Chandra, P.K. Mohan

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General Considerations

Disorders of the central nervous system secondary to pathological, processes involving the blood vessels are very common after the fifth decade of life. Sudden neurological deficit due to ischemia or bleeding involving one or more cerebral blood vessels is called stroke. Vascular disorders are characterized generally by their abrupt onset. Strokes are broadly divided into 'ischemic' and 'hemorrhagic' types. Ischemic strokes include transient ischemic attacks, thrombotic stroke and embolic stroke. Hemorrhagic stroke may be caused by intracerebral and subarachnoid hemorrhage. When the supply of oxygen and glucose to the brain is interfered with due to vascular

occlusion, ischemic necrosis and infarction develop. Obstruction of an artery may be either by a thrombus or an embolus- cerebral thrombosis or cerebral embolism. Sometimes gross impairment of the cerebral circulation may result from hypotension produced by cardiac failure or shock and this may also lead to cerebral ischemia when the mean arterial blood pressure falls below 60 mm Hg. The cerebral blood flow depends upon the gradient between the mean arterial blood pressure and intracranial pressure.

Strokes are common in India. Though it is predominantly a disease beyond the age of 50 years strokes in the young occurring below the age of 40 years are not uncommon. Before the advent of CT scan, it was thought that 75% of strokes are ischemic and the rest hemorrhagic. Now it is realized that several pathological processes can lead to stroke and their etiology differs in the different age groups.

Complete Stroke

Incidence of stroke types:

Thrombosis	:	40%
Embolism	:	30%
Lacunes	:	20%
Hemorrhage	:	10%

Causes of Stroke in Persons above the Age of 50 Years

Atherosclerosis of the cerebral arteries: This accounts for the majority of cases. Lesions may be in the

intracranial portions of the arteries, particularly the striate branches of the middle cerebral artery and perforating branches of the basilar artery, or in the cervical portions of the internal carotid and vertebral arteries. Atherosclerosis may be complicated by thrombosis, embolization of subintimal plaques or hemorrhage. Platelet aggregates and atheromatous emboli arising from the carotid bifurcation are common causes of transient ischemic attacks (TIA) and further cerebral infarction. Cardiac sources of emboli in ischemic heart disease, atrial fibrillation and cardiomyopathies account for a good number of ischemic strokes in elderly subjects.

An epidemiological study conducted by the Indian Council of Medical Research (ICMR) in 1986 revealed that the main risk factors for stroke are hypertension, tobacco smoking and low hemoglobin levels. The combination of hypertension and tobacco smoking increases the risk of stroke twenty times. Increase in the systolic and diastolic blood pressures correlate with the risk. Carotid and vertebral artery atherosclerosis is associated with hypercholesterolemia. In many of them atherosclerosis of the coronary and peripheral arteries also occurs. Other known risk factors are diabetes mellitus, dyslipidemias, obesity, polycythemia and use of oral contraceptive drugs.

Causes of Stroke in the Young (Under 40 years)

Nonspecific aortic arteritis which is common in India accounts for many cases. Endarteritis occurring in syphilis, meningitis, brain abscess and other infective conditions may be complicated by arterial thrombosis and cerebral infarction. Embolism complicating several cardiovascular diseases is a common cause, the chief among them being rheumatic mitral stenosis with atrial fibrillation. Postpartum cerebral venous thrombosis and hematological disorders such as sickle cell disease and thrombophilia are also common causes for stroke in the young. Hyperhomocysteinemia is an accepted cause for stroke in all age groups. Hyperhomocysteinemia may be acquired as in deficiency of folate and vitamins B₁₂ and B₆ or may be an inborn error of metabolism. The intima becomes coarse and predisposes to thrombosis.

Pathogenesis

The brain tissue is most vulnerable to ischemia and the sequence of events leading to neuronal death sets in and proceeds rapidly following vascular occlusion. Normal blood flow is 50 mL/100 g of brain tissue per minute. At this rate of blood flow hemodynamic changes in any of the feeding arteries is compensated by autoregulatory mechanisms so that the cerebral blood flow is not compromised.

Fall of blood flow to 30 mL/mt: Autoregulation fails. Patients become stuporose and focal neurological deficits may occur.

Fall of blood flow to 20 mL/mt: Electrical changes occur. Normal EEG rhythm changes to slow wave activity. Focal neurological deficits worsen.

Fall of blood flow to 10 mL or less/mt: Irreversible brain damage.

Within ten seconds of arterial occlusion or circulatory arrest the patient becomes unconscious.

Neuronal ischemia may be due to disease or hemodynamic changes in the major arteries (macrocirculation) or the arteriolar circulation (microcirculation). 80% of ischemic strokes occur in the anterior circulation and 20% in the posterior circulation.

The electrical activity ceases within twenty seconds. Maximum affection occurs at the epicenter of the infarcted territory. Towards the periphery where some amount of oxygen may be available from neighbouring tissues or collateral circulation the ischemic damage may be less severe and these tissues may not be irreversibly damaged. It is now recognized that this “**ischemic penumbra**” may recover if therapeutic measures are instituted early to limit the extent and severity of brain damage.

The net effect of arterial occlusion on the cerebral tissue depends upon the available amount of collateral blood flow to the affected zone. The circle of Willis normally provides adequate blood flow in the event of occlusion of any artery proximal to it such as the occlusion of the internal carotid artery. There may be a retrograde anastomotic flow from the external carotid artery through the ophthalmic artery. In addition to the patency of the collateral vessels, the speed of occlusion also influences the collateral supply. Gradual narrowing of a vessel allows time for collateral channels to open up. Presence of hypotension or hypoxia at a critical moment may render the anastomotic channels ineffective.

With the progress of neuronal death, the ischemic area becomes edematous. This may lead to rise in intracranial tension (ICT) which will further impair the blood supply to the affected region. Other complications such as uncal herniation can occur.

Rise of ICT is even more pronounced with hemorrhagic strokes. In these, vasospasm may supervene and lead to extensive damage to nervous tissue. Hemorrhagic strokes are caused by extravasation of blood into the brain tissue due to rupture of arteries, veins or vascular anomalies such as arteriovenous malformation and aneurysms. In addition, any type of infarction of the brain may lead to softening of the infarcted tissue and secondary bleeding from unsupported blood vessels. The blood that extravasates ploughs its way through nervous tissue leading to its destruction. It may also rupture onto the

surface of the brain or into the cerebral ventricles leading to secondary subarachnoid hemorrhage.

The course of development of neurological events often gives clue to the type of stroke. In cerebral embolism, the deficit starts dramatically, reaching its peak within minutes, and thereafter recovery starts. Cerebral thrombosis also has an abrupt onset but it evolves slowly over a period of several minutes, hours, or days in a series of steps rather than in a smooth course. Cerebral thrombosis generally occurs when the blood pressure and cerebral blood flow are low as in sleep. The patient may notice the disability on waking up. In cerebral hemorrhage, the deficit usually manifests from the moment of onset of hemorrhage and steadily progresses over a period of minutes or hours. Cerebral hemorrhage occurs more commonly during the height of physical activity or emotional outburst. Though it was thought that cerebral hemorrhage inexorably proceeds to end fatally, it is now known with the advent of CT that in several cases the progress may be arrested and the lesion may even regress. However, the clinical presentation of cerebral infarction and hemorrhage may overlap, and diagnosis based on clinical features alone is bound to be inaccurate in many cases.

Neurovascular Syndromes Caused by Arterial Occlusion

CLINICAL FEATURES

Occlusion of arterial supply to the brain gives rise to diagnostic clinical features. Though as a general rule the infarcted area corresponds to the vascular supply, this may not be the case in many instances. Clinical localization, therefore, has its own limitation (Table 193.1).

Internal carotid artery (ICA): The ICA supplies the eye as well as the anterior two-third of the cerebral hemi-

sphere, via the anterior and middle cerebral arteries. The clinical features of ICA include:

- a. Contralateral paralysis of the limbs and face (hemiplegia),
- b. Contralateral hemisensory loss (hemianesthesia)
- c. Aphasia (if the lesion is in the dominant hemisphere),
- d. Visuospatial disturbance (if the lesion is in the non-dominant hemisphere), and
- e. Ipsilateral monocular blindness (due to occlusion of the ophthalmic artery).

Ipsilateral blindness occurring with contralateral hemiplegia is called **carotid hemiplegia**. The common carotid and ICA in the neck are accessible for direct examination. Palpation of the carotid pulse is a valuable method to identify occlusion of these arteries. Though the occluded common carotid artery can be palpated in the neck, palpation through the tonsillar fossa is a more reliable method to assess pulsation of the ICA. Severe atherosclerotic narrowing of the carotid artery gives rise to a bruit detectable by auscultation. The site of the bruit indicates the site of stenosis. A bruit heard over the angle of the jaw indicates stenosis of the carotid siphon . If it is heard lower in the neck, it is in the common carotid artery. In a severe stenosis bruit may not be heard over the affected side, but on the normal side a bruit may be heard due to compensatory increase in blood flow. Therefore, full reliance cannot be given to the bruit alone in determining the side of occlusion. Availability of doppler studies has facilitated the study of blood flow in these arteries.

Middle cerebral artery (MCA): The MCA which is the largest branch of the ICA supplies the entire lateral surface of the cerebral hemisphere excluding the motor area for the leg. It may be occluded in its stem or in its deep penetrating or superficial cortical branches. Occlusions of the MCA are mostly embolic, especially those of the cortical branches. The clinical picture in MCA stem

TABLE 193.1			
Distinctive clinical features in stroke			
	Thrombosis	Embolism	Hemorrhage
Age group	Elderly	Young or old	Younger
Time of onset	Sleep	Activity	Activity
Waking the patient during sleep	No	No	Yes
Headache	Present due to vasodilation of extracranial vessels	Not much	Sudden bursting headache
Seizures	Occurs late, when gliosis develops	Solitary seizures at onset	Recurrent seizures
Disturbance of consciousness	Minor	Minor or nil	Often severe
Recovery	Slow, mortality less, morbidity more	Good recovery	Mortality more, but in survivors morbidity is less

occlusion is similar to ICA occlusion except for the absence of monocular blindness. However, most of the emboli entering the MCA tend to drift into the cortical branches and very rarely to the deep penetrating vessels. Smaller emboli tend to occlude smaller branches so that the clinical picture tends to be less complete. Thus patients may present with weakness limited only to the face and arm (*facio-brachial paralysis*). The right or left hemispheric lesion is accompanied usually by contralateral homonymous hemianopia.

Anterior cerebral artery (ACA): This supplies mainly the medial surface of the anterior three-fourth of the cerebral hemisphere, anterior four-fifth of the corpus callosum and the anterior limb of the internal capsule. There is no serious disturbance in occlusion of the ACA proximal to the anterior communicating artery since adequate collateral flow develops from the opposite ACA. However, if the occlusion is distal to the anterior communicating artery, it results in weakness of the contralateral lower limb and slight weakness of the upper limb. The face is spared. Sometimes both the anterior cerebrals arise from a common stem. In such instances, occlusion produces paraplegia, incontinence of urine and abulia in which there is slowness of reaction and reduction of all activity.

Posterior cerebral artery (PCA): The anterior branches of the PCA supply the sensory nuclei of the thalamus through the thalamogeniculate branches, central midbrain through the paramedian branches and parts of the basal ganglia through the thalamoperforate branches. Occlusion of these branches results in characteristic syndromes. Infarction of the thalamus causes severe sensory loss and mild hemiparesis contralaterally. After sometime sensations begin to return and patient complains of pain and *hyperpathia* on the affected side. The term *hyperpathia* indicates an increased threshold to pain, but once pain is produced it is severe (*thalamic syndrome of Dejerine and Roussy*).

Infarction of the midbrain results in ipsilateral third nerve palsy and contralateral hemiparesis (**Weber's syndrome**). Sometimes ataxia on the side of hemiparesis occurs (*ataxic hemiparesis*). This indicates involvement of the cerebellar connections. Hemiballismus, hemichoreoathetosis or tremors result from occlusion of the thalamoperforate branches.

The cortical branches supply the calcarine cortex as well as the inferomedial portion of the temporal lobe. Bilateral occipital infarction causes total blindness of the cortical type. Here the pupillary reflexes are preserved and the fundus is normal. Many a time the patient is unaware of his blindness. This type of blindness has to be distinguished from hysterical blindness. Infarction involving the inferomedial portions of the temporal lobe

causes impairment of memory, especially for recent events (**Korsakoff's amnesic state**).

Vertebral artery: The two vertebral arteries supply the medulla. It is not uncommon for one of the arteries to be congenitally hypoplastic. In such instances occlusion of the dominant vertebral artery may produce significant bilateral disturbances. Sometimes in occlusion of the subclavian artery proximal to the origin of the vertebral, exercise of the ipsilateral upper limb results in syphoning of blood from the vertebral to the distal part of the subclavian. This retrograde flow of blood from the vertebral artery renders the brainstem ischemic and symptoms of vertebro-basilar insufficiency develop (**subclavian steal syndrome**).

In occlusion of posterior-inferior cerebellar artery supplying the lateral aspect of the medulla a characteristic syndrome called the **lateral medullary syndrome (Wallenberg's syndrome)** develops. This is perhaps the most common mode of presentation of vertebral artery occlusion. The resultant neurological features consist of sensory impairment over the face, Horner's syndrome and ataxia on the ipsilateral side, and impaired pain and temperature sensations on the contralateral side. In addition, vertigo, nausea, vomiting, dysphagia, hoarseness of voice, and hiccups also occur in many cases. In the pure form of this syndrome there is no weakness or pyramidal tract dysfunction.

In the medial medullary syndrome there is paralysis of the ipsilateral half of the tongue with contralateral hemiparesis. The face is spared. In addition, there is impaired proprioceptive sensations contralaterally. In total unilateral vertebral occlusion a combination of both medial and lateral medullary syndromes may be present.

Basilar artery: The basilar artery supplies essentially the pons, the middle and superior cerebellar peduncles and through the cerebellar arteries the cerebellar hemispheres. Basilar artery stem occlusion is usually due to thrombosis. Emboli usually lodge at the basilar bifurcation or in one of the posterior cerebral arteries. Total occlusion of the basilar artery is fatal, but rare. More frequently its branches are occluded. Often the deficit includes bilateral long tract signs with variable abnormalities of the cranial nerves and cerebellum. The patient is usually comatose (Table 193.2).

Transient Ischemic Attacks (TIA)

These are focal neurological deficits due to vascular cause developing suddenly and disappearing completely within 24 hours, without any residual abnormality. The common presentations are uni or binocular visual loss, paralysis of one or more limbs, aphasia, disturbances of cognition and /or numbness and sensory disturbances lasting for a

TABLE 193.2

Pattern of clinical features in various vascular syndromes				
Middle cerebral artery (MCA)	Anterior cerebral artery (ACA)	Common carotid artery (CCA)	Internal capsule (IC)	Vertebro-basilar artery (VBA)
Upper limbs weaker than lower	Lower limbs weaker than upper	Ipsilateral eye and contralateral hemiparesis resembling MCA, ACA or both	Equal weakness of upper and lower limbs	Bilateral affection
Aphasia if lesion is on the dominant side	Nil	±	Nil	Nil
Hemianopia often present	Absent	Present	Present	Present if PCA is affected
Hemianesthesia present	Cortical sensory loss in lower limbs	Hemianesthesia +	Present	Crossed anesthesia
Rarely cerebellar signs +	Absent	Absent	Rarely present	Cerebellar signs common
Recovery poor in patients with Wernicke's aphasia and hemianopia	Recovery poor due to frontal lobe infarct. Apathy and lack of drive	Variable	Variable	Recovery variable

few to several minutes. If the disability persists beyond 24 hours and upto 72 hours, it is called *Reversible Ischemic Neurological Deficit*- (RIND). If the disability persists beyond 72 hours but still recovers completely it is called *Prolonged Ischemic Neurological Deficit* (PIND). In more than 90% of cases the symptoms last for < 10 minutes. Recurrent TIA s should suggest critical narrowing of the feeding artery by atherosclerosis or other pathological processes and recent thrombo-embolic overlay. Since TIA s may be followed by total occlusion of the arterial supply, they are medical emergencies demanding assessment of the vascular status and immediate therapy.

The common sources of emboli are the following

- 1. Atheromatous plaques and platelet emboli from the aorta and the carotid or vertebro-basilar arteries.
- 2. Atrial appendage in atrial fibrillation.
- 3. Mural infarcts in myocardial infarction.
- 4. Cardiac valves and others.

Recurrent TIA s in the same territory suggest lowered arterial blood flow, often due to recurrent emboli. Presence of cervical spondylosis predisposes to the development of TIAs. At the stage of TIA s it is possible to prevent major strokes which may follow.

Differential diagnosis of TIAs include aural vertigo, arterial dissection, subdural hematoma, thrombophilia, seizure disorders, postural hypotension, hypoglycemia and cerebral venous thrombosis.

Management: Start antiplatelet drugs such as aspirin in a doses of 150 mg/daily oral and clopidogrel 75 mg qid on first day oral without delay, later reduce it to once daily. Anticoagulation with conventional heparin or preferably

with low molecular weight heparin should be started, and followed up with warfarin to keep the prothrombin time at INR 2.5.

Investigations for the underlying causes should be instituted simultaneously. These include Doppler studies of the carotid and vertebral systems, digital subtraction angiography of the major arteries in the neck and intracranial cavity, C T and /or MRI imaging of the brain, MRI angiography and investigations to detect cardiac and aortic lesions.

COMPLETED STROKE

Generally, occlusion of major artery is preceded by one or more transient ischemic attacks. Sometimes abrupt focal neurologic deficit occurs without preceding TIAs. The term completed stroke denotes the condition where there is no further progression of the neurological deficit over the previous 48 hours. The paralysis tends to be complete. If the neurologic deficit progresses over several hours or days, it is called “stroke-in-evolution”. In the initial 48 hours there is gradual deterioration of neurological status due to extension of the infarct and the development of cerebral edema. The patient may become comatose during this period and the condition may end fatally.

LACUNAR INFARCTS

This term is applied to infarcts smaller than 2 cm in diameter caused by occlusion of the deep penetrating arterial branches. Lacunes > 1.5 cm in diameter are called giant lacunes.



Fig. 193.1: Hemiplegia left—boy, hemiplegia right—woman see the characteristic posture

Lacunar infarcts are seen commonly in the internal capsule, basal ganglia and pons, usually in hypertensive individuals. Clinical features may be absent and if at all they occur, they are mild. The lacunar syndromes are characterized by a combination of motor, sensory and speech deficits depending upon the location of the lesions. Ataxic hemiparesis is a common presentation. The other clinical presentations include pure motor hemiparesis, pure hemianesthesia, dysarthria and 'clumsy hand syndrome'. Pure motor paralysis shows prompt recovery within a week.

Neurological Deficits Caused by Cerebral Infarction

CEREBRAL THROMBOSIS

Involvement of Cerebral Cortex and Subcortical Areas

This leads to hemiplegia, hemisensory loss of cortical type and hemianopia on the contralateral side, aphasia, abnormality of higher functions such as unconsciousness, and altered behavior. In many cases pattern may be stroke in evolution (Fig. 193.1).

Internal capsule: This is probably the most common site for infarction and the lesion gives rise to dense hemiplegia with upper motor neuron type of facial palsy on the opposite side of the lesion. Depending on the posterior extension of the lesion, sensory and visual phenomena may be evident.

Some capsular infarctions may extend to involve the lenticular nucleus and thalamus. This results in hemichoreoathetosis or hemitremor of the paralysed side. This is called striatal hemiplegia.

Brainstem: Lesions in the brainstem give rise to crossed hemiplegia. Midbrain lesions give rise to ipsilateral LMN palsy of the oculomotor nerve and contralateral hemiplegia — **Weber's syndrome**. Pontine lesions give rise to ipsilateral LMN facial palsy and contralateral hemiplegia. Medullary lesions give rise to ipsilateral LMN palsy of the tongue (XII nerve) and contralateral hemiplegia.

The course of the stroke is often unpredictable. Deterioration of the condition is usually due either to extension of the thrombus along the vessel, progressive stenosis of the artery, or acute brain edema. Intercurrent infections of the respiratory or urinary tract are constant dangers, which lead to rapid deterioration if they set in. On the other hand, patients with lacunar infarcts with pure motor hemiparesis start improving within hours and recover completely in a week. Delay in recovery suggests a poor prognosis.

Poor prognostic factors include:

1. Persistent gaze palsy
2. Persistent hypotonia
3. Sensory aphasia
4. Hemianopia and
5. Symptoms on one side with signs on the other side.

The paralysed limbs are flaccid in the acute stage and this flaccidity persists for the first few days or weeks. Gradually spasticity develops and the tendon jerks become brisk. The upper limb assumes a flexed adducted posture while the lower limb remains extended.

Investigations: Diagnosis of cerebral thrombosis should be suspected when a focal neurological deficit develops abruptly. Investigations help to confirm the nature of underlying pathology and extent of the disease. CT scan of brain is the investigation of choice in stroke. It may be useful even upto 48 hours after the onset of cerebral vascular occlusion. It confirms the nature of underlying brain pathology and also indicates the location and extent of brain damage. The infarcted area is seen as a low density lesion (black). CT scan may be normal in about 3-5% of cases if it is done too soon after the onset of cerebral vascular occlusion. However, early CT scan helps to exclude cerebral hemorrhage. Further improvements on CT scan include contrast enhanced CT scan, perfusion scan and CT angiography after IV administration of iodinated contrast.

In a few cases, in order to exclude meningitis and subarachnoid hemorrhage LP and CSF analysis have to be undertaken, preferably after a CT examination to exclude any serious contraindication for LP. Occasionally, LP may reveal subarachnoid hemorrhage even when the CT scan is normal.

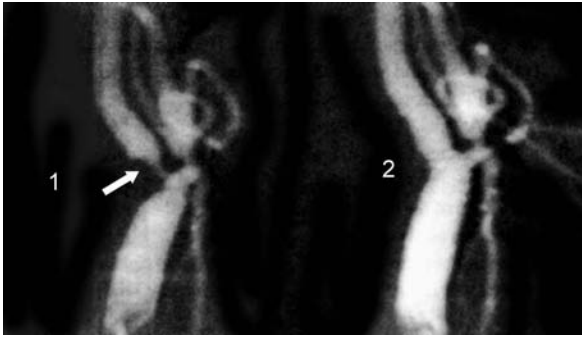


Fig. 193.2: Internal carotid artery stenosis, arteriogram
(1) Note the narrowing—arrow (2) after correction

The electroencephalogram which may show low voltage records of a lower frequency over the infarcted area is neither diagnostic nor specific.

MRI gives the details better about the ischemic zone. Radionuclide scans and positron emission tomography (PET) reveal the infarct even before it is recognized by CT.

Intravenous digital subtraction angiography is a non-invasive investigation which demonstrates the occlusion clearly. When the carotid lumen is reduced to 25% or less, the distal flow is compromised. Information on carotid blood flow can also be obtained noninvasively by periorbital directional doppler ultrasonography, phonoangiography, or a combination of multi-gated pulsed doppler ultrasonography and high resolution B-mode scanning (*duplex system*) (Fig. 193.2).

Investigations for risk factors of stroke should be carried out.

Management of Thrombotic Stroke

The undisputed therapeutic principles in the management of brain ischemia are: (i) restoration of normal systemic blood pressure, (ii) adequate oxygenation, (iii) avoidance of hypercapnia, and (iv) abolition of seizures, if present. In the acute stage the aim is to ensure adequate cerebral perfusion and to avoid all factors that interfere with cerebral blood flow. The patient is nursed in the recumbent posture, carefully avoiding the upright posture. Coexistent disorders like anemia or polycythemia should be corrected. In chronic hypertensive patients, higher than normal blood pressure may be needed to maintain cerebral perfusion. Cerebral blood flow may come down if the blood pressure is lowered below 150 mm Hg systolic. Therefore, careful watch is necessary while administering antihypertensive therapy. Blood pressure should not be lowered in the acute phase unless it is above 200/120 mm Hg. Exceptions include, concomitant aortic dissection, acute myocardial infarction, severe heart failure or hypertensive encephalopathy. Rapid reduction of BP is indicated urgently in hypertensive encephalopathy. It is controversial in cerebral hemorrhage. In other forms of stroke it is better to wait for 48-72 hours after the onset,

for instituting antihypertensive therapy to reduce blood pressure. When drug therapy is required, useful agents include sodium nitroprusside, labetalol and calcium channel blockers. Further rise in blood pressure can be prevented by oral doses of atenolol or nifedipine.

Mannitol 200 mL of 20% solution given in a dose of upto 1.5 g of mannitol/kg bw given intravenously rapidly within 20 minutes helps to reduce cerebral edema. Barbiturates in high doses lower cerebral metabolic activity and help to mitigate the ischemic damage independent of their antiepileptic action.

Hypothermia reduces cerebral metabolism and oxygen demand. In ideal situations this can be tried. Seizures increase the metabolic demands of brain tissue. Hence, antiepileptic drugs are employed if seizures occur.

The use of anticoagulants: They have a role in patients with recurrent TIAs or 'stroke in evolution' in arresting further thrombosis. When cardiac embolism is evident, these drugs are clearly indicated. It is important to exclude intracranial hemorrhage by CT scan before starting anticoagulants. Mild to moderate hypertension is not an absolute contraindication.

Anticoagulants are used with advantage in the following conditions:

1. Thromboembolic stroke
2. Venous sinus thrombosis
3. Progressive thrombosis
4. Thrombophilias and
5. TIAs
6. Possibility of peripheral venous thrombosis.

The anticoagulants are maintained at dosage levels needed to keep INR 2-3.

The usual regime is to start heparin 5000 units 4 h intravenously for 1-2 weeks. Low molecular weight heparin is a safe alternative but more expensive. Heparin therapy is followed up with oral anticoagulants of the coumarin group for 8-16 weeks. Since anticoagulation is always associated with the risk of hemorrhagic lesions in the brain, this form of therapy should be undertaken only in specialized centres, preferably in "**acute stroke care units**". They have no role in completed stroke.

Thrombolytic therapy is recommended as a modality of treatment in acute ischemic stroke. However selection of cases has to be meticulous and individualized. Thrombolytic therapy employs recombinant tissue plasminogen activator (rtPA) given IV. The time of administration is crucial in bringing out good outcome. In carotid territory strokes it has to be given IV within 3 hours of onset. In the vertebro-basilar territory rtPA is useful if given up to 12 hours from the onset or even later if intra-arterial injection is given. Dose is 0.9 mg/kg body weight up to a maximum of 90 mg. Ten percent of the drug is to be given as a bolus and the rest as IV infusion over 60 minutes. Intra-arterial administration is associated with

slightly higher risk of bleeding. CT evaluation is mandatory. CT evidences of massive infarction such as subdural effacement, mass effect, edema are all contraindications.

Other contraindications include:

1. Rapidly progressing neurological deficit
2. Seizures at the onset of stroke
3. Presence of systolic BP > 180 mm Hg and diastolic BP > 110 mm Hg
4. Prior occurrence of intracranial bleeding
5. Occurrence of previous stroke or head injury within 3 months
6. Major surgical procedure within the preceding two weeks.

Relative contraindications include

- a. Concurrent anticoagulant therapy
- b. Age above 80 years
- c. Blood glucose levels < 50 mg/dL or > 400 mg/dL
- d. Platelet counts < 100,000/cmm
- e. Rapidly improving stroke and
- f. Those who wake-up from sleep due to stroke.

If employed under ideal conditions rtPA produces better outcome in the immediate post-stroke period and also quality of life at the end of 2-3 months. rtPA leads to bleeding complications intracranially and also outside the cranium. The drug is very expensive cost—Rs. 35000 for one injection of 50 mg and it has to be used only in tertiary care centers, by personnel experienced in its use. Measures to improve the efficacy of rtPA such as use of ultrasound energy to facilitate thrombolysis are under trial. Direct administration of rtPA into the artery gives better results. In view of the adverse side effects and high cost other, thrombolytic drugs are being developed.

Physiotherapy is to be started early to facilitate movement and rehabilitation. Early ambulation is advocated, since this helps to avoid the development of contracture, periarthritis, and bedsores.

Surgical treatment: Whenever recurrent TIAs are associated with demonstrable significant (>75%) stenosis due to atheroma or ulcerating plaques in the internal carotid artery or the arch of aorta, surgical intervention is indicated. Thromboendarterectomy or bypass graft of the carotid, innominate or subclavian arteries has been employed to revascularise the part. Present evidence suggests that prophylactic endarterectomy reduces the risk of subsequent strokes. Results of Medical Research council (MRC UK) Asymptomatic Carotid Surgery Trial (ACST) 2002 showed that in asymptomatic patients younger than 70 years who have 70% or more reduction of carotid artery diameter, immediate carotid endarterectomy reduced the risk of stroke at 5 years follow-up, by 50% (12% vs 6%). Perioperative mortality risk is 3%. Stenting of the carotid artery in the neck or intracranially

is also done. The long-term results seem to be encouraging (Fig. 193.2).

Prevention: Since ischemic stroke is largely a preventable disease, the present stress is on prevention. Attention to the risk factors for atherosclerosis and correction of lesions giving rise to embolic episodes form the mainstay for primary prevention.

Proper control of hypertension is the most effective prophylactic intervention in the prevention of ischemic as well as hemorrhagic strokes.

Aspirin in a dose of 150 mg should be started as early as possible after the diagnosis of ischemic stroke as a treatment and for prophylaxis against recurrence. Clopidogrel, given orally in a dose of 75 mg od is also an effective antiplatelet drug. This can be given as the sole antiplatelet drug or can be combined with aspirin for better results.

Dyslipidemia is corrected by life style modifications and the use of statins.

Cerebral Embolism

Cardiogenic embolism to brain: 15-20% of cerebral emboli are cardiovascular in origin.

Major risk factors include atrial fibrillation, prosthetic heart valves, mitral stenosis, recurrent myocardial infarction, left ventricular thrombus, atrial myxoma, infective endocarditis, non-ischemic dilated cardiomyopathy and marantic endocarditis. In India where rheumatic heart disease is still prevalent it is a frequent cause for the occurrence of stroke in the young. Atrial fibrillation, irrespective of the cause increases the risk of embolic stroke. Risk of embolism in patients above the age of 60 years with atrial fibrillation is 5-8% annually. In the presence of structural abnormalities such as valvular defects or infarcted myocardium the risk is increased several folds. In ischemic heart disease embolism occurs commonly in the week following acute infarction. In patients with persistent ventricular thrombi the risk is 10% in the initial 6-12 months.

Minor risk factors are mitral valve prolapse, severe mitral annulus calcification, patent foramen ovale, atrial septal defect and calcific aortic stenosis.

Probable sources with minimal risk include carotid artery stenosis narrowing the lumen to 50% or less, left ventricular aneurysms, sick-sinus syndrome and peripartum cerebral venous or arterial thrombi.

Paradoxical embolism may occur in atrial septal defect, ventricular septal defect and pulmonary arteriovenous fistulae. Patent foramen of ovale is a possible source for cerebral embolism.

Risk for mechanical prosthetic valves is 2-4% yearly. Rates are higher for valves in the mitral position than in the aortic.

Emboli commonly consist of platelet thrombi, atheromatous plaques, cardiac vegetations and calcareous particles, but rarely fat, air and tumour tissue may be seen. The clinical setting in which embolism occurs often provides the clue to the nature of the embolus. When an embolus lodges in an artery, it leads to distal thrombosis along the ramifying vessels or it may fragment and get impacted in smaller vessels. Infarcts caused by emboli are often hemorrhagic since the blood flowing into damaged vessels escapes into ischemic or necrotic brain tissue. The middle cerebral artery territory is most frequently involved in embolism. The most common cause is chronic atrial fibrillation occurring in either rheumatic or atherosclerotic heart disease. The other causes include mural thrombi from myocardial infarction, vegetations on prosthetic valves, bacterial endocarditis and rarely mitral valve prolapse. Iatrogenic causes include complications during arteriography or surgery of the neck and thorax.

The clinical picture depends on the artery involved. Usually the embolus lodges in one of the branches rather than the mainstem of an artery. Thus it is more common to produce a focal deficit like monoplegia or motor aphasia rather than a complete hemiplegia. Often the deficit is transitory since the embolus passes distally into smaller vessels. Occurrence of distal thrombosis leads to extension of the infarct.

Investigations: Cerebral ischemia is confirmed by a CT scan. Detection of the source for embolus strengthens the diagnosis of embolism.

Management: Prevention of cerebral embolism is more important than its treatment. Restoring atrial fibrillation to normal sinus rhythm and long-term anticoagulant therapy in patients with myocardial infarction and cardiac valve prosthesis prevent embolic complications. However, once the embolism results in infarction, it is necessary to exclude a hemorrhagic infarct before anticoagulant therapy is started. Low dose heparin therapy started early and followed up with oral warfarin anticoagulation, the prothrombin time being kept at INR 2.5–3.5 reduces the risk of recurrent stroke by 75%.

In cardioembolic stroke secondary hemorrhage into the infarct may develop, and therefore, anticoagulation therapy should be deferred for at least 48 hours after the stroke. Large infarct, i.e. infarct with 2/3 or more involvement of the occluded arterial territory is a contraindication for starting heparin, since there is a high risk of hemorrhagic transformation. In such cases anticoagulant therapy may be deferred for upto 2 weeks.

In cerebral embolism complicating bacterial endocarditis, it is advisable to withhold anticoagulants because of the danger of intracranial bleeding. Effective antibiotic therapy reduces the risk.

Intracranial Hemorrhage

Hemorrhage in the intracranial cavity may be extracerebral, intracerebral, or intraventricular. Extracerebral hemorrhage may be extradural, subdural or subarachnoid in location. Hypertension is the most common cause of non-traumatic intracranial hemorrhage, followed by ruptured aneurysms, and vascular malformations. Hemorrhage may result from bleeding disorders or inflammatory disease of the cerebral arteries but it is less common.

INTRACEREBRAL HEMORRHAGE

Syn: Spontaneous nontraumatic-intracerebral hematoma

Intracerebral bleeding is most common in the sixth and seventh decades of life. Analysis of 100 consecutive cases at the Medical College Hospital, Trivandrum, revealed that hypertension, arteriovenous malformation, eclampsia, brain tumours, arteritis and anticoagulant medication accounted for a total of 50% of the cases. In the others no causal factor was demonstrable. Among the known causes, hypertension was the most frequent. Rarely the blood pressure may be in the normal range when first examined after the stroke.

Other causes include amyloid angiopathy in patients above 70 years, A-V malformation, angiomas, tumours, dural venous sinus thrombosis, coagulopathies and bleeding into ischemic area. The extravasated blood accumulates to form a circular or oval mass and behaves like a space occupying lesion displacing the midline structures to the opposite side. *The common sites of hypertensive hemorrhage* in the order of frequency are: (i) putamen and internal capsule, (ii) cerebral white matter, (iii) thalamus, (iv) cerebellum, and (v) pons. Majority of intracerebral bleeds develop due to rupture of minute aneurysms (**Charcot-Bouchard aneurysms**) seen in hypertensives.

CLINICAL FEATURES

The onset is usually abrupt with rapid evolution of symptoms. Hemorrhage generally occurs while the patient is up and active. Recurrence of bleeding is rare. The clinical signs depend on the location and size of the hematoma. Headache is a common symptom preceding the attack.

In hemorrhage into the putamen, internal capsule and lobar white matter, there is contralateral hemiplegia becoming complete within 5-30 minutes. The level of consciousness worsens and the patient lapses into coma. Upper brainstem signs appear in large lesions.

In thalamic hemorrhage hemisensory loss equals or even outstrips the motor deficit. The characteristic ocular abnormality is the skew deviation of the eye with the

opposite eye deviated downward and medially. In pontine hemorrhage the patient is deeply comatose with pin-point, but reacting pupils.

In cerebellar hemorrhage the patient complains of occipital headache and repeated vomiting, followed by vertigo and ataxia. There is ipsilateral sixth and seventh nerve palsy with paralysis of conjugate lateral gaze to the side of hemorrhage.

Once deep stupor or coma has supervened, patients rarely survive. Sometimes the hemorrhage extends into the ventricles or it produces secondary brainstem compression leading to coma. Death occurs in about 60-70% of cases. In those with smaller hemorrhages the hematoma resolves and in such patients the prognosis is better than that of infarction.

Investigations: With the advent of the CT scan, localization of the site of hemorrhage has become very easy and accurate, and this is the investigation of choice. The area of hemorrhage on CT scan appears as hyperdense (white) lesion and the surrounding brain edema as hypodense (black) lesion.

MRI, CT angiography and conventional X-ray angiography are used when the cause of intracranial hemorrhage is uncertain, particularly if the patient is young or not hypertensive and the hematoma is not in the usual site for hypertensive hemorrhage.

MANAGEMENT

The immediate management of an unconscious patient with intracranial hemorrhage consists of assistance to ventilation, fluid restriction, and measures to reduce intracranial tension such as intravenous administration of 20% mannitol or 200 mL given IV as a rapid infusion within 10 minutes, and repeated fourth hourly.

Blood may compress brain tissue in the acute stage. Surgical evacuation of the hematoma is indicated in patients who are not comatose, (i) if the hemorrhage lies near the cortex, and (ii) in cerebellar hematoma and intraventricular hematoma. In deeply comatose patients surgery carries high risk. In those showing improvement with medical management, it may not be considered necessary. In addition to the general measures instituted in comatose patients, proper control of hypertension is also important. The mean BP should be kept above 70 mm Hg by appropriate therapy. Recombinant factor VII a has been used IV to arrest progression of hematoma.

Summary of Treatment Options in Acute Strokes

1. Improve and stabilize cerebral perfusion—Avoid hypotension, cardiac failure and cardiac arrhythmias.
2. Control of cerebral edema — Rapid IV infusion of 20% mannitol initially and followed up with oral

glycerine 15 mL 6 h help to prevent the rise of intracranial tension.

3. Hemorrhheological methods to improve microcirculation.
Controlled hemodilution,
4. Antiplatelet drugs to prevent platelet aggregation and thrombosis—These are more useful for prevention of recurrence.
5. Anticoagulants — indicated in cardio-embolic stroke, stroke in evolution and recurrent TIAs.
6. Thrombolysis — in carefully selected patients within 3 hours of onset.
7. Tissue protectors—these are employed to protect the jeopardized neural tissue from further damage. Metabolism of brain cells can be reduced by inducing barbiturate coma. Partially affected neurons may undergo reperfusion injury especially as a result of free-radical accumulation. Free-radical scavengers like vitamin E have been tried with a view to reduce this damage.
8. Surgical measures such as removal of the extravasated blood are indicated when these can be undertaken with safety. When the hematoma is localized within the brain and gives rise to pressure effects surgical evacuation is life-saving.

Preventive Strategies to Avoid Recurrence of Ischemic Stroke

Correction of dystepidemia and stopping of tobacco smoking should be instituted forthwith.

Aspirin in a dose of 75-150 mg daily is recommended in thromboembolic strokes. Clopidogrel is an alternate drug which is to be considered in those who are intolerant to aspirin. Its cost is higher. Combination of aspirin and clopidogrel gives synergistic effects.

Warfarin or other anticoagulants may be employed in those who have potential for recurrent cardiogenic embolism.

The period for which prophylactic therapy has to be continued is not standardized. This decision should be made in each case depending on its merits.

Subarachnoid Hemorrhage

Bleeding into the subarachnoid space constitutes subarachnoid hemorrhage (SAH). The ICMR collaborative study (1988) revealed that subarachnoid hemorrhage is not uncommon in India. Males are affected more (M : F = 1 : 0.73). Maximum prevalence was in the fifth and sixth decades. 46.7% were due to berry aneurysms, and 9.4% due to arteriovenous malformations (AVM).

Other less common causes of subarachnoid hemorrhage include malignant tumours, trauma, bleeding disorders like thrombocytopenic purpura and hemophilia excessive anticoagulation, and hemorrhagic meningitis. In

these cases the clinical evidence of the underlying disorder will be evident.

Aneurysms develop at sites of developmental defects in the media and elastica of the cerebral arteries. Often they are multiloculated and sometimes, multiple. These are called berry aneurysms. They are usually located at bifurcations and branchings of the vessels. Approximately 90% of the aneurysms are located on the anterior part of the circle of Willis.

The common sites include the anterior communicating artery, origin of the posterior communicating artery (PCA), major bifurcations of the middle cerebral artery (MCA), and the bifurcation of the internal carotid artery (ICA) into MCA and ACA (anterior cerebral artery). Other sites include ICA in the cavernous sinus and bifurcation of the basilar artery.

Aneurysms are not present at birth. They develop after the period of adolescence and some of them continue to grow. Those above 3 mm in diameter tend to rupture. If they grow bigger (10 mm or more) they give rise to pressure symptoms and their tendency to rupture also increases.

Genetically determined conditions may be associated with increased occurrence of intracranial aneurysms.

These include:

1. Autosomal dominant polycystic disease of the kidney
2. Ehlers-Danlos syndrome type IV
3. Neurofibromatosis type I
4. Marfan's syndrome.

As compared to sporadic aneurysms, the familial cases tend to rupture earlier even when they are smaller. Such patients also develop fresh aneurysms on follow-up.

In addition to congenital defects, arterial wall may be weakened by emboli developing in infective endocarditis (mycotic aneurysms). Many of these aneurysms may not rupture at all. When they do so, the rate and amount of bleeding is highly variable.

PATHOPHYSIOLOGY

When an artery ruptures into the subarachnoid space there is rapid rise of intracranial pressure (ICP) which may reach arterial pressure levels. This impairs normal cerebral blood flow and leads to coma. If the bleeding stops spontaneously the ICP falls and coma passes off. If the ICP remains high for considerable periods, brain death follows and patient does not recover from coma. Intracerebral hemorrhage and herniation of brain due to ICP worsen the problem further. Blood collecting at the base of the brain obstructs the foramina of fourth ventricle leading to obstructive hydrocephalus. The portion of the arteries bathed in subarachnoid blood go into vasospasm leading to infarction of the brain. This results in delayed ischemic neurological deficit. Blood which has entered the CSF undergoes defibrination and hemoglobin

undergoes further changes with release of bilirubin which makes the CSF xanthochromic (yellow colour).

Other clinical presentations result from mass effect due to the size of the aneurysm and features of cerebral ischemia.

CLINICAL FEATURES

Before Rupture

Most of the aneurysms are asymptomatic until they rupture. They may, however, become symptomatic by causing pressure on the adjacent structures. A large aneurysm of the ICA may produce compression of the optic chiasma, third, fourth and sixth cranial nerves, and ophthalmic division of the fifth cranial nerve. Posterior communicating artery aneurysms may press upon the ipsilateral oculomotor nerve.

After Rupture

Rupture of an aneurysm results in subarachnoid hemorrhage. The patient usually presents with excruciating headache of sudden onset followed by loss of consciousness. Sometimes consciousness is lost without any premonitory symptoms. Rarely the leak is small and only mild headache may develop without further progression. The sensorium may improve within a few hours but usually confusion lasts for ten days or more. In many cases focal neurological signs may not be present. When present, these signs help to localize the aneurysm. Signs of meningeal irritation like neck rigidity, Kernig's sign, and Brudzinski signs are usually present. Examination of the fundus frequently reveals pre-retinal or subhyaloid hemorrhages. In those with raised intracranial tension papilledema may develop. Reversible electrocardiographic abnormalities such as T wave inversion, ST depression, prolongation of QT interval and others may be seen in about 80% of cases.

INVESTIGATIONS

Imaging Studies

Subarachnoid hemorrhage should be suspected when an otherwise healthy individual suddenly develops severe headache associated with features of meningeal irritation without fever or other signs of infection. CT scan is the investigation of first choice wherever available. In the early phase of the bleed, CT is the most sensitive diagnostic test. The blood from the CSF is rapidly cleared and so the sensitivity of CT scanning falls to 80% at 3 days, 50% at 2 weeks and 30% at 3 weeks. MRI is less sensitive than CT in the early stages, but later in the course of the disease it becomes more diagnostic. MRI reveals parenchymal pathology such as arteriovenous malformations, cavernomas or vasculitis, which can all lead to SAH.

Lumbar Puncture

In those cases that come late even if the CT scan is negative, if the clinical suspicion is high, a diagnostic LP may be necessary to confirm the diagnosis. However LP is a risky procedure which should be undertaken only when facilities for management of brainstem herniation are ready at hand. The CSF shows uniform blood staining and on centrifuging the supernatant is xanthochromic if the hemorrhage is of at least 6 hours duration. Occurrence of xanthochromia is a highly suggestive point favoring SAH. On standing, the blood does not clot, and the erythrocytes settle at the bottom. This has to be distinguished from blood staining of the CSF caused by accidental injury to veins during the LP (traumatic hemorrhage). In this condition the CSF clears-up as it flows out, the initial samples being more bloodstained than the later ones. On standing the blood clots and on centrifugation the supernatant is not xanthochromic. After a bout of subarachnoid hemorrhage the xanthochromia persists for at least three weeks.

Cerebral Angiography

If CT or LP shows positive evidence of SAH and if there is no other obvious cause, four-vessel angiography is indicated to exclude aneurysm. The most frequently used investigations to delineate intracranial aneurysm are **digital subtraction angiography**, MRI angiography and helical (also called spiral) CT angiography. DSA or conventional angiography of the cerebral vessels is the gold standard, but are associated with the risks of TIA in 4%, permanent ischemic damage in 1% and death in 0.1%. Three dimensional DSA angiography is available in a few centers. By this technique full details of the intracranial aneurysms can be obtained. Angiography will reveal site, size and number of patent aneurysms, arteriovenous malformations, midline shifts and other abnormalities. In some cases initial angiography may be negative due to vasospasm. If the clinical suspicion is strong a second

angiography undertaken 2-6 weeks later may reveal the underlying cause in such cases (Fig. 193.3).

Course

Approximately 10-15% die before seeking medical attention. 40% of hospitalized patients die within a month. More than a third of the survivors develop major neurological deficits.

Initial mortality is 20-25% in spontaneous subarachnoid hemorrhage. Aneurysms tend to re-bleed after initial hemostasis at the rate of 4% on the first day and thereafter 1-2% daily for the first two weeks during which time the risk is highest. Thereafter the risk comes down. Recurrent bleeds tend to be more severe and are accompanied by higher mortality.

The Hunt and Hess Grading System of SAH

- Grade 1 Asymptomatic or minimal headache and neck rigidity.
- Grade 2 Moderately severe headache, nuchal rigidity, no neurological deficit other than cranial nerve palsy.
- Grade 3 Drowsiness, confusion, mild focal deficit.
- Grade 4 Stupor, moderate to severe hemiparesis, possibly, early decerebrate rigidity and disturbance of vital functions.
- Grade 5 Deep coma, decerebrate rigidity, moribund appearance.

Management

Definitive treatment of the aneurysm is surgical. Once subarachnoid hemorrhage is diagnosed and aneurysms are identified by angiography, the next step is to decide the time of surgery. In deeply comatose patients, surgery carries a high risk. Hence it is better to operate when the patient's general condition has improved. General management in such instances consists of absolute bed rest,

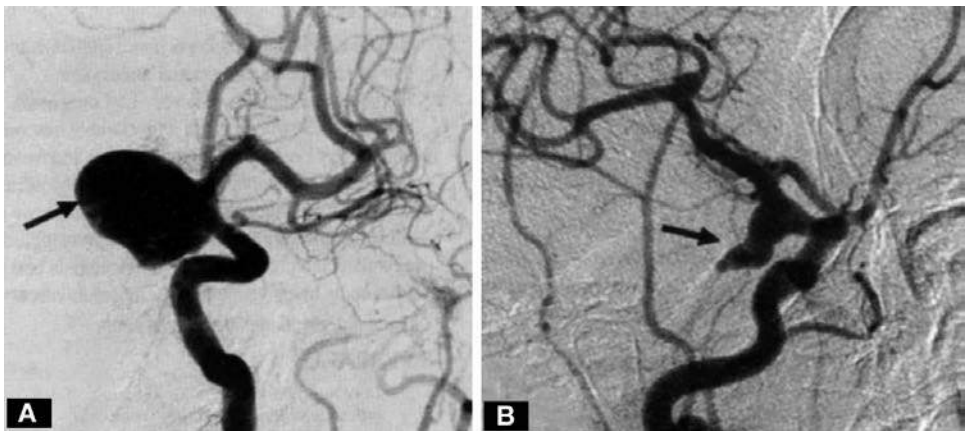


Fig. 193.3: Carotid angiography. A and B show berry aneurysm—arrows

continuous sedation, and control of hypertension and seizures if present.

Nimodipine given orally in a dose of 60 mg every four hours helps to relieve cerebral vasospasm and improve the circulation. Nimodipine can also be given IV in a dose of 3 mg/hour.

Another approach which is also experimental is to increase blood volume by giving IV infusions and improve perfusion pressure using dopamine infusions.

Early surgery is more beneficial. Suitability for surgery is best assessed by a modified Glasgow Coma Scale, recommended by the World Federation of Neurological Societies (WFNS).

World Federation of Neurologic Societies Grading system of SAH		
Grade	Glasgow coma scale	Motor deficit
Grade 1	15	No
Grade 2	13-14	No
Grade 3	13-14	Yes
Grade 4	7-12	No or Yes
Grade 5	3-6	No or Yes

The tendency at present is to clip the aneurysm using operating microscope within 96 hours of hemorrhage in patients in grades 1 and 2. In patients with intracranial hematoma early evacuation is life-saving. Operation between the 4th and 10th day of ictus carries heavy risk of ischemic neurological deficit.

Careful monitoring to avoid undue fall in blood pressure is essential. Liquid paraffin 10 mL may be given twice daily to keep feces soft and avoid straining. Once the general condition is stabilized, surgical ligation or clipping of the aneurysm is advised to prevent recurrence of bleeding. Other surgical procedures include occluding the aneurysm by introducing coils into the aneurysmal sac and inducing thrombosis by embolization; or strengthening the sac by fascial or muscle covering.

Prophylaxis

Close relatives of patients who had subarachnoid hemorrhage due to aneurysms and those who have genetic predisposition have been subjected to screening test with a view to detect aneurysms before they rupture. Marginal benefit has been reported.

Arteriovenous Malformation (AVM)

These developmental anomalies consist of abnormal communications between the arterial and venous systems resulting in a cluster of dilated vessels. There are no capillary vessels between the two systems.

They vary in size from a few millimeters to huge masses lying in the cortex or white matter, usually in the

posterior half of the cerebral hemispheres. They usually become symptomatic in the second or third decade. They present initially as subarachnoid or intracerebral hemorrhage, focal epilepsy, vascular headache, hemiparesis or any focal neurological deficit. The combination of epilepsy with subarachnoid hemorrhage should suggest this possibility. The annual risk of hemorrhage is 1.3-4%. History of previous bleed and hypertension increase the risk.

X-ray skull may reveal abnormal linear (rail track) or crescentic calcification. CT scan and MRI will confirm the diagnosis. Arteriography delineates the abnormal vessels.

Indications for radical treatment include seizures resistant to drugs, progressive neurological deficit and intractable headache. Microsurgical resection is the gold standard of treatment. Other modalities include endovascular embolisation and radio-surgery.

Secondary Subarachnoid Hemorrhage

This occurs when blood from cerebral hemorrhage enters the general subarachnoid space by rupturing the cerebral cortex or rupturing into the ventricles.

Intracranial Venous Thrombosis

Etiology

In India this is one of the common causes of stroke in the young. It may be secondary to bacterial thrombophlebitis or simple cerebral phlebothrombosis secondary to congenital or acquired thrombophilic states. Bacterial thrombophlebitis complicates infections on the face, neck, scalp, and particularly the central part of the face. Other causes of thrombophilia include postpartum and postoperative states, polycythemia, sickle cell disease, severe dehydration in children and the aged, vasculitis, deficiencies of protein C, protein S, antithrombin-III, Factor V Leyden, mutation of the prothrombin gene and myeloproliferative conditions. They predispose to venous thrombosis in different sites. Use of oral contraceptives aggravates this tendency. A stroke occurring in the background of such a clinical setting is suggestive of cerebral venous thrombosis. Sometimes, even in the absence of intracranial infection, occlusion of the superior sagittal sinus or lateral sinus develops with rise of intracranial tension.

CLINICAL FEATURES

Intracranial thrombophlebitis is usually secondary to infections in the middle ear, paranasal sinuses, mastoids or skin over the face. In such instances, high grade fever and toxemia are present. The lateral sinuses, cavernous sinuses and superior longitudinal sinus are commonly involved.



Fig. 193.4: Cerebral venous thrombosis

In lateral sinus thrombosis, the infection spreads to involve the jugular bulb to give rise to the **jugular foramen syndrome** with paralysis of IX, X and XI cranial nerves. In such patients compression of the ipsilateral jugular vein fails to produce rise of CSF pressure during lumbar puncture and the Queckenstedt's test. The CSF pressure rises if the patent jugular vein on the opposite side is compressed. Venous thrombosis evolves more slowly compared to arterial occlusions and it has a greater tendency to produce seizures and hemorrhagic infarcts, compared to the latter.

Cavernous sinus thrombosis is usually secondary to infections of the ethmoid or maxillary sinuses or the skin around the eyes and nose. The clinical features include high grade fever, chemosis of the conjunctiva, proptosis,

and edema of the ipsilateral eyelid. Later the fundus shows papilledema with retinal hemorrhages. Unilateral or bilateral paralysis of the third, fourth, sixth, and ophthalmic division of the fifth cranial nerves develop. Within a few days the infection spreads to the other cavernous sinus through the interconnecting vessels (Fig. 193.4). Sooner or later meningeal infection supervenes and meningitis develops.

In superior longitudinal sinus occlusion, symptoms start with unilateral convulsions and hemiplegia. Subsequently the occlusion spreads to involve the superficial cortical veins.

Treatment: Treatment consists of attention to the primary cause and anticoagulant therapy. When infection is suspected the mainstay of treatment consists of high doses of appropriate antibiotics and measures to prevent or reduce cerebral edema and convulsions. Once the infection is controlled, the focus of infection in the offending ear or paranasal sinus should be tackled surgically to prevent recurrence. At present intravenous injection of thrombolytic agents have been used to dissolve the clot and restore patency.

Anticoagulants: Role of anticoagulants in infective thrombosis is controversial. Anticoagulants are indicated in the absence of any hemorrhagic lesion. Except in the presence of infection anticoagulant therapy has to be started with low molecular weight heparin and maintained with oral anticoagulants at INR 2-3, for periods upto one year or longer, depending on the condition.

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Intracranial Space Occupying Lesions

Ananda Kumar, P.K. Mohan

Chapter Summary

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General Considerations

The term 'intracranial space occupying lesion' (ICSOL) includes lesions which expand in volume to displace normal neural structures and lead to increase in intracranial tension.

Intracranial space occupying lesions encompass tumours, parasitic cysts, abscesses, granulomas,

lymphoma, large infarcts and hematomas in the brain. All these conditions are fairly common in India. Around 5-6% of neurological disorders in India are constituted by space occupying lesions.

These lesions give rise to the following three groups of symptoms in general.

- 1. **Neurological phenomena caused by irritation or destruction** of brain tissue, e.g. focal seizures (Jacksonian epilepsy) and paralysis.
- 2. **Features of raised intracranial tension (ICT):** The rate of increase of tension and its level depend upon the nature of the lesion and its location. For example, rapidly growing tumours and multiple secondaries give rise to rapid rise in ICT whereas slow growing tumours and cysts may be accommodated within the cranium for considerable periods without symptoms. Moreover, in general, posterior fossa lesions lead to more rapid rise in tension than supratentorial lesions.
- 3. **False localizing signs:** (a) These are neurological phenomena arising from secondary effects of the lesions. As a result of herniation of brain tissue under the falx cerebri or downward herniation through the tentorium cerebelli and foramen magnum, pressure effects on other parts of the brain develop. (b) *Countre-coupe effect:* This is pressure effect caused on the side opposite to the side of lesion when a space occupying lesion expands. The midline

structures such as brainstem may be pushed against the opposite free margin of the tentorium cerebelli to give rise to focal neurological deficit ipsilateral to the space occupying lesion.

In addition to these general features different lesions may produce symptoms specific to their nature. For example, brain abscess may be associated with fever and other signs of infection. Secondary subarachnoid hemorrhage may be associated with signs of meningeal irritation. Table 194.1 gives the common ICSOLs.

Clinical Features

- 1. *Persistent headache* not due to any other detectable cause and unresponsive to simple medication should suggest the possibility of ICSOL. The headache may be felt in the midline over the head or at times it may be referred over the site of lesion, e.g. meningioma. It may be continuous and progressive, paroxysmal (as in migraine), or aggravated by coughing, stooping forward or changing postures.
- 2. *Vomiting and visual loss:* In many cases projectile vomiting is a usual symptom. The term projectile vomiting refers to vomiting unassociated with nausea. Projectile vomiting may be mistaken for gastrointestinal or psychiatric disturbances. Visual disturbances due to papilledema develops with time.
- 3. Recent onset of behavioral changes.
- 4. *Late onset seizures:* Any type of seizure occurring for the first time after the age of 15 years should suggest the possibility of ICSOL and this demands full investigation.
- 5. Onset of neurological deficits.

TABLE 194.1

Common intracranial space occupying lesions

- 1. *Congenital:* Dermoid, epidermoid, hamartoma, and teratoma.
- 2. *Traumatic:* Subdural and extradural hematomas.
- 3. *Inflammatory:* Abscesses (acute and chronic), tuberculomas, syphilitic gumma, fungal granulomas.
- 4. *Parasitic causes:* Cysticercosis, hydatid cyst, amebic abscess, *Schistosoma japonicum*.
- 5. *Neoplasms:*
 - a. *Tumours arising from neural structures*
Gliomas—astrocytoma, ependymoma, oligodendroglioma, mixed glioma, medulloblastoma, medulloepithelioma, sarcoma, pinealoma.
 - b. *Tumours arising from appendages*
Meningioma, neurilemmoma (Schwannoma, e.g. acoustic neuroma), chordoma, osteoma.
 - c. *Pituitary tumours*
Adenomas of the pituitary which are intracellular, and craniopharyngiomas which arise from remnants of the *Rathke's pouch*— which are suprasellar.
- 6. *Vascular lesions:*
Angioma, hemangioblastoma, hemangiopericytoma, and papilloma of the choroid plexus.
- 7. *Secondary neoplasms:*
The brain is a common site of secondaries from carcinoma of the lung, kidney, breast and alimentary tract. In addition, acute leukemias and lymphomas cause infiltration and tumour formation in the central nervous system leading to rise in ICT.

Intracranial Hematomas

Hematomas are common complications following injury to the skull. Blood may collect in the extradural space or subdural space.

EXTRADURAL HEMATOMA

This is collection of blood between the dura and the skull. The blood may be derived from injury to the middle meningeal vein, middle meningeal artery, diploic vein, dural venous sinuses or small vessels lying between the dura and the skull. The commonest site is the temporal fossa. Other sites include the frontal, subfrontal and occipital regions, vertex and posterior fossa.

Pathogenesis: The initial collection of blood in the extradural space results in stripping of the dura from bone. Further oozing from the damaged vessels increases this space and the hematoma enlarges. Clinically significant hematomas exceed 25 mL in volume. The extent and location of the hematomas are determined by the ease of

stripping of the dura; the site of injury and its severity, and the presence of fissured or depressed fractures of the skull.

Clinical features: Extradural hematomas are seen in 1-2% of patients suffering from head injuries. It is uncommon in children below 3 years of age and in old age. In the latter, adherence of the dura to the skull prevents its easy stripping.

Immediately following trauma there may be a period of loss of consciousness, after which there is a period of apparent normalcy with clear consciousness (*lucid interval*). This is again followed by deterioration of the mental state. If the bleeding is rapid, this lucid interval may be absent.

Classical features include rise in intracranial tension leading to progressive deterioration of the level of consciousness, pupillary abnormalities and contralateral hemiparesis.

Pupillary changes: The pupil on the side of lesion constricts initially, then it dilates. As the ICT rises, the opposite pupil also dilates. This sequence of events is referred to as **Hutchinson's pupillary reaction**.

In children massive bleeding into the cranium may lead to pallor.

Diagnosis: Intracranial bleeding should be suspected when there is change in the level of consciousness, rise in ICT. Pupillary abnormalities and focal neurological deficits following major or even minor head injuries. Presence of fracture of the skull strengthens this suspicion. The most reliable methods to demonstrate the hematoma are CT scan and MRI. Cerebral angiography may be required in some cases to demonstrate the cause of hematoma, especially in atypical locations (Fig. 194.1).

Course and prognosis: Progressive collection of blood leads to rise in ICT and death. Early diagnosis and treatment are rewarded by full recovery. Therefore, the investigations should not be delayed when intracranial hematomas are suspected. Though early treatment ensures full recovery, seizures may develop as a sequel in some cases.

Treatment: Medical treatment consists of measures to lower intracranial tension and anticonvulsant medication. Definitive therapy consists of surgical evacuation of the hematoma through burr holes.

SUBDURAL HEMATOMA

This is collection of blood between the dura and the arachnoid. This may follow injuries which may be apparently trivial or even unnoticed. The development of the hematoma may be acute (within 3 days), subacute (within two weeks) or chronic (within months). Chronic subdural hematomas are more common in alcoholics, epileptics, patients receiving anticoagulation therapy and in dehydrated children. Sudden reduction of ICT following shunt surgery for hydrocephalus or even lumbar puncture may give rise to subdural hematoma.

Common cause of subdural hematoma is bleeding from superficial veins or venous sinuses but it may also develop as a complication of cerebral hemorrhage or cortical tumours. The usual sites are the frontal, anterior temporal, and parietal region. The lesion is bilateral in 10% cases. The hematoma may consist of fluid or clotted blood or blood mixed with CSF (*subdural hygroma*).

Pathology: The hematoma consists of fluid blood covered on the inner and outer aspects by layers of fibrin. The blood is defibrinated on account of the constant pulsation

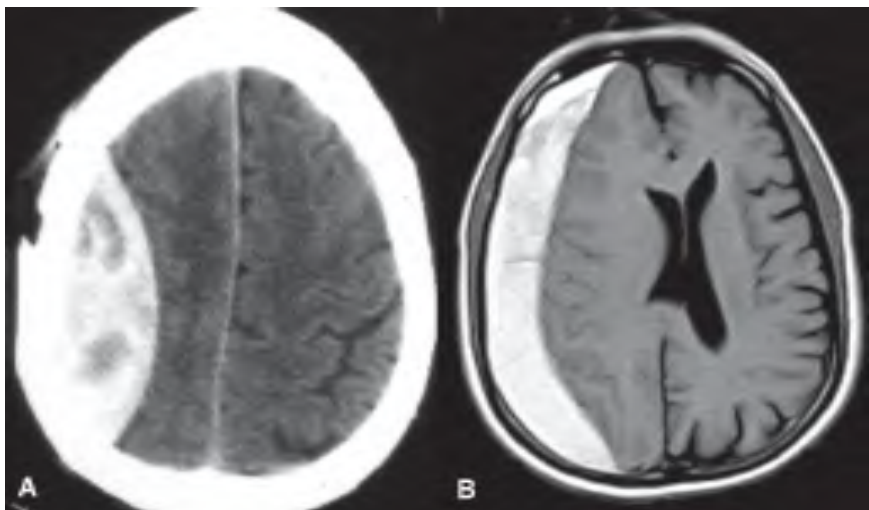


Fig. 194.1: C T scan showing (A) extradural and (B) subdural hematomas. Note the hematoma compressing the brain tissue and leading to pressure effects (i.e.) distortion of the ventricles and shift of mid line structures

of the brain. The high protein content of the fluid makes it hyperosmotic. It absorbs fluid from the surroundings and enlarges, thereby increasing the ICT. Subdural hematoma may be the only lesion in many patients. In others it may coexist with extradural hematoma or intracerebral hemorrhage. Acute and subacute subdural hematomas are often associated with cerebral contusion, laceration or edema.

Clinical features: The symptoms, in general, are similar to those of extradural hematoma but less dramatic and often atypical.

Chronic subdural hematoma differs in symptomatology from the acute and subacute varieties. It presents as dementia, altered behaviour, psychiatric manifestations, or focal neurological deficits. The level of consciousness fluctuates. History of trauma may be doubtful or may be absent in many cases. In the middle aged and elderly, headache, contralateral hemiplegia and papilledema are the prominent features. Children present with vomiting, restlessness, irritability, refusal to feed, anemia, seizures, and failure to thrive.

Diagnosis: In the acute and subacute form diagnosis may be easy. Around 60% of cases of fracture of the skull show accompanying subdural hematoma.

A high degree of clinical suspicion is necessary for the diagnosis of chronic subdural hematoma in the elderly and children, especially so if history of trauma is not forthcoming. CT scanning shows up the hematoma clearly in almost all cases and this is the investigation of choice (Fig. 194.1). The hematoma appears as a clear avascular zone between the compressed brain below and the skull above on cerebral angiography.

Course and prognosis: Acute subdural hematoma which is often associated with underlying injury to the brain is associated with a mortality of 40-60%. Subacute and chronic subdural hematomas act as progressive space occupying lesions and end fatally, if left untreated. If treated in time, recovery is complete and prognosis is excellent.

Treatment: Surgical evacuation should be undertaken without delay, after locating the hematoma. Medical therapy consists of measures to lower intracranial tension and anticonvulsants.

Intracranial Tumours

These may be primary or secondary. Primary tumours arise from the brain parenchyma, the cerebral blood vessels, the cranial nerves, the meninges, the pituitary gland and the skull. They may be benign or malignant. Secondary tumours are due to hematogenous metastases from malignant tumours at distant sites. Intracranial metastasis

may be lodged in the brain parenchyma, skull vault or the meninges. The common primary tumours that give rise to intracranial metastases are carcinoma of the lungs, breasts, thyroid and the abdominal and pelvic viscera. Most of the intracranial metastatic lesions are solid. Some may be cystic or hemorrhagic. Neoplastic cells from the abdominal and pelvic viscera can also reach the intracranial structures directly through the vertebral venous plexus (*Batson's system of veins*).

PRIMARY INTRACRANIAL NEOPLASMS

Among the primary tumours gliomas which arise from glial cells are the commonest. They are more common in men. Astrocyte, being the most common glial cell, astrocytomas is the most common among glial tumours. The other glial tumours are oligodendrogliomas, ependymomas and medulloblastomas in the order of frequency. Depending on their histology, these tumours are classified into four grades (I to IV) grade I being the least and grade IV the most malignant neoplasm.

Next to gliomas meningiomas are common. These are slow growing benign tumours arising from dural covering of the brain. They are usually located in the parasagittal regions. Unlike gliomas, the meningiomas are more common in women.

Depending on the age of the patient and the intracranial location of the tumour, the nature of the lesion can be inferred accurately in many cases.

Age	Supratentorial brain tumours	Infratentorial brain tumours
Infancy and adolescence	Glioma	Cerebellar astrocytoma
	Craniopharyngioma	adolescence
	Choroid plexus papilloma	Medulloblastoma
	Pinealoma	Brainstem glioma
Middle age	Optic nerve glioma	Ependymoma of fourth ventricle
	Glioblastoma	Metastases
	Meningioma	Acoustic neuroma
	Astrocytoma	Meningioma
	Metastases	
Elderly age	Pituitary adenoma	
	Metastases	Metastases
	Glioblastoma	Acoustic neuroma
	Meningioma	Meningioma

GENERAL CLINICAL FEATURES

Clinical presentation of a patient with intracranial tumour depends upon:

- i. The site, size and rate of growth of the tumour,
- ii. The rate of rise in intracranial pressure, and
- iii. The mass effect on the neighbouring structures.

Rapidly growing tumours in the posterior cranial fossa may present as an acute emergency while slow growing tumours such as meningiomas and oligodendrogliomas in the supratentorial region may remain silent for long periods. As a rule, the symptoms produced by an intracranial tumour are generally progressive over a period of weeks to months but occasionally they may appear more rapidly or abruptly. Cerebral edema around the tumour, hemorrhage into the tumour or displacement of brain structures are the usual causes for rapid worsening of symptoms in some cases. ***The constellation of headache, vomiting and papilledema are the classic clinical features of an established intracranial tumour.*** However, these findings are inconstant in many cases and may be even late to appear in the course of the illness, but when they do occur, especially in association with progressive neurological deficits such as dysphasia, diplopia, blurring of vision, sphincter incontinence or altered state of consciousness they invariably indicate the presence of a brain tumour or any other intracranial space occupying lesion.

The classic description of tumour headache is that it usually starts as mild episodic dull ache at night or on rising-up from sleep in the morning. It becomes worse by coughing or straining and gets better as the day progresses or the patient assumes erect posture. Over a period of time the headache becomes continuous and intense. In one-third of the cases, the headache may occur as an early symptom. However, it should be remembered that cases with headache due to tumour account for only a small proportion of the total number of headaches seen in clinical practice. Neither the location, nor the intensity of the headache correlates directly with the level of intracranial pressure (ICP). Even when the ICP is within the normal range, headache may result from traction or pressure on the dura mater, major cerebral blood vessels or pain sensitive cranial nerves.

Vomiting occurs in one-third of the cases with intracranial tumour. It is more common and early in onset, when the tumour is located in the posterior cranial fossa. Like headache, vomiting also usually occurs soon after getting up from sleep.

Papilledema is a common and sinister finding in intracranial tumours, as it reflects the raised intracranial pressure. It is often bilateral but it can be unilateral or asymmetric at times. Blurring of vision and constriction of the visual fields are early symptoms. Objective testing of vision reveals concentric constriction of the visual fields and enlargement of the blind spot.

Focal or generalised seizures occur in 25-30% of the cases with brain tumours. They are more common with supratentorial tumours.

The neurological deficits caused by brain tumours depend upon:

1. The location of the tumour.
2. The level of the intracranial pressure, and
3. The presence or absence of complications such as brain herniation.

When the tumour is located in the frontal lobe or is associated with significant hydrocephalus, it may manifest as dementia, altered behavior, mood or personality in the early stage. Sometimes, the patients may present with hallucinations, delusions or confusional state. Sometimes, false localising neurological signs may develop due to herniation of brain structures. The medial part of the temporal lobe (uncus) ipsilateral to a supratentorial tumour may be displaced downwards and medially through the tentorial notch. This is called ***transtentorial uncal herniation.***

This leads to the following sequence of neurological phenomena:

1. Compression of the third cranial nerve on the side of the tumour results in pupillary dilatation and ptosis which are the earliest clinical signs of uncal herniation.
2. Compression of the posterior cerebral artery ipsilateral to the tumour gives rise to ischemia of the occipital cortex and hemianopia on the contralateral side.
3. Compression of the cerebral peduncle on the side opposite to the tumour (countre-coup effect) leads to hemiparesis on the side of the tumour.
4. Compression of the midbrain on the side of the tumour leads to contralateral hemiplegia. When this occurs along with the compression of the cerebral peduncle on the opposite side, bilateral upper motor neuron signs develop.

Downward displacement of the brain may also occur due to raised ICP in the supratentorial compartment (brainstem herniation). This stretches the bulbar cranial nerves leading to their dysfunction.

In many cases, even without brain herniation, unilateral or less commonly bilateral VI cranial nerve palsy may occur as a false localising sign.

Special Clinical Features

Gliomas: These constitute half of all the neural tumours. Depending on the histological features, they are pathologically divided into grades I to IV depending on the malignant nature of the neoplasm. Grade I is the least malignant whereas Grade IV is the worst. Grade IV gliomas are known as glioblastoma multiforme and they form 80-90% of all gliomas. In 20-30% of cases the tumours are multicentric and bilateral. The common locations for gliomas are the cerebral hemispheres, brainstem, cerebellum, and spinal cord.

Astrocytomas: These are slow-growing tumours, seen more commonly in the cerebrum, cerebellum, thalamus,

pons, and optic chiasma. Cavitation and/or calcification may develop in many cases. Malignant change may supervene later.

Oligodendrogliomas: These are rare, slow growing tumours, usually seen in the cerebrum, often with calcification.

Ependymomas: These grow inside the fourth ventricle and less commonly in other sites. They are more frequent in children.

Meningiomas (endotheliomas): These benign tumours arise from the dural covering of the brain particularly seen in sites having arachnoid granulations. The sites of predilection are para-sagittal regions, olfactory groove, tuberculum sellae, sylvian fissure, sphenoidal wing, occipital region, and the spinal cord. Older age groups are affected more. More than 90% of meningiomas are associated with abnormalities of chromosome 22.

The tumours are firm, lobulated, highly vascular and adherent to the dura. They compress subjacent brain tissue and lie embedded in it without actual invasion. Commonly the tumours may be calcified. The overlying bone may show erosion or more commonly hyperostosis. Arterial bruit may be heard over highly vascular meningiomas. Surgical removal of meningiomas gives very satisfactory results.

Medulloblastoma: This term is a misnomer which has been handed down by common usage, because medulloblasts are not identifiable in these lesions. These are rapidly growing primitive neuroectodermal tumours affecting the vermis of the cerebellum and giving rise to widespread metastases in ventricles, spinal cord, and meninges. The course and progress are rapid so that clinically these tumours may resemble inflammatory lesions. Children are affected more.

Schwannoma syn: Neurofibroma, neurinoma, neurilemmoma: These are benign, slow growing tumours arising from nerve sheaths with maximum frequency in the fourth and fifth decade. The commonly affected nerve is auditory nerve (**acoustic neurinoma**) and less commonly the trigeminal. The extramedullary part of the VIII nerve is affected and the tumour is located in the cerebellopontine angle (C-P angle) in the posterior cranial fossa. Bilateral acoustic neuromas are seen to be strongly associated with neurofibromatosis type 2.

Acoustic neurinomas produce a characteristic progression of symptoms which depend on the anatomical configuration of this region. The onset is with tinnitus, vertigo, or deafness. Later on there is rise in intracranial tension. As the lesion extends, there is progressive compression of the VII, V, IX and X cranial nerves sequentially. Compression of the brainstem may cause contralateral hemiplegia and hemianesthesia. As the

compression progresses, counter-coup pressure on the side opposite to the brainstem gives rise to the development of hemiplegia and sensory disturbances on the same side as well. The tumour is highly vascular. The internal auditory meatus is often eroded and this can be demonstrated by X-ray of the base of the skull (**Towne's view**). Isolated 10th nerve palsy, raised intracranial tension and even post papilledematous optic atrophy can be the presenting feature of acoustic neurinoma. This occurs as it is a slow growing tumour and compensatory mechanisms mask the localizing features and even the symptoms of raised ICT. CT or MRI scan visualises the lesion. Treatment is surgical removal.

Other tumours in the C-P angle region include meningiomas, trigeminal schwannomas, cholesteatomas, arachnoid cysts and aneurysms.

Tumours in the Region of the Pituitary Fossa

Tumours arising from the pituitary start within the sella turcica. These may be chromophobe or chromophil adenomas. They produce enlargement of the sella turcica and as they grow big, the diaphragm sellae is eroded and the tumour may press on the under aspect of the optic chiasma. In addition to pressure effects determined by their location, endocrine manifestations are also seen. Overproduction of hormones by the tumour gives rise to features such as acromegaly, gigantism, and hyperprolactinemia, depending on the type of neoplasm. Many a time pressure of the tumour on the surrounding normal tissue may lead to pituitary hypofunction.

Craniopharyngioma: Suprasellar tumours and cysts arise commonly from the remnants of the pituitary stalk. These are called *Rathke's pouch tumours*. These are midline tumours occurring at variable distances above the diaphragm sellae. In addition to local pressure effects, they lead to bitemporal hemianopia and later on total blindness and optic atrophy as a result of pressure on the optic chiasma from above. Pressure on the region of the hypothalamus gives rise to somnolence, hyperphagia, obesity, and diabetes insipidus.

Stunted growth with papilledema in a child, should make one suspect craniopharyngioma. It can present in the fifth decade with features of dementia and visual loss.

Suprasellar tumours are generally very slow-growing. Many show calcification in skull radiographs. CT and/or MRI will delineate the lesion.

Pineal Tumours: See section 11, Chapter 97

Patency of the normal foramina of the fourth ventricle allows free communication between the ventricular and subarachnoid CSF spaces. These foramina may be congenitally blocked as in *Dandy-Walker syndrome*. It may occur as acquired phenomenon in basal meningitis or tumours.

Tumours that invade the base of the skull from below: *Nasopharyngeal carcinoma* infiltrates several cranial nerves arising from the medulla and pons.

Glomus jugutare tumours arise from glomus tissue embedded in the external coat of the jugular vein. These tumours may grow into the jugular foramen leading to pressure effects on the VIII, XII, IX, X and VII cranial nerves. Glomus tumours give rise to intense pain. Erosion of the jugular foramen can be demonstrated by CT scan.

Secondary deposits: Carcinomas of the lungs and breast are prone to produce cerebral metastases. Other primaries include carcinomas of the kidney and alimentary tract. Acute lymphatic leukemia and to a lesser extent acute myeloid leukemia may produce lesions in the central nervous system. Lymphomas also may produce neurological manifestations by infiltration. See section: 15 Chapter 159.

MANAGEMENT OF INTRACRANIAL TUMOURS

Early diagnosis is very essential. A high index of clinical suspicion is absolutely essential to plan the appropriate investigation. Proper history and clinical examination including funduscopy should enable the physician to arrive at a provisional diagnosis, not only of the possibility of a brain tumour, but also its site and nature.

Investigations

CT or MRI scan of the brain provides the diagnosis promptly and noninvasively in almost all cases of brain tumour and hence these are the investigations of choice whenever available. MRI is superior to CT in detecting small or isodense tumours, tumours located in the posterior cranial fossa or tumour close to the skull vault or skull base. MRI also picks up multiple metastatic lesions that may be missed by CT.

A thorough search for the primary should be made when intracranial metastases are suspected. A radiograph of the chest should always be obtained in order to exclude carcinoma of the lung which is a common source of intracranial metastases.

Conventional cerebral angiography is seldom done to diagnose a brain tumour. However, in some cases if it is required to elucidate the vascular pattern of the tumour and its relation to the major blood vessels CT angiography or MRI angiography are done. These are relatively non-invasive procedures which will give valuable clues. This helps in the surgical procedure when needed and also helps to exclude the possibility of a giant intracranial aneurysm presenting as a tumour.

Lumbar puncture is contraindicated when an intracranial tumour or other space occupying lesion is clinically suspected or confirmed on CT or MRI scan because of the risk of fatal brain herniation.

Apart from electron microscopy and immunocytochemistry other techniques have evolved as regards the diagnosis of intracranial neoplasms. These include specific markers for glial cells, neurons and epithelial cells. There are also methods to identify gene structure and gene localization by molecular probes.

Differential Diagnosis

Whenever a brain tumour is suspected, other intracranial space occupying lesions such as subdural hematomas, brain abscess, tuberculoma, cysticercosis, fungal granulomas, large demyelinating plaques, large cerebral infarcts and cerebral hematomas should be considered in the differential diagnosis. Sometimes, conditions like hydrocephalus and benign intracranial hypertension (BIH) may masquerade as tumours.

TREATMENT, COURSE AND PROGNOSIS

The course and prognosis of a brain tumour depend upon its site, size, degree of malignancy, rate of growth, invasiveness and the response to treatment. Less than 20% of the patients with glioblastoma survive 1 year after the onset of symptoms. Survival can be prolonged by a few months by radiotherapy. Chemotherapy increases survival to a limited extent. Less malignant tumours such as astrocytomas are more amenable to surgery and radiation therapy. Their survival is 5-6 years. Tumours confined to the cerebellum have better survival rates.

Meningiomas, and acoustic neuromas can be removed by surgery completely. However if the surgical resection is incomplete recurrence is likely.

Symptomatic medical therapy aims at reducing intracranial tension with IV steroids (dexamethasone), mannitol and frusemide. Antiepileptic drugs should be given to control seizures.

The present day management of brain tumour is not uniformly ideal. Recent advances in refined microsurgical techniques, radiation therapy and chemotherapy have made the therapeutic regimen more acceptable and effective. In recent years conventional surgery is being replaced by destruction of the tumour using gamma knife, wherever it is available. The principle is to destroy the lesion by radiation, applied to the target precisely by computed focussing. Use of the gamma knife is limited since it can be employed only for few tumours satisfying specific criteria.

Gene therapy, gene transfer therapy and immunotherapy with monoclonal antibody are promises for the future.

Hydrocephalus

Syn: Hydroencephalus

Dilatation of the ventricular system of the brain due to accumulation of CSF is called hydrocephalus. This may

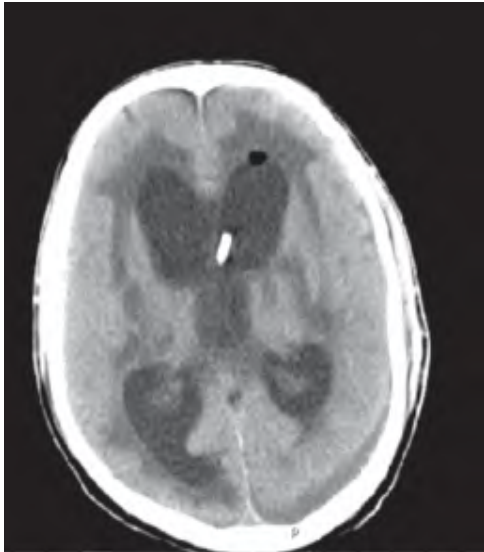


Fig. 194.2: CT scan showing hydrocephalus
Note: The dilated ventricles and thinned cortex

be congenital or acquired. If the communication between the ventricular system and the subarachnoid space remains patent, it is called **communicating hydrocephalus**. If this communication is blocked, it is termed **obstructive hydrocephalus**. In some cases the hydrocephalus may be normotensive, i.e. the pressure in the ventricular system may be normal, in others it may be raised. Tissue loss resulting in compensatory ventricular enlargement without obstruction is called *hydrocephalus ex vacuo* (Fig. 194.2).

In congenital hydrocephalus and those developing in early infancy the fontanelle and skull sutures separate and the head is enlarged. The eyeballs are depressed and optic atrophy may develop. The brain and skull are thinned out. Percussion over the skull may give a cracked-pot note.

NORMAL PRESSURE HYDROCEPHALUS (NPH)

Normal pressure hydrocephalus (NPH) denotes a chronic, communicating adult onset hydrocephalus. Typical presentation is with a triad of mental impairment, gait disturbance and incontinence. Although called NPH, long term monitoring shows intermittent elevation of pressure. In selected patients shunt surgery may help to alleviate symptoms.

Causes of Hydrocephalus Developing in Infancy

1. Bleeding into the brain during delivery and subsequent adhesions.
2. Congenital absence of arachnoid granulations.
3. Stenosis of the aqueduct.
4. Improper development of the mantle layer of the brain. In the early stages of embryonal development the ventricular system is relatively larger. As the mantle layer develops and the brain grows this relative

TABLE 194.2

Surgical procedures and their principles	
Type of surgery	CSF diverted into
Ventriculo-peritoneal shunt	the peritoneum
Ventriculo-atrial shunt	the right atrium
Ventriculo-sinus shunt	the sagittal sinus
Theco-peritoneal shunt	draining the spinal subarachnoid space into the peritoneum.

disparity disappears. In conditions where the mantle layer does not develop normally, hydrocephalus persists.

5. Arnold-Chiari malformation.
6. Obstruction to the foramina of Magendie and Lushka.

Course and prognosis: If the obstruction is not relieved, the condition progresses. Mental deficiency, optic atrophy, and convulsions may develop in many.

Treatment: Surgical procedures are available to divert CSF from the ventricles and relieve tension using suitable valves, in case of obstructive hydrocephalus. Endoscopic third ventriculostomy is another surgical method employed (Table 194.2).

Causes of Hydrocephalus in Adults

- Subarachnoid hemorrhage
 - Basal meningitis
 - Neoplasms obstructing the aqueduct.
- The basal foramina may be obstructed in meningitis and subarachnoid hemorrhage. The skull is not enlarged if hydrocephalus occurs after closure of the fontanelle. Rise of intracranial tension leads to radiological features such as resorption of the clinoid processes and thinning of the skull vault giving rise to a ‘*silver beaten*’ appearance.

INCREASED INTRACRANIAL TENSION

Persistent increase in tension of CSF above 180 mm CSF (or water) in the recumbent posture constitutes *raised intracranial tension* (ICT). The normal contents of the cranium are the nervous tissue, circulating blood and CSF. Rise in intracranial tension may result from increase in the contents of the cranium, e.g. clots, tumours, abscesses or edema of the brain or due to obstruction to the flow of CSF or impaired CSF absorption by the arachnoid granulations. Some degree of compensation is possible to normalize the intracranial tension in health and disease. These mechanisms include (1) displacement of CSF from the cranium, and (2) drainage of blood by the emissary veins. When rise of intracranial tension proceeds, these compensatory mechanisms fail.

Common Causes of Raised ICT

1. Space occupying lesions: Tumours, abscesses, granulomas, cysts, subdural hematomas.
2. Inflammation: Meningitis, encephalitis, cerebral edema.
3. Vascular accidents: Cerebral and subarachnoid hemorrhage, thromboembolic episodes giving rise to cerebral infarctions, cerebral venous thrombosis.
4. Obstruction to flow of CSF: Hydrocephalus.
5. Miscellaneous causes: Systemic hypertension, especially malignant hypertension; chronic respiratory failure, water intoxication, high altitude cerebral edema.

Pathogenesis: Rise in intracranial tension leads to disturbances of hypothalamic vasomotor regulatory mechanisms. These lead to the development of bradycardia and systolic hypertension (*Cushing's vasomotor phenomena*). Further rise in tension results in displacement of the brain.

If the rise in tension is caused by a unilateral lesion in the cerebral hemisphere, the ipsilateral hemisphere is pushed to the opposite side under the falx cerebri—*subfalcine herniation*. The medial part of the temporal lobe is pushed down through the tentorial hiatus—*transtentorial herniation*. This gives rise to paralysis of the third nerve. Pressure on the ipsilateral cerebral peduncle gives rise to contralateral hemiparesis. *Countercoup pressure* on the opposite cerebral peduncle by the free margin of the tentorium cerebelli gives rise to hemiparesis of the ipsilateral side as well. As the tension increases further, both the pupils dilate, both the cerebral peduncles are compressed with loss of consciousness and the picture is one of decerebrate rigidity. Opisthotonic seizures may develop. When the intracranial tension reaches that of arterial blood pressure, cerebral blood flow is considerably diminished. Medullary centres are depressed. The cerebellar tonsils herniate down the foramen magnum (tonsillar herniation) compressing the medulla and this leads to respiratory paralysis and death. Lesions in the posterior-cranial fossa give rise to ICT earlier than supratentorial lesions.

CLINICAL FEATURES

Headache: The earliest symptom is headache, which is dull initially and it tends to worsen in the mornings. Later it becomes persistent and assumes a bursting character. Sharp rise in intracranial tension caused by coughing, straining at stools or stooping forwards gives rise to aggravation of the headache. Later the headache may become so constant that the patient may not even complain of it unless specifically asked for.

Vomiting: Stimulation of midline structures in the medulla (vomiting centre) gives rise to effortless and projectile vomiting. In projectile vomiting nausea is usually absent.

Visual symptoms: As the ICT rises, vision deteriorates. Initially, there will be transient episodes of visual blurring. Later visual symptoms, defects in the visual fields, diplopia, and total blindness may follow. Funduscopy shows papilledema and later on, optic atrophy. Papilledema occurs when CSF pressure is > 200 mm CSF.

Mental changes: These include apathy, abnormal behavior and lack of attention to personal details. With further rise in ICT the patient may become comatose.

Seizures: These may be the presenting symptom in many. These may be generalized motor or partial seizures with or without secondary generalization.

Focal neurological deficits: These occur if the ICT is due to a focal ICSOL.

Hypothalamic disturbances: Endocrine disturbances develop in long-standing cases where the rise in ICT is gradual and prolonged. These may result in disturbance of the hypothalamus, pituitary or both. Symptoms include amenorrhea, precocious puberty, obesity, gigantism, somnolence, and hyperphagia.

In children constipation is frequent and this results from the fear to defecate since the act of defecation causes rapid worsening of the headache.

Investigations: Apart from general investigations to exclude systemic disorders, specific investigations include radiological studies, electroencephalography, CT scanning, MRI, isotope studies, and CSF examination. It is to be remembered that lumbar puncture is a risky procedure in the presence of raised ICT and this should not be performed without neurosurgical assistance. When LP is contraindicated, CSF can be obtained for tests by ventricular puncture.

MANAGEMENT

General Measures

Anti-edema agents: Administration of 20% mannitol solution 200 mL as an intravenous drip within 30 min helps to draw fluid from the brain and transfer it to the vascular compartment. This leads to a temporary fall in ICT. Other hyperosmotic solutions such as 3% saline and glycerol act by the same principle but they are less efficient. Dexamethasone in a dose of 4-12 mg given intravenously every 6 h also serves to lower ICT.

Specific management: Treatment of the cause relieves the raised ICT also. Surgical measures may be required in some cases.

IDIOPATHIC INTRACRANIAL HYPERTENSION (IIH)

This is a condition (previously known as benign intracranial hypertension – BIH) in which there is rise in

intracranial pressure, often above 200-250 mm of water, in the absence of any space occupying lesion. It is more common in young obese women. Majority of the cases are idiopathic and no specific etiology is detectable. Secondary IIH may result from the use of steroids or withdrawal of steroid therapy, hypoparathyroidism, cortical venous sinus thrombosis, hypervitaminosis A and use of drugs such as outdated tetracycline, phenytoin therapy oral contraceptive pills and others. Pathologically there is obstruction to the arachnoid granulations and this prevents absorption of CSF into the venous sinuses.

Clinically, patients with IIH present with headache, vomiting and visual disturbances. Except for gross papilledema with retinal hemorrhage as on funduscopy and occasionally VI cranial nerve palsy, there is no other neurological deficit.

Diagnosis

Although as a general rule LP is contraindicated when there is papilledema, in IIH, it is relatively safe and should be performed after excluding intracranial space occupying

lesion. LP helps to exclude meningitis and also to record the high CSF pressure, often >250 mm of water. Otherwise it is normal in cytology and biochemistry.

CT scan or MRI scan shows slit like lateral ventricles and normal brain parenchyma. MRI brain scan and MR venogram are the gold standard investigations to diagnose IIH. The former helps to exclude space occupying lesions, particularly cysticercosis which is prevalent in many states of India and which can present as isolated raised ICT. MR venogram helps to exclude cortical venous thrombosis which can also present as isolated raised ICT. Simple CT study often fails to identify these conditions.

Treatment: Some cases are self-limiting and the condition may regress. They may be left alone and observed. In the others repeated LP may have to be done to drain out CSF.

CSF production can be inhibited by acetazolamide 250-500 mg tid or prednisolone 1 mg/kg body weight. These drugs may give partial benefit when tried sequentially. In cases of impending visual loss, optic nerve sheath fenestration has to be undertaken.

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Multiple Sclerosis and Other Demyelinating Lesions

Anand Kumar, P.K. Mohan

Chapter Summary

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- Multiple Sclerosis 1290
- Acute Disseminated Encephalomyelitis 1293
- Schilder's Diffuse Cerebral Sclerosis 1294

General Considerations

Myelin is a membrane that ensheathes the axons to improve their ability to conduct electrical action potentials. Oligodendrocytes make myelin and wrap it around axons. The myelin sheath of an axon is not continuous. There are gaps at variable intervals called

nodes of Ranvier, where membrane ionic channels are concentrated. These can generate powerful axon potentials. Loss of myelin leading to exposure of the axons is called demyelination. Demyelination prevents depolarisation due to insufficient flow of ions through the ionic channels. This in turn leads to non-conduction of an action potential across the damaged nerve segment, rendering the nerve functionless.

The term 'demyelinating diseases' refers to a group of acquired disorders where the myelin sheath is destroyed with relative sparing of the other elements of nervous tissue like axis cylinders, nerve cells and supporting tissues. This should not be confused with disorders where myelin is not formed adequately at birth, which are referred to as dysmyelination, e.g. leukodystrophy.

Classification of Diseases of Myelin

Autoimmune

Acute disseminated encephalomyelitis (ADEM).

- Post-infectious: Following viral, bacterial, mycoplasma and rickettsial infections
- Post-vaccinal, e.g. following rabies, smallpox vaccination.

Acute hemorrhagic leukoencephalopathy

Multiple sclerosis

- Chronic relapsing encephalomyelopathic form
- Acute multiple sclerosis
- Diffuse cerebral sclerosis (Schilder's disease, concentric sclerosis of Baló)

Infections

Progressive multifocal leukoencephalopathy

Toxic/ metabolic

Carbon monoxide

Vitamin B₁₂ deficiency

Mercury intoxication (Minamata disease)

Alcohol/ tobacco amblyopia

Central pontine myelinolysis, a complication of rapid correction of hyponatremia

Marchiafava- Bignami syndrome

Hypoxia

Radiation.

Vascular

Binswanger's disease

Reversible posterior leukoencephalopathy

Hereditary disorders of myelin metabolism (Dysmyelination)

Adrenoleukodystrophy due to defect in metabolism of long chain fatty acids. Metachromatic leukodystrophy due to deficiency of arylsulphatase enzyme. Krabbe's globoid leukodystrophy.

Alexander's disease

Canavan's disease

Phenylketonuria.

Multiple Sclerosis

Multiple sclerosis (MS) is the most common demyelinating disease in the west, however, it is less common in India and other Asian countries. In India, MS constitutes 0.05% of all diseases seen in neurology services in the southern and 1.5% in the northern parts of the country. The disease is characterized by neurological deficits due to involvement of optic nerves, cerebrum, cerebellum, brainstem and the spinal cord, to varying extents. It usually affects women between 20-35 years and men between 35-45 years. It is rare before the age of 14 years and after the age of 60 years. Women are more often affected than men

(F:M=2:1). Sometimes it appears to be familial, the first degree relatives having 10 to 20 times increased risk of developing MS.

Etiology: The exact cause of this disease is not clear. However, several epidemiological factors have been clearly established. The disease has a prevalence of less than 1 in 100,000 in equatorial areas, 6 to 14 in 100,000 in southern USA, and 30 to 80 in 100,000 in Canada. The increasing risk of developing multiple sclerosis with increasing latitude has been confirmed by many studies. Also persons who migrate from a high risk to a low risk zone carry with them at least a part of the risk of their country of origin. Those who migrate before the age of 15 carry the risk of developing multiple sclerosis similar to the country of settlement, while the risk in those who migrate after the age of 15 is similar to that of their country of origin. The importance of environmental factors in the genesis of multiple sclerosis is clear. There is no definite inheritance pattern for the disease. HLA-A3,-B7, and DW2 appear to have a possible relationship.

Immunopathogenesis of Multiple Sclerosis

The presence of T and B lymphocytes, macrophages and activated microglia in MS lesions is proof to the fact that immune mechanisms play a role in the genesis of MS plaques. What triggers the immune cascade in MS is still unclear.

Immunopathogenesis in MS is evidenced by the following factors:

1. Presence of immune reactive cells
2. Inflammatory cytokines in serum, CSF and brain
3. Immunomodulators are effective therapeutically
4. MS is initiated by immune cells in animal models.

An antigen presenting cell [APC] engages the antigen in the groove present on the major histocompatibility antigen [MHC]. Antigen presenting cells are usually dendritic cells, macrophages or microglia. T cells with receptors programmed for the antigen proliferate and differentiate into effector subsets of T cells named as Th1 and Th2. These cells produce cytokines. Th 1 and Th 2 cells produce proinflammatory and anti-inflammatory cytokines respectively. T cells with receptors specific for myelin proteins are present in healthy individuals. They are kept suppressed in normal individuals. The mechanisms responsible for the same are decreased activity of suppressor regulator cells and the presence of molecular mimicry. Many pathogens and foreign antigens can activate the myelin reactive T cells. This explains the exacerbations in MS due to multiple triggers. Currently there is evidence to implicate role of B cells in the pathogenesis of MS as well.

Myelin reactive T cells gain entry into the central nervous system by crossing the blood-brain barrier. For

this to happen, adhesion molecules on T cells and endothelial cells are upregulated. After crossing the endothelial barrier the cells reach the outer basement membrane. Matrix metalloproteases (MMP) alter the basement membrane for easy passage of T cells. Later on, chemokines also help in the migration of T cells.

Multi-level loss of tolerance in MS can be due to:

1. Activation of quiescent myelin reactive T cells
2. Influx of T cells into CNS
3. Priming CNS for inflammatory response.

Pathology: The gross appearance of the brain and the spinal cord is normal. The cut surface of the brain shows numerous scattered lesions which are slightly depressed and stand out from the surrounding white matter by virtue of their pinkish grey colour due to loss of myelin. The lesions vary from less than 1 mm to several centimeters in size and are located in the periventricular areas of the brain in relation to the veins.

Histopathological hallmarks are the breach in the integrity of blood-brain barrier; up-regulation of adhesion molecules on the endothelium of brain and spinal cord and further pathological processes. Leukocytes enter the normal immunologically privileged CNS. If lymphocytes programmed to react with myelin antigen enter the tissues, acute inflammatory demyelinating lesions ensue. These lesions primarily involve white matter where the primary targets are the myelin sheath and the myelinating cell which is the oligodendrocyte. However, gray-matter lesions are also known to occur where the primary target is still the myelin antigen.

During an attack of MS, inflammation occurs in areas of white matter of CNS in random patches called 'plaques'. This process is followed by destruction of the myelin sheath which insulates the nerve fibers in the brain and spinal cord. The central problem seems to be the autoimmune destruction of myelin in the CNS.

CLINICAL PRESENTATIONS

MS is a heterogeneous disease both etiologically and clinically. However, based on its clinical course, MS is classified into the following subtypes:

1. **Relapsing:** Remitting type (R-R type): Most common (85%)
2. **Progressive type:** Deterioration continues for at least 1 year
 - a. **Primary progressive (PPMS):** In this type, the neurological deficit is progressive from the onset without acute exacerbation, plateau or remissions.
 - b. **Progressive-relapsing (PRMS):** Consists of patients with primary progressive disease who later in their course develop acute relapses with or without full recovery.

- c. **Secondary progressive (SPMS):** Illness starts as a relapsing-remitting MS, but later assumes a progressive course.

There are distinct ethnic differences in the clinical presentation of MS. Mainly, they are categorized as:

- i. Western type MS
- ii. Asian type MS

Western type MS shows lesions disseminated widely throughout the CNS including the cerebrum, cerebellum and brainstem whereas lesions in Asian type are mainly confined to the optic nerves and spinal cord-opticospinal MS. The opticospinal MS differs from western type MS in the following aspects:

- i. A higher frequency of female patients
- ii. Older age of onset
- iii. More frequent exacerbations
- iv. Fewer number of lesions in the cerebrum on MRI
- v. Higher cell counts and total proteins in the CSF
- vi. Low frequency of oligoclonal bands (OB) or increased IgG index in the CSF, i.e.: (OB negative MS) and
- vii. A benign course.

This large difference in the clinical presentation among ethnic groups is probably due to differences in the HLA class II molecules. The CNS antigens presented to T cells in these two ethnic types may also be different, thereby producing marked differences in the distribution of CNS lesions.

Following the initial acute attack of MS, about one-third of cases recover completely, one-third improve, though not completely, and the remaining cases show no improvement. The most dramatic symptom is visual loss caused by optic neuritis. Loss of vision may be total or partial, acute or subacute and usually unocular, rarely binocular. Some cases present with weakness or numbness in one or more limbs. Other modes of presentation are unsteadiness of gait, brain stem symptoms—diplopia, vertigo, vomiting and bladder disturbances. Dementia, aphasia, seizures, and extrapyramidal movements are rare. Once established, the disease is characterized by remissions and relapses at multiple sites at varying intervals. Due to the presence of heavily myelinated fibres, posterior column deficits and pyramidal involvement are common in MS. Polysynaptic reflexes such as the superficial reflexes may be affected early. Optic atrophy, spastic paraparesis, cerebellar signs like intention tremor or ataxia, and internuclear ophthalmoplegia due to involvement of the medial longitudinal fasciculus are some of the distinctive findings. Bilateral trigeminal neuralgia is characteristic of MS. Rarely a combination of cerebral, brainstem and spinal manifestations evolve over a few weeks rendering the patient stuporous or comatose. In such cases death may occur within a few weeks.

Diagnosis: Clinically definite MS is diagnosed when there are at least two attacks separated in time by at least one month with clinical evidence of at least two separate lesions in the central nervous system or two attacks with clinical evidence of one and investigational evidence of another separate lesion. The clinical attacks should indicate objective involvement of white matter in the CNS. If the attacks are two or more in the relapsing-relapsing type, they should occur in two or more separate anatomical sites.

In the progressive type the duration of illness should be more than one year. In both types there should be no other evident reason to account for the neurological deficit.

There is no pathognomonic laboratory test for MS. CSF may show lymphocyte pleocytosis, up to 20 cells/cmm during the acute attack. Slight rise in total protein (up to 100 mg/dL) may occur. Sugar level is normal. The IgG component in CSF is increased above 13% of the total CSF protein, the total protein being normal or only moderately raised. Electrophoresis of CSF IgG in multiple sclerosis reveals a restricted number of bands called the “oligoclonal bands”. Higher levels of IgG and greater number of *oligoclonal bands* are seen in severe and chronic cases. During the acute phase, high levels of myelin basic protein and myelin debris can be found in the CSF.

In early stage, methods to establish the presence of other asymptomatic lesions are of great help in diagnosis. This is done by recording the evoked potentials by visual, auditory, and somatosensory stimuli. Thus identification of abnormal visual evoked response in a case of paraplegia might help in the diagnosis of multiple sclerosis, even though clinical examination of the visual pathway is normal.

MRI imaging clearly brings out the plaques of demyelination and the lesion can be demonstrated non-invasively (Fig. 195.1).

It is important to exclude other conditions before the diagnosis of MS is established. In India, it still remains a diagnosis by exclusion.

Prognosis: Depends on the type of disease and its progression. Single and localized attacks may remain with partial recovery for varying periods of time but relapses are the rule. Each attack leaves behind residual disability to varying extent. In progressive types severe disability may result, crippling the patient.

TREATMENT OF MULTIPLE SCLEROSIS

There are three main categories in the treatment of MS

- Treatment of exacerbations
- Disease modifying therapy
- Symptomatic treatment.

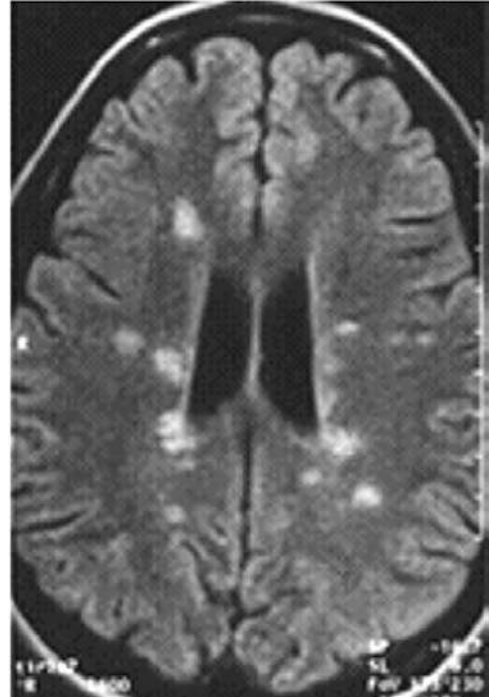


Fig. 195.1: MRI showing periventricular lesions in MS
Note: The demyelinated plaques

Treatment of Exacerbations

In 1970, Ross and colleagues used ACTH in MS and found a beneficial effect as compared to placebo. Currently most centers use intravenous methyl prednisolone in dose of 1 g per day for a three or five day course often followed by a rapid tapering course of oral steroids. There are also studies claiming equal efficacy for high dose oral steroids. The use of adhesion molecule blockers, has not yielded much benefit.

Plasmapheresis: At least one study has demonstrated significant functional improvement in patients treated with plasmapheresis who had failed to respond to corticosteroids.

Disease Modifying Therapies

There are five approved agents, belonging to three different classes of drugs, presently available as disease modifying therapies for MS. These agents are effective in relapsing remitting MS and in clinically isolated syndromes that do not satisfy the criteria for MS.

Interferon β 1b: Interferon β 1b (IFN β 1b) given in dose of 8 mIU every other day has been shown to reduce the relapse rate in MS by 30%. The proportion of patients remaining exacerbation free and median time to first exacerbation were favourably affected by IFN β 1b. MRI data from patients on IFN β 1b showed a dramatic effect with a reduction in the rate of new lesions and the number

of patients free of new lesions. MRI lesion burden calculated from T2 weighted images was also less in the treated group. The most common side effects of IFN β 1b are flu like syndrome and elevation of liver enzymes. As regards the role of interferon beta in secondary progressive MS two major studies have given conflicting results.

Interferon beta -1a (IFN β 1a) Studies on IFN β 1a have shown beneficial effect in slowing progression of disease, preventing relapses and in delaying second attack in clinically isolated syndromes. MRI data also showed improvement. One study has shown slowing of progression in secondary progressive MS. However, the study used a new outcome measure. The dose used is 30 mcg IM every week and the side effect profile is similar to IFN β 1b.

Glatiramer Acetate Two placebo controlled studies have shown favourable results with glatiramer as regards relapse rate and progression of MS. Glatiramer achieved a reduction in MRI disease burden in another study.

One problem with the use of disease modifying agents is the emergence of neutralizing antibodies (NAB). Relapses are more frequent in patient, with NAB. They occur more in low dose treated group, and many patients lose them over time.

Mitoxantrone is a cytotoxic anthracenedione which has been approved for use in worsening forms of relapsing MS. These include relapsing remitting, progressive relapsing and secondary progressive MS. The dose used is 12 mg/m² IV every three months and the major toxicity is cardiac.

Repetitive courses of steroids: A recent study used pulses of IV methyl prednisolone in relapsing remitting MS, every four months for three years and every six months for two years. There was less disability and evidence of reduction of neuronal loss in the treated group.

Intravenous immunoglobulin (IVIG): The data on the use of IVIG in MS is not convincing, but definitely encouraging. There is no consensus on the dose or frequency of administration of IVIG.

Selective therapy: Natalizumab, a recombinant monoclonal antibody against α_4 integrins is employed for treatment of relapsing MS. It is effective as a short term and medium term (2-3 years) therapy. It reduces relapses and also reduces the lesions seen on MRI. There was a fear of progressive multifocal leucoencephalopathy (PML) developing as a complication of the drug, but this risk is low.

The dose is 300 mg by IV infusion, once in four weeks for more than 2 years.

Fingolimod is a new oral immunomodulating agent being evaluated for the treatment of relapsing MS. Initial results

on its efficacy in reducing clinical disease activity and MRI abnormalities are encouraging. The dose used was 1.5 mg and 5 mg for patients with one lesion or three lesions, respectively, given oral daily for six months (Ludwig Kappos et al Oral Fingolimod (FTY720) for Relapsing Multiple Sclerosis N Engl J Med 2006, 355: 1124-1140).

Bone Marrow/ Stem cell transplantation: Only anecdotal reports are available on the use of this mode of therapy for MS. This is likely to be put to use in the future.

Symptomatic Management

- Amantadine—for fatigue
- Baclofen, dantrolene and diazepam—to allay spasticity
- Clonazepam and high dose INH—to allay intention tremors
- Oxybutinin and propantheline—to reduce urinary frequency and urgency.

VARIANTS OF MS

Devic's Disease (Neuromyelitis optica)

It is a combination of symptoms and signs resulting from spinal cord and optic nerve involvement. Brain is spared, both clinically and on neuroimaging. MRI of spinal cord shows striking lesions of demyelination.

The CSF shows neutrophil pleocytosis and elevated protein.

Balo's Concentric Sclerosis

It occurs more commonly in Philippines and China where the demyelinating attack effects young adults and lasts for a few months. Concentric bands of intact myelin and demyelination zones are present in the CNS.

Marburg's Disease

It is an acute fulminant, progressive disease with extensive destruction of myelin and axon cylinders.

Monophasic Demyelinating Syndromes

These may take the form of optic neuritis, transverse myelitis, acute inflammatory brainstem syndromes or acute disseminated encephalomyelitis (ADEM).

ACUTE DISSEMINATED ENCEPHALOMYELITIS

Acute disseminated encephalomyelitis (ADEM) is an autoimmune, monophasic, demyelinating disease generally associated with preceding viral infection. The disease has an immunological basis and is thought to be secondary to molecular mimicry and formation of T-cell

and B-cell response to endogenous proteins in the myelin layer. Although most cases begin within a few days of a preceding infection or vaccination, at times there is no history of antecedent event. It may be difficult to differentiate ADEM from the first attack of multiple sclerosis, and the two may have a similar underlying pathophysiology. ADEM is a monophasic illness as opposed to multiple sclerosis, which is polyphasic or progressiv. Recently multiphasic ADEM (MDEM) has also been reported.

Infectious agents thought to precede the development of ADEM include the following:

1. **Measles** which is most common, 1/1000 measles cases, with autoreactive T-cells and antibodies to myelin basic protein.
2. **Other viruses** such as rubella, corona virus, mycoplasma, influenza, parainfluenza, CMV, EBV, HHV-6, Varicella, and nonspecific upper respiratory pathogens.
3. **Vaccinations:** ADEM also follows vaccination to several diseases such as smallpox, rabies, mumps, rubella and influenza.

These various triggers may initiate immune responses within the CNS, or uncover myelin proteins not previously detected by the immune system, resulting in a vigorous inflammatory response.

The clinical course is highly variable, ranging from a slow progression over weeks to a fulminant course over hours to days. A clinical hallmark of the condition is its monophasic course, differentiating it from multiple sclerosis.

Neurological signs and symptoms are variable and nonspecific, but evidence of upper motor neuron dysfunction invariably occurs. Headache, meningism, and altered mental status with confusion progressing to lethargy and coma are common. Cranial nerve involvement, particularly optic neuritis, is common. Motor involvement ranges from focal spastic weakness to quadriplegia. Sensory findings and cerebellar dysfunction are also common.

Laboratory evaluation typically shows a CSF pleocytosis with up to 150-200 WBCs, generally with a lymphocytic predominance. Sometimes polymorphonuclear cells predominate in the CSF (a finding that initially suggests meningitis rather than ADEM). The protein level is usually elevated, but generally not higher than 180 mg/dL.

MRI images show multiple white matter lesions on T2 and flair sequences with gadolinium enhancement on T1. These findings are typical, but not diagnostic, of inflammatory demyelinating lesions as seen in multiple

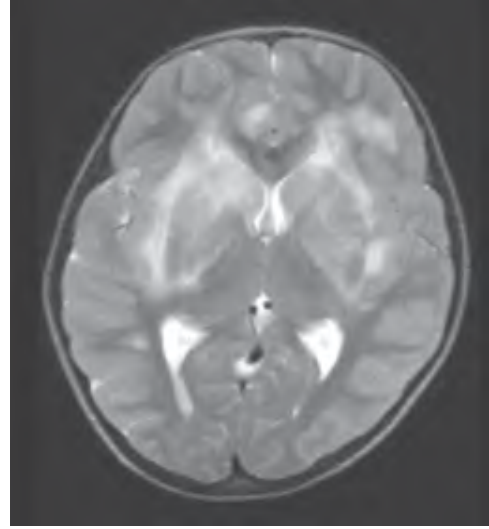


Fig. 195.2: Showing white matter and basal ganglia lesions in ADEM

sclerosis. They are frequently more confluent and larger in size than typical MS plaques. Lesions may occur in basal ganglia and thalamus which are not seen in MS. Cortical lesions may occur. Frequently, the posterior fossa and spinal cord are involved, with uniform enhancement of lesions (suggesting active disease) unlike MS in which there are often multiple lesions of different ages (Fig. 195.2).

CSF examination: There is no elevation of CSF IgG unlike in MS.

Prognosis: In milder cases, 90% of patients recover completely. In more severe cases, mortality may be as high as 5-20%; and 50% of patients so affected are left with permanent neurological disability.

Treatment is with high dose corticosteroids such as IV methyl prednisolone 1g daily for 3 to 5 days. Plasma exchange and IV IG have also been employed with benefit.

Schilder's Diffuse Cerebral Sclerosis

This is a rare familial disease encountered in children and young adults. Pathologically it is characterized by sharply outlined, asymmetrical foci of myelin destruction involving one or both cerebral hemispheres. It is clinically characterized by a progressive course of dementia, seizures, homonymous hemianopia, cortical blindness, varying degrees of hemiplegia, quadriplegia, and pseudobulbar palsy. In majority of cases death occurs within a few months or years.

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General Considerations

Motor neuron disease (MND): This term refers to disorders in which the primary pathology is degeneration of motor neurons. They include a wide variety of clinical conditions.

Etiology: The exact nature of the disease is not known, though it is generally considered to be a degenerative disease. Several etiological factors have been postulated from time to time. These include chronic toxicity due to aluminium and manganese, slow virus infection, low intake of calcium and magnesium and auto immunity. Another hypothesis is that glutamate, which is a primary excitatory neurotransmitter in the central nervous system, accumulates to toxic levels at synapses and causes the neurons to die, probably through a calcium dependent mechanism and free radical production.

Pathology: The motor neurons in the cerebral cortex, brainstem and spinal cord show atrophy and their axons show degenerative changes. Muscles show groups of atrophic fibers amidst groups of normal fibers.

The clinical pattern may follow the classical description in most of the cases, but some may show atypical features. Variant forms of the disease have been described from different geographical regions, including Madras (Chennai).

Classification of Motor Neuron Disorders

- A. *Non-familial or sporadic forms*
 - I. *Of unknown etiology—Motor Neuron Disease (MND)*
 - With UMN and LMN involvement
 - (a) In the spinal cord—amyotrophic lateral sclerosis
 - (b) In the brain—progressive bulbar and pseudo-bulbar palsy
 - With predominantly UMN involvement
 - (a) in the spinal cord—primary lateral sclerosis
 - (b) in the brain—progressive pseudobulbar palsy
 - With predominantly LMN involvement
 - (a) in the spinal cord—progressive muscular atrophy
 - (b) in the brain—progressive bulbar palsy
 - II. *Of known etiology*
 - Infections—polio, tetanus, herpes zoster, HIV
 - Toxins—lead, aluminum, manganese
 - Immunological—plasma cell dyscrasias
 - Metabolic—hypoglycemia, hyperthyroidism, hyperparathyroidism
- B. *Familial/Hereditary/Genetically transmitted forms*
 - I. *Of unknown mechanism*
 - Spinal muscular atrophy (SMA)
 - Infantile onset—Werdnig-Hoffmann disease
 - Childhood onset
 - Adolescent onset—Kugelberg-Welander disease
 - Familial amyotrophic lateral sclerosis
 - Progressive juvenile bulbar palsy
 - Hereditary spastic paraplegia
 - II. *Of known metabolic basis*
 - Hexosaminidase A and B deficiency
 - Superoxide dismutase deficiency
 - Hyperlipidemia
 - Hyperglycemia
- C. *Atypical variants:*
 - Madras motor neuron disease
 - Mill's variant- hemiplegia variant
 - Monomelic atrophy
 - Hirayama type -both upper limbs
 - Gourie Devi's – upper limb
 - Chopra's – lower limb
 - MND with dementia
 - MND with Parkinsonism

Motor Neuron Disease (MND)

Syn: Maladis de Charcot (named after Charcot who first described the condition in 1869) lou Gehrig's disease.

The term 'Motor neuron disease' refers to progressive involvement of upper and/or lower motor neurons usually with little or no clinical involvement of sensory or other non-motor tracts. Five types of MND can be identified on the basis of their clinical, pathological and prognostic characteristics. These are referred to as classic or sporadic forms. MND occurs all over the world, the incidence being 1/100,000. In the islands of Guam and some other regions, the incidence exceeds 50-100/100,000. This is probably due to exposure to an yet unidentified toxin. In some countries the term ALS and MND are used synonymously.

AMYOTROPHIC LATERAL SCLEROSIS (ALS)

This is the most common type of MND. The disease sets in insidiously by the age of 50-55 years, males suffer twice as commonly as females. Average age of onset is 45 years in India, a decade younger than in the West. It is not uncommon to find several members of a family affected. The classic form starts with wasting of the small muscles of the hand, deltoid and shoulder girdle muscles and then progresses to involve the other muscles of the limb. In the majority of cases the affection is bilateral, though asymmetrical. Rarely the manifestations may remain unilateral for considerable periods of time. Still minor manifestations such as fasciculations can be observed over more extensive areas. Bulbar muscles are affected later. Finally all muscles of the body may be involved. The wasted muscles show fasciculations readily, whereas they are less prominent in the apparently unaffected muscles. *Fasciculations* can be made more prominent by exerting the muscle, exposure to cold air or subcutaneous injection of 0.5 mg neostigmine. Atrophy of small muscles of the hand gives rise to claw hand in which there is extension of the metacarpophalangeal joints and flexion of the interphalangeal joints. In the feet, atrophy of the intrinsic muscles gives rise to pes cavus (exaggeration of the arch of the foot), when the feet are in the resting position. As the condition proceeds, trunk muscles and other major muscles of the limbs may also be affected giving rise to considerable wasting and paralysis. Some muscles show evidence of UMN lesion in the form of spasticity and exaggeration of deep tendon reflexes, and also evidence of LMN lesion in the form of fasciculations and atrophy. Affection of the bulbar muscles gives rise to LMN lesion of the tongue, leading to its atrophy, and UMN lesion of the soft palate and pharynx giving rise to exaggeration of gag reflex and dysphagia. The jaw jerk is exaggerated. The plantar responses are bilaterally extensor indicating UMN lesion.

Sensations and mental functions are unaffected. Oculomotor nuclei are spared for some unknown reason. Autonomic functions such as micturition and defecation remain intact, for considerable periods. Speech is affected early. Spastic dysarthria develops with time. In the advanced case, the picture is of extreme wasting. Death is due to respiratory infection, aspiration pneumonia, nutritional inadequacy or cardiovascular causes.

Course and prognosis: The course is one of relentless progression to produce severe disability and death in 4-5 years. Known prognostic factors include age, site of initial involvement, extent and severity of wasting, severity of bulbar muscle dysfunction and respiratory functions.

VARIANT FORMS

1. Madras pattern of MND: Weakness and wasting may be uni- or bilateral, proximal or distal, and asymmetrical. Bulbar muscles may be involved in 60% of cases. Unilateral or bilateral sensorineural deafness, younger age of onset with ALS-like features and a benign course are characteristic of this condition. Indian workers have incriminated defects of glucose utilization by spinal motor neurons to have a causative role (Valmikinathan).

Although this condition was initially described in patients from Madras in South India, similar cases are now encountered in many parts of India.

2. Monomelic amyotrophy: This is a non-familial, insidiously progressive condition, usually affecting adolescents and adults. It is characterised by weakness, wasting and fasciculations restricted only to one extremity—either upper or lower. In some cases, the involvement may be only focal or segmental in one extremity—focal or segmental MND. UMN signs are usually absent. The course is benign. Although clinically one limb is affected, electromyographically subclinical involvement of lower motor neurons in other limb muscles may be evident.

3. Juvenile MND: The typical features of classical ALS may sometimes occur even in young adults.

4. Western Pacific form: It is clinically similar to classic form of ALS, but neuropathologically distinct with neurofibrillary changes and granulovacuolar bodies.

5. Familial form of ALS: About 5 to 10% of ALS cases occur in families suggesting a dominant inheritance pattern. Younger age of onset and a 1:1 sex ratio differentiate this form from classical ALS. A defect in a gene on chromosome 21 has been identified.

6. Amyotrophic lateral sclerosis-parkinsonism—dementia complex, described from Guam islands.

PROGRESSIVE MUSCULAR ATROPHY

In this condition there is selective LMN degeneration leading to weakness and wasting in one upper extremity (75%) or one lower extremity (25%) and this becomes generalized over a period of 3-5 years. Fasciculations are visible but less common. Despite the marked wasting, reflexes are preserved normally or they may even be brisk, but there will be no other signs of UMN involvement.

PRIMARY LATERAL SCLEROSIS

It is an uncommon form of MND in which only signs of UMN lesion in the limbs are present. These signs may persist for many years before the development of bulbar or LMN signs. Disease progression varies between patients. Fifty percent die within 3 years of onset of symptoms. Majority of deaths is due to respiratory failure.

PROGRESSIVE BULBAR PALSY

This is the most serious form of MND since it terminates life within a period of 1 year. There is LMN paralysis of cranial muscles as evidenced by wasting of the muscles of the tongue, muscles of mastication and face. Fasciculations are most marked in the tongue. Progressive involvement of the palatal, pharyngeal, and laryngeal muscles leads to difficulty in speech and deglutition. Patient develops dysarthria and inability to swallow and cough. Emaciation develops rapidly. The jaw reflex is normal or absent. There is no emotional lability.

PROGRESSIVE PSEUDOBULBAR PALSY (SPASTIC BULBAR PALSY)

In this form of palsy the affection of the bulbar muscles is of the UMN type. There is weakness of the bulbar muscles. The palatal muscles, tongue and pharyngeal muscles are spastic. Palatal movements are slow, but the gag reflex is brisk. Speech becomes slurred due to spastic dysarthria. Jaw jerk is exaggerated. Emotional lability is common. Other signs of amyotrophic lateral sclerosis may be associated with progressive bulbar palsy and pseudobulbar palsy.

SPINAL MUSCULAR ATROPHIES (SMA)

These are pure anterior horn cell degenerations with a definite genetic pattern of inheritance, and hence can be considered as hereditary motor neuronopathies. They are subdivided into various types depending on the pattern of muscle involvement, age of onset and mode of genetic transmission.

- i. Werdnig-Hoffmann disease—when the onset is in infancy
- ii. Childhood onset SMA

Spinal Muscular Atrophies Clinical Features			
Distribution	Age of onset	Mode of inheritance	Remarks
Generalised	Infancy	AR	Werdnig-Hoffmann's disease, rapidly progressive Death before the fourth year
Proximal	Childhood	AR	
	Adolescence	AR, AD	Kugelberg-Welander's disease
Distal	Childhood to adult life	AD, AR?	Rare
Scapulo-peroneal	20-60 years	AD, AR ?	Rare
Facioscapulo-humeral		X-linked (?)	
		AD	Rare
Note: AD—autosomal dominant AR—autosomal recessive			

- iii. Kugelberg-Welander disease—when the onset is in adolescence.

Werdnig-Hoffmann disease: This form of progressive muscular atrophy is seen in infancy. It runs a more rapid course.

Kugelberg-Welander disease: This is one of the forms of spinal muscular atrophy characterized by affection of the proximal muscles of all four limbs, starting at adolescence. This has a benign chronic course.

Other forms of spinal muscular atrophy: These occur at any age after infancy. They manifest as asymmetrical uni- or bilateral weakness and wasting of muscles with predominantly LMN features. The affection may be proximal or distal and the former may be mistaken for muscular dystrophy. The diaphragm may be affected early in the disease.

Diagnosis: Motor neuron disease has to be suspected under the following circumstances:

1. Insidious onset of selective motor system involvement characterized by affection of the lower and upper motor neurons.
2. Weakness and atrophy of muscles and fasciculations.
3. Electromyographic abnormalities manifesting as:
 - a. fibrillation and fasciculations at rest,
 - b. reduction in the number of motor unit potentials, and
 - c. giant potentials with increased duration and amplitude.

The motor and sensory nerve conduction velocities are normal. Serum muscle enzymes (CK) and CSF studies are normal.

Differential Diagnosis

Carcinomatous neuromyopathy may resemble MND. In diabetic amyotrophy wasting of the proximal muscles of the lower limbs may develop. This is correctable with proper control of diabetes. In syphilitic amyotrophy there is wasting of the muscles of the hands with upper motor neuron lesion of the lower limbs. Compression of the cervical cord occurring in tumours and cervical spondylosis may present as wasting of hands and spastic paralysis of the lower limbs. In cervical spondylotic myelopathy C₅₋₆ segments are more affected and hence the proximal muscles are more wasted than the hands as in motor neuron disease. Sensory manifestations are usually present in these conditions.

Motor neuropathy with multifocal nerve conduction block is an autoimmune peripheral neuropathy affecting young males, especially the upper limbs. Nerve conduction velocity is affected in motor nerves. GM-1 antibodies develop against the myelin components. GM-1 antibodies may be present in serum. This condition promptly responds to I.V. immunoglobulin. This has to be differentiated from the spinal forms and variant forms of MND.

Myopathies and chronic polymyositis may present with muscle wasting and atrophy. In these fasciculations are absent. Muscle biopsy is diagnostic. Electromyography

helps to distinguish myopathy from MND. Muscle enzymes like CK are elevated in myopathies.

Treatment

At present none of the known modalities arrest the progress of the disease. Palliative measures include physiotherapy, use of orthotic devices to help functioning of the limbs and treatment of intercurrent illness and ventilatory support.

Drugs that modulate the glutaminergic system have been proposed for therapy of MND. Riluzole (2-amino-6-trifluoromethoxy benzathiole) has given encouraging results in arresting the progression temporarily, especially in the bulbar forms of MND. The drug crosses the blood brain barrier. It is an inhibitor of glutamate release and it exerts its beneficial effect by reducing the neurotoxicity of glutamate. The dose is 100 mg a day. It is available as 50 and 100 mg tablets.

It postpones the onset of ventilatory failure and ventilator-dependence by a few months. The drug is available with Sun pharma.

Cyclophosphamide given in doses of 1.5 g/m² body surface in divided doses IV has been shown to relieve bulbar symptoms temporarily, by Indian workers. The effect wanes off after varying periods.

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Diseases of the Cerebellum

Anand Kumar, P.K. Mohan

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General Considerations

The cerebellum lies below the tentorium cerebelli in the posterior cranial fossa. It consists of two cerebellar hemispheres on either side, connected by the vermis in the middle. The cerebellar hemispheres consist of three lobes.

TABLE 197.1

Autosomal dominant ataxia – Harding’s classification		
Type	Clinical phenotype	Common genotypes
ADCA I	Cerebella ataxia plus other symptoms: extrapyramidal symptoms, neuropathy	SCA 1, 2, 3, 4, 12, 17, 21, 23 and 25
ADCA II	Cerebellar ataxis plus retinal degeneration	SCA 7
ADCA III	Cerebellar ataxia-pure	SCA 5, 6, 8, 10, 11, 14, 15, 16 and 22
ADCA: Autosomal dominant cerebellar ataxia; SCA: Spinocerebellar ataxia		

The cerebellum consists of the outer grey matter, inner white matter and four deep nuclear masses—fastigial, globosus, emboliformis and dentate nuclei. The cerebellar cortex consists of the outermost molecular layer, middle Purkinje cell layer and inner granular layer.

The three lobes are:

- 1. Anterior lobe—functionally related to the gross movements of heads and neck
- 2. Middle lobe—related to fine voluntary movements
- 3. Floculonodular lobe related to equilibration.

The vermis controls the midline structures of the body and trunk, whereas the lateral hemispheres control the limbs of the same side.

The cerebellum is connected to the brainstem by three peduncles (superior, middle and inferior) through which afferent and efferent fibers connect to various parts of the brain and spinal cord.

Blood supply is derived from three pairs of arteries—superior cerebellar and anterior inferior cerebellar arteries from the basilar artery and posterior inferior cerebellar arteries from the vertebral arteries.

Functions of the Cerebellum

- 1. Coordination of voluntary and reflex movements
- 2. Modulation of muscle tone and
- 3. Maintenance of body posture.

The clinical features of cerebellar disease and testing for cerebellar function are described in Chapters 182 and 183. Acute lesions of the cerebellar system produce sudden, severe and disabling symptoms. Chronic lesions lead to insidious deterioration of function.

HEREDOFAMILIAL ATAXIAS

These include a wide spectrum of degenerative diseases which are progressive, familial and manifesting in early life, with their main brunt on the cerebellar pathways. Variable degrees of involvement of the spinal cord, brainstem and cranial nerves also occur. The exact etiology is not known but recent evidence points to defects in mitochondrial energy systems and pyruvate metabolism as probably important factors. Hereditary ataxias are of many types, the most common being Fiedreich’s ataxia.

HEREDITARY ATAXIAS

Hereditary ataxias are broadly defined by mode of inheritance - autosomal dominant, autosomal recessive, or X-linked. With better understanding of the molecular basis and pathogenesis of these diseases, other classification schemes have been suggested. These classifications are based on disorders of trinucleotide repeat expansions or toxic “gain of function” due to abnormal proteins and accumulation of polyglutamine inclusions, channelopathies, mitochondrial dysfunction, defective DNA repair and metabolic disorders. Autosomal dominant cerebellar ataxias (ADCA) were initially classified according to phenotype and accompanying signs by Harding, as given in Table 197.1. Genetic advances have led to modification of these criteria as specific genes and mutations responsible for cerebellar ataxias have been discovered.

SPINOCEREBELLAR ATAXIA (SCA)

SCA is characterized by cerebellar ataxia manifesting with gait ataxia, dysarthria, slow saccades, nystagmus, corticospinal tract signs, neuropathy and later on with ophthalmoplegia and bulbar dysfunction (dysphagia, tongue fasciculations). Extrapyramidal signs may be seen but cognitive deficits are not typically present. Age of onset varies from adolescence to late adulthood with the average age of onset around third to fourth decades. SCA1 is due to an expansion of an unstable trinucleotide CAG repeat on chromosome 6p23.

So far about 25 types of autosomal dominant ataxias have been described and the list is likely to extend further.

Friedreich’s Ataxia

This is an autosomal recessive disorder. Prevalence in European population is 1/50,000. The locus of genetic defect is on chromosome 9. The gene which encodes a protein ‘frataxin’ undergoes mutation.

Frataxin is a mitochondrial protein taking part in energy metabolism. Defect in frataxin leads to abnormal accumulation of iron in the mitochondria followed by cell death. There is neuronal loss in the motor and sensory systems.

Pathology: There is degeneration of the spinocerebellar tracts, posterior columns, Clarke's columns, and the pyramidal tracts. Cardiac involvement occurs in many, taking the form of interstitial myocarditis and conduction defects.

CLINICAL FEATURES

The onset is in the first or second decade of life. Cardinal features of Friedreich's ataxia include ataxia of all four limbs, cerebellar dysarthria, areflexia in the lower limbs, sensory loss and pyramidal signs. Earliest manifestations are ankle areflexia and gait ataxia due to loss of posterior column sensations and cerebellar disturbances. Later, other signs of cerebellar disease and posterior column dysfunction are evident. Ankle jerks are lost earlier than the knee jerks. Loss of vibration and proprioceptive sensations are more evident in the lower limbs. Skeletal deformities such as kyphoscoliosis and pes cavus (increased convexity of the arch of the foot) are common. Optic atrophy and muscle wasting may develop in some cases. Diabetes develops in 10% of cases. Features of cardiomyopathy may develop in those with cardiac involvement.

DIAGNOSIS

It is entirely clinical. Insidious onset of ataxia with signs of cerebellar and posterior column dysfunction, absence of ankle jerks, and presence of Babinski's sign in the first two decades of life should suggest this diagnosis. Associated congenital defects such as kyphoscoliosis and pes cavus are further suggestive. Presence of the disease or other stigmata in family members strengthen the diagnosis. Relatives of the patient may show abnormalities such as pes cavus, kyphoscoliosis, loss of ankle jerks, nystagmus or upper motor neuron signs.

Differential Diagnosis

Several neurological disorders may resemble Friedreich's ataxia superficially. These include multiple sclerosis, other forms of ataxias, craniovertebral junction anomalies, intracranial tumours, tabes dorsalis, and diabetic neuropathy.

Course and Prognosis

The disease progresses steadily over several years, but rate of progression may vary widely between cases. In many cases considerable disability in gait, speech, and daily activities develops, though lifespan is not shortened. Interstitial myocardial fibrosis and cardiac conduction defects may occur in some cases and this may account for premature death in such cases.

Treatment

Specific therapy is not available. Physiotherapy to improve coordination is beneficial. Occupational therapy to

rehabilitate these patients is to be instituted early. High doses of choline have been claimed to allay progress of the disease.

Other Forms of Heredofamilial Ataxias

These rare forms include:

1. **Roussy-Levy syndrome:** It is characterized by sensory ataxia, wasting of extremities, areflexia and pes cavus, without nystagmus.
2. **Sanger-Brown's ataxia:** It manifests as ophthalmoplegia, optic atrophy, and spasticity with nystagmus and pes cavus.
3. **Marie's cerebellar ataxia:** Occurs in the 3rd and 4th decades of life, with cerebellar ataxia and optic atrophy without posterior column deficits.
4. **Primary cerebellar degeneration:** This is clinically characterized by nystagmus, dysarthria and ataxia. The cerebellar cortex and olivocerebellar fibers of the inferior peduncle show atrophy.
5. **Olivopontocerebellar atrophy (OPCA):** It is a large heterogeneous group characterized by degeneration of pontine arcuate and olivary nuclei and middle cerebellar peduncles together with loss of white matter and Purkinje cells in the cerebellar hemispheres. The clinical presentation varies considerably. This occurs sporadically and is seen after the age of 45 years. There is atrophy of the superior and middle cerebellar peduncles, Purkinje cells, olive and pontine nuclei. The disease presents with ataxia of the trunk and extremities, titubation, unsteadiness, and dysarthria. Some patients develop urinary incontinence, parkinsonism and cognitive decline.

Familial, essentially autosomal dominant cerebellar ataxia associated with slow saccadic eye movements. It has been described by N.H. Wadia from (Bombay) as a distinct subgroup of hereditary ataxias. There are up to 21 varieties of familial autosomal dominant spinocerebellar degenerative disorders leading to ataxia.

CEREBELLAR ATAXIAS RESPONSIVE TO SPECIFIC THERAPY

Most of these have a metabolic abnormality caused by congenital or acquired defects of enzymes which take part in the metabolism of amino acids.

These disorders usually present in early life but can also manifest in later life. The presentation can be acute or recurrent, static or progressive.

Acute Recurrent Ataxia

Familial episodic ataxia is an autosomal dominant disorder of uncertain etiology.

Clinical features include paroxysmal ataxia, nausea and vertigo. There are two types; type 2 is more common.

Attacks begin in late childhood or adolescence and are precipitated by stress, exertion and fatigue. Duration is from hours to days. The episodes may be superimposed on mild form of chronic progressive truncal ataxia. The disease predominantly affects the vestibulo-cerebellum. Diagnosis is made by the episodic nature of attacks, positive family history and MRI evidence of cerebellar vermis atrophy. Therapy is with acetazolamide which reduces the frequency and severity of episodic ataxia. Type 1 is earlier in onset with briefer attacks and absence of signs between attacks. Myokymia of the hands and face can occur.

Maple Syrup Urine Disease (MSUD)

MSUD is an autosomal recessive disorder due to deficiency of branched chain ketoacid dehydrogenase. The intermittent form of MSUD can present with episodic ataxia and encephalopathy. Infection and excess dietary protein precipitate attacks and diagnosis is established by finding increased levels of branched chain amino and ketoacids in plasma and urine. Dietary restriction of branched chain amino acids and use of thiamine are the modes of treatment.

Hartnup Disease

Hartnup disease is an autosomal recessive disorder resulting from defective transfer of neutral amino acids. Affected individuals present with episodic ataxia, personality change and pellagra like skin rashes. There is increased excretion of neutral amino acids and indole products in the urine. Treatment is by giving high protein diet and nicotinamide.

Multiple Carboxylase Deficiency

Multiple carboxylase deficiency is an autosomal recessive disorder due to deficiency of biotinidase [biotin recycling enzyme] or biotin containing carboxylase. The disorder often presents in the first six months of life with seizures, alopecia and decreased hearing. Milder forms may present in later life. Diagnosis is by finding reduced levels of biotin in serum and urine and lactic acidemia. Treatment is oral biotin 10 mg per day.

Urea Cycle Disorders

Urea cycle disorders present in infancy with ataxia, seizures, vomiting and varying levels of altered sensorium. They are autosomal recessive disorders with the exception of ornithine transcarbamylase deficiency which is X-linked. Altered function of several enzymes involved in the urea cycle can present with increased levels of ammonia and abnormality in levels of specific amino

acids. Insulin-glucose regime, sodium benzoate and sodium phenylacetate are used to bring down ammonia. Severe cases may require dialysis.

CHRONIC PROGRESSIVE ATAXIA

Abetalipoproteinemia

Abetalipoproteinemia is an autosomal recessive disorder presenting with steatorrhea in infancy followed a few years later by ataxia, peripheral neuropathy and retinitis pigmentosa. There is absence of apolipoprotein B resulting in fat malabsorption and deficiency of Vitamins A,E and K. Investigations reveal acanthocytes in peripheral smear, low serum cholesterol and triglycerides and absence of apolipoprotein in serum. Treatment is by giving vitamins A,E and K. Diet should be low in long chain fatty acids.

Ataxia due to Vitamin E Deficiency

This is an autosomal recessive disorder presenting in the second decade of life with progressive ataxia, areflexia and proprioceptive loss. Diagnosis is made by finding low serum levels of Vitamin E and treatment is vitamin E supplementation.

Refsum's disease is an autosomal recessive disorder due to deficiency of the enzyme *phytanic acid alpha hydroxylase*. Ataxia, Polyneuropathy, retinitis pigmentosa and deafness are the common clinical manifestations. Phytanic acid levels are increased in blood and urine. Treatment is by giving diet low in phytanic acid. During acute exacerbations, plasmapheresis may be required.

Cerebrotendinous Xanthomatosis

This is an autosomal recessive disorder due to deficiency of chenodeoxycholic acid which is necessary for the synthesis of bile acids. Presentation is in adolescence or early childhood with ataxia, spasticity, neuropathy and dementia. Diagnosis is suggested by the typical association of tendinous xanthomas and cataract. Serum cholesterol level is increased and treatment is by giving chenodeoxycholic acid.

Wilson's disease an abnormality of copper metabolism, may be present with cerebellar ataxia (see Chapter 32).

von Hippel-Lindau Syndrome

von Hippel-Lindau syndrome is an autosomal dominant disorder presenting with hemangioblastoma of the cerebellum and angioma of the retina. Other associations include renal cell carcinoma, renal and pancreatic cysts, pheochromocytomas and polycythemia.

Ataxia Telangiectasia

Syn: Madame-Louis-Bar syndrome

This is an autosomal recessive condition occurring in children and manifesting by the age of 10 years. The features are cerebellar ataxia, wasting of legs and areflexia. The bulbar conjunctiva shows telangiectasia. There is deficiency of immunoglobulins and this leads to repeated sino-pulmonary infection. The condition is associated with poor prognosis.

Hereditary Spastic Paraplegia

In this form, the predominant lesion is degeneration of the pyramidal tracts with minor involvement of the spinocerebellar tracts and posterior columns. It is inherited as autosomal dominant disorder and the disease manifests clinically between 3 and 15 years of age. In the fully evolved form the picture is one of spastic paraplegia with lesser affection of the upper limbs, dysarthria, and pseudobulbar palsy.

Cerebellar Tumours

The cerebellum may be the seat of tumours such as medulloblastoma, cystic astrocytoma, and oligodendroglioma, which are common in children. Medulloblastoma affects the midline structures of the cerebellum more often. Astrocytoma affects the lateral hemispheres more. Hemangioblastoma and metastatic deposits usually occur in adults.

Inflammatory Lesions of the Cerebellum

Cerebellum may be involved in viral and bacterial meningo-encephalitis, chickenpox and postvaccinal encephalitis. Cerebellar abscess may occur as a complication of otitis media. Tuberculomas are not uncommon in the cerebellum, especially in children (See Chapter 49).

Vascular Lesions of the Cerebellum

Cerebellum is the seat of hemorrhage in 5-10% of all hemorrhagic strokes occurring in hypertension. The patient presents with headache, neck rigidity, nystagmus, vomiting and ataxia. If the bleeding increases or edema develops, other features such as ocular palsy, loss of sensation in the trigeminal territory, facial palsy, and coma may set in. Surgical evacuation of the clot is life-saving. If left untreated, 50% die within a week. Occlusive lesions of the vertebrobasilar system lead to cerebellar infarction.

OTHER CAUSES OF CEREBELLAR DYSFUNCTION

Alcoholism: Acute alcoholic bout may lead to ataxia, nystagmus, and dysarthria. Cerebellar degeneration as a complication of chronic alcoholism results in ataxia of gait and stance, often without nystagmus and dysarthria.

Multiple sclerosis: The cerebellum and its connections are affected in multiple sclerosis.

Subacute cerebellar cortical degeneration: This may occur as a nonmetastatic complication of malignancy, especially bronchogenic carcinoma. The cerebellar lesion manifests as ataxia, dysarthria, rarely nystagmus, depression of tendon reflexes, and Babinski's sign.

Metabolic disturbances: Cerebellar ataxia may occur in hypoglycemia, hypothyroidism, hypoxia and hyperthermia. In the early stages this is reversible.

Drugs: Drugs like phenytoin may lead to reversible cerebellar disturbances such as dysarthria, ataxia, and nystagmus. In advanced cases the Purkinje cells may show degeneration and the condition becomes irreversible.

Nutritional deficiencies: Thiamine and niacin deficiency (pellagra) produce cerebellar deficit similar to chronic alcoholism.

Developmental anomalies: Arnold-Chiari malformation, basilar invagination, Dandy-Walker cyst and cerebellar aplasia cause cerebellar dysfunction along with other deficits.

Diseases of the Spinal Cord, Nerve Roots and Plexus

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General Considerations

The spinal cord extends from the foramen magnum to the lower border of first lumbar vertebra. Pia and arachnoid mater extend to the 2nd sacral vertebra and dura further below to merge with the periosteum of coccyx. The pia mater, which extends down as a connective tissue filament, is called *filum terminale*. The length of the spinal cord is 45 cm (male) and 40 cm (female) and consists of 31 segments: eight cervical, twelve dorsal, five lumbar,

five sacral and one coccygeal. From each spinal segment, the anterior and posterior roots arise which join to form the spinal nerve. The spinal roots exit the spinal canal through neural foramina formed by adjacent vertebrae. The spinal cord is shorter than the spinal canal, and therefore, vertebral bodies and the spinal cord segments do not correspond with each other. The first seven cervical roots exit above their corresponding cervical vertebral bodies and the eighth cervical root exits below the seventh cervical vertebra. The other spinal roots exit below their corresponding vertebral bodies. The lumbar and sacral roots are long because they descend from their respective cord segment to their exit points in the spinal canal. These descending roots form a bundle termed as *cauda equina* (horse's tail). The spinal segment corresponding to each vertebra is determined as follows:

For cervical vertebrae add 1, e.g. spinal cord segment corresponding to C5 vertebra is C6.

For thoracic (dorsal) vertebrae, 1- 6 add 2

For thoracic vertebrae 7-9, add 3

10th thoracic vertebral arch overlies L1 and L2 segments

11th thoracic arch overlies L3 and L4 segments

12th thoracic arch overlies L5 segment

1st lumbar arch overlies sacral and coccygeal segments.

Group of muscles and area of skin supplied by a spinal cord segment is called *myotome* and *dermatome*, respectively. Knowledge of the segmental innervation of muscles and skin is essential to determine the level of affection of spinal cord disease.

The spinal cord is supplied by one anterior and 2-4 posterior spinal arteries. The anterior spinal artery is formed by the confluence of two branches arising from the vertebral arteries and it descends in the anterior median fissure throughout the length of the spinal cord. The two posterior spinal arteries arise from the corresponding vertebral or posterior inferior cerebellar arteries and descend along the entire length of the cord. Anterior spinal artery supplies the anterior 2/3 of the spinal cord including anterior horn, central canal and anterolateral columns,

whereas the posterior spinal arteries supply the posterior 1/3 including posterior horn and posterior columns. The spinal arteries send descending branches to supply the cauda equina. The anterior spinal artery is reinforced by 4-8 radiculomedullary arteries derived from the vertebral, intercostal and lumbar arteries. The feeder vessels of the lower cervical and lower thoracolumbar regions are most important. **The artery of Adamkiewicz** (arteria radicularis magna) is a major radicular artery that arises from the aorta and enters the cord between T10 and L3 segments and supplies the lower thoracic and lumbar spinal cord. As the feeder vessels in the thoracic region are small in caliber and sparsely distributed, the thoracic cord (especially T4 to T8 regions) is vulnerable to ischemia during global hypoperfusion and hence this region represents a watershed zone in the spinal cord. The direction of blood flow along the spinal arteries varies and can depend on various factors such as changes in posture and intra abdominal and intrathoracic pressure. Veins draining the cord are situated dorsally and ventrally as six longitudinal channels. They drain rostrally into the vertebral veins.

The motor neurons supplying different groups of muscles are arranged in the anterior horn of the spinal cord in a definite manner:

Muscle groups	Position of neuron in the anterior horn
Distal muscles of the extremities	Lateral
Proximal muscles of the extremities	Medial
Extensors and abductors	Anterior
Flexors and adductors	Posterior

The sensory and motor tracts passing through the spinal cord are shown in Table 198.1 and Figure 198.1 The pathway for bladder and bowel control is located in the lateral column.

TABLE 198.1		
Tracts of the spinal cord		
Tract	Location in spinal cord	Function
Fasciculus gracilis Fasciculus cuneatus	Dorsal column	Proprioception, vibration sense, touch
Pyramidal	Lateral column – deep and anteromedial	Voluntary muscle contraction
Lateral spinothalamic	Venterolateral column	Pain and temperature
Anterior spinothalamic	Anterior column	Touch
Spinocerebellar	Lateral column - superficial	Muscle position, tone

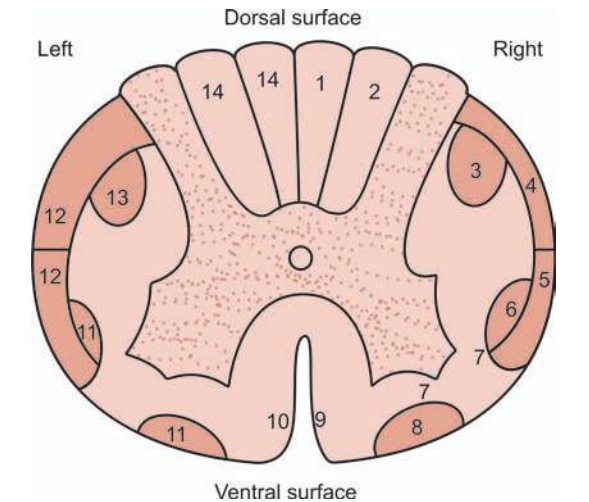


Fig. 198.1: Spinal cord section—diagrammatic representation

Functional Representation	Anatomy of tracts
10. and 13. Voluntary movement	1. Fasciculus gracilis
11. Pain, temperature and touch	2. Fasciculus cuneatus
12. Equilibration	3. Lateral (crossed) pyramidal tract
14. Position sense, vibration sense, touch	4. Posterior spinocerebellar tract
	5. Anterior spinocerebellar tract
	6. Lateral spinothalamic tract
	7. Extrapyramidal tracts
	8. Anterior spinothalamic tract
	9. Anterior (uncrossed) pyramidal tract

Fibers in the spinal cord tracts are arranged in a specific pattern, called as laminations. In the dorsal columns, sacral fibers are medially placed while thoracic and cervical fibers are arranged more laterally. In the lateral spinothalamic and pyramidal tracts, the arrangement of fibers is reverse, sacral fibers being more lateral and cervical fibers medial.

Clinical Features of Spinal Cord Disease

Motor phenomena: Interruption of the descending corticospinal (pyramidal) tract gives rise to UMN type of paralysis below that level, characterized by distal weakness and spasticity. At the level of lesion, LMN type of paralysis may occur, manifesting as wasting and fasciculation of muscles supplied by that spinal cord segment. Weakness of upper and lower limbs is called quadriplegia (tetraplegia) and weakness of lower limbs alone is paraplegia. Pattern of muscle weakness may vary depending on the degree of spinal cord compression. Classically, patients may present with **paraplegia in extension** if the pyramidal tract is solely damaged and **paraplegia in flexion** if both the pyramidal and extra-

pyramidal tracts are damaged. As the spinal cord lesion progresses, the lower limbs assume a position of flexion and persistent shortening and contracture of muscles. With involvement of both pyramidal and extrapyramidal tracts, the paralyzed limbs may develop frequent spasms (*flexor spasms*) that may occur either spontaneously or in response to external stimuli. With cord lesions at T₁₀ level, upper abdominal muscles are normal while lower abdominal muscles are weak and maneuvers that require contraction of the abdominal muscles results in pulling up of the umbilicus, resulting in **Beevor's sign**.

Sensory phenomena: Interruption of ascending sensory tracts may lead to various patterns of sensory deficits. Involvement at a particular spinal cord level results in bilateral impairment of sensations with a distinct level that separates it from the region of normal sensation above. Interruption of spinothalamic tracts results in loss of pain and temperature sensations. Lesion of the dorsal column results in loss of proprioception and vibration sense. Compression of posterior spinal roots gives rise to root pains (*radicular pain*) and loss of sensations in the corresponding dermatome. **Radicular pain** is characterized by unilateral, sharp dermatomal pain exacerbated by cough, sneeze or Valsalva maneuver and results from root irritation. **Vertebral pain** arises from the vertebrae and is characterized by aching pain localized to the point of the spine involved by the lesion and is often accompanied by point tenderness. **Funicular pain** (tract pain) is a deep ill-defined painful dysaesthesia usually occurring away from the affected spinal cord level and is caused by involvement of spinal tracts. Lesions of the dorsal column may result in tingling or vibratory paraesthesias. Patients may complain that the skin is "too tight" or an extremity is "wrapped in bandages". Lesions of the spinothalamic tracts may result in pain that is poorly characterized or localized.

Neck flexion at times may give rise to an electric shock like sensation down the spine due to stretching and irritation of nerve fibers in the dorsal column of the cervical cord. This is referred to as **Lhermitte's sign**. It occurs in cervical spondylotic myelopathy and demyelinating diseases affecting the cervical cord.

Reflex changes: Deep tendon reflexes are exaggerated below the level of lesion in localized spinal cord lesions. If the substance of the cord is destroyed over long segments, the tendon reflexes mediated by these segments are also lost. Following acute lesions which interrupt the motor pathways completely, there is a period of flaccidity and areflexia. This period of **spinal shock** may last from a few hours to days after which, tone and reflexes return. Spasticity then develops, initially in the extensor group of muscles of the lower limbs and flexor group of muscles of the upper limbs. The *mass reflex* consists of widespread

reflex contraction of the muscles of the lower limbs and trunk, sweating, and evacuation of the bladder, rectum and seminal vesicles in response to noxious stimuli.

Autonomic Disturbances

Sweating is lost below the level of complete transection of the cord. Rarely, excessive sweating may occur.

Blood pressure fluctuations may also occur in myelopathies. Lesions above T5 spinal segment leads to impaired vasomotor control, resulting in orthostatic hypotension. Such patients may also have episodic autonomic dysreflexia characterized by excessive sweating, cutaneous flushing, hypertension, pounding headache and reflex bradycardia following any noxious stimulus.

Bladder disturbances are common in spinal cord disease. Parasympathetic and sympathetic fibers mediate the voiding and storage functions of urinary bladder while somatic fibers are responsible for voluntary control. Bladder receives parasympathetic fibers from intermediolateral zone of S2, S3 and S4 spinal segments that travel via pelvic nerves and innervate the detrusor muscle, bladder neck and internal sphincter. Sympathetic fibers arise from L1 and L2 spinal segments and reach the bladder via hypogastric nerves. They predominantly innervate the bladder neck and internal sphincter. External sphincter is under voluntary control and is supplied by somatic efferent fibers arising from S2, S3 and S4 spinal segments (Onuf's nucleus) that travel via the pudendal nerve. Sensory impulses from the bladder pressure receptors are carried by somatic (pudendal nerve) and autonomic (pelvic and hypogastric nerves) fibers. Micturition is mediated by a supraspinal reflex with pontine micturition centre and its initiation and termination are under voluntary control. Voiding of urine occurs by relaxation of the sphincters and contraction of detrusor muscle, mediated by the parasympathetic system. Once micturition is complete, detrusor muscle relaxes and sphincters contract due to parasympathetic inhibition and sympathetic system facilitation. Subsequently, the bladder begins to store urine. Voluntary control of initiation and termination of micturition is mediated by the paracentral motor region of frontal cortex via descending fibers in the lateral columns of spinal cord. Bladder sensations are carried via the spinothalamic tracts. Lesions of the spinal cord above the sacral segments results in an upper motor neuron type of neurogenic bladder characterized by increased contractions of the detrusor muscle (detrusor hyperreflexia) and lack of coordination between contraction of the detrusor and sphincter muscles (detrusor sphincter dyssynergia). This results in the symptoms of urgency, urge incontinence, frequency of micturition and

hesitancy. However, initially in the acute phase, the patient may present with retention of urine and reduced detrusor muscle activity due to the stage of spinal shock. Lesions of the sacral segments results in the symptoms of hesitancy of micturition, chronic retention, continuous dribbling of urine due to overflow incontinence, inability to initiate micturition and reduced bladder sensations.

Sexual dysfunction is also common in myelopathies and may result in impotence (failure to obtain erection sufficient enough to perform the sexual act). Penile erection, mediated by parasympathetic pathways, is often affected in lesions of spinal cord. Psychogenic erection is mediated by impulses passing from spinal segments T12 to L3. Reflex erection resulting from penile stimulation, is mediated by S2, S3 and S4 spinal segments. In lesions above T12 segment, psychogenic erection is lost while reflex erection persists, whereas both are lost in lesions affecting the sacral segments. Occasionally, patients may manifest with priapism, characterized by sustained erection without psychological sexual stimuli. In females, disturbances of sexual function manifest commonly as loss of the sexual drive and dyspareunia, often difficult to assess objectively.

Disturbances of defecation are less severe and often transient in myelopathies. Common complaints include constipation and loss of rectal sensation. Fecal incontinence is rare and may occur in lesions of the conus medullaris. It is associated with patulous rectal sphincter as appreciated during digital examination and loss of anal reflex.

Diseases of the Spinal Cord

Several disease processes affect the spinal cord and cause varying degrees and patterns of neurological dysfunction. These are referred to as *myelopathies*. Myelopathies can be approached syndromically based on the constellation of symptoms and signs. The common spinal cord syndromes include:

Complete transverse section: Syndrome of complete transverse section at a particular level of the spinal cord results in symmetric UMN paralysis, sensory loss and autonomic disturbance below the level. This syndrome is classically seen in transverse myelitis, but can occur in post-traumatic spinal cord injury and acute spinal cord compression.

Unilateral transverse section: Syn: *Brown-Sequard syndrome*. This syndrome of hemisection of spinal cord results in ipsilateral UMN paralysis and loss of sensation for vibration and proprioception and contralateral loss of appreciation of pain and temperature. Otherwise known

as the *Brown-Sequard syndrome*, it most commonly occurs following spinal cord trauma or compression due to tumour.

Central cord syndrome: Intramedullary lesions damage the decussating fibers of the spinothalamic tract that carry sensations of pain and temperature at that level, resulting in dissociated sensory loss. This is characterized by loss of pain and temperature sensations and preserved appreciation of joint and proprioception sensations. Because of the arrangement of fibers in the spinothalamic tract, sacral sensations are usually preserved resulting in a *suspended pattern* of sensory loss. Common causes include syringomyelia, intramedullary tumours and post-traumatic hematomyelia or contusion.

Anterior spinal artery syndrome: Occlusion of the anterior spinal artery results in a characteristic constellation of signs due to infarction of spinal cord parenchyma supplied by it. It is characterized by involvement of anterior horn cells and anterolateral tracts leading to motor paralysis, loss of bowel, bladder and sexual functions and sensory disturbances characterized by loss of appreciation of pain and temperature sensations and preservation of joint and proprioception sensations. This can occur following vascular and thoraco-abdominal surgeries.

Anterior horn and pyramidal tract syndrome: Disturbance of anterior horn and pyramidal tract function with preservation of sensory and autonomic nervous system function can occur in motor neuron disease (MND).

Combined Posterior and Lateral Column Disease: Syndrome of loss of joint and proprioception sense with UMN pattern of weakness leads to spastic ataxic gait and is seen in vitamin B₁₂ deficiency (subacute combined degeneration). Friedreich's ataxia, neurosyphilis and HIV myelopathy may show signs of loss of pyramidal tract, posterior columns, lateral columns and spinocerebellar tract functions.

For practical purpose of evaluation and management, myelopathies can be broadly categorized into compressive or non-compressive, based on whether or not myelopathy is caused by a lesion that is compressing the spinal cord. General clinical features that are usually seen in compressive myelopathy include:

- Asymmetric onset
- Steadily progressive symptoms
- Asymmetric symptoms and signs
- Presence of flexor spasms
- Well-defined sensory, reflex or motor level
- Bladder dysfunction.

The lesion compressing the spinal cord may be either extramedullary, arising outside the spinal cord, e.g.

TABLE 198.2
Causes for myelopathy
• Tumour • Infections-tuberculosis, syphilis • Trauma • Degenerative disc diseases • Congenital anomalies • Diseases of vertebral column, e.g. tuberculosis, epidural malignant lesions, primary and secondary; pachymeningitis, arachnoiditis

meningioma, or may be intramedullary, arising from within, e.g. ependymoma. Differentiation between the two may be difficult clinically, though presence of certain symptoms and signs may be helpful. Table 198.2 and Figure 198.2 give a simple approach to the patient presenting with myelopathy. The common causes of myelopathy are enlisted in Table 198.2.

MYELOPATHY

Myelopathy may be caused by compressive or non-compressive lesions.

COMPRESSIVE MYELOPATHIES

The spinal cord may be the seat of compression in several pathological entities on account of its location within a narrow, restricted bony canal —the spinal canal. *Source of the spinal cord compression may be extramedullary in 80% and intramedullary in 20%.* The common causes are enlisted in Table 198.3.

TABLE 198.3
Causes for compressive myelopathy
Intramedullary Primary tumours (astrocytoma, ependymoma) Metastasis Syringomyelia, hematomyelia Infections: spinal cord abscess, tuberculoma, cysticercosis
Extramedullary and intradural Primary tumours: neurofibroma, meningioma Vascular: AV malformation Metastases: leukemia, lymphoma, myeloma Infections: syphilitic pachymeningitis, arachnoiditis, e.g. tuberculous
Extramedullary and extradural Infections: epidural abscess, tuberculosis of the vertebrae (Pott's disease) Metastases: breast, lung, GI tract, prostate, thyroid, myeloma Congenital anomalies: craniovertebral junction anomalies Epidural hematoma Trauma: vertebra fracture Spondylosis cervical and lumbar/intervertebral disc prolapse Fluorosis

Two-third of extramedullary tumours are situated on the dorso-lateral aspect of the cord, and one-third ventrally. Damage to the spinal cord may result from direct pressure of the tumour, and/or pressure on the arteries leading to infarction or edema caused by venous obstruction. In slow spinal compression, the corticospinal

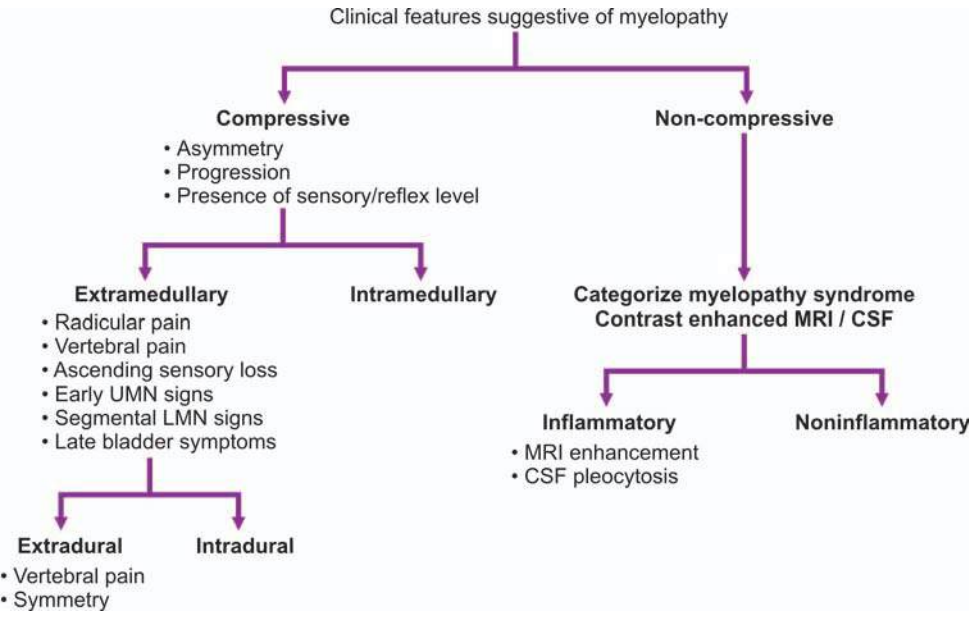


Fig. 198.2: Clinical approach to a patient with myelopathy

TABLE 198.4

Clinical guidelines to differentiate intramedullary from extramedullary compressive lesions

Symptom/ sign	Intramedullary lesion	Extramedullary lesion
Radicular pain (girdle pain)	Unusual	Common, may occur early
Vertebral pain	Unusual	Common
Funicular (tract) pain	Common	Less common
Upper motor neuron signs	Yes, late	Yes, early
Lower motor neuron signs	Prominent and diffuse	Unusual; if present, segmental distribution
Progression of pain/temperature sensation loss	Descending (sacral sparing)	Ascending
Dissociation of sensory loss	Present	Absent
Bladder disturbances	Early	Late

tracts are more susceptible to compression and ischemia and only later are the posterior column and spinothalamic tracts affected (Table 198.3).

CLINICAL FEATURES

Onset of symptoms may be acute, subacute or insidious and clinical features depend upon the site and cause of compression Table 198.4 SCA—spine-cerebellar ataxia.

In extramedullary compression, the initial symptom is pain felt over the spine or in the distribution of the spinal root. Coughing, sneezing or movements of the spine may aggravate this pain in the case of extradural lesions. As the compression proceeds, paresthesias and numbness develop over the limbs as a result of compression of the spinothalamic tracts and posterior column. Motor symptoms consist of heaviness, stiffness and weakness of the lower limbs if the lesion is below T1 level. Upper limbs will also be involved if site of compression is cervical spinal cord. **Classically, the march of paralysis in cervical cord extramedullary compression is initially ipsilateral upper limb, then ipsilateral lower limb, opposite lower limb, and finally opposite upper limb (Elseberg rule).** This sequence is due to initial compression of the ipsilateral corticospinal tract and as it progresses, subsequent compression of the contralateral corticospinal tract by *contre-coup* pressure. Involvement of bladder occurs late, as the fibers subserving bladder function are placed deep in the spinal cord.

Intramedullary compression causes disturbance of bladder function early. Sensory loss generally takes the form of dissociated anesthesia. Dissociated sensory loss may develop either as a result of pressure on the crossing sensory fibers in the anterior commissure or compression on the lateral spinothalamic tracts. In the former case, sensory loss is confined to the segment affected. Since the lateral spinothalamic tract is compressed from within, cervical lesions cause loss of sensation in the upper limb first and then only lower limb. Thus sacral sensations are spared till late in the disease, called **sacral sparing**. Root pains are uncommon.

Lesions at the level of foramen magnum and upper cervical cord lead to a constellation of symptoms and signs. These include suboccipital pain (C2 distribution), loss of pain and temperature sensation of face, lower cranial nerve palsies (9,10,11,12), cerebellar signs, diaphragmatic weakness, downbeat nystagmus, papilledema and cruciate hemiplegia (contralateral upper limb and ipsilateral lower limb weakness).

LESIONS OF THE CONUS MEDULLARIS AND CAUDA EQUINA

Lesions of the cauda equina and conus medullaris cause similar symptoms and it is often not possible to differentiate between the two. When the cauda equina is affected, symptoms and signs are attributed to root involvement. Common conditions include neoplasms, prolapsed intervertebral discs and spinal arachnoiditis. Lumbar canal stenosis may lead to the additional symptom of intermittent neurogenic claudication. Lesions of the **conus medullaris** (S3,4,5,coccygeal spinal segments) are characterized by early loss of sphincter functions. Common conditions include neoplasms such as ependymoma and demyelination. Lesions of the **epiconus** affect the L4, 5, S1 and S2 spinal segments. Table 198.5 enlists the points useful to differentiate between conus medullaris and cauda equina lesions

DIAGNOSIS (SEE FIG. 198.2)

Diagnosis of compressive myelopathy involves the following steps:

1. Determining the level of compression
2. Determining whether compression is extra- or intramedullary
3. Ascertaining the pathological nature of the lesion.

X-rays of the spine may reveal vertebral or disc pathology. Enlargement of the intervertebral foramina suggests the presence of neurofibroma. CT scan can demonstrate the spinal canal and identify the cause of compression. MRI is superior to CT to reveal spinal cord lesions and whenever available is the investigation of choice.

TABLE 198.5

Clinical features useful to differentiate conus medullaris and cauda equina lesions

Clinical feature	Conus medullaris	Cauda equina
Onset	Sudden, bilateral	Usually gradual, unilateral
Motor weakness	Symmetric, minimal	Asymmetric, may be severe, fasciculations common
Sensory loss	Saddle anaesthesia, symmetric	Asymmetric
Spontaneous pain	Unusual, not severe	Prominent, severe, asymmetric
Neurogenic claudication	Absent	May be present
Dissociated sensory loss	Present	Absent
Sphincter incontinence	Early and marked	Late, less severe
Erectile dysfunction	Early	Late, less severe
Loss of anal and bulbocavernosus reflexes	Early	Late
Ankle jerk	Preserved	May be lost

Role of lumbar puncture is limited, and presence of elevated protein levels suggest significant cord compression. L.P. is contraindicated in cord compression due to tumours since it may worsen the paralysis due to leakage of CSF and inspissation of the tumour at the site. In cases of obstruction of the spinal canal **Froin's syndrome** characterized by xanthochromia and elevated CSF protein, may develop.

Differential diagnosis: When the signs and symptoms of myelopathy are associated with spinal pain, tenderness and deformity or nerve root pains, it strongly suggests a remediable surgical etiology. Figure 198.2 is useful to localize the source of compression. Sometimes, clinical distinction between extra- and intramedullary lesions may be difficult.

Spinal cord compression has to be distinguished from other intrinsic disorders such as syringomyelia, motor neuron disease and multiple sclerosis.

MANAGEMENT OF SPINAL CORD COMPRESSION

Whenever spinal cord compression is confirmed by MRI, CT scan or myelography, neurosurgical intervention should be sought without delay. Surgical treatment should be undertaken early to avoid permanent damage to the cord by direct compression or vascular occlusion. Early treatment restores function but if compression is allowed to persist for long periods, secondary changes develop in the cord. Late surgery is often unrewarding and the functional results are poor. Conditions such as tuberculosis of the vertebrae may resolve to a great extent with medical therapy. Acute cord compression leading to sudden onset paraplegia is a neurosurgical emergency. Appropriate and prompt decompressive surgery reverses

the neurological damage. The prognosis for recovery depends upon the severity and the duration of the neurological deficit prior to surgery. Therefore, it is important to make an early diagnosis.

MYELOPATHY IN TUBERCULOSIS

Tuberculosis can present as myelopathy in several ways. Spinal tuberculosis commonly affects the dorsal spine and can lead to *Pott's paraplegia* due to spinal cord compression. X-ray shows anterior wedging of adjacent vertebrae with loss of intervening disc space, which can be confirmed by CT or MR imaging. Table 198.6 enlists the causes for myelopathy in tuberculosis.

TABLE 198.6

Myelopathy due to tuberculosis

Due to extramedullary lesions	Due to intramedullary lesions
Cold abscess, granulation tissue	Myelitis
Sequestered bone and disc fragment	Tuberculoma
Pathological subluxation of vertebra	Thrombosis of anterior spinal artery (rare)

Spinal Epidural Abscess

It commonly presents as subacute progressive compressive myelopathy associated with fever. However, it may occasionally present as acute paraplegia. Epidural abscess develops as a result of septic emboli reaching the epidural space during systemic infection. Root pains may develop. Fever is highly variable and some patients may have mild fever while others may have hectic fever and appear toxic. *Staphylococcus aureus* is the causative organism in 50%

of cases. Diagnosis is established by MRI and confirmed by evacuation of pus and culture/sensitivity. At times, the condition will be diagnosed when pus is aspirated during a lumbar puncture for other indications.

INJURY TO SPINAL CORD

Spinal cord damage is a common complication of injuries to the vertebral column. When the spinal cord is injured by forces occurring during violence without fracture, dislocation of the spine or structural cord damage, it is termed *concussion*. *Contusion* is the term used to denote bruising of the cord without rupture of the pia arachnoid. More severe injury results in *laceration* of the cord in which the pia is ruptured and often the cord may even be completely transected. Clinical features depend upon the site and type of injury. Injury to the cervical cord above C4 is fatal due to associated paralysis of the diaphragm and intercostal muscles.

Management: On the first suspicion of spinal cord injury, further movements of the spine should be prevented by proper splinting. Transportation to a neurosurgical center should be done without delay. Surgical decompression is undertaken if conservative measures such as immobilization of the spine and traction are unsuccessful.

Spinal cord lesions are not uncommon in dysbarism (caisson disease). This should be borne in mind when injury is associated with activities under water (see Chapter 14).

HEMATOMYELIA

Bleeding into the substance of the spinal cord is termed *hematomyelia*. Though bleeding into the cord may follow injuries, the term *hematomyelia* is reserved for those conditions where there is no obvious precipitating factor.

Etiology

- 1. Transmitted violence
- 2. Intramedullary telangiectasia or angioma
- 3. Spontaneous hemorrhage into the cavity of syringomyelia
- 4. Hemorrhagic disorders, especially purpura.

Common site is the cervical cord enlargement. The bleeding is primarily into the central grey matter and the long tracts are compressed by the hematoma.

Clinical features: The onset may be sudden or gradual and progressive. The condition is clinically characterized by the syndrome of partial or complete transection of the cord, depending on the extent of the hematoma. Usually, patients gradually improve as the hematoma resolves. Rarely the condition may be fatal if the hematoma extends to the cervical cord leading to diaphragmatic paralysis.

Treatment: This consists of complete rest and immobilization of the neck in a collar or suitably made splints. The underlying cause should receive appropriate treatment.

Syringomyelia

This is a chronic disorder pathologically characterized by progressive cavitation (*syrix*) and gliosis of the central portions of the spinal cord. Usually the syringomyelic cavity is longitudinal and extends over a few segments and rarely the entire length of the cord. Transversely, it tends to extend irregularly into the anterior horns and lateral columns. Dorsal columns are late to be involved. The contours of the cavity are irregular and its walls are formed by gliosis. When the lesion extends into the medulla, it is called *syringobulbia*. The condition may be primary (congenital) or secondary (acquired) (Table 198.7). In about 50% of cases of primary syringomyelia, there are associated bony and soft tissue abnormalities at the craniovertebral junction.

Pathogenesis: No theory adequately explains the pathophysiology of syringomyelia. Disruption of CSF circulation at the level of foramen magnum is seen in many cases of syrix. Pressure waves develop at the foramen magnum due to periodic downward displacement of the cerebellar tonsils during systole and results in compression and elongation of the syrix. Following trauma and infection such as tuberculous arachnoiditis, scarring results and leads to altered CSF dynamics and tethering of the cord.

Pathology: The site of predilection of primary or congenital syringomyelia is the lower cervical region, but the cavity may extend for several segments down into the thoracic region or up into the medulla. Lumbosacral cord may be affected either by extension of the cavity or by independent cavities. Usually the cavity starts as enlargement of the central canal of the spinal cord, which extends forward and laterally to involve the anterior commissure, anterior horns, and lateral columns. The anterior horn cells and the segmental fibers carrying pain

TABLE 198.7	
Causes for syringomyelia	
• Foramen magnum obstruction – Arnold Chiari malformation, basilar invagination • Spinal cord tumour: astrocytoma, ependymoma, hemangioblastoma • Myelomalacia and loss of spinal cord parenchyma • Intracranial communicating hydrocephalus • Post-traumatic • Post-infectious, post-inflammatory • Idiopathic	

and temperature, which cross in the anterior commissure, are affected early. The corticospinal and lateral spinothalamic tracts are involved subsequently. The posterior columns get involved only late in the disease or not at all.

CLINICAL FEATURES

The age of onset is usually between 25-40 years in the primary form. Initial symptoms in cervicothoracic syringomyelia consists of loss of pain and thermal sensation in the cervicothoracic segments (especially C8, T1) associated with weakness, wasting and even fasciculations of the small muscles of the hands. Loss of pain and temperature sensation with preservation of touch (*dissociated anesthesia*) in an irregular distribution is the hallmark of syringomyelia. The patient may not appreciate burns and injuries. Depending upon the level of interruption of the crossing fibers and the lateral spinothalamic tracts, the distribution of dissociated sensory loss varies. In high cervical lesions, the spinal tract of the trigeminal nerve is affected and this also gives rise to dissociated anesthesia over the face. Trophic changes develop as a result of loss of pain sensation. These include painless perforating ulcers and neuropathic joint (*Charcot's joints*). Destructive changes in joints induced by denervation was described by Jean Martin Charcot (French physician) in 1868. The affected joints undergo degenerative changes due to hypermobility and laxity of the capsule and ligaments, and the articular surfaces may disintegrate. Commonly, elbow and shoulder joints are also affected. Radiological changes of destruction are demonstrable in these joints. Patients may complain of vague pains and paraesthesias over the affected parts. In some, sensory symptoms may be the most troublesome presenting symptom.

Horner's syndrome occurs due to involvement of the sympathetic fibers in the cervical cord or medulla. Function of bladder and rectum are generally not affected. When the cavity extends into the brainstem, patients develop multiple cranial nerve palsies.

Course and prognosis: The condition is slowly progressive and causes significant disability over several years. Some cases are self-limiting. In a few, rapid worsening may be due to bleeding into the syrinx.

Diagnosis: The combination of lower motor neuron paralysis, dissociated sensory loss at the level of the lesion and upper motor neuron features below the level of lesion should raise the possibility of syringomyelia. Intramedullary tumours, vascular lesions and hematomyelia have to be excluded. Syringomyelia and craniovertebral anomalies may coexist in some cases. MRI is the investigation of choice. In all cases therefore, it is necessary to

investigate the craniovertebral region with X-ray, and CT scan or MRI.

Treatment: Treatment depends upon the cause. Syrinx due to Arnold Chiari malformation is managed by foramen magnum decompression. Syrinx associated with hydrocephalus is managed with ventricular shunt. Tumour removal is the treatment of choice for tumour related syrinx. Syrinx related to trauma and infection is managed by adhesiolysis and duroplasty. Second line treatment for syringomyelia includes syringostomy, which drains the syrinx cavity into the spinal subarachnoid space.

Non-compressive Myelopathies

However in some cases of myelopathy, despite extensive investigations, the cause may still remain obscure (myelopathy of undetermined etiology) (Table 198.8).

TABLE 198.8

Causes for non-compressive myelopathy

- Inflammatory
 - Infections: enterovirus, herpes zoster, herpes simplex, mumps, HIV, HTLV-1 (tropical spastic paraplegia), tuberculosis, syphilis, mycoplasma
 - Non-infectious: transverse myelitis, multiple sclerosis, neuromyelitis optica, vasculitis, SLE, Sjögren's disease, antiphospholipid antibody syndrome, Eale's disease
- Nutritional
 - Vitamin B₁₂ deficiency, Vitamin E deficiency, Pellagra
- Vascular
 - Spinal artery occlusion, arteriovenous (A-V) malformation
- Heredofamilial/degenerative
 - Hereditary spastic paraparesis, spinocerebellar ataxia, motor neuron disease, adreno-myelo-neuropathy
- Toxins
 - Lathyrism, triorthocresyl phosphate, subacute myelo-optic neuropathy (SMON)
- Physical
 - Lightning, electricity, radiation
- Paraneoplastic
 - Lymphoma, carcinoma breast, ovary

Transverse Myelitis

Inflammatory disease affecting the grey and white matter of the cord is called myelitis. Involvement of the anterior horn is called *poliomyelitis*. Selective involvement of the white matter is called *leucomyelitis*. When the disease is localised over several segments of the cord, it is called transverse myelitis. The cord lesion may occur alone or as part of a more extensive disease such as meningitis or encephalitis (encephalomyelitis).

TABLE 198.9

Causes for transverse myelitis

- a. Demyelinating illnesses**
Postinfectious/postvaccinial myelitis: allergic response to infection or vaccination, e.g. antirabies vaccine, smallpox vaccine
Multiple sclerosis
Neuromyelitis optica
- b. Direct infections**
Virus: enterovirus, herpes zoster, rabies
Bacteria: syphilis, pyogenic infection, tuberculosis
- c. Vasculitis**
SLE, Sjögren's disease, antiphospholipid antibody syndrome

Table 198.9 enlists the cause for transverse myelitis. However in nearly 40% of cases no specific cause may be detectable even after investigations.

Pathology

The affected segment of the cord becomes hyperemic and edematous. Histologically there is perivascular inflammation, edema, vascular thrombosis, and in the chronic stage, neuroglial proliferation.

CLINICAL FEATURES

Transverse myelitis usually affects thoracic segments of the spinal cord. Initial symptoms may be nonspecific such as fever, malaise, backache and root pains. Spinal cord involvement results in a syndrome of complete or partial transection of the cord. Patient presents with sudden weakness and sensory loss involving the lower limbs extending up to the trunk and upper limbs, depending upon the upper level of involvement. Neurological deficits are often asymmetric. Bladder and bowel disturbances occur early. Within 24-48 hours, paralysis and sensory loss are fully manifest and a clear upper level of sensory and reflex loss is definable which indicates the level of the lesion. The initial phase is one of spinal shock in which there is flaccidity and areflexia. The spinal shock period extends for a few days to weeks and is followed by hyperreflexia and spasticity.

CSF shows moderate lymphocytic pleocytosis and rise in proteins (up to 400 mg/dL). CSF sugar remains normal. MRI is the investigation of choice and confirms the diagnosis and facilitates identification of etiology. MRI shows hyperintense lesions in the spinal cord, representing myelitis and demyelination.

Course and prognosis: Improvement occurs with time and complete or near complete recovery occurs in most cases.

Differential diagnosis: Transverse myelitis should be considered when the syndrome of complete cord

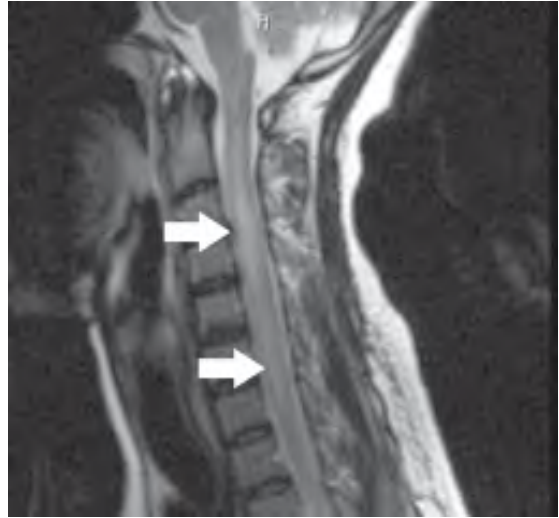


Fig. 198.4: MRI cervical spine showing demyelinating lesions in a patient with transverse myelitis. Note: (1) General swelling of the cord and (2) Hyper intense (whitish) lesions

transection develops within hours or a few days. Acute cord compression can present similarly. This may be seen in conditions such as epidural abscess, tuberculosis, metastasis, bleeding or edema into spinal cord tumour, bleeding from a vascular malformation or occlusion of the anterior spinal artery. MRI is useful to distinguish these conditions (Fig. 198.4). Occasionally, Guillain-Barré syndrome may mimic acute myelopathy.

Occasionally, postinfectious/postvaccinial demyelination may affect other regions of the nervous system as well and patient may have encephalopathy, ataxia or brainstem signs in addition. This condition is called as **acute disseminated encephalomyelitis (ADEM)**.

Management: Investigations (blood and CSF) should be done to exclude conditions such as multiple sclerosis, vasculitis or any infections such as herpes zoster, HIV, HTLV -1, tuberculosis, syphilis, etc. If a specific cause is identified, appropriate treatment can be initiated. When no specific cause is detectable or when immune mediated disease is suspected, trial of high dose corticosteroids such as intravenous methyl prednisolone may be given. Plasma exchange and intravenous immunoglobulin have also been used in refractory cases. General management of paraplegia consists of attention to nutrition, frequent change of position and skin care to avoid bedsores, proper positioning of the limbs to avoid contractures, physiotherapy to prevent venous thrombosis and to improve muscle tone and drainage of urine using an indwelling catheter. Constipation is treated using laxatives or small enemas. Flexor spasms can be controlled by avoiding stimuli to the lower limbs and administering medications such as diazepam 5 mg b.d or baclofen. As the patient improves, active physiotherapy and occupational therapy are instituted.

Anterior Spinal Artery Occlusion

The anterior spinal artery supplies the anterior 2/3 of the cord. The artery may be occluded by thrombosis or embolism leading to ischemia and infarction in the vascular territory. Arterial occlusion may be due to vascular disease of aorta, generalized atherosclerosis, vasculitis, cardiac arrest and global hypoperfusion, diseases of the vertebral artery such as dissection, aortoarteritis or descending aorta aneurysm repair. Embolism may occur as a complication of infective endocarditis or ischemic heart disease. Clinical features depend on the level of arterial occlusion. Recovery may start within a few days of onset and improvement may occur with time.

Subacute Combined Degeneration of the Spinal Cord

Subacute combined degeneration of the spinal cord represents the commonest cause for metabolic myelopathy. This condition results from vitamin B₁₂ deficiency. Further account is given in chapters 151 and 187.

Neuromyelitis Optica (Devic's disease)

This is a syndrome of acute severe transverse myelitis with bilateral simultaneous or sequential optic neuritis occurring in close temporal succession and resulting in paraplegia and blindness. There is no evidence of clinical disease outside the optic nerve or spinal cord. Aetiopathogenesis and natural history are controversial. Recently anti-aquaporin-4 antibodies have been implicated.

HIV Related Myelopathy

Subacute or chronic myelopathy occurs late in HIV infection. It affects predominantly the posterior and lateral columns and clinical presentation has a striking resemblance to subacute combined degeneration of spinal cord secondary to vitamin B₁₂ deficiency. Usually upper limbs are spared. As per the pathological changes, vacuolar myelopathy is also used to describe this condition. It may coexist with other manifestations of neuroAIDS such as dementia and distal painful sensory neuropathy. CSF shows mild lymphocytic pleocytosis and MRI may reveal spinal cord atrophy. Diagnosis is established after ruling out opportunistic infections and malignancy that may also cause myelopathy in AIDS.

Eale's Disease

This is an idiopathic inflammatory venous disorder manifesting as retinal perivascular phlebitis and subsequent vitreous hemorrhage. Neurological manifestations are rare and subacute or acute myelopathy is described. There may be an association with tuberculosis.

Tropical Spastic Paraplegia

This condition, commonly seen in tropical areas and in Japan, is characterized by chronic progressive spastic paraplegia associated with mild impairment of proprioception and vibration in 50% of patients. Visual impairment occurs in 15%. The condition is caused by infection by a retrovirus, HTLV-1, and hence it is also called HTLV-1 associated myelopathy. Diagnosis is established by the demonstration of anti-HTLV-1 antibodies in CSF.

Lathyrism

It is a form of spastic paraparesis produced by excessive intake of the chickling pea or grass pea (khesari dal, toor dal), lathyrus sativus. It is found in north and central India. Beta oxalyl amino alanine (BOAA) is the toxin implicated. Being drought resistant, lathyrus sativus becomes the chief constituent of diet during famines. It commonly manifests as a chronic spastic paraparesis. The degree of disability has been staged according to the amount of support with walking stick that is required for ambulation: no stick stage, one stick stage and two stick stage. Objective sensory loss does not occur (See Chapter 24).

Hereditary Spastic Paraplegia

Otherwise known as *Strumpell-Lorraine* syndrome or familial spastic paraplegia (FSP), HSP comprises a heterogeneous group of inherited disorders in which the chief clinical feature is progressive spasticity of lower limbs. Inheritance can be autosomal dominant, autosomal recessive or X-linked. Onset may be below the age of 35 years, or later. Clinical features are dominated by spasticity and UMN pattern of weakness, predominantly in the lower limbs. Sensory loss and micturition disturbances are variable. Complicated HSP is the term applied when there are additional systemic or neurological deficits such as optic atrophy, retinopathy, amyotrophy, dementia, deafness or ataxia.

Diseases Affecting the Spinal Roots

Nerve roots are susceptible to local compressive lesions as well as many of the disorders affecting peripheral nerves. Otherwise known as radiculopathies, their clinical features include radicular pains, paresthesias, dermatomal distribution of sensory loss, myotomal loss of muscle power and diminished segmental deep tendon reflexes. Involvement of multiple roots is called polyradiculopathy. Common causes for radiculopathy are enlisted in Table 198.10

Radiculopathies are evaluated according to the clinical presentation. Investigations include nerve conduction study, CSF study and MRI.

TABLE 198.10
Common causes of radiculopathy
1. Degenerative disc disease
2. Traumatic root avulsion
3. Inflammation: Guillain-Barré syndrome, CIDP, vasculitis
4. Neoplasms/paraneoplastic syndrome
5. Infections: Herpes zoster, tuberculosis, cytomegalovirus
6. Diabetes mellitus
CIPD: Chronic inflammatory demyelinating polyradiculopathy

Neurogenic Claudication
(Pseudoclaudication)

This is a syndrome in which pain is felt in the regions supplied by the lumbosacral segments of the spinal cord. The symptoms typically consist of exercise (walking)-induced pain in the gluteal, thigh or leg regions and weakness in the legs. Symptoms and signs promptly recover with cessation of exercise in the early stages but later on deficits persist even at rest. Symptoms may be confused with vascular claudication and Table 198.11 lists points to differentiate between the two. Neurogenic claudication is caused by lesions that narrow the spinal canal and compress the nerve roots of the cauda equina. This most commonly arises due to **lumbar canal stenosis**, which may be congenital or acquired. Congenital causes include achondroplasia and acquired causes include spondylosis, fractures or degenerative spondylo-lithesis. Symptoms are attributed to the compressive effects on the nerves of the cauda equina, impaired arterial supply and venous stasis and hypertension. During exertion there is a 50-100% rise in nerve tissue metabolism when action potentials begin to fire. Exercise in the setting of compromised nerve roots causes pain due to accumulation of metabolites such as lactic acid. After stopping exercise, reduction in metabolic demand is associated with improvement of pain and neurological symptoms and signs.

Treatment: If narrowing of the spinal canal can be demonstrated by MRI, CT imaging or myelography, surgical decompression is undertaken. The results are often gratifying.

Disorders of Nerve Plexuses (Plexopathy)

Disorders of the brachial plexus and lumbosacral plexus manifest with characteristic clinical syndromes. Lesions of the upper trunk of brachial plexus manifest with LMN weakness and sensory loss in a C5 C6 distribution. Lesions of lower trunk produce deficits in a C8 and T1 distribution.

Common causes for plexopathies are enlisted in Tables 198.12 and 198.13. Investigations include nerve conduction study and MRI.

TABLE 198.11		
Differentiating neurogenic from vascular claudication		
Clinical manifestation	Neurogenic	Vascular
Distribution of exertional pain	Thigh and buttocks	Calf
Symptoms when using bicycle	No effect	Reproduces symptoms
Symptoms when walking incline	Worse coming down	Worse climbing up
Symptoms when standing	Reproduces symptoms	No effect
Weakness after exertion	Present often	Nil
Sensory deficits after exertion	Occasionally	Nil
Diminished reflexes after exertion	Occasionally	Nil
Back hyper-extension	Reproduces symptoms	Nil
Pain relief	Stopping activity, sitting, leaning forward	Stopping activity
Time required for relief	Variable (5-15 min)	Prompt (15-20 sec)
Preventive measures	Leaning forward using a support while walking	Walking slower
Peripheral pulses	Preserved	Usually absent

TABLE 198.12	
Causes for brachial plexopathy	
<i>Structural causes</i>	<i>Non –structural causes</i>
Traumatic	Radiation
Cervical rib/associated bands – thoracic outlet syndrome	Diabetes
Brachial plexopathy due to metastatic / infiltrating lesions	Idiopathic Hereditary

TABLE 198.13	
Causes for lumbosacral plexopathy	
Structural causes	Non-structural causes
Hematoma	Diabetes mellitus
Pregnancy	Radiation
Psoas abscess	Vasculitis
Trauma	Idiopathic
Metastatic/infiltrating tumours	
Aneurysm	
Following endovascular interventions	

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Diseases of the Vertebral Column Causing Neurological Lesions

Anand Kumar, P.K. Mohan

Chapter Summary

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TABLE 199.1

Classification of craniovertebral anomalies

- I. *Skeletal anomalies*
 - a. Basilar invagination—primary or secondary
 - b. Platybasia
 - c. Occipitalisation of atlas
 - d. Atlantoaxial dislocation—congenital or acquired.
 - e. Klippel-Feil anomaly
- II. *Neuraxial anomalies*
 - a. Arnold-Chiari malformation
 - b. Dandy-Walker syndrome, i.e. failure of the foramina of Magendie and Luschka to open, associated with cerebellar hypoplasia
 - c. Occipitocervical meningocele
 - d. Cysts in the posterior fossa
- III. *Combined neural and skeletal anomalies*

Craniovertebral Anomalies

Definition: Craniovertebral anomalies are developmental defects involving the bony and/or neural structures at the occipitocervical transition zone. These defects manifest clinically in a variable manner as craniospinal deformities and/or neurological deficits. Secondary changes such as repeated trauma, pressure effects, and vascular occlusion aggravate the neurological disability and lead to its progression. Several major and minor abnormalities have been described. Common features which should draw attention to the presence of craniovertebral anomalies are short neck (total body height/neck length ratio > 13.86), low hairline (posterior hairline below C4 spine level) and facial asymmetry. Neck movements may also be abnormal.

Classification: The more important anomalies have been classified in Table 199.1.

Basilar Invagination (Basilar impression)

In this condition, there is invagination of whole or part of the margins of the foramen magnum into the posterior cranial fossa. Although most often it is a developmental anomaly, it may also be acquired because of softening of the bones as in osteomalacia, Paget's disease of the bone, osteogenesis imperfecta, achondroplasia and gargoylism.

Clinical features: Primary basilar invagination may present at any age and may be symptomatic or asymptomatic. In symptomatic cases, occipital headache, and hyperalgesia in the distribution of the second cervical nerve roots are common features. Episodic vertigo, diplopia and drop attacks reflect circulatory disturbances in the vertebrobasilar territory. **Drop attacks** are sudden episodes of loss of tone in the limbs leading to falls. Motor weakness with pain and paresthesiae in the limbs may progress gradually or in a stepwise manner. Dysphagia, dysarthria, dysphonia, and ataxia are the other well recognized symptoms. Nystagmus, ataxia, and intention tremors occur due to cerebellar involvement. Paralysis of the lower cranial nerves occurs due to compression along their course. Among the pressure effects on the cervicomedullary region of the cord, pyramidal tract involvement is the commonest. This manifests as spastic quadriparesis or rarely hemi- or monoparesis. Weakness and wasting of the small muscles of the hands may develop in some and this has been attributed to ischemic myelopathy. Posterior column disturbances are maximum in the distal aspects of the limbs. Dissociated sensory disturbances may occur in some cases which may suggest coexisting *syringomyelia* or *secondary hydromyelia*. This

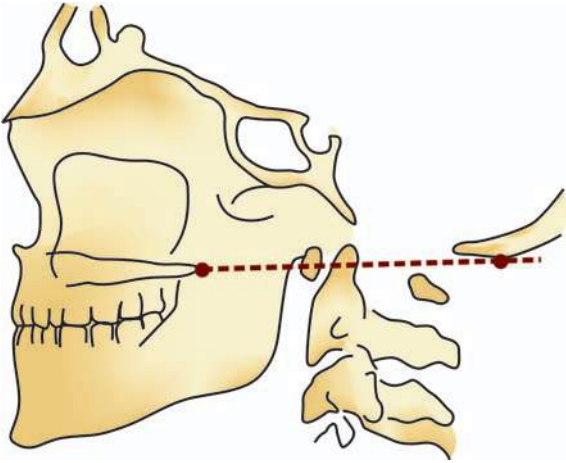


Fig. 199.1: McGregor's line—Line from posterosuperior margin of hard palate to the lowermost point of the occipital bone in the midline. Tip of odontoid does not project more than 3 mm above this line in normal individuals

association is seen in about 30% of cases. Sphincteric disturbances are uncommon but they may develop late in the disease.

Diagnosis: The clinical diagnosis is confirmed by radiological studies of the craniovertebral region and MRI.

Lateral View of Skull and Cervical Spine in the Skiagram

McGregor's line: This imaginary line joins the posterior tip of the hard palate and the most caudal point (inferior tip) on the occipital squama. Normally, the tip of the odontoid is below or up to 3 mm above this line. In basilar impression the tip of the odontoid lies at a higher level than normal (Fig. 199.1).

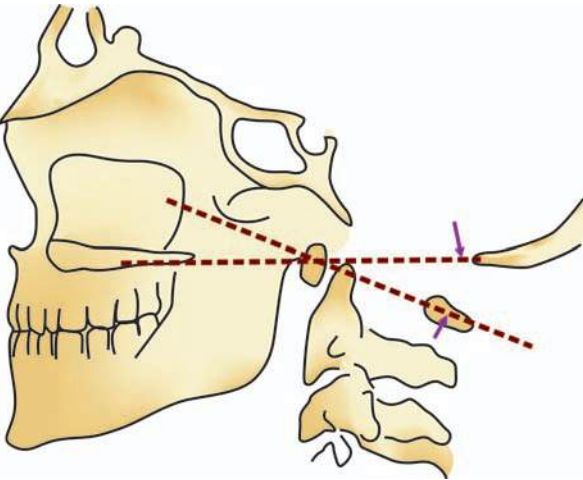


Fig. 199.2: Bull's—angle formed between: 1. Line drawn along the plane of the hard palate, and 2. Along the plane of the atlas. If this angle (indicated by arrows) exceeds 13°, the position of the odontoid is abnormal

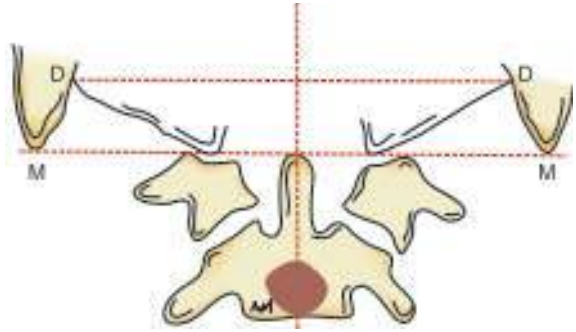


Fig. 199.3: Inter-mastoid (MM) and digastric (D.D) lines. The intermastoid line (MM) joins the tips of the mastoid processes. The digastric line joins the two digastric grooves lying medial to the bases of the mastoid processes. Tip of odontoid should always be below these lines

Bull's angle: The line drawn extending the hard palate backwards and the line drawn through the plane of the atlas subtend an angle less than 13°. Increase in this angle is suggestive of basilar invagination (Fig. 199.2).

Antero-posterior view of skull and craniovertebral junction: The tip of the odontoid lies at or below a line joining the tip of both mastoid processes in normal individuals. If it lies above this line it suggests basilar impression (Fig. 199.3).

Platybasia

It is defined as flattening of the base of the skull. As a result, there is an increase in the angle subtended by lines (1) joining the nasion to the tuberculum sellae, and (2) from the tuberculum sellae to the anterior lip of the foramen magnum. (In normals this angle ranges between 115° and 140°). Values above 148° are abnormal. This angle can be measured in a true lateral X-ray of skull. This condition per se is asymptomatic. It may be associated with other craniovertebral anomalies.

Occipitalisation of Atlas

This refers to the bony fusion of whole or part of the atlas to the occipital bone. This may occur as an isolated lesion or as part of multiple anomalies. It is often accompanied by congenital atlantoaxial dislocation.

Atlantoaxial Dislocation

The transverse ligament of the atlas holds the dens (odontoid) of the axis against the anterior arch of the atlas and prevents posterior subluxation in normal subjects. The apical and the two alar ligaments fix the tip of the dens to the occiput. They limit the degrees of rotation and lateral flexion. Abnormal mobility of the atlas on the axis

may be due to congenital or acquired causes. Congenital anomalies include non-fusion of the odontoid with the axis, agenesis of part of the odontoid, or agenesis of the transverse ligament of the atlas. Acquired causes may be traumatic, or may follow vertebral tuberculosis, rheumatoid arthritis and ankylosing spondylitis. Atlantoaxial dislocation has been classified radiologically depending on the presence or absence of occipitalization of the atlas and state of the odontoid process.

Types of Atlantoaxial Dislocation (Wadia)

Type IA— Odontoid normal with occipitalisation of atlas

Type IB— Odontoid normal without occipitalisation of atlas

Type II— Odontoid detached from body of axis or agenesis of part or whole of odontoid.

Due to subluxation, the odontoid presses on the cervico-medullary region of the spinal cord in certain positions of the head. This gives rise to pressure effects, secondary vascular changes and progressive degenerative changes in the lower part of the medulla and upper part of the spinal cord. Neurological symptoms may be abrupt such as drop-attacks and quadriplegia, or slowly progressive due to degenerative changes in this region.

CLINICAL FEATURES

Symptoms may begin abruptly or gradually, but once symptoms start, they show stepwise progression. Trivial trauma may precipitate the symptoms in many patients. Suboccipital pain, painful restriction of neck movements and clicking sounds on movements of the neck are the local symptoms.

Spastic quadriplegia, paresthesia and sensory disturbances in the extremities, and wasting and fasciculations of the small muscles of hands constitute the other manifestations. Lower cranial nerve palsies and cerebellar disturbances are less common than in basilar impression. Horner's syndrome may be present.

DIAGNOSIS

Once atlantoaxial dislocation is suspected, violent movements of the head over the neck, with a view to elicit the "click", should not be attempted. Diagnosis is confirmed by radiology. Lateral view pictures are taken with the neck in full flexion and extension to visualize the atlantoaxial joint. In atlantoaxial dislocation the distance between the posterior surface of the anterior arch of atlas and the anterior surface of the dens is increased (normal distance is less than 3 mm in adults). In addition, the morphology of the odontoid can also be studied. An open mouth view in an anteroposterior projection gives a good picture of the odontoid process. MRI gives a clear picture of the whole abnormality.

Klippel-Feil Syndrome

Syn: Block vertebra

Fusion of two or several of the cervical vertebral bodies or their spines occurs in Klippel-Feil syndrome. This may be associated with congenital hemivertebrae, kyphoscoliosis, limitation of neck movements, short-neck, low hairline and facial asymmetry. *Mirror movements* of the upper limbs may be seen in this condition i.e. any movement initiated by one hand is involuntarily initiated by the other. The exact pathogenesis of this remains unclear, though anomalous decussation of the cortico-spinal tracts is a possible explanation in some cases. Various other congenital abnormalities involving the nervous, musculoskeletal, cardiopulmonary, gastrointestinal, and excretory systems may be associated with Klippel-Feil syndrome.

Arnold-Chiari Malformation

This is characterized by herniation of the cerebellar tonsils with or without the medulla and fourth ventricle into the cervical spinal canal. In some patients this is associated with cervical meningocele and syringomyelia. This is one of the causes of hydrocephalus in infancy. Other features are cerebellar and lower cranial nerve involvement which may develop in older patients. Contrast myelography done with the patient in the supine position demonstrates obstruction to the flow of dye and kinking of the cord in the cervical region due to the herniated cerebellar tonsil. CT scan studies give details about the neurological and vertebral abnormalities. MRI gives a more vivid picture of the total abnormality (Fig. 199.4).

Principles of Management of Craniovertebral Anomalies

Mild and asymptomatic cases may be left alone with advice to avoid violent neck movements, weight-bearing

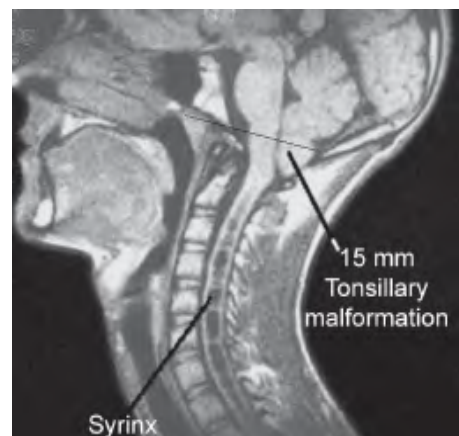


Fig. 199.4: MRI showing Arnold-Chiari malformation. Note the herniation of the cerebellar tonsils through the foramen magnum.

on the head and to continue physiotherapy of the neck to strengthen the neck muscles. Conservative measures like graded cervical traction and cervical collar may be used in atlantoaxial dislocation. Surgical decompression and fixation is required only when the above measures fail. Surgical treatment has to be undertaken in symptomatic patients. The surgical procedures include methods to reduce the compressive effects on the neural structures and measures to limit abnormal mobility. Surgical treatment of Arnold-Chiari malformation is accompanied by good clinical improvement.

Cervical Spondylosis

Degenerative changes develop in the vertebral column with advancing age. The nucleus pulposus of the intervertebral discs undergoes degeneration with reduction in their fluid content, and this results in their collapse and narrowing of the intervertebral spaces. The annulus fibrosus also shows degenerative changes and they protrude backwards behind the vertebral bodies to form ridges. Osteophytes develop from the vertebral bodies and laminae resulting in compression of the nerve roots in the intervertebral foramina.

The cord may be compressed by osteophytic bars formed in the midline behind the vertebral bodies or the roots may be compressed by osteophytes growing into the intervertebral foramina. Degenerative changes are seen most markedly and symptoms are more frequent in the cervical and lumbar regions of the vertebral column. In addition to the higher mobility of the spine in these regions which accounts for greater predilection to degenerative changes, it is also likely that subjects who develop cervical spondylotic myelopathy have congenitally narrower spinal canal.

In addition to the bony changes, soft tissue changes also develop. The ligamenta flava loses its elasticity and tends to buckle forwards when the cervical spine is extended. This leads to compression of the posterior aspect of the cord. In the intervertebral foramina, fibrosis of the dural sheaths contributes to further pressure on the spinal nerves and their roots. Pressure on the spinal arteries and the vertebral arteries occurs during their course in the bony structures of cervical vertebrae. This leads to secondary vascular changes which cause vascular occlusion and ischemic damage to the cord and lower brainstem. The clinical presentation may vary widely from that of a myelopathy, radiculopathy or both. The site of cord dysfunction may be at the actual level of compression, or even distant from that, on account of vascular occlusion.

Neurological Complications: Clinical Features

Cervical radiculopathy: This condition develops when the intervertebral foramina are grossly narrowed. In the cervical region, maximal degenerative changes are seen between the fifth, sixth and seventh cervical vertebrae and these nerve roots are most frequently affected.

Cervical spondylosis is a common condition seen in day-to-day practice. Though the older age groups are more affected by osteoarthritis, many patients even in the fourth and fifth decades of life may suffer from this disease and this fact should be borne in mind in all cases presenting with painful symptoms in the neck and around the pectoral girdle. Initial symptoms consist of paresthesia and pain in the distribution of fifth to the eighth cervical dermatomes, pain being felt most frequently over the shoulder, arm, scapular region, forearm, and hands. Movements of the neck, travel, and adoption of certain postures aggravate the pain, which may be intermittent or even constant. In the majority of patients objective sensory loss to pin-prick may be demonstrable. Motor phenomena consist of weakness and wasting of the deltoid, triceps, biceps or forearm muscles. Wasting of small muscles of the hand is rare in pure cervical spondylosis. Involvement of the C5 segment gives rise to *inversion of the supinator jerks*. Fasciculations may be seen over the affected muscles. Tendon reflexes of the affected roots are diminished. The lesion may be unilateral or asymmetrically bilateral.

Compressive myelopathy: This develops as a result of compression of the spinal cord by the osteophytic bars in front and ligamentum flavum behind. Most frequent site of compression is the C5-C6 region. Ischemia further enhances the damage.

The clinical picture is one of insidious onset of spastic paraparesis with motor and sensory symptoms. Pressure on the posterior columns is more common than the spinothalamic tract and this gives rise to sensory ataxia. Bladder and bowel dysfunction is less common.

Vertebrobasilar ischemia: The vertebral artery which ascends through the foramina in the transverse processes of the cervical vertebrae and passes over the atlas to enter the foramen magnum is kinked, compressed and stretched, when the vertebral column loses height and spondylotic changes occur. In addition, atherosclerotic changes develop early. These changes result in vertebrobasilar ischemia.

Diagnosis: Cervical spondylosis has to be suspected in all cases presenting with cervical cord or root symptoms in persons above the age of 40 years. Differential diagnosis includes other causes of cord compression, syphilitic pachymeningitis, arachnoiditis, syringomyelia,



Fig. 199.5: X-ray cervical spine / cervical spondylosis

and motor neuron disease. In some cases of cervical spondylosis, flexion or extension of the cervical spine causes “electric shock-like sensation” over the segments affected. This is called **Lhermitte’s sign**. This may occur in other causes of cervical cord compression as well.

The clinical diagnosis should be confirmed by radiological studies of the spine. X-ray taken in the lateral view with the neck in straight, flexed, and extended positions and oblique views reveal the abnormalities well. Radiological changes include narrowing and irregularity of the intervertebral spaces, osteophytes, and encroachment of the intervertebral foramina. In young subjects bony outgrowths may not be evident, but alteration in the alignment of cervical vertebrae, especially loss of the cervical curvature caused by spasm of neck muscles should be taken as a suggestive sign (Fig. 199.5). Myelography reveals the narrowing of the spinal canal and compression of the cord. A-P diameter of the spinal cord in the cervical region is 9-10 mm. If the spinal canal is less than 10 mm in the lateral view X-ray cord compression is likely. MRI clearly brings out the total picture of vertebral changes and compression of the neural structures. Somatosensory evoked potentials help to evaluate physiological and anatomical malfunction of the posterior column of spinal cord.

It has to be borne in mind that radiological changes in the cervical spine are seen in a high proportion of elderly subjects without neurological damage and the mere presence of such changes is not adequate to establish the diagnosis of cord compression as due to vertebral disease. Cervical spondylosis may coexist with other disorders involving the spinal cord such as motor neuron disease, tumours and syringomyelia.

Treatment: In the early stages of spondylotic radiculopathy proper positioning of the neck, physiotherapy and use of a cervical collar to restrict neck movements help to relieve root pains. Exercises designed to strengthen the shoulder girdle muscles, especially elevators of the scapula help to relieve traction on the nerve roots and prevent recurrence of symptoms. Persons who have had symptoms should be advised to wear cervical collar during long journeys, so as to prevent recurrence of the symptoms. Graded cervical traction may help to relieve pressure on the nerve roots. Nonsteroidal anti-inflammatory drugs are of some benefit. If definite bony ridges are demonstrable causing root or cord compression surgery is indicated to relieve pressure and to prevent further neurological deterioration. Presence of motor phenomena such as paresis, or muscle wasting is an indication for early surgery. Before surgery all cases should be fully investigated to exclude other causes of myelopathy which may also present with similar clinical picture.

Treatment has to be based on individual considerations. There is no general agreement on any standard therapy.

Lumbar Disc Lesions

The lumbar intervertebral discs are particularly vulnerable to injury and degenerative damage, irrespective of age. Males engaged in heavy manual work and weight-lifting are particularly affected. Sudden jerky movements, unaccustomed lifting of heavy weights and heavy falls on the gluteal region or back may lead to sudden rupture of the annulus fibrosus even in otherwise normal persons. The nucleus pulposus herniates through ruptured annulus fibrosus to impinge upon the nerve roots. The L4-5 or L5-SI discs are more often affected. The onset is generally abrupt with severe radicular pain in the lumbosacral dermatomes in the sciatic distribution (*sciatica*). The pain is aggravated by flexion of the spine, coughing, sneezing or jolting movements. Motor weakness of spinal root distribution will occur if the anterior roots are impinged upon.

Flexion of the spine is more restricted than extension. Objective neurological findings of root compression may be evident. In acute cases the normal lumbar lordosis is obliterated. Local tenderness may be elicited over the affected region and the paraspinal muscles may exhibit spasm. Straight *leg raising test* is positive—*Lasegue’s sign*. This sign is elicited by passively lifting up the lower limb held straight by the examiner when the patient is in supine position. In normal subjects the limb can be brought to near-vertical position without discomfort. In lumbosacral root irritation due to disc prolapse this movement is restricted by severe pain.

Diagnosis: Low back pain, especially aggravated by coughing or sneezing, should suggest the possibility of lumbar disc prolapse. X-ray spine may reveal narrowing of the inter-vertebral spaces. CT scan, MRI and myelography bring out the actual pathology distinctly.

Course and prognosis: This is variable. In mild cases the condition may improve with rest and conservative measures. Progressive neurological disability may develop in some cases. In many, sudden onset of sciatica may be very disabling.

Management: Conservative measures include uninterrupted rest in bed with slight extension of the back on a hard non-sagging bed for periods of two to three weeks, traction on the legs, exercises to strengthen the paraspinal muscles and to prevent wasting of the affected muscles and use of spinal braces to limit spinal movement. Analgesics and muscle relaxants like diazepam help in the acute stage or intractable pain.

Presence of progressive neurological damage or intractable pain is an indication for surgical treatment which consists of laminectomy and removal of the prolapsed disc.

Modern surgical techniques employ keyhole procedures to remove the damaged disc without conventional laminectomy.

Lumbar Canal Stenosis

The term *spinal canal stenosis* covers any type of narrowing of the spinal canal, but it usually affects the lumbar spinal canal. Most often it is congenital, but the patient becomes symptomatic later in life due to the development of other pathological changes that result in the compression of neurovascular tissues. The compression may be due to any of the following causes:

1. Prolapse of the intervertebral disc,
2. Hypertrophic changes of the ligaments within the narrowed spinal canal,
3. Angulation of vertebrae due to loss of disc height,
4. Spondylolisthesis,

5. Paget's disease of bone,
6. Neural arch degeneration (spondylolysis),
7. Bony and ligamentous compression at the exit foramina.

In addition to mechanical compression, the arterial supply of the cord may also be compressed. Multiple factors may operate in the same case. Males are generally affected more than females, except in case of spondylolisthesis. L5 and S1 roots, which run a long oblique course within the spinal canal before changing direction to emerge through the exit foramina, are most affected.

Clinical features: Symptoms fall into three categories. These are:

1. lumbago (backache) in almost all cases,
2. lumbosacral radicular symptoms in a third, and
3. neurogenic claudication in another third of cases. Cases with neurogenic claudication get pain when bending backwards or on walking. Such patients assume a stooping posture to avoid pain. Both postural and exertional claudication result in transient root pain, paresthesia, weakness or numbness. Dermatomal sensory loss, muscle weakness and other motor deficits may be present. All these symptoms temporarily subside following rest. Straight leg raising test is positive in a third of the cases, especially if tested after exertion.

Diagnosis: Clinical diagnosis should be supported by radiography. The narrowed lumbar canal may be demonstrable in lateral and A-P view skiagrams. MRI demonstrates the narrowing precisely. Electromyographic demonstration of segmental muscle denervation in the legs gives diagnostic localization and this procedure is done routinely before surgical decompression.

Treatment is preferably surgical decompression by a partial undercutting facetectomy with decompression of the nerve root canal by removal of the hypertrophied bony fragments, ligamentum flavum and degenerated disc. The results are excellent in majority of cases.

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Diseases of the Peripheral Nervous System

Anand Kumar, P.K. Mohan

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General Considerations

Functionally, the peripheral nervous system consists of the anterior horn cells, anterior nerve roots, posterior root ganglion cells, posterior roots, the part of the nerve fascicles within the spinal cord and the peripheral nerves up to the myoneural junctions. But for practical purposes the extent of the peripheral nervous system (PNS) is limited to the part of the nervous system outside the pia-arachnoid. The cranio-sacral and thoracolumbar outflows contribute the parasympathetic and sympathetic fibers to the peripheral nerves.

The peripheral nerves consist of axons invested by the Schwann cells. There are two types of fibers—the myelinated and the unmyelinated. The myelinated nerve fiber has a single axon surrounded by Schwann cells which spiral round the axon and provide the myelin sheath. There are gaps in the myelin sheath where the axon is exposed. These are called the *nodes of Ranvier*. The myelinated nerve fibers conduct impulses at a faster rate than the unmyelinated nerve fibers. They are also prone to acquire diseases which affect myelin. These include: (1) the demyelinating diseases where there is destruction of myelin sheath, and (2) the dysmyelinating diseases where there is deposition of abnormal myelin, e.g. leukodystrophies.

In the case of unmyelinated nerve fibers the Schwann cells do not provide the myelin sheath and several axons are accommodated by the same Schwann cell. According to the fiber diameter, the nerve fibers may be grouped into *small diameter fibers* and *large diameter fibers*. Large diameter fibers carry sensations like touch, vibration and joint sense. Pain and temperature are carried by the small diameter fibers. Several diseases affect the small or large diameter fibers selectively, e.g. leprosy and amyloidosis affect the small diameter fibers. The response of the nerve fiber to different forms of pathological injury is limited. The neural reaction may take the form of axonal degeneration where there is destruction of axons, segmental demyelination where there is patchy loss of myelin, or both. In polyneuropathies the disease process affects the nerve cell body, which loses its ability to maintain the integrity of the axon. It undergoes degeneration, starting from the most distal part and spreading proximally. The lower limbs are affected earlier than the upper limbs, since the axons supplying the lower limbs are longer.

Apart from the myelin and axons, the peripheral nerve has investing layers of connective tissue which form the endo-, epi-, and perineurium. The peripheral nerves have a rich anastomosis of blood vessels around them. When disease processes affect these elements, they may lead to interstitial neuropathy and ischemic neuropathy respectively. Moreover, since the anterior and posterior roots are bathed in the cerebrospinal fluid (CSF), abnormalities of the CSF may result in dysfunction of the PNS as well.

A nerve can be damaged by injury to the myelin, the axon, the cell body or the vasa nervorum. There are three basic mechanisms underlying nerve injuries.

1. Degeneration in which both the axon and myelin are affected, e.g: transection of a nerve
2. Segmental demyelination in which only the myelin is affected leaving the axon relatively intact, and
3. Axon degeneration in which damage to the cell body leads to death of the distal part of the neuron.

In segmental demyelination, because the axon is intact, there is no denervation and hence there is no muscle

atrophy whereas in axonal degeneration there is muscle atrophy. Recovery from nerve damage is slow and incomplete in axonal neuropathies.

CLINICAL SYMPTOMATOLOGY

Clinical features are due to affection of the sensory, motor autonomic fibers alone or in combination.

Sensory Phenomena

These may be positive, i.e. irritative in nature; or negative, i.e. due to loss of function.

Hyperpathia: These are excessively painful or unpleasant sensations from noxious stimulation of skin.

Causalgia: This is a severe, dysaesthetic pain, associated with autonomic disturbances probably due to erratic transmission (cross talk) in damaged nerves.

Neuralgia: This refers to paroxysmal pain in the distribution of a nerve e.g. trigeminal neuralgia, sciatica.

Positive phenomena

1. **Spontaneous pain:** This occurs due to irritation of the small fibers which carry pain or due to loss of large fibers which usually inhibit the pain sensation carried by the small fibers.
2. **Paresthesia** in the form of pins and needles.
3. **Contact dysesthesia**—where contact with the affected part elicits a disturbing sensation.
4. **Hyperalgesia:** Increased appreciation of pain resulting from decrease in the sensory threshold for pain.
5. **Burning feet:** This is a frequent symptom but its mechanism is not clear. It may occur in neuropathies, accompanying alcoholism, diabetes and beriberi.
6. **Lancinating pains:** These are sharp and paroxysmal pains occurring usually in the transverse plane in the lower limbs in patients suffering from tabes dorsalis and diabetes.

Negative phenomena

Numbness is an important negative symptom which indicates that at least 50% of the nerve fibers are destroyed. Patients may have a feeling as though they are walking on cotton wool. They may have unsteadiness of gait, particularly in the dark due to loss of joint and position sense. Nonhealing painless ulcers and neuropathic joints develop due to loss of pain and temperature sensation and loss of protective reflexes. When the protective influence of pain is lost, the joints undergo minor and major trauma due to overuse and injuries. Degenerative and destructive changes of joint structures develop, leading to disorganization of the joint (*Charcot's joints*). Such joints may occur in severe peripheral neuropathy and also in tabes dorsalis and syringomyelia.

The pattern of sensory loss differs depending upon the site of affection. In posterior radiculopathies, the

sensory loss is segmental. When a single peripheral nerve is affected the sensory and motor abnormalities occur in the distribution of that nerve (**mononeuritis**). Affection of several nerve trunks in an asymmetrical fashion is termed **mononeuritis multiplex**, e.g., leprosy. In classic polyneuropathies, there is symmetrical distal sensory loss in the extremities, described as *glove and stocking* anesthesia. All the nerve fibers in the distal part of the limbs are affected irrespective of the peripheral nerve to which they belong.

Motor Phenomena

These also may be negative or positive. Weakness is a negative phenomenon. Fasciculations, cramps, spasms and neuromyotonia are positive symptoms. Compared to diseases affecting the anterior horn cells, fasciculations are much less marked in peripheral nerve damage.

The tendon reflexes are lost early in peripheral neuropathies which affect the large fibers. The reflexes may be spared in neuropathies which affect the small fibers alone, e.g. leprosy.

Autonomic Phenomena

This manifests as loss of sweating, postural hypotension, and trophic disturbances. Pupillary changes, bladder and bowel dysfunction and impotence point to central lesions, these do not occur in pure peripheral neuropathy.

CLINICAL APPROACH TO A PATIENT WITH PERIPHERAL NERVE DISEASE

The clinical features of peripheral nerve disease depend upon a number of factors. These factors are important not only in the production of various clinical features in different neuropathies but also in the clinical diagnosis. The clinical features which are most helpful in the clinical diagnosis are given below.

1. Onset and rate of progression:

Acute: Less than 1 week, e.g: Guillain-Barré syndrome, porphyria, toxins.

Subacute: Less than 1 month, e.g: Acquired demyelinating polyneuropathies, toxins, metastatic lesions.

Chronic: More than 1 month, e.g: Toxic neuropathies, metabolic neuropathies, chronic inflammatory demyelinating polyneuropathies, hereditary neuropathies, diabetic neuropathy, paraproteinemic neuropathy. They may continue to exist over several years.

Relapsing: Multiple episodes occur, e.g: relapsing forms of neuropathy, repeated exposure to toxins.

2. Clinical pattern:

Mononeuropathy: Involvement of one nerve, e.g: nerve entrapments and nerve injuries.

Mononeuritis multiplex: Asymmetrical simultaneous or sequential affection of more than one nerve e.g: systemic vasculitis, cryoglobulinemia.

Polyneuropathy: Symmetric involvement of multiple nerves, e.g. diabetic polyneuropathy.

Radiculopathy: Involvement of isolated spinal nerve root.

Polyradiculopathy: Involvement of several isolated spinal nerve roots.

3. Clinical deficit

Sensorimotor: Many of the common neuropathies show involvement of sensory and motor functions.

Motor predominant: Lead, porphyria, Guillain-Barré syndrome, diphtheritic neuropathy, dapsone induced neuropathy.

Autonomic predominant: Diabetes, demyelinating neuropathies.

4. Initial distribution in the limbs

Distal: Common pattern of most of the neuropathies.

Proximal: Rare.

5. Type of sensory impairment

- a. Selective loss of pain and temperature—small fiber neuropathy.
- b. Impaired proprioceptron: Large fiber neuropathy.
- c. All sensory modalities: Involvement of all fibers.

Peripheral nerves may be palpably hypertrophic in conditions such as leprosy, amyloidosis, acromegaly, neurofibromatosis, and Refsum’s disease.

Table 200.1 lists the common causes.

TABLE 200.1	
Causes of peripheral neuropathy	
Hereditary	Hereditary sensory-motor neuropathies
Metabolic	Diabetes mellitus, hepatic failure, renal failure porphyria
Endocrine	Hypothyroidism
Toxic	Alcohol, organophosphates, arsenic, lead, gold, thallium, lithium
Drugs	Vincristine, INH
Immune mediated	Guillain-Barré syndrome
Chronic idiopathic demyelinating polyneuropathy (CIDP)	
Infections	Leprosy, diphtheria
Vasculitis	Polyarteritis nodosa, other forms of vasculitis in sarcoidosis, Wegener’s granulomatosis, Behcet’s syndrome
Nutritional	Vitamin deficiencies, e.g. Vit B ₁₂ , B ₁ , B ₆
Miscellaneous	Lymphomas, paraneoplastic syndromes, critical illness neuropathy

Guillain-Barré Syndrome (GBS)

Syn: Acute idiopathic polyneuropathy, Acute inflammatory polyneuropathy, postinfective polyneuropathy

Guillain-Barré syndrome is a symmetrical, predominantly motor polyneuropathy or polyradiculopathy, frequently involving facial and bulbar muscles, with areflexia. The weakness develops abruptly and reaches its peak within four weeks of the onset and the illness follows a monophasic course with more or less complete recovery in majority of patients. There is no specific cause for this illness, but commonly it is preceded by a viral infection of the respiratory or less commonly, the gastrointestinal tract. Particular temporal association with herpes viruses, cytomegalovirus, Epstein-Barr virus, mycoplasma and *Campylobacter jejuni* infections are present in some cases (14-18%). Vaccinations for rabies, typhoid and tetanus may be followed by this syndrome. All age groups and both sexes are affected. Male to female ratio is 1.25. Most of the cases are sporadic but small epidemics have been reported. Infection leads to activation of antigen specific T and B cells. Antibody reaction and cell mediated immune processes lead to toxic damage to Schwann cells resulting in demyelination and axonal degeneration. Anterior nerve roots are most commonly affected.

Pathogenesis: In cases where there is preceding infection, immunological reactions involving T-cells directed against peptides from myelin proteins, antibodies and complement take place and lead to the neural lesion. Experimental studies have shown that components of the bacterial wall of *C. jejuni* contains ganglioside-like structures which trigger neuropathy, resembling acute motor axonal neuropathy in rabbits. The lesions in GBS include at least four subtypes of acute peripheral neuropathy.

These include:

- 1. Acute inflammatory demyelinating polyradiculoneuropathy (AIDP).
- 2. Acute motor axonal neuropathy (AMAN).
- 3. Acute motor and sensory axonal neuropathy (AMSAN)
- 4. Miller Fischer syndrome

The distribution of ganglioside may explain the distribution of lesions and symptoms in GBS.

Clinical Features

Sudden onset of paresthesia and pain in the back and the extremities without fever is the most common initial presentation. These sensory symptoms are soon followed by symmetrical, predominantly proximal muscle weakness in the lower limbs which rapidly ascends to involve the upper limbs and some times facial and bulbar muscles as well. Rarely the weakness is distal or appears first in upper limbs. The paralysis may remain mild and stable or it may

rapidly progress to total quadriplegia and respiratory paralysis within a few days. The cranial nerves that are commonly involved are facial (40%), bulbar (30%) and ocular (10%). The tendon reflexes are usually absent or reduced even in the early stage of the illness. There is associated hypotonia. Sensory impairment is mild with impairment of all modalities of sensation, especially in a glove and stocking distribution. Sphincters are involved only rarely. Dysautonomic features may be present in the form of brady- or tachycardia and rapid fluctuations in blood pressure.

The disability may progress steadily to reach its peak within three weeks, by which time 60% of patients are unable to walk. Respiratory function is impaired in about 50% of patients of which about 15-20% will require assisted ventilation. Almost 80% make good recovery. Some (10-20%) may be left with residual paralysis.

Diagnosis

Onset of rapid or subacute symmetrical polyradiculoneuropathy should suggest the possibility of Guillain-Barré syndrome. Differential diagnosis at this stage includes toxic polyneuritis, poliomyelitis, transverse myelitis, demyelinating diseases, acute myopathies associated with polymyositis, hypokalemic paralysis, botulism and myasthenia. Neurotoxic snake bite particularly *krait* may give rise to diagnostic problem, especially if the bite occurs during sleep. Pure sensory syndrome, a definite sensory level over the trunk, severe and persistent sphincteric disturbances and more than 50 cells/cmm in the CSF make the diagnosis of GB syndrome unlikely.

Investigations: Blood counts and blood chemistry are non-contributory. Cerebrospinal fluid characteristically shows albuminocytological dissociation if examined about a week after the onset of the disease. This abnormality may persist for a few weeks. The term *albuminocytological dissociation* refers to the rise in proteins without a corresponding rise in cell count. EMG and nerve conduction studies help to distinguish the condition from myopathies and poliomyelitis.

Prognosis: In about 10% of cases with rapid onset and progress, respiratory failure may threaten life. Mortality is around 5%. Vast majority of patients start improving after a week or so of onset and recovery is complete within 6 weeks and in about 25% of cases resolution is slow. In a smaller number, severe paralysis may persist and the patient may become crippled for life. Presence of axonal degeneration and occurrence of the disease at the extremes of age are associated with bad prognosis. About 3% of cases will have a relapse or second episode.

Management

Early recognition and treatment of respiratory failure is of utmost importance. As respiratory paralysis may occur very rapidly, close observation with monitoring of vital capacity is essential. Assisted ventilation through endotracheal intubation or tracheostomy should be given when respiratory paralysis sets in. Although steroids are still used by some physicians, neither oral prednisolone nor intravenous methyl prednisolone has proved to be of definite benefit in clinical trials.

Plasmapheresis is indicated in all patients who have severe disability such as inability to walk. Plasma exchange at the rate of 50 mL/kg body weight during each session, up to a total of five sessions over 7-14 days is sufficient in the majority.

Intravenous immunoglobulin (I.V.I.G.) in a dose 0.4 g/kg body weight daily for 5 days has emerged as an effective alternative to plasmapheresis, with good functional recovery.

Since patients may be paralysed for prolonged periods, careful nursing care with regular turning in bed, attention to pressure areas, proper care of the eyes when there is facial palsy, care of the oral cavity, and attention to bowel and bladder are of great importance. Lung and urinary tract infections should be treated promptly. As deep vein thrombosis and pulmonary emboli are recognised complications, prophylaxis with heparin in a dose of 5000 units twice daily as sub-cutaneous injections is advisable.

Autonomic disturbances are complications demanding emergency intervention. Continuous ECG and BP monitoring in an intensive care unit is essential in such cases. On recovery, physiotherapy and rehabilitation should be started.

Variants of GB Syndrome

- i. Miller-Fischer syndrome: This is characterised by the triad of acute ophthalmoplegia, ataxia and areflexia without significant weakness or sensory symptoms or signs. This presentation is more frequently associated with *Campylobacter jejuni* infection. This condition has a benign course and complete recovery is the rule.
- ii. Acute sensory ataxia with areflexia.
- iii. Acute autonomic neuropathy.
- iv. Acute polyneuritis cranialis.

Chronic Inflammatory Demyelinating Polyradiculoneuropathy [CIDP]

The presentation of CIDP is with signs of motor and sensory polyneuropathy that evolves subacutely over more than eight weeks or chronically over many months. There is weakness in proximal and distal muscles and

involvement is usually symmetrical, accompanied by sensory deficits and paresthesias. Pain is a rare symptom. CIDP can begin at any age and the course is either progressive, step wise progressive or relapsing. Patients can become considerably disabled. Spontaneous remissions are rare and CIDP can occur in the presymptomatic phase of HIV infection.

Work up for CIDP includes: detailed electrophysiological examination of all four limbs, lumbar puncture to look for CSF protein elevation and pleocytosis (in HIV related CIDP), serum and urine protein electrophoresis to rule out monoclonal gammopathy and skeletal survey to exclude myeloma. A nerve biopsy and teased fiber analysis will be confirmative. If required, a genomic DNA testing can be done for exclusion of hereditary demyelinating neuropathy.

There are two main forms of therapy for CIDP. As there is clinical and laboratory support for autoimmune etiology, immunosuppressive drugs and plasma exchange form the mainstay of treatment. High dose steroid is required in initial dose of 60-80 mg per day for 6 to 8 weeks with subsequent tapering by 10 mg per month and then switching to alternate day regime. Plasma exchange is equally efficacious for selected cases of CIDP. More recently, high dose intravenous immunoglobulins [IVIG] have been introduced for immunomodulation in CIDP. The dose is 0.4 gm per Kg body weight to be given for five consecutive days. IVIG and plasma exchange are safe but expensive. Prednisolone although cheap, takes time to act and long-term complications are to be anticipated. Current practice is to recommend IVIG or plasma exchange as primary treatment.

Vasculitic Neuropathy

Many forms of vasculitis cause widespread destruction of epineural arterioles with resultant ischemic damage to peripheral nerves. Peripheral neuropathy can be an early manifestation of vasculitis and diagnosis can be established by nerve biopsy. The three major categories of diseases that cause vasculitic neuropathy are:

1. Systemic lupus erythematosus and rheumatoid arthritis.
2. Systemic necrotizing vasculitis, e.g. Polyarteritis nodosa.
3. Non-systemic vasculitic neuropathy.

Clinically the most common presentation is as mononeuritis multiplex caused by segmental nerve trunk infarction. Radiculopathies, distal sensorimotor neuropathy and cutaneous neuropathy are other manifestations of vasculitic neuropathy. Cranial neuropathies are common in Wegener's granulomatosis and sarcoidosis. Painful paresthesias can be severe and disturbing and difficult to treat. Specific treatment is directed at the vasculitis itself.

Hereditary Motor Sensory Neuropathies

Hereditary motor sensory neuropathies (HMSN) are complex clinically and genetically heterogeneous group of disorders that cause slowly progressive degeneration of peripheral nerves. Recent advances in the understanding of the molecular basis of hereditary neuropathies have resulted in a new genetic classification of HMSN. This is important for genetic counselling and planning future research for effective therapy. Type I and II are known as **Charcot-Marie-Tooth disease** 1 and 2 [CMT1 and CMT2]. CMT1 is the more common demyelinating form with loss of muscle stretch reflexes, hypertrophy of nerves and a markedly slow conduction velocity in the nerves. Genetic studies have revealed subtypes under each group depending on the chromosome affected. Thus there are four subtypes of type 1 CMT. CMT 2 is the less common neuronal form where there is no nerve hypertrophy or delayed conduction. Muscle stretch reflexes are usually preserved. There are six subtypes of autosomal dominant type 2 CMT.

The disease is transmitted as an autosomal dominant or recessive trait and sex linked forms. The two forms are distinguishable based on electrophysiological studies. These are;

Type 1: Nerve conduction velocity is slowed and tendon reflexes are absent. This type is probably a defect of the Schwann cells. It follows an autosomal dominant inheritance pattern.

Type 2: Nerve conduction velocity is normal and tendon reflexes are also normal. The defect is in the axon.

Neuropathy of Dejerine and Sottas is an autosomal recessive demyelinating sensory neuropathy in which the onset is much earlier and the disease progresses to make the patient bed ridden by the age of 20-30 years. The nerves are thickened. Sensory impairment is more marked. It may be associated with other neurological abnormalities such as optic atrophy, deafness, retinitis pigmentosa and spastic paralysis.

Clinical Features

The symptoms of CMT1 appear in the first decade or early second decade. Toe walking, gait abnormalities, loss of balance and foot deformities are common presentations. Weakness of peroneal and anterior tibial muscles results in foot drop with high stepping gait. Pes cavus deformity and hammer toes are relatively late manifestations. Atrophy of legs give the classical *inverted champagne bottle* appearance. Vibratory sense is the usual sensory modality affected. Diagnosis is made based on the family pedigree, neurological examination, electrophysiological studies and DNA analysis. As of now there is no effective

treatment. Steroid responsive forms of CMT1 and hereditary neuropathy with liability to pressure palsy have been described.

Neuropathy in Systemic Diseases

DIABETIC NEUROPATHY

This manifests as four main types.

- 1. Distal symmetrical neuropathy—sensory, motor, autonomic or mixed—most common.
- 2. Proximal neuropathy—(a) symmetrical proximal sensori-motor neuropathy, and (b) asymmetrical proximal neuropathy.
- 3. Mononeuritis and mononeuritis multiplex: (a) cranial nerves, and (b) peripheral limb and trunk nerves.
- 4. Entrapment neuropathies.

Several of these neuropathic manifestations and autonomic neuropathy may co-exist in the same patient. The major pathological finding is axonal degeneration. Proper control of diabetes with all-time euglycemia helps to reduce the frequency and severity of neuropathies.

See also section: 10 chapter 90.

Other systemic diseases like hypothyroidism, chronic liver failure, porphyria, uremia, connective tissue disorders, malignancy and paraproteinemias may be associated with peripheral nerve involvement (Table 200.2).

Several disorders of the peripheral nervous system termed ‘**paraproteinemic neuropathies**’ are closely

connected with the presence of excessive amounts of abnormal immunoglobulins in blood which can be detected by immunoelectrophoresis or the more sensitive immunofixation test. The neuropathies may precede or occur concurrently along with benign monoclonal gammopathies or conditions like multiple myeloma, Waldenstrom’s macroglobulinemia, osteosclerotic myeloma, primary amyloidosis, Castleman’s disease, other lymphatic diseases and chronic leukemias. The polyneuropathy of cryoglobulinemia is due to vasculitis in numerous nerve fascicles. The final picture is the sum total of incomplete multiple mononeuropathies. Sensorimotor neuropathy also develops. Treatment of the primary condition halts the progress of the neuropathy also.

Toxic and Drug Induced Neuropathies

Exposure to several toxins like alcohol, lead, arsenic, triortho-cresyl phosphate and organophosphorus compounds and drugs like dilantin sodium, INH, nitrofurantoin, methotrexate and vincristine can lead to polyneuropathies.

Entrapment Neuropathies

These result from compression of the nerve trunks by normal anatomical structures at certain sites. The common entrapment neuropathies are **carpal tunnel syndrome** caused by compression of median nerve under the flexor retinaculum at the wrist and **meralgia paresthetica** caused

TABLE 200.2

Salient features of the common types of peripheral neuropathy

Disease	Type of onset	Distribution	Pattern	Fiber affected	Pathology
Diabetes melitus	Acute or chronic	Proximal or distal	Polyneuropathy or mononeuropathy	Small and large	AD and SD
Porphyria	Acute	Proximal/diffuse	Polyneuropathy	-do-	AD
Vitamin B ₁₂ deficiency	Chronic	Distal	Polyneuropathy	-do-	AD
Lead poisoning	Subacute	Distal	Mononeuropathy	-do-	AD
Arsenic poisoning	Subacute	Distal	Polyneuropathy	-do-	AD
Leprosy	Subacute or chronic	Mononeuritic or distal symmetrical	Mono- or poly-neuropathy	Small	AD and SD
Diphtheria	Acute	Distal, proximal or diffuse	Poly- or mononeuropathy	Small and large	SD
Connective tissue disorders and vasculitis	Chronic or acute	Distal	Poly- or mono-neuropathy	-do-	SD
Guillain-Barré syndrome	Acute	Proximal or diffuse	Polyneuropathy	-do-	SD
Paraneoplastic	Chronic	Distal	Poly- or mononeuropathy	-do-	AD
Hereditary sensori-motor neuropathy	Chronic	Distal	Polyneuropathy	-do-	AD

Note: - AD – Axonal degeneration; SD – Segmental demyelination.

by compression of lateral cutaneous nerve of thigh between the anterior superior iliac spine and inguinal ligament.

Carpal tunnel syndrome (CTS) presents as pain and paresthesia in the lateral three fingers, worsened at night. The pain may spread proximally. Shaking the hand in the air gives relief (flick test). Sensations over the median nerve distribution are dulled. This may be accompanied by weakness of the thenar muscles. In about half the cases the condition is primary. In the others some underlying cause is evident.

Carpal tunnel syndrome may occur in acromegaly, myxedema, multiple myeloma, rheumatoid arthritis, and in pregnancy.

Flexion of the wrist for 60 seconds causes pain—**Phalen's sign**. **Tinel's sign** is the occurrence of sharp shooting pain along the distribution of the median nerve when the flexor retinaculum is tapped gently.

Electrophysiological studies facilitate the diagnosis but the results may be inconclusive.

Treatment: When the condition is curable with medical treatment as in pregnancy or myxedema, splinting of the hand, use of diuretics and local instillation of hydrocortisone acetate may give temporary relief. Decompression of the nerve by surgical splitting of the flexor retinaculum gives permanent relief.

Meralgia paresthetica presents as pain and paresthesia in the lateral aspect of the thigh. There are no motor signs in this disorder. This responds to surgical decompression. Other nerves likely to be compressed in other sites are the radial, suprascapular, femoral, obturator, posterior tibial, plantar and intercostal nerves.

Neuralgic Amyotrophy

Syn: *Brachial neuralgia*

This disorder is thought to be caused by demyelination occurring secondary to several causes such as infection, immunization and surgery. The patients complain of sudden severe pain in the shoulder region. This is followed by weakness and wasting of muscles around the shoulder joint. Most commonly muscles supplied by the axillary nerve (circumflex nerve) or long thoracic nerve (nerve to serratus anterior) are affected. Objective sensory signs are minimal. Recovery occurs within six months to one year.

NEUROFIBROMATOSIS

This entity consists of two distinct subgroups designated as **von Recklinghausen's neurofibromatosis** (VRN or Type 1), and **bilateral acoustic neurofibromatosis** (BANF or Type 2). The former used to be called peripheral neuro-



Fig. 200.1: Café au lait lesions in VRN type-I

fibromatosis and the latter central. Both entities are genetically and clinically distinct.

Peripheral Neurofibromatosis

Syn: von Recklinghausen's (VRN Type I)

Peripheral neurofibromatosis has a prevalence of one in 3000 adults. It is inherited as an autosomal dominant condition with 100% penetrance. The abnormal gene is located on chromosome 17. About 50% of cases arise as new mutations without family history. Clinical picture is varied. This includes dermatological features such as *café au lait patches* which grow with age, *Lisch nodules* (brown hamartomas seen in iris) and *dermal neurofibromas* which appear during puberty and continue to grow throughout life. *Plexiform neurofibromas* may produce local hypertrophy and physical disfigurement. Rare associations include congenital defects in the posterior orbital wall, proptosis due to orbital neurofibroma, pseudo-arthroses of tibia and ulna and vertebral lesions giving rise to kyphoscoliosis. Neurofibromas in the spinal roots or in the intracranial structures, gliomas and meningiomas may occur but the risk is much less than in the central type (Fig. 200.1).

Acoustic neuromas are extremely rare, but optic nerve or chiasmal gliomas may occur. Plexiform neurofibromas may develop malignancy, but not dermal neurofibromas. Two rare associations include pheochromocytoma and renal artery stenosis.

Central Neurofibromatosis

Syn: Type II or Bilateral acoustic neurofibromatosis (BANF)

This is much rarer than Type 1 (1 in 100,000), transmitted by a different autosomal dominant gene located on chromosome 22 with a 95% penetrance so that 50% of offsprings develop the disease. There is a very high prevalence of bilateral acoustic neuromas (Schwannomas). The

TABLE 200.3

Diagnostic criteria in neurofibromatosis

Type I	Type II
Two or more of the following must be present	At least one criterion must be present for diagnosis
1. Cafe-au-lait macules with the greatest diameter 5 mm in prepubertal and 15 mm in postpubertal patients, atleast six in number.	1. Bilateral eighth nerve tumours seen by imaging techniques.
2. Two or more neuro-fibromas of any type or one plexiform neuroma	2. Parent, sibling or child with neurofibromatosis-2 showing neurological tumours or juvenile posterior lenticular opacity.
3. Presence of optic glioma	
4. Two or more Lisch nodules	
5. Bony lesion in sphenoid or long bones	
6. Parent, sibling or child with neurofibromatosis	

early symptoms manifest in the second or third decades with eighth nerve dysfunction. Rarely the condition may be unilateral.

Other CNS tumours such as Schwannomas in other sites, gliomas and meningiomas may occur simultaneously. Management consists of surgical removal of the tumours and genetic counselling. Patients with BANF and their close relatives should avoid underwater swimming.

Diagnostic criteria are given in Table 200.3.

Critical-illness Neuropathy

It is a type of sensory-motor neuropathy that develops in about 50% of patients who stay in critical care units for more than 2 weeks, for a variety of critical illnesses. They also have past or current infections and multiple organ failure. Difficulty to wean the patient off the ventilator raises the suspicion of this type of neuropathy. Prognosis is good in those who survive the original illness.

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Autonomic Nervous System

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Chapter Summary

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- Clinical Features and Diagnosis 1329
- Management of Autonomic Neuropathy 1331

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General Considerations

Autonomic Nervous System (ANS)

Definition: This is the part of the nervous system which functions autonomically with very little role for voluntary control. Autonomic neuropathies are common. They may occur more often along with other forms of neuropathy

such as diabetic neuropathy and systemic amyloidosis or autonomic neuropathy may be the predominant or only manifestation as in acute pan-dysautonomia.

Anatomically, the ANS can be divided into cortical, peripheral and enteric components.

Centers in the brain include orbito-frontal cortex, cingulum, amygdala, insula, claustrum which converges on the hypothalamus, bulbar reticular formation, and nucleus tractus solitarius.

The highest control of the autonomic nervous system (ANS) is from the hypothalamus and this is influenced by the orbitofrontal cortex and limbic system. The autonomic nervous system innervates smooth muscles of viscera and secretory glands. It consists of the sympathetic and parasympathetic nerves.

The afferents to the ANS include:

- 1. All the sensory pathways,
- 2. Carotid and aortic sinus baroreceptors via the IX and X cranial nerves and
- 3. Cardiopulmonary baroreceptors, skin, muscles, and the viscera.

Sympathetic system: The peripheral sympathetic system is formed by fibers leaving the spinal cord from C8 to L3 segments. Fibers emerging from the C8 and T1 segments pass up through the inferior and middle cervical ganglia and synapse in the superior cervical ganglion. Postganglionic fibers from these ganglia pass along with the branches of the internal and external carotid arteries to supply cranial structures.

The thoracolumbar outflow consists of fibers which arise from neurons in the intermediolateral column of the cord from T1 to L3 segments. The preganglionic fibers (myelinated) pass out along with the ventral roots and reach the paraspinal sympathetic ganglia chain in the white rami communicantes. Unmyelinated postganglionic fibers (grey rami) leave these ganglia to reach the various organs along with the spinal nerves.

The paraspinal sympathetic chains consist of three cervical, eleven thoracic, four lumbar and four sacral ganglia which are all paired, and a single unpaired coccygeal ganglion. The upper limb is supplied through the stellate ganglion by fibers arising from the upper thoracic segments. Cardiac fibers arise from the upper thoracic segments. The greater splanchnic nerve derived from T5 to T10 ganglia reaches the celiac plexus. Lesser splanchnic nerve (T9 to T10) reaches the aortorenal plexus. These supply the digestive tract and other abdominal organs.

Parasympathetic system: The centers are situated in special visceral nuclei in the brainstem and in the lateral horns of S2-S4 segments of the spinal cord. Fibers from these nuclei leave along the cranial nerves (III, VII , IX and X) or the sacral nerves and synapse in the ganglia situated near the viscera which receive their supply. The sacral fibers supply the urinary bladder, colon, and other viscera.

Functions: The sympathetic and parasympathetic systems have complementary roles. The former is more active during wakefulness and activity whereas the latter is more active during sleep. *Sympathetic nervous system consists of adrenergic nerve fibers, with the exception of fibers to sweat glands which alone are cholinergic.* The important actions mediated by adrenergic nerves are pupillary dilatation, cardiac acceleration, splenic contraction, vasoconstriction in the skin and viscera, coronary vasodilatation, inhibition of intestinal motility, bronchodilatation, sweating, ejaculation of semen, contraction of sphincters, and hepatic gluconeogenesis and glycolysis.

Parasympathetic fibers are cholinergic. Their main actions include pupillary constriction, slowing of the heart rate, vasodilatation in the skin and viscera, secretory activity of glands, bronchoconstriction, increasing peristalsis and secretion of the gastrointestinal tract, contraction of urinary bladder, penile erection, and increased secretion of insulin.

Visceral pain is carried by the ANS, the stimuli being distension of viscera, hypermotility, and inflammation. This is poorly localized and diffuse. Often it is felt as referred pain over cutaneous areas supplied by the spinal nerves arising from the same spinal segment, e.g. hepatic pain is referred to the right shoulder and cardiac pain is referred to the inner aspect of the left arm.

The two systems show differences

Parasympathetic system	Sympathetic system
1. Pre-ganglionic and post ganglionic fibers are cholinergic	Postganglionic fibers are adrenergic except for sweat glands.
2. Ganglia close to target	Away from the target
3. Specific function	Different effects

The enteric system, also called the *minibrain* consists of the Auerbach's and Meissner's plexuses and the Henle's plexus. They sense parameters such as wall tension, osmolality of the luminal contents, pH and others, and activate the neural network for performing programmed digestive behaviour by providing information, generating output signals via the motor nerves to muscles, secretory apparatus and vasculature of the gut.

Preganglionic fibers are small lightly myelinated B' fibers and postganglionic fibers are unmyelinated C' fibers. Since these fibers are small, generally abnormalities of nerve conduction may not be evident on clinical testing.

Autonomic nerves subserve almost all organs and take part in all involuntary and reflex activities taking place in the body. The terms autonomic neuropathy (ANP) denotes the autonomic disturbances arising out of diseases of the peripheral autonomic nervous system

AUTONOMIC NEUROPATHY

Most of the ANPs have features of both sympathetic and parasympathetic dysfunction, manifesting in varying degrees. The onset and course are generally insidious and chronic in conditions such as diabetes and leprosy. It may be acute and even fulminant in conditions such as acute intermittent porphyria, Guillain-Barre syndrome, acute pan-dysautonomia, botulism and diphtheria. The course also varies. In diabetes mellitus ANP progresses to cause severe disability. In the acute forms it may recover completely, or to varying extent (Table 201.1).

Clinical Features and Diagnosis

Clinical suspicion of the presence of autonomic neuropathy (ANP) is essential to make a diagnosis (Table 201.2).

TABLE 201.1

Causes of autonomic neuropathy	
A. Secondary to other diseases	
1. Systemic disease	– Diabetes mellitus, uremia, hepatic failure, acquired amyloidosis, porphyrias.
2. Infections	– Leprosy, diphtheria, botulism, Chagas disease, HIV.
3. Drug induced	– Vincristine, cisplatin, taxols, amiodarone, perhexiline.
4. Toxic	– Alcohol, heavy metals, organic solvents.
5. Immune-mediated	– Guillain-Barre syndrome, paraneoplastic syndromes (Eaton-Lambert syndrome), connective tissue disorders, inflammatory bowel diseases, chronic inflammatory demyelinating polyneuropathy, acute pan-dysautonomia.
6. Nutritional	– Vit B ₁₂ deficiency.
B. Primary autonomic neuropathies	
1. Primary affections of autonomic nervous system	– Progressive autonomic failure (<i>Bradbury and Eggleston syndrome</i>). – Progressive autonomic failure with multiple system atrophy (<i>Shy-Drager syndrome</i>). – Progressive autonomic failure with Parkinson's disease.
7. Hereditary	– Hereditary sensory and autonomic neuropathy (HSAN). Fabry's disease, Tangier's disease, Allgrove's syndrome, multiple endocrine neoplasia (MEN).
8. Idiopathic	– Idiopathic distal small fiber neuropathy, chronic idiopathic anhydrosis.

TABLE 201.2

Shows the manifestations specifically attributable to autonomic neuropathy	
1. Cardiovascular system	– Orthostatic hypotension, syncope, labile hypertension, brady-tachy arrhythmias
2. Gastro intestinal	– Constipation, fecal incontinence, bloating of abdomen, gastroparesis, episodic diarrhea, dysphagia, abdominal pain and vomiting.
3. Urogenital	– Impotence, ejaculatory failure, retrograde ejaculation, vaginal dryness. Urinary retention and/or incontinence, urgency, precipitancy, nocturia, enuresis, incomplete evacuation of urine.
4. Secretomotor disturbances	– Anhidrosis, hypohydrosis, hyperhidrosis mainly of hands feet and face, gustatory sweating, xerostomia, ptyalism, dryness of the eyes, bronchorrhea.
5. Skin	– Feeling of coldness, flushing and warmth, pallor, acrocyanosis, mottling, loss of hair, thickening and discolouration of nails.
6. Bones and joints	– Charcot's joints, rarefaction and destruction of bone, analgesia or pain in joints.
Thermo regulation	– Hypothermia, hyperpyrexia.
Eyes	– Horner's syndrome, Argyll Robertson pupils. Adie's pupil, mydriasis.

Features Suggestive of Autonomic Neuropathy (ANP)

<i>Skin and mucous membranes</i>	– Dry skin, nail changes, loss of hair, trophic changes, vasomotor disturbances, dryness of mucous membranes or excess secretions.
<i>Pupils</i>	– Horner's syndrome, Adie's pupil, Argyll Robertson pupil.
<i>Cardiovascular</i>	– Orthostatic hypotension, abolition of sinus arrhythmia, absence of heart rate and blood pressure changes to Valsalva maneuvers and exercise.
<i>Urogenital</i>	– Impotence, other forms of sexual dysfunction, disorders of micturition.

TABLE 201.3

Tests employed to detect ANP
A. <i>Tests for parasympathetic functions</i> Recording of sinus arrhythmia and blood pressure (BP) 1. Heart rate response to Valsalva maneuver.
B. <i>Tests for sympathetic adrenergic and cholinergic functions</i> 2. Heart rate and BP responses to standing. 3. BP response to Valsalva maneuver. 4. Cold pressor test – BP rises. 5. Isometric exercise test-BP rises. BP response to drugs such as noradrenaline, angiotensin II, atropine and neostigmine
C. <i>Tests for sympathetic cholinergic functions</i> 6. Thermoregulatory sweat test. 7. Quantitative sudomotor axon test. 8. Sympathetic skin response. 9. Sweat imprint methods.
D. <i>Test for lacrimal secretion (parasympathetic)</i> 10. Schirmer's test. 11. Test for cutaneous flare response. Subcutaneous histamine injection or scratch test 12. Tests for pupillary responses. Instillation of drugs such as homatropine, cocaine, pilocarpine –response depends on the type of drug instilled.

Several Tests are Available for Detecting ANP

See Table 201.3.

Importance of Autonomic Neuropathy

Several diseases lead to ANP. Occurrence of ANP increases the risk of fatal complications e.g. diabetic autonomic neuropathy. They impair the quality of life e.g.

TABLE 201.4

Principles of symptomatic management of autonomic neuropathy	
Condition	Therapy
Orthostatic hypotension	Oral fluids, salt intake, mineralocorticoid fludrocortisone 0.1 to 0.3 mg/day or alpha receptor agonist like midodrine 2.5-10 mg tabs daily
Bowel disorders	Adjustment of diet, prokinetics
Erectile failure	Sildenafil 25-100 mg oral
Urinary dysfunction	Timed voiding, cholinergic drugs self catheterisation
Labile hypertension	Beta blockers
Tachyarrhythmias	
Hyperhidrosis	Trihexyphenidyl, glycopyrrolate

sexual dysfunction, urinary and fecal incontinence, orthostatic hypotension and others.

Syndromes of Primary Autonomic Failure

- 1. Primary orthostatic hypotension- fall in blood pressure severe enough to cause syncope on assuming the erect posture is indicative of sympathetic dysfunction.
- 2. Shy-Drager syndrome—This has features of chronic autonomic failure along with parkinsonism, cerebellar and pyramidal features.

Management of Autonomic Neuropathy

All primary underlying conditions should be treated. Chances of recovery of autonomic functions are variable. Proper control of the primary disease may prevent deterioration.

In symptomatic cases, management aims at treating the symptoms (Table 201.4).

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Myasthenia Gravis 1332

Neonatal Myasthenia 1334

Congenital Myasthenic Syndromes 1334

Myasthenic Reactions 1334

The term myasthenia denotes muscle weakness. In practice the weakness aggravates with repeated action.

Myasthenia occurs due to defective impulse transmission at the neuromuscular junction. The most common among the neuromuscular disorders is myasthenia gravis.

Myasthenia Gravis

Myasthenia gravis (MG) is a disease characterised by weakness and easy fatigability of skeletal muscles with predilection for cranial and limb muscles. The disease improves after administration of cholinergic drugs.

Etiopathogenesis: The defect in myasthenia gravis is at the neuromuscular junction where acetylcholine is the principal neurotransmitter. In normal muscle, acetylcholine released in the synaptic cleft binds to acetylcholine receptors located on the muscle membrane and depolarize them. In myasthenia gravis, the primary abnormality is the autoimmune mechanism leading to blocking and destruction of acetylcholine receptors. Antibodies against acetylcholine receptors do not allow acetylcholine to bind with the receptors, thus blocking the chemical transmission. There is also gross reduction in the number of acetylcholine receptors. Patients may have only 1/3 the number of acetylcholine receptors compared to normals. IgG antibodies are demonstrable in the serum. Family members of MG are 1000 times more susceptible to develop MG than the general population.

It is possible that the thymus gland may act as the source of antigen directing the humoral and cellular immune response. Moreover, the normal homeostasis of the immune system by the T-cell suppressor system is also

altered. Around 85% of myasthenic patients have thymic hyperplasia and 15% have thymoma, especially those in whom the onset is below 40 years.

Myasthenic syndromes can develop in several other conditions as a result of formation of humoral factors which block the action of the receptors, e.g. bronchogenic carcinoma.

Classification of Myasthenia gravis (MG)—(Osserman)**A. Adult MG:**

- Group 1. Ocular myasthenia (20%)
- Group 2. Generalized myasthenia (60%)
 - a. Mild-generalised
 - b. Generalised with bulbar involvement
 - c. Severe-generalised
- Group 3. Acute fulminant myasthenia with early involvement of respiratory muscles (10%).
- Group 4. Late severe myasthenia developing after at least 2 years of group 1 or 2 symptoms (10%).

CLINICAL FEATURES

Myasthenia may start at any age but the peak incidence is around 20-30 years and females are more often affected. 5-7% of cases are familial. In 10% of cases spontaneous remissions occur. Genetic susceptibility is associated with certain HLA types. Muscle weakness may or may not be present at rest but occurs or increases after sustained or repetitive exercise. The hallmark of myasthenia is easy fatigability of skeletal muscles, worsened on exercise and this disability is relieved after short rest. The weakness has diurnal variation, being less in the morning and worse in the afternoon or evening. Diplopia, ptosis, ophthalmoplegia, dysphagia, and dysphonia commonly occur due to involvement of muscles supplied by the cranial nerves. The disease then involves the proximal muscles of the lower and upper limbs. There are no sensory symptoms or signs. Deep tendon reflexes are normal. Muscle weakness is not accompanied by wasting or fasciculations.

In many cases the onset is insidious and severity is mild to moderate. The common presentations are diplopia,

weakness of voice, inability to chew food or progressive fatigue on doing repetitive activities, particularly towards the latter part of the day. Less commonly the onset may be subacute or in a few cases it may even be acute. Infections, emotions, insomnia and menstruation may aggravate myasthenia leading to myasthenic crisis. Many drugs such as quinidine, quinine, aminoglycosides, polymyxin, procainamide, penicillamine, oral contraceptives, opiate analgesics, propranolol, calcium channel blockers, diazepam, muscle relaxants, anti-epileptic drugs, chloroquine and colistin also worsen myasthenic symptoms.

Diagnosis

Diagnosis of myasthenia is clinical. It can be confirmed by investigations.

Pharmacological Tests

- Tensilon test—Tensilon (edrophonium chloride) given intravenously in a dose of 2 mg initially as a test dose followed by 8 mg slowly, improves myasthenic weakness dramatically within 60 seconds. Atropine should be available at hand to terminate unpleasant side effects. Complications include syncope and respiratory distress.
- Recovery of muscle strength within 15-30 minutes on injecting neostigmine in a dose of 0.04 mg/kg body weight S.C is also diagnostic.
- Acetylcholine receptor antibodies can be detected in serum by radioimmunoassay tests. Presence of the antibody confirms the diagnosis but its level in the serum and clinical severity do not correlate. These antibodies are present in 80% of cases of generalized and severe forms of MG. In ocular MG and MG in remission this frequency is much lower. Antibodies to striated muscle in the serum are also present in some cases. Anti-muscle antibody positive MG constitutes 8-10% of seronegative MG in children.
- Repetitive nerve stimulation and EMG*: In myasthenia, on repetitive stimulation of the peripheral motor nerves in the limbs at a rate of 3 stimuli per second, the amplitude of the evoked motor action potentials progressively diminishes (>10%). This is called decremental response. On single fiber—EMG examination there will be increased jitter.
- X-ray, CT scan or MRI of the chest help to demonstrate enlargement of the thymus, pulmonary lesions and other abnormalities.

Differential diagnosis: Myasthenia has to be differentiated from hysterical conversion reaction, motor neuron disease, myositis and myopathies. Precipitation or aggravation of symptoms by emotion may suggest a diagnosis of hysterical conversion reaction. The bulbar type of motor neuron disease and polymyositis seldom

involve the external ocular muscles. The absence of fatigability and presence of fasciculations in motor neuron disease and occurrence of muscle tenderness in polymyositis help to differentiate these diseases from myasthenia.

In myopathy involving the cranial muscles, especially ocular myopathy, the weakness is confined to the affected muscles and there is no worsening with repeated activity.

Complications

Myasthenic crisis and cholinergic crisis are two acute complications which may develop. These are characterized by sudden occurrence of severe degree of paralysis affecting several muscles in the body including respiratory paralysis. The former is due to aggravation of myasthenia due to precipitating causes. The latter is caused by over use of anticholinesterase drugs.

Clinically both may appear similar, except for the history of drug administration and presence of fasciculations in the latter. Unless emergency measures are instituted to tide over the paralytic episode, the condition may prove fatal. A simple test to distinguish the two types is the I.V administration of 2 mg edrophonium (available as Tensilon) which rapidly relieves myasthenic crisis, but not cholinergic crisis.

Irrespective of the cause, all such patients need intensive care management with ventilatory support. Myasthenic crisis is usually precipitated by intercurrent infections.

Cholinergic crisis is caused by excessive dose of anticholinesterase drugs.

Course and Prognosis

Many cases are only mild to moderate in severity and the patients learn to manage themselves with optimal drug therapy. The severity may show fluctuations from time to time. In about 10% of cases spontaneous remission may occur during the first few years. Purely ocular myasthenia runs a mild course. Prognosis is worse for acute fulminant and late onset cases. Cases associated with thyrotoxicosis show a see-saw relationship with the severity of the latter. Occurrence of crisis is a fatal complication if not managed promptly. Patients suffering from myasthenia may develop other autoimmune diseases.

TREATMENT

- Onset of MG before the age of 60 years:** Thymectomy is the preferred modality of treatment, even in those who do not have thymoma. In some cases pretreatment with plasmapheresis or anticholinesterase drugs may be required to reduce severity of the symptoms before surgery. After thymectomy if the result is not satisfactory, high doses of prednisolone or other immunosuppressant drugs may be necessary. Some patients require anticholinesterase drugs.

B. **Onset of MG after the age of 60:** Anticholinesterase drugs along with prednisolone or immunosuppressant drugs are preferred. Plasmapheresis or intravenous human immunoglobulin (I.V.I.G.) should be considered for severe exacerbations of the symptoms and during myasthenic crises until the drugs take effect. Thymectomy should be reserved for those who do not respond to medications.

C. In patients with thymoma, thymectomy should be performed, irrespective of the age at which the diagnosis is made.

The commonly used anticholinesterase drugs are:

1. **Neostigmine** (15 mg tablet) 60-200 mg/day in divided doses.
2. **Pyridostigmine** (60 mg tablet) 1 tablet given every 4 hours.

The dose and frequency of administration of these drugs have to be tailored to the patient's requirement.

Corticosteroids are indicated:

- i. in those cases where there is insufficient response to anticholinesterase drugs,
- ii. when ocular symptoms are predominant and
- iii. in older males. Oral prednisolone is the preferred steroid which is given in a high dose—100 mg daily to start with and then on alternate days. Once remission of symptoms occurs, it is slowly tapered off over 6-12 months. Initial worsening of the myasthenic symptoms may occur with steroids in some cases.

Immunosuppressant drugs may be required for those cases of MG that are resistant to thymectomy and steroids. These include azathioprine, cyclophosphamide and cyclosporine in the usual dosage. Mycophenolate mofetil, in doses of 2 g/daily orally is a good immunosuppressant which acts as an adjunctive therapy in MG. It helps to reduce the dose of corticosteroids.

Treatment of myasthenic crisis: Injection of edrophonium chloride in a dose of 2 mg relieves myasthenic crisis within one minute. If the weakness aggravates, cholinergic crisis should be diagnosed. In such a case all drugs should be withdrawn and the patient's respiration should be maintained by artificial ventilation till the condition passes off.

In cases of myasthenic crisis further doses of anticholinesterase drugs should be given with care. If there is no relief two options are available. (1) **emergency plasmapheresis** and (2) **I.V human immunoglobulin** in a dose of 0.4 g/kg/body weight daily for 3-5 days. Both have been tried extensively in different centers and found to be quite effective. The former requires expensive equipment and donor plasma, the latter is more expensive (Rs 80,000 to 1, 00,000 per course).

Treatment of the underlying cause should be instituted simultaneously.

Myasthenia Gravis in Pregnancy

Usually when pregnancy occurs the myasthenia abates. Neostigmine is quite safe during pregnancy. Cytotoxic drugs should be avoided.

The newborn may show transient myasthenia lasting for a few hours to days due to passive transfer of maternal antibodies. Oral administration of pyridostigmine corrects the condition.

Neonatal Myasthenia

Transient neonatal MG may be present in 15% of babies born to mothers with MG due to trans-placental transfer of antibodies. Usually the condition clears in a few days. These babies need specific management during the myasthenic phase.

Congenital Myasthenic Syndromes

Neonates and infants manifest with myasthenic symptoms which persist into adult life. Anti-acetylcholine receptor (AChR) antibodies are not demonstrable. Mothers do not have MG. Several congenital myasthenic syndromes have been described. These are hereditary disorders of neuromuscular transmission. Most of them except a few (e.g. slow channel syndrome) are autosomal recessive: They are characterized by ophthalmoplegia, muscle weakness and fatigue. They may have delayed milestones in infancy, and respiratory distress which may extend into childhood. Repetitive nerve stimulation shows decremental response, especially at slow rates of stimulation. The defect may be presynaptic, synaptic or postsynaptic. Genetic studies are available to identify the defect.

Treatment: Some patients benefit with anticholinesterases such as neostigmine. Drugs like quinine and fluoxetine are beneficial in slow- channel syndrome. Thymectomy has no role in this condition.

Myasthenic Reactions

Syn: Secondary myasthenia

A clinical picture closely resembling myasthenia gravis may develop as a paraneoplastic phenomenon, particularly in oat cell carcinoma of the lung (**Eaton-Lambert syndrome**). This is caused by immunological reaction at the neuromuscular junctions by antibodies developing against the membrane proteins of the tumour cells which may resemble antigen present in normal nervous tissue and receptors at the neuromuscular junction. Immunological injury leads to damage to calcium channels and results in failure of release of acetylcholine at motor and autonomic nerve terminals. Other manifestations of carcinomatous neuromyopathy may also be evident in many cases. Though it superficially resembles myasthenia gravis, it differs in that the ocular muscles are not affected. So, also muscle wasting and loss of tendon reflexes may be seen. Unlike in MG, the muscle weakness in these

patients improves with exercise (**reverse myasthenia**). The electromyographic pattern also shows marked difference. Removal of the primary tumour leads to symptomatic remission. Guanidine in a dose of 35 mg/kg given orally is beneficial. Another drug found to be useful in this condition is 3,4 diamino pyridine.

Myasthenic reaction may develop in thyrotoxicosis, snake bites, (especially cobra and krait) and use of drugs

like aminoglycosides, penicillamine and others. AchR antibodies may be present in penicillamine induced myasthenia.

Recognition of this complication in snake bites and anticholinesterase therapy along with ventilatory support are life saving. In neoplastic conditions, treatment of the neoplasm relieves the myasthenia too. Drug induced myasthenia subsides on withdrawal of the drug.

203

Diseases of Muscles

A.S. Girija, P.K. Mohan

Chapter Summary

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GENERAL CONSIDERATIONS

Study of the diseases of muscles (clinical myology) has advanced considerably in the last few decades as a result of improvement in investigations like biochemical tests, electrophysiology, histological studies, electron microscopy, histochemistry and genetic studies.

Skeletal muscle is composed of several muscle fibers that run along its longitudinal axis. Each muscle fiber represents a separate anatomic and physiologic unit. The cytoplasmic membrane is called sarcolemma and the

cytoplasm is called sarcoplasm. Sarcoplasm contains myofibrils which in turn are composed of contractile myofilaments—actin and myosin. Connective tissue invests the muscle fibers, fasciculi and the entire muscles and this is known as endomysium, epimysium, and perimysium respectively. The integrity of the muscle depends upon its adequate blood supply and intact nerve connections. Muscle disorders may be caused by affection of one or more of these components, i.e. enzyme systems in the sarcoplasm, abnormalities in connective tissue coverings, ischemia or loss of trophic influences. By special staining techniques, two types of muscle fibers are recognized. Type I fibers are richer in oxidative enzymes and they are abundant in muscles which are intended for sustained contraction for long periods, e.g. muscles which maintain posture. Type II fibers are high in phosphorylase enzyme activity. They are present more in muscles which are intended for fast action, e.g. hand muscles. Both fiber types are present in all the muscles in differing proportions.

Type I fibers are also known as *slow twitch* or *red fibers* and *Type II* fibers are known as *fast twitch* or *white fibers*.

The muscle fiber, like any other cell, has a resting action potential (RAP). An action potential is triggered off when the sodium permeability of the sarcolemma increases. Potassium moves out of the cell and sodium moves in. The intracellular sodium releases calcium, which activates the ATPase enzyme in the presence of

magnesium (Mg^{++}). The release of energy-rich bonds in turn produces a sliding movement of the actin-myosin filaments, resulting in mechanical contraction. The whole process is called excitation-contraction coupling. Changes in ionic concentration of Na^+ , K^+ , Ca^{++} , Mg^{++} and others can influence activity of the muscle fiber.

Damage to the sarcolemma gives rise to leak of sarcolemmal enzymes into the general circulation. Transaminases, lactic dehydrogenase (LDH), aldolase and creatine kinase (CK) appear in large amounts in blood in muscle diseases. Since other tissues like the heart, liver, brain and others also contain similar enzymes, rise in the level of these enzymes in blood may result from damage to other tissues as well. But in each case the specific isoenzyme can be identified by appropriate methods. This helps to identify the affected tissue more specifically.

Creatine is found in large amounts in muscle and it is required for the formation of energy-rich phosphate bonds. Creatinine is the metabolic product of creatine. Normal sarcolemma is highly impermeable to creatine, but not to creatinine. In disease states permeability to creatine increases, resulting in rise in serum creatine levels and appearance of creatine in urine (creatinuria).

The muscle plasma membrane is a trilaminar structure which houses thousands of proteins forming various channels, pores, receptors and anchoring proteins, all performing specific functions. The various structural components of muscles are genetically determined and each has a distinct function to perform. Classification of inherited muscle diseases is based on the abnormal component. Terms such as dystrophinopathies, sarcoglycanopathies and lamininopathies are being used to denote the underlying pathology of muscle disorders.

SYMPTOMATOLOGY OF MUSCLE DISEASES

Muscle disorders often present with weakness and wasting of proximal muscles. Some diseases of muscles may show hypertrophy, pseudohypertrophy (apparent increase in bulk due to overgrowth of fat and connective tissue) or contractures. Unlike in neuropathy, tendon reflexes are usually preserved until late in the disease and sensations are normal although sensory symptoms like aches, cramps and painful muscle spasms may occur in some patients. Fasciculations are not present, though there are exceptions.

Myotonia is the failure of relaxation after contraction and this is a feature of some muscle disorders. *Action myotonia* is failure to relax after voluntary action such as shaking hands with the examiner. *Percussion myotonia* is the persistence of contraction after tapping the muscle, best demonstrated in the muscles of the tongue or hand.

Myoedema is a localized bulge of the muscle on tapping, found in hypothyroidism and cachexia.

Bilateral weakness of the gluteus medius and minimus muscles produces **waddling gait**. Proximal muscle weakness in the lower limbs gives rise to difficulty in getting up from the squatting posture, and the patient gets up with the assistance from his hands over the thighs. This is known as **Gower's sign**. Weakness of the iliopsoas and paraspinal muscles gives rise to exaggeration of lumbar lordosis and protuberance of the abdomen. Winging of scapulae occurs due to weakness of the serratus anterior, lower part of trapezius and rhomboids. Muscles supplied by the cranial nerves may be affected in some forms of myopathies (e.g. ocular myopathies). Muscle tenderness may be present in myositis.

Some patients may not use the term weakness for their symptoms but instead describe them as difficulty in combing hair, rising out of chair or climbing up a stair case. The distribution of these symptoms or weakness offers a clue to the diagnosis. Proximal limb weakness without significant wasting is the presenting symptom in polymyositis, mitochondrial myopathies, glycogen or lipid storage myopathy and Lambert-Eaton myasthenic syndrome. Proximal limb weakness with significant wasting is seen in facioscapulo-humeral, limb girdle, Duchenne and Becker types of muscular dystrophies and juvenile spinal muscular atrophy.

Distal limb weakness presents with difficulty in performing fine coordinated movements or weakness of hand grip, going over a step or going down stairs. Myotonic dystrophy, scapulo-peroneal muscular dystrophy, distal myopathy, distal spinal muscular atrophy and amyotrophic lateral sclerosis are the conditions with predominantly distal weakness. Ptosis and ophthalmoplegia occurs in myasthenia gravis, hyperthyroid ophthalmopathy, oculopharyngeal muscular dystrophy and mitochondrial myopathies. Generalised wasting without focal weakness is seen in cachexia and malnutrition. Focal weakness and wasting of hand muscles without pain is an early manifestation of motor neuron disease or syringomyelia. Accompanying pain in the hand and forearm suggests cervical radiculopathy or peripheral nerve entrapment. Frank enlargement of calf muscles is seen in Duchenne and Becker types of muscular dystrophy, myopathy due to congenital hypothyroidism and cysticercosis. Generalised muscular hypertrophy occurs in myotonia congenita.

Classification

Diseases of the muscle that cause acute, subacute or chronic weakness, wasting, myalgia, muscle cramps and stiffness, asthenia and easy fatigue or myoglobinuria are called myopathies. Several schemes of classification of myopathies have been followed by different authors. Earlier classifications were based on the pattern of muscle

TABLE 203.1

Classification of myopathies

A. Genetically determined myopathies	
1. Muscular dystrophy (MD)	
a. X-linked	
i. Severe form	: Duchenne type (DMD)
ii. Mild form	: Becker type (BMD)
b. Autosomal recessive	: Limb-girdle type
c. Autosomal dominant	: Facioscapulohumeral type. Syn: Landouzy-Dejerine type,
d. Localized types	: Distal MD Ocular MD Oculopharyngeal MD
2. Congenital myopathies, e.g. congenital muscular dystrophy, nemaline myopathy, central core disease, myotubular myopathy	
3. Myotonic disorders, e.g. dystrophia myotonica, myotonia congenita (Thomsen's disease)	
4. Glycogen storage disorders	
5. Mitochondrial myopathies	
6. Myopathies associated with disordered lipid metabolism	
7. Familial periodic paralysis	
B. Inflammatory myopathies: Polymyositis, dermatomyositis	
C. Myopathies due to endocrine and metabolic disorders	
a. Thyrotoxicosis	
b. Myxedema	
c. Cushing's disease	
d. Addison's disease	
e. Hyperparathyroidism	
f. Primary aldosteronism	
g. Acromegaly	
h. Osteomalacia	
i. Nutritional myopathy	
j. Drugs: Steroids, clofibrate, chloroquine, phenformin, d-penicillamine, zidovudine.	
D. Myopathy in malignant diseases — Carcinomatous myopathy	
A detailed description of all these disorders is beyond the scope of this chapter. Hence brief descriptions of the more common disorders are attempted here. The student may refer monographs on muscle diseases for further details.	

groups involved and the mode of inheritance, e.g. limb-girdle dystrophy and facioscapulohumeral myopathy. Later, myopathies where electrical abnormalities were demonstrable by electromyography (EMG) were added, e.g. congenital myopathies. Classification of metabolic myopathies takes into consideration the enzymic defects occurring in muscle metabolism. A simplified system of classification is given below for purpose of clarity. Several terms have been employed to indicate muscle disorders. These are muscular dystrophy, myopathy and myositis (Table 203.1).

“Myopathy” is a broad general term that includes all diseases of the muscles. Muscular dystrophies are myopathies that are characterised by a specific pattern of inheritance. Myositis is a type of myopathy where inflammation is the predominant feature.

The muscular dystrophies are inherited myogenic disorders characterized by progressive muscle wasting and weakness, of variable distribution and severity. These are genetically determined and each type shows a unique pathology. In them the structural proteins are defective and classification of the muscular dystrophies is based on the abnormality of the structural proteins.

CLINICAL APPROACH TO THE PATIENT WITH MUSCLE DISEASE

A muscle disorder is first suspected when a patient presents with muscle wasting and weakness, predominantly proximal in distribution or in one of the characteristic patterns. The important differential diagnosis includes spinal muscular atrophy and motor neuropathies. Absence of deep tendon reflexes, presence of fasciculations and insidious course of the disorder help to distinguish spinal muscular atrophy from muscular dystrophy. Peripheral neuropathies commonly affect the distal muscles, contrary to muscular dystrophy which affects the proximal muscles more. Pure motor neuropathy is extremely rare and in many cases of neuropathy sensory abnormalities are demonstrable. Investigations like muscle enzymes, EMG, and nerve biopsy help to make a definite diagnosis in most cases and these should be done in all cases for confirmation. These investigations should be done for the family members also to detect subclinical cases and carriers in cases of suspected genetically transmitted myopathies. Muscle histochemistry and electron microscopy may help in the diagnosis of early cases even when routine muscle histology on light microscopy is not confirmatory.

Muscle enzymes estimation should be done before EMG examination as the needle pricks spuriously elevate these enzymes. For muscle biopsy, a muscle which is not submitted to EMG examination should be selected to avoid needle injury artefacts on histology.

Duchenne Muscular Dystrophy (DMD)
Syn: Pseudohypertrophic muscular dystrophy

The disease manifests only in males whereas females act as carriers. It is transmitted as an X-linked recessive trait. The Duchenne Muscular Dystrophy (DMD) locus is in Xp21 region. At present specific DNA probes are available to identify this locus. Duchenne and Becker type dystrophies are due to defects in the same gene locus and its product “dystrophin” is probably required for

maintaining the stability of muscle membrane. Mutations of dystrophin gene, usually deletion or gene inversions; lead to total or near-total loss of dystrophin protein from skeletal muscle causing early and progressive loss of muscle function. Dystrophin is part of a multifunctional transmembrane protein complex; the dystrophin-glycoprotein complex. This acts as a scaffold for adhesion and signalling of cytoskeletal proteins. Disruption of this complex leads to death of muscle cells from apoptosis and necrosis. Milder defects lead to Becker's muscle dystrophy. Since the genetic defects in Duchenne's muscular dystrophy and Becker's muscular dystrophy are the same, these disorders together are called *dystrophinopathies*.

CLINICAL FEATURES

Whereas DMD is rapidly progressive and incapacitating before reaching adolescence, the progress in Becker type is slow and the patient can be ambulant even up to the age of 60 years. The frequency of DMD is one in 3000-5000 male children. Onset of the disease is usually before the fourth year. Symmetrical involvement of pelvic girdle muscles occurs. The initial complaint is that the child falls frequently while walking. *Gower's sign* is demonstrable at this stage. This is followed by weakness of the muscles of the shoulder girdle. Pseudohypertrophy of the calf muscles is an important clinical finding at this stage. Involvement of the muscles is selective at first, later it becomes generalized. Weakness of muscles progresses and within 10 years of onset of the disease, the child is disabled considerably. About 20% of affected boys have IQ below 40%. About 5-10% of female carriers may have some degree of muscle weakness and enlargement of the calf muscles.

Cardiac involvement occurs invariably, and manifests as persistent tachycardia or sudden death due to cardiac failure. Characteristic ECG changes may occur. These include tall R-waves in right precordial leads and deep Q-waves in the limb leads and left precordial leads. Skeletal changes take the form of severe scoliosis, exaggerated lumbar lordosis, and increased tendency for fractures.

DIAGNOSIS

This is confirmed by markedly elevated serum CK level, myopathic pattern on EMG and characteristic muscle biopsy. Since genetic studies are now available for diagnosis, muscle biopsy is required only rarely. The EMG shows brief duration small amplitude motor unit potentials with complete interference pattern. These investigations are marginally abnormal in carriers and this helps in carrier detection. There is no effective treatment at present. It is possible to diagnose affection of the fetus prenatally. Genetic counselling and prenatal diagnosis should be undertaken in affected families.

Differential diagnosis includes other causes of myopathies, myositis, Hoffman's syndrome in myxedema and rarely S₁ radiculopathy.

Though generally damage to spinal nerve roots or peripheral nerve causes muscle atrophy, at times S₁ spinal root radiculopathy may give rise to unilateral calf swelling. Histology of the muscle shows hypertrophy, pseudo hypertrophy or focal myositis. Evidence of myositis such as elevation of serum creatine kinase (CK) may be evident. The condition generally resolves spontaneously. Rarely decompression of S₁ spinal root may be needed.

Course and Prognosis

The course is one of steady progression to involve all muscles in the body and death occurs in 10-12 years as a result of malnutrition, respiratory infection or respiratory failure.

Management

Supportive care maintenance of nutrition, proper schooling as long as it is possible, avoidance and prompt treatment of respiratory infections, proper physiotherapy and use of appropriate appliances for daily life help to maintain mobility and preserve the morale.

Early recognition and prevention: The growth and development of affected boys are slow, they start walking only around 18 months and their speech is slow. Serum creatine kinase is elevated. Early diagnosis helps in proper genetic counselling.

Clinical manifestations such as muscle weakness and dilated cardiomyopathy can be detected by investigations in 20% of carriers of DMD and BMD. 40% may show left ventricular dilatation.

Limb-Girdle Muscular Dystrophy

This is transmitted as an autosomal recessive trait and it occurs in both sexes. The disease manifests in the second and third decades of life as primary involvement of the pelvic or shoulder girdle muscles. Hypertrophy of muscles may be seen in some cases. Most patients are severely disabled by middle life. In the upper limbs, the muscles usually affected are serratus anterior, trapezius, rhomboids, latissimus dorsi and sternal head of pectoralis major. Deltoids are spared until late in the disease. Cardiac involvement is rare.

Different types of limb girdle muscular dystrophy occur; depending on their genetic abnormality. They differ in

1. the pattern of inheritance
2. clinical pattern— age and distribution of lesions
3. the chromosomal defect and
4. type of muscle protein affected.

Facioscapulohumeral Muscular Dystrophy

This disease is usually transmitted as an autosomal dominant trait. The onset of the disease may be at any age from childhood to adult life. The facial and shoulder girdle muscles are involved first. Muscular hypertrophy, contractures and skeletal deformities are rare. Life expectancy is normal as the disease runs an insidious course.

Congenital Myopathies

Different types of congenital myopathies have been recognized with the advent of muscle histochemistry and EMG. These diseases are transmitted as autosomal dominant or recessive traits. Proximal muscles are usually involved. Congenital myopathy leads to severe hypotonia in the infant. The disease is slowly progressive and muscle enzymes are seldom elevated.

Emery-Dreifuss muscular dystrophy: This is a X-linked recessive disease. Autosomal dominant and recessive forms are also seen. There is absence of emerin in muscles. The defect is in the STA gene in chromosome q 28 which encodes emerin. The clinical triad includes:

1. Early occurrence of contractures
2. Slowly progressive muscle wasting and weakness with a humero-peroneal distribution and
3. Cardiomyopathy with conduction defects.

Ocular Myopathy

This is due to affection of the external ocular muscles. It starts with bilateral ptosis and progressive ophthalmoplegia which becomes almost complete over a period of several years. Diplopia is only rarely complained of. Some cases may be associated with dysphagia resulting from involvement of pharyngeal muscles.

Myotonic Disorders

Myotonia is defined as the continued active contraction of a skeletal muscle which persists even after the cessation of voluntary effort or stimulation. Myotonia is an abnormality of the muscle fiber itself and it persists even after interrupting the nerve. Myotonic disorders may be genetically determined or acquired.

1. Genetically Determined Myotonias

- a. Autosomal dominant—Myotonia congenita (*Thomsen's disease*)
- b. Autosomal recessive—Myotonia congenita (*Becker type*)
- c. Myotonic dystrophy (*Stemert's disease*)
- d. Paramyotonia congenita (*von Eulenberg disease*)

- e. Chondrodystrophic myotonia (*Alberfeld Hinter-Buchner Schneider disease*)

2. Acquired myotonias

- a. Drug induced
- b. Toxins e.g.: Weed killers containing monocarboxy aromatic acids.

Myotonia is now recognized to be a channelopathy.

Channelopathies are disorders caused by inherited mutations in ion channels. Several diseases occur in this group. Most channelopathies affect either muscle or the nervous system. Despite phenotypic heterogeneity, a striking feature is the association with paroxysmal dysfunction. Periodic paralysis and non-dystrophic myotonias are also classified as channelopathies.

Ion channels are transmembrane glycoprotein pores that control cell excitability by regulating ion flow into and out of cells. The channels are composed of distinct proteins called channel subunits. Different genes encode each subunit. Two mutations within the same gene can result in different physiological defects. The concept that different mutations in the same gene can cause different phenotypes is termed *phenotypic heterogeneity*. For example, mutations in the same muscle sodium channel gene can result in hyperkalemic periodic paralysis, hypokalemic periodic paralysis or paramyotonia congenita. Genetic heterogeneity is manifested where different mutations in the skeletal muscle sodium channel cause the hyperkalemic periodic paralysis phenotype. Hypokalemic periodic paralysis can also occur due to α -type calcium channel mutations.

Dystrophia Myotonica (Myotonic Dystrophy)

This is an autosomal dominant disorder mediated by a mutant gene located on chromosome 19. It is an example of triplet repeat disease, the repeated triplet being CTG.

It is characterized by myotonia and dystrophic changes in muscles demonstrable histologically. Both sexes are affected. Usual age at onset is 20-30 years. Main brunt of disease falls on facial muscles, temporalis, masseter, sternomastoid, shoulder girdle muscles, quadriceps and distal muscles of the limb. Both action myotonia and percussion myotonia are demonstrable. The muscles show wasting. The facial appearance is distinctive. Ptosis, frontal baldness, and wasting of the facial muscles and sternomastoid give a characteristic appearance.

Systemic manifestations include posterior subcapsular cataract, cardiomyopathy, gonadal failure, bone changes, respiratory failure and endocrinopathies. Intellectual impairment may develop. Males develop impotence and females suffer from amenorrhea. Usually the disease lasts for 15-20 years, death occurring due to cardiac or respiratory causes.

The EMG shows diagnostic abnormalities consisting of electrical after-discharge after cessation of voluntary effort. Phonographic recording of these discharges give the characteristic pattern described as *dive bomber* phenomenon and this is diagnostic of myotonia. Histopathological investigations may reveal widespread nervous system abnormalities especially affecting the peripheral large diameter motor and sensory fibers and small diameter sensory fibers.

Management: Myotonia responds to procainamide, mexilitine or phenytoin given orally in the usual doses. Avoidance of cold environment, overexertion and stressful situations help to prevent exacerbation. Quinine sulphate in a dose of 600 mg twice or thrice a day is beneficial in some cases. Myotonia may be relieved by drugs, but not the muscle weakness.

Patients with mild degrees of myotonia are able to manage themselves by adjusting their life styles.

MYOTONIA CONGENITA

Syn: *Thomsen's disease*

This disorder is transmitted as an autosomal dominant disorder and is usually present at birth. There is severe action myotonia. Myotonia congenita is due to mutation in the chloride channel. The muscles are all hypertrophied. Mexilitine and procainamide are helpful in myotonia congenita and paramyotonia.

Chondrodystrophic Myotonia

This is associated with myotonia, skeletal deformities, and short stature.

Polymyositis

This is a non-suppurative inflammatory disorder of the skeletal muscles of presumed autoimmune etiology. When the pathological process affects only the muscles it is called polymyositis (PM) and when it is associated with characteristic skin rash it is known as dermatomyositis (DM). Various connective tissue disorders may be associated with polymyositis in 1/3 of cases and malignancy in 1/10 of cases. Based on the presence or absence

of skin lesions and other associated conditions, the disease has been classified as follows.

- Group I: Primary, idiopathic polymyositis
- Group II: Primary, idiopathic dermatomyositis
- Group III: Poly- or dermatomyositis with neoplasia
- Group IV: Childhood dermato- or polymyositis with vasculitis
- Group V: Poly or dermatomyositis with collagen vascular disease

Inflammatory myopathy may also be seen in sarcoidosis, AIDS and other infections due to toxoplasma, spirochetes, viruses and trichinella.

Staphylococcal and streptococcal infections of the muscles lead to suppurative inflammation which is referred to as pyomyositis. Sometimes instead of diffuse involvement of the muscles, there may be rapidly developing painful focal inflammatory nodules in the muscles. This condition is called focal nodular myositis. *Inclusion body myositis* (IBM) is another condition which mimics polymyositis, but differs from that with onset at age above 50 years, distal muscle involvement and a longer course of illness that does not usually respond to either steroids or cytotoxic drugs.

CLINICAL FEATURES

The peak incidence of PM is between 20-60 years. Females are more frequently affected. The disease presents with subacute symmetrical weakness, and pain and tenderness of the muscles of the proximal parts of the limbs and trunk and neck muscles. The pharyngeal and laryngeal muscles are frequently involved. Ocular muscles are not affected. Muscle tenderness may be elicited in about 50% of cases (Table 203.2).

The course is gradual and slow, extending from weeks to months and this contrasts with muscular dystrophies which extend over years. Rarely the course may be acute.

Diagnosis

The muscle enzyme CK is markedly elevated more than 10 times. The EMG findings are abnormal. Diagnosis is established by demonstrating inflammatory changes in histological specimen of muscle biopsy. The course and progress depend on the type of myositis. Muscle

TABLE 203.2

Clinical features of the different types of myositis			
	DM	PM	IBM
Age	All	Second decade	Above 50 yrs
Sex	Females more	Females more	Males more
Distribution of muscle weakness	Proximal	Proximal	Distal
	Symmetrical	Symmetrical	Symmetrical
DM—Dermatomyositis; PM—Polmyositis; IBM—Inclusion body myositis			

TABLE 203.3

Summary of the features of common myopathies					
Muscle disorder	Age of onset	Pattern of involvement	Muscle enzymes	EMG	Prognosis
1. Duchenne muscular dystrophy (DMD)	Before 4 years	Proximal muscles	Markedly elevated	Myopathic	Gross disability in 10 years
2. Congenital myopathy	Infancy	Proximal muscles	Normal or marginally elevated	Myopathic	Insidious course
3. Limb-girdle dystrophy	2nd or 3rd decade	Proximal muscles	Mild to moderate elevation	Myopathic by middle age	Severe disability
4. Facioscapulohumeral dystrophy	Childhood to adult life	Facial and shoulder girdle muscles	Mild to moderate	Myopathic	Normal life expectancy
5. Dystrophia myotonica	20-30 years	Facial muscles, temporalis, masseter, quadriceps and distal limb muscles	Mild elevation	Myotonic pattern "dive-bomber phenomenon"	Severely disabled in 15-20 years
6. Polymyositis	20-60 years	Proximal limb muscles, trunk muscles, neck pharyngeal and laryngeal muscles	Markedly elevated	Myopathic, spontaneous activity in the form of fibrillations	Responds to corticosteroids and immuno-suppressants

histochemistry and electronmicroscopy may help in the diagnosis of early cases even when routine muscle histology on light microscopy is not confirmatory (Table 203.3).

Treatment: Prednisolone in high doses at 1-2 mg/kg body weight/day gives the best results, which takes 1-4 weeks to set in.

Where there is good improvement the dose of prednisolone may be gradually tapered off at a rate of 5 mg every 4 weeks. In the majority of patients maintenance dose of prednisolone, either daily or on alternate days is required for several years. Cytotoxic drugs such as azathioprine, cyclophosphamide, methotrexate or cyclosporine are indicated under the following conditions.

1. Steroids fail to bring improvement in 1-3 months
2. Severe disease
3. Relapses occur while on steroid treatment.

In resistant cases, plasmapheresis or high dose intravenous immunoglobulin therapy may be useful. Bed rest during the acute phase and remedial physiotherapy subsequently, help to hasten recovery.

Prognosis: Inclusion body myositis is resistant to treatment. The others respond favourably and attain functional recovery.

METABOLIC MYOPATHIES

These result from abnormalities in muscle metabolism caused by deficiency or abnormalities of the enzymes concerned with metabolic process. The immediate source of energy for muscle contraction is the hydrolysis of ATP to ADP. Availability of fuel and the rate at which energy

can be produced are the limiting factors for exercise. Muscles utilize carbohydrates in the form of muscle glycogen and lipids in the form of free fatty acid as fuel. Glycogen can be metabolized both aerobically and anaerobically, whereas lipids can be metabolized only aerobically.

Metabolic myopathies result from abnormalities of enzymes concerned with metabolism of carbohydrates or lipids. The clinical picture is different for each type. Deficiency of the enzyme carnitine palmitoyl transferase leads to abnormalities of lipid metabolism. Deficiency of phosphofructokinase leads to abnormality of glycogen metabolism. This occurs in **McArdle's syndrome**.

Several toxic myopathies may result from exposure to toxins. **Eosinophilia-myalgia syndrome** is characterized by peripheral blood eosinophilia and scleroderma like features. Possible etiological factor is toxic chemicals contaminating tryptophan which is consumed as a health food.

Mitochondrial Disorders

The mitochondrial disorders represent a group of diseases in which defects in the oxidative metabolism are found due to inborn defects in the mitochondria. Although these defects affect all cells in the body, organs with a high demand for energy such as brain, muscle and heart are most affected clinically.

Mitochondria are responsible for the utilization of oxygen and conversion of fatty acids, carbohydrates and proteins into energy, by producing adenosine triphosphate (ATP). Mitochondria have their own DNA (mtDNA). They

are also influenced by DNA in the nucleus (n-DNA). Defects in either type of DNA can seriously affect the vital functions of mitochondria. When mutations occur which affect mitochondria the vital supply of ATP is disrupted and the systems or organs begin to fail.

Understanding of mitochondrial disorders was scanty until recently, but with advances in molecular genetics, mitochondrial disorders are increasingly being recognized. Frequency of mitochondrial dysfunction is one in 4000 of the population. Mitochondrial disorders have a wide variety of symptoms. Different persons having exactly the same defect in their mtDNA may differ in their clinical manifestations. Some mitochondrial disorders are not manifest until adulthood and some never cause symptoms. Some are so severe that the victim dies in infancy itself.

Individuals with mitochondrial disorders may present with a wide spectrum of clinical manifestations. These include the following neurological features:

- i. Poor growth and development
- ii. Loss of motor control
- iii. Muscle weakness
- iv. Visual or hearing impairment
- v. Mental retardation
- vi. Seizures

In addition, affection of other organ systems such as cardiac disease, gastrointestinal diseases, respiratory disorders, diabetes mellitus, liver diseases, renal dysfunction and susceptibility to infection may manifest.

Three types of inheritance can occur:

- i. Maternal inheritance due to defects such as point mutations, deletions or duplication in the mtDNA, derived from the mother.
- ii. Autosomal (dominant or recessive) inheritance due to defects in the n-DNA contributed by both parents.
- iii. X-linked inheritance due to defect in the X chromosome.

Mitochondrial Myopathies

The historical term 'mitochondrial myopathy' is too restrictive since in most patients muscle is not the only tissue affected. Hence it has now been replaced by the more general term—*mitochondrial encephalomyopathy*, which includes the occurrence of widespread CNS and systemic involvement.

The symptoms of mitochondrial encephalomyopathies include muscle weakness or exercise intolerance, dementia, movement disorders, stroke like episodes, deafness, blindness, seizures and ataxia. The disorders range in severity from progressive weakness to premature death. The age of onset ranges from birth to adulthood and the majority of cases occur by the age of 20 years. Some of the more common mitochondrial disorders include:

- i. **Kearns-Sayre syndrome:** Progressive external ophthalmoplegia, pigmentary retinopathy, heart block, cerebellar syndrome and increase in CSF protein (> 100 mg/dL)
- ii. **Myoclonic epilepsy** with ragged red fibers (MERRF)
- iii. **Mitochondrial encephalopathy**, lactic acidosis and stroke-like episodes (MELAS)
- iv. **Leber's optic atrophy**
- v. **Progressive external ophthalmoplegia** (PEO).

Muscle biopsy tissue, when stained with Gomori trichrome stain reveals characteristic muscle fibers with structurally abnormal mitochondria, known as ragged red fibers (RRF) because of the staining appearance.

There is no specific treatment for any of the mitochondrial encephalomyopathies. Occupational therapy and physiotherapy serve to keep the muscles functional for longer periods. Vitamin therapies such as riboflavin, coenzyme Q, vitamins C and K and carnitine may improve muscle function in some patients. Prognosis varies greatly depending upon the type of the disorder and other individual factors.

Dermatology

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Structure of the Skin

The skin is a major organ in the body with a surface area of 1.8 square m in an adult, constituting up to 16% of the total body weight. Skin is composed of three layers, the epidermis, dermis and subcutaneous tissue.

Epidermis

The epidermis which originates from ectoderm, is a stratified squamous epithelium about 0.1 mm thick. The thickness varies in different parts of the body. Its main function is to act as a protective barrier. Epidermis is mainly composed of keratinocytes, which produce a protein called keratin. It is devoid of blood vessels and lymphatics. It gets its nutrition from the underlying dermis. Histologically, the epidermis consists of four layers, the stratum basale, stratum spinosum, stratum granulosum and the stratum corneum.

Stratum basale (basal cell layer) is composed of columnar cells. This layer rests on a basement membrane, which attaches it to the dermis. These cells are attached to the basement membrane by attachment plaques called hemidesmosomes. 30% of basal cells divide. One of the daughter cells moves into the suprabasal layer and differentiates and synthesizes keratin. Stem cells reside amongst the basal cells and divide in response to injury.

Melanocytes, seen as clear cells in between the basal keratinocytes, constitute about 5-10% of the basal cells. They arise from the neural crest. Melanocytes synthesize melanin and transfer it to neighbouring keratinocytes via the dendritic processes. Melanin granules are uniformly distributed in the stratum corneum and they reduce the ultraviolet radiation penetrating the skin. In the deeper layers of the epidermis, the melanin granules form a

protective cap over the outer part of the nucleus of the keratinocyte.

Stratum spinosum (prickle cell layer) is composed of 5-8 layers of polygonal cells called keratinocytes. These keratinocytes are interconnected by desmosomes which are seen as prickles on light microscopy. These desmosomes are specialized attachment plaques that contain desmoplakins, desmogleins and desmocollins. Auto-antibodies to these proteins are responsible for the various autoimmune blistering disorders. Tonofilaments are small fibres running from the cytoplasm to the desmosomes. Bundles of tonofilaments are called tonofibrils. In the superficial spinous layer, **lamellar granules** or **Odland bodies** which are derived from the golgi apparatus appear. They contain phospholipids, cholesterol and glucosylceramides, which are discharged into the intercellular space of the granular cell layer. These are the precursors for the lipids in the superficial layers which are very important for the barrier function of the skin.

Langerhan's cells are found mostly in this layer. These dendritic cells, derived from the bone marrow are the outermost sentinels of the cellular immune system. These cells are characterized by unique cytoplasmic organelles known as **Birbeck granules**, on electron microscopy.

Stratum granulosum (granular layer) is composed of 2-3 layers of flattened cells containing coarse basophilic keratohyaline granules which merge with the tonofibrils. These keratohyaline granules contain proteins like involucrin, loricrin and profillagrin. In the outer layers, these granules break up and their contents are dispersed throughout the cytoplasm, leading to keratinization. This tough peripheral protein coating is called the horny envelope.

Stratum corneum (horny layer) is composed of sheets of overlapping, flattened, non- nucleated, cornified, dead cells. The barrier function of the skin is due to the special properties of the horny layer. The cytoplasm is packed with keratin filaments embedded in a matrix with a peripheral tough protein coat inside the cell. These proteins bind to the lipids in the intercellular space by transglutaminases.

This envelope gives the corneocytes its toughness to withstand all the chemical and mechanical insults.

Keratinization

The epidermal keratinocytes undergo characteristic changes as they ascend and transform from undifferentiated columnar basal cells to fully differentiated horizontally aligned corneal cells. As the basal keratinocytes mature toward cornified cells, they lose their nuclei and cytoplasmic organelles and become filled with tonofilaments. This process is called *cornification* or *keratinization*.

Dermo-epidermal Junction

It is a highly specialized attachment between the epidermis and the papillary dermis. The various structures of the dermo-epidermal junction such as tonofilaments, hemidesmosomes, trilaminar plasma membrane, lamina lucida, anchoring filaments, basement membrane, anchoring fibrils, type III collagen and microfibrils provide attachment and support between the dermis and epidermis and also regulate the permeability across the junction.

Dermis

The dermis is a tough supportive connective tissue matrix found immediately below the epidermis. Its thickness varies from 0.6 mm on the eyelids to about 3 mm on the palms and soles. It is made up of connective tissue fibers like collagen (70%) and elastin in a ground substance of glycosaminoglycans.

The thin upper layer of the dermis is called papillary dermis which interdigitates with the epidermal rete ridges. The deeper thick layer is called reticular dermis with coarse bundles of collagen. The dermis also contains fibroblasts (which synthesize collagen, elastin, and the ground substance) dendritic cells, mast cells, macrophages and lymphocytes. The dermis shows epidermal downgrowths of hair follicles, the sebaceous glands and sweat glands. It also contains an extensive network of blood vessels and nerves. The caliber of the dermal blood vessels can be controlled by arteriovenous anastomoses that act as shunts. The blood vessels are under neural and hormonal control as in other parts of the body. This mechanism ensures a proper supply of blood to the cutaneous appendages like hair bulbs, sweat glands and sebaceous glands and also plays a major role in temperature regulation.

The cutaneous nerves in the dermis are both autonomic and sensory. The arterioles are supplied by adrenergic sympathetic nerves that mediate vasoconstriction. The adrenergic sympathetic fibers also supply arrectores pilorum muscles. The myoepithelial cells of the

apocrine and eccrine sweat glands are cholinergic sympathetic. The skin is devoid of any demonstrable vasodilator nerves. Free sensory nerve endings are seen in the dermis, also extending to the epidermis. There are specialized receptors called Pacinian corpuscles to detect pressure and vibration and Meissner's corpuscles in the skin of hands and feet, which detect touch. The free nerve endings that transmit pain also subserve the sensation of pruritus, the intensity of the stimulus being low.

Glands of the Skin

Sebaceous glands: These are of epidermal origin seen in close proximity of the hair follicles at the upper part of the dermis. They are most numerous on the scalp, face, front of the chest and back and they are absent on the palms and soles. Their secretion- sebum is formed by disintegration of the lining cells and this is not under neural control. The sebum is discharged to the surface through the hair follicle. The major components of sebum are triglycerides, wax esters, squalene, cholesterol esters and cholesterol. Sebum that is present on the skin surface inhibits microbial proliferation. The sebaceous glands hypertrophy during puberty under hormonal influences.

Apocrine glands: They are large coiled tubular glands opening into the hair follicles and their function is not clearly known. They are seen in the axillae, around the nipples, perineum and genital regions. Specialized apocrine glands are seen in the eyelids, and in the ear canal. Apocrine glands are surrounded by contractile myoepithelial cells that help to expel their contents. These myoepithelial cells derive their innervation from adrenergic twigs that respond to emotional stimuli.

Eccrine glands: Eccrine sweat glands are small coiled glands in the dermis whose ducts empty directly on to the cutaneous surface. Eccrine sweat produced in the gland by merocrine secretion (only the contents of the secretory vesicles are discharged, unlike in a holocrine secretion, the cells disintegrate to liberate their secretion) is colorless and odorless. They are more numerous over the forehead, axillae, palms, and soles though they are widely distributed throughout the body.

Heat and emotional stress are the main stimuli for sweat secretion. The temperature control center in the hypothalamus is able to detect minute changes in temperature and when excited, stimulates the number and the activity of sweat glands via sympathetic non-myelinated class C nerve fibers. Excessive body heat is dissipated by evaporation of sweat. Aldosterone prevents the loss of electrolytes in sweat by inducing re-absorption of sodium in the sweat ducts. Sweat moistens the skin of palms and soles and provides grip. Substances like griseofulvin, lead, mercury, ethanol and ketoconazole are excreted by eccrine glands. In healthy persons sweat contains all the

electrolytes found in the plasma or interstitial fluid but to a lesser extent.

Hair

Hairs are found over the entire surface of the skin with the exception of the glabrous skin of the palms, soles, glans penis and vulval introitus. The density of the follicles is greatest on the face. Embryologically, hair is developed from the primordial epithelial germ cells formed from the ectoderm. Hair follicle is formed by an invagination of the epidermis into the dermis.

In longitudinal sections a mature hair follicle consists of an infundibulum, isthmus, stem and bulb. The germinative cells are in the hair bulb, interspersed with melanocytes. The bulb encloses the follicular papilla which organizes and maintains the function of the hair follicle. Cut section of the hair shaft shows an outer cortex and an inner medulla.

The growth of hair is cyclical and different phases of follicle are, growing phase (anagen) which lasts for 3-10 years, involuting phase (catagen) which lasts for 2-3 weeks and the resting phase (telogen) which lasts for 3-4 months. The stem and the bulb shrink to form a thin column of epithelial cells in the catagen phase. When a new cycle of anagen phase begins, these residual undifferentiated epithelial cells proliferate and generate a new follicular matrix. At least 85% of hair follicles are in anagen phase at any one time.

There are three types of hair:

1. **Lanugo hairs** are fine and long and are formed in the fetus at 20 weeks of gestation. They are normally shed before birth, but may be seen in premature babies.
2. **Vellus hairs** are short, fine light coloured hairs that cover most body surfaces.
3. **Terminal hairs** are long, thick and dark and are found on the scalp, pubic and axillary regions, beard area, upper trunk and limbs. They originate as vellus hair and change into terminal hair at puberty under the influence of androgens.

Nails

The nail is a phylogenetic remnant of the mammalian claw and consists of hardened and densely packed keratin. It protects the finger tip, facilitates grasping and tactile sensitivity in the finger pulp. The nail matrix contains dividing cells which mature, keratinize and form the nail plate. The pink colour of the nail is due to the dermal capillaries and the white lunula is the visible distal part of the matrix. The nail plate rests on the nail bed. The nail plate grows at a rate of 0.1 mm/day for finger nail and the toe nails at a rate of 0.03 mm/day.

Functions of the skin: The skin has many vital functions.

1. The skin acts as a mechanical barrier to protect the deeper structures from external injury and invasion by microbes.

2. The eccrine sweat glands and the blood vessels of the skin play a major role in temperature regulation.
3. The skin regulates the loss of body fluids by altering the rate of perspiration.
4. Melanin pigment protects the skin from the harmful effects of ultraviolet rays.
5. Skin acts as a major sensory organ receiving all superficial sensations.
6. Vitamin D synthesis occurs in the skin on exposure to sunlight. Twenty minutes of exposure can supply the day's need of vitamin D.
7. Dendritic cells in the skin play a major role in immune surveillance.
8. Sebum has antimicrobial properties.
9. Several drugs and chemicals are absorbed through the skin when applied in suitable vehicles. This property has been made use of in therapeutics.

Clinical Examination

Skin disorders are widespread in India contributing to 20-25% of the total attendance in any general hospital. The skin closely reflects the disorders occurring in the internal organ systems and several cutaneous disorders have systemic manifestations. Therefore, clinical examination of the skin is not complete without a full systemic examination. Examination should be done under conditions of proper lighting, preferably natural light.

Descriptive Terms

The initial lesions that herald the onset of any dermatological disorder are called primary lesions. Secondary lesions are those that develop during the course of the disease.

Primary Lesions

Macule: is an alteration of color of the skin up to 1 cm in diameter and is flush with the surrounding normal skin. A macule more than 1 cm is called a *patch*.

Papule: is a solid elevated lesion up to 1 cm in diameter. A papule more than 1 cm is called a *plaque*.

Vesicle: is a clear fluid filled lesion up to 1 cm. A vesicle more than 1 cm is called a *bulla*.

Pustule: is a small vesicle containing pus. An *abscess* is a deeper and localized collection of pus in a cavity more than 1 cm in diameter.

Nodule: This is a solid elevated mass, more than 1 cm in diameter and depth, better palpated, than seen.

Wheal: is an evanescent edematous skin lesion. It may be erythematous, skin colored or pale.

Purpura: is a hemorrhagic macule or papule that does not blanch on pressure. Larger lesions are called *ecchymoses* and pinpoint lesions are called *petechiae*.

Burrow: is a tunnel produced by the movement of a parasite within the tissue. It is seen as a straight or zigzag line that may be grayish.

Comedones: are dark plugs seen inside the opening of a hair follicle.

Telangiectasia: is the visible dilatation of the small cutaneous blood vessels.

Secondary Lesions

Scales: Visible dry exfoliation of the horny layer.

Crust: Dried up discharges such as serum, pus or blood.

Erosion: An area of denuded skin due to a complete or partial loss of the epidermis.

Ulcer: Discontinuity in the skin due to a loss of epidermis as well as part or whole of the dermis.

Excoriation: Superficial denudation of the skin due to scratching.

Atrophy: Thinning of the skin (epidermis, dermis or subcutaneous fat). With epidermal atrophy, the skin becomes shiny, translucent and wrinkled. Atrophy of the deeper tissues leads to depression in the skin.

Fissure: A slit or linear tear in the epidermis.

Scar: The replacement of normal structures by fibrous tissue when a tissue heals at the site of injury.

Lichenification: Visible and palpable thickening of the epidermis with accentuated skin markings.

Induration: Thickening of the dermis that makes the skin feel more thick and firm.

Principles of Therapy

Locally applied drugs as well as systemic drugs are employed for the treatment of dermatological diseases. The fact that locally applied drugs exert their action in addition to systemic drugs is an added advantage. Many disorders respond to local therapy, some require a combination of local and systemic therapy, while a third group requires only systemic therapy. In a limited number of cases surgical as well as electrosurgical measures may also be necessary.

Local therapy: The advantages of local therapy are: (i) achievement of a high concentration of the drug at the site of lesion, which is not generally obtainable by systemic therapy, (ii) freedom from serious adverse side effects, and (iii) even drugs which cannot be administered systemically can be given locally. Though drugs applied over the skin are not absorbed significantly, systemic toxicity becomes a problem with many drugs, especially if applied over extensive raw areas for prolonged periods.

Modes of local therapy: *Compresses, soaks and baths:* These help in mechanically removing the exudates, poorly formed crusts, tissue debris, remnants of previously applied medicines, etc. The absorption of a drug from the local site is facilitated if it is administered after applying compresses, soaks or baths. Compresses and soaks are given for localized lesions, whereas baths are given for more extensive and generalized disorders.

Potassium permanganate, sodium chloride, liquor picis carbonis, ichthyl or sodium bicarbonate is added to the compresses, soaks and baths to enhance their therapeutic value.

Vehicle or base: For local applications, the active ingredients are dissolved or suspended in a vehicle called the base, the main function of which is to keep the ingredients in contact with the lesion. The base is selected according to the type and location of the lesion and also the solubility and compatibility of the active ingredients with the base. Commonly used vehicles are water, glycerine, alcohol, cream, petrolatum, and talcum.

Astringents: These are agents which when applied on raw areas of the skin, react with tissue proteins to form a protective covering on the surface. They help to reduce the pain. Liquor aluminium acetate, liquor plumbi subacetate and silver nitrate are commonly used astringents.

Soothing agents: These are applied to relieve pain, burning, and pruritus, generally associated with inflammation of the skin. Alleviation of these symptoms is achieved by the evaporation of the water component of the medication which produces a cooling effect and vasoconstriction. All aqueous preparations can act as soothing agents, e.g. calamine lotion and cream.

Emollients: These form a thin greasy layer over the surface of the skin and prevent evaporation of water from the stratum corneum. Vaseline, oils, cream, and glycerine are the commonly used emollients.

Antipruritic agents: Itching is the most common and troublesome complaint in dermatological disorders. No doubt, specific therapy is the ideal way to abolish this symptom, but when this is not possible or immediate relief is to be provided, symptomatic therapy is indicated. Chloretone (butyl chloral) which is an analogue of chloral hydrate is a safe antipruritic agent in a concentration of 3-5%. Menthol, camphor, and phenol in acceptable concentrations are also effective.

Keratolytic agents: These are employed for promoting desquamation of scales or removal of thickened stratum corneum. They are useful in the treatment of disorders like palmoplantar keratoderma, ichthyosiform dermatoses, psoriasis, and dermatitis associated with lichenification. Salicylic acid, urea and resorcin are commonly used keratolytic agents.

Anti-inflammatory agents: These agents reduce the severity of inflammation and minimize tissue damage when employed with other specific therapy. Though mild inflammatory processes can be controlled with soothing agents, severe inflammatory responses demand the use of drugs like corticosteroids, gentian violet and ichthyol. The commonly used corticosteroid preparations include betamethasone valerate (0.12%), flucinolone acetonide (0.025%), fluticasone propionate 0.05% hydrocortisone 1%, clobetasol propionate 0.05% and others.

Antibacterial agents: Topical antibacterial agents play an important role in the treatment and prophylaxis of microbial infections of the skin, especially infections of the epidermis and dermis. The commonly used topical antibacterial agents are neomycin, polymyxin, framycetin, gentamicin, silver sulfadiazine, fusidic acid and mupirocin.

Hexachlorophene, povidine iodine, benzalkonium chloride and chlorhexidine have been used as antiseptics, particularly in the context of disinfection of skin prior to surgical procedures. Topical antibacterial agents are used prophylactically in trauma, cuts, wounds and burns.

Sun screens: These are used to protect the skin from sunlight. These may act as reflectors or absorbers of light. Reflectors help to prevent the rays from entering the skin whereas chemical absorbers absorb sunlight. Agents like para-aminobenzoic acid, benzophenones, avobenzones, tannic acid, titanium dioxide, and zinc oxide are usually employed as sun screens.

Occlusive dressings: These are employed when a drug is to be applied in close contact with the skin and it is to be kept in position to favour absorption and prolonged action. Moreover, the moisture released by the skin helps to soften the lesions and favour resolution, e.g. psoriasis.

205

Infections of the Skin and Appendages

Usha Vaidhyathan

Chapter Summary

- Normal Microbial Flora 1348
- Bacterial Infections 1349
- Viral Infections 1350
- Fungal Infections 1352

Normal Microbial Flora

A healthy normal skin is colonized by a variety of non-pathogenic microorganisms. This constitutes the normal flora of the skin. It is classified into resident flora and transient flora. Resident flora includes bacteriae that grow on skin and are relatively stable in number and composition. Some organisms linger briefly on the skin in small numbers before disappearing, unable to multiply and thrive in the relatively inhospitable environment. These are labelled as temporary residents or transients. Most of the organisms reside on the surface of the stratum corneum in the crevices between squames in the

loose outermost layers. The hair follicles are inhabited by anaerobes like *propionibacterium* species. Streptococci are usually absent, but may be found as transient residents on perioral skin, from the mouth. Coagulase positive *S. aureus* should not be considered as a resident on healthy skin although it is frequently found in the anterior nares and perineum and on damaged skin in eczema or psoriasis. Of the coagulase negative staphylococcus species, *S. epidermidis* and *S. hominis* are the most important. Other resident flora are *micrococcus* (intertriginous areas and scalp), *corynebacterium* species (axilla), *propionibacterium* species (face, scalp, axilla), gram negative organisms (axilla, toe webs, nose) and fungi like *pityrosporum* (scalp) and *candida* species (intertriginous areas). The resident flora prevents colonization by pathogenic organisms and also other commensal flora.

An intact stratum corneum is the most important defense against invasion by pathogenic bacteriae. Skin infection results when the skin defenses are compromised

due to physical factors such as excessive hydration, occlusion and systemic factors like immunosuppression.

BACTERIAL INFECTIONS

Pyoderma

Pyoderma is an infection of the skin caused by pyogenic organisms. *Staphylococcus aureus* and group A beta hemolytic *streptococcus* are the most common. Less commonly *Pseudomonas*, *E. coli* and other organisms can also invade the skin. Pyoderma may be primary or secondary.

Primary pyoderma occurs in previously normal skin. It is caused by a single group of organisms and has a characteristic morphology.

Secondary pyoderma occurs in skin previously damaged by other diseases such as scabies, fungal infection, eczema and others.

Primary Pyoderma

Impetigo: Impetigo is a superficial infection of the epidermis due to *Staphylococcus aureus* and occasionally Group A beta hemolytic streptococci. There are two types—non-bullous (impetigo contagiosa) and bullous impetigo.

Impetigo contagiosa commonly affects the face of small children, but any site can be involved. It begins as transient superficial small vesicles or pustules on an erythematous base that soon rupture and form erosions and crusting (golden yellow crusts) (Fig. 205.1). If the lesions persist, central clearing can occur and may become confluent. Complications include cellulitis and post-streptococcal glomerulonephritis.

Bullous impetigo is common in neonates and infants, but can occur at any age. 80% are caused by *Staphylococcus aureus*, phage group 2, type 71 and 55. Vesicles and bullae containing yellow fluid arise on normal appearing skin

without surrounding erythema and persist for a few days. Lesions rupture and varnish like yellow crusts are formed. Lesions can occur anywhere and commonly involves intertriginous areas.

Ecthyma: Commonly it affects the distal extremities. The infection extends up to the dermis. It presents as a purulent tender indurated ulcer with adherent crust and surrounding erythema. Healing occurs with scarring.

Folliculitis: Folliculitis is the infection of the hair follicle mostly due to *Staph. aureus* and appears as pustules with a hair or follicular orifice at the center. Chronic folliculitis of the legs is a common problem in India. Mostly it affects the shin of young males. The pustules are chronic, recalcitrant and cause atrophy on healing. A deep folliculitis involving the whole depth of the hair follicle, affecting the beard (*sycosis barbae*) and nape of the neck (*sycosis nuchae*) is also described.

Furuncle: Infection of the hair follicle and perifollicular region is called furuncle or boil. It is an extremely painful follicular nodule that may suppurate and become an abscess. Common sites are neck, face, scalp, axilla, perineum, buttocks and thighs.

Carbuncle is a deep infection extending up to the subcutaneous tissue, involving a group of contiguous follicles, with multiple discharging points on the surface. The common sites are the back of the neck, shoulders, hips and thighs. It is frequently associated with diabetes mellitus and immunocompromised states.

Erysipelas: is an acute streptococcal infection of the dermis. Streptococci can enter only through a damaged skin. It presents as an erythematous, edematous, elevated, indurated and well-demarcated lesion, commonly on the face and the legs. There may be vesiculation at the periphery in acute cases.

Cellulitis is an acute, sub-acute or chronic streptococcal infection affecting the deeper subcutaneous tissue. The margins are indistinct, and not elevated unlike as in erysipelas. Common sites are the legs but any area can be involved.

Treatment: Majority of the cases need systemic antibiotics. Cloxacillin 500 mg qid or first generation cephalosporins like cephalexin 500 mg qid are preferred. Supportive therapy includes improvement of local hygiene, elimination of any predisposing factors, saline compresses for crusted lesions and topical antibiotics.



Fig. 205.1: Impetigo on the leg

Points to remember

- Intact stratum corneum is the most important defense against invasion by pathogenic bacteriae.
- Staphylococcal infections include impetigo, ecthyma and folliculitis.

- Streptococcal infections are erysipelas and cellulitis.
- Staphylococci and streptococci cause secondary infection of eczema or leg ulceration.
- Cloxacillin and first generation cephalosporins are preferable.

Viral Infections

Verrucae (syn: warts)

Warts are common benign epithelial hyperplasia due to infection with human papilloma viruses (HPV). Papilloma viruses are double stranded DNA viruses of the PAPOVA class with host and tissue specificity. They infect squamous epithelia of the skin and mucous membrane causing cell proliferation. The virus infects the basal layer of the epithelium, but viral replication takes place in fully differentiated cells of upper stratum spinosum and stratum granulosum. After initial infection, HPV may persist in a latent form and may be reactivated later leading to recurrence of lesion. More than 150 types of HPV have been identified and some types have a role in the oncogenesis of cutaneous malignancies. The virus infects by direct inoculation and spreads by skin-to-skin contact. Common clinical patterns are:

Common warts: These present as dome shaped papules with verrucous surface commonly on the hands (Fig. 205.2) and feet, but can affect any site. Some warts are *filiform* with fine digit like projections (Fig. 205.3).

Verruca plana: These are smooth flat topped papules, often multiple, commonly seen on the face and dorsa of the hands and these resolve spontaneously. Koebner's phenomenon is seen frequently (i.e.) new warts forming over sites of trauma.

Plantar warts: are seen on the pressure points of the soles of the feet. They are painful. When pared, reveals dark punctate spots due to thrombosed capillaries. Multiple warts can coalesce to form a *mosaic wart*.

Genital warts: are sexually transmitted, but sometimes the transmission may be non-venereal. Genital warts have a high infectivity. In one study, around two-thirds of sexual



Fig. 205.3: Filiform wart on the thigh

contacts of patients with genital warts developed lesions within 9 months. They affect the penis in males, perianal area in homosexuals and the vulva, perineum and vagina in females. The warts may be small or may be large cauliflower like *condylomata acuminata*. Rectal and cervical warts have to be identified and followed up because of the risk of malignant change. Sexual partners should be examined.

Management: In children, 30-50% of common warts resolve spontaneously within 6 months. The common modalities of treatment for different types of warts are as follows.

Hand and foot warts: Salicylic acid and lactic acid in a liquid formulation is applied daily till resolution. Other modalities of treatment include cryotherapy (liquid nitrogen at -196°C) sprayed on to the lesions and intralesional bleomycin for resistant warts. Periungual and subungual warts are difficult to treat and relapses are common.

Genital warts: Podophyllin (25%) applied under supervision weekly till resolution or podophyllotoxin (0.5%) self application, twice daily for 3 days/week for 4 weeks yields good results.

Filiform and large perineal warts: Curettage and electro-desiccation are effective.

Laser surgery is a very specialized treatment at present for any type of wart.

Points to remember

- Hand and foot warts are common and often resolve spontaneously. Duofilm application and cryotherapy are effective treatments.
- Plane warts on the face are treated by electro-surgery
- Plantar warts are painful and when pared reveals dark punctate spots.
- Genital warts are transmitted sexually. Treated by podophyllin or cryotherapy.

Note: Liquid formulation containing salicylic and lactic acids is marketed as duofilm by Stiefel Ltd.



Fig. 205.2: Verrucae on the index finger



Fig. 205.4: Molluscum contagiosum on the left knee. Note the central umbilication on the papule

Molluscum Contagiosum

Molluscum contagiosum is a self limiting epidermal viral infection caused by Molluscum contagiosum virus, a DNA pox virus. It mainly affects children or young adults. Spread is by contact, fomites or sexual route.

It presents as discrete, multiple, grouped, umbilicated, pearly, dome shaped papules with a central punctum and if squeezed, releases a cheesy material (Fig. 205.4). Lesions are commonest on the face, neck and trunk.

Diagnosis can be confirmed by incising one of the papules, smearing the contents between two slides and staining with gram's stain. *Molluscum bodies* or *Henderson Patterson bodies*, which are cytoplasmic masses of virions, appear as ovoid, homogenous inclusion bodies. The host cell is pushed to the periphery giving a signet ring appearance to the cell.

In healthy individuals, molluscum lesions persist for 6 months to 2 years and then undergo spontaneous regression. Such lesions undergoing spontaneous regression have an inflammatory erythematous halo. In HIV infected individuals, lesions persist and proliferate even after aggressive therapy. Lesions resolve with highly active anti retroviral therapy (HAART). Painful aggressive therapy is not indicated. Lesions spread by autoinoculation and cause cosmetic disfigurement. Treatment includes curettage, phenol cautery, cryotherapy, duo film (avoided on the face lesions) and electrodesiccation.

HERPES SIMPLEX

(See also Section: 6)

Herpes simplex is a primary or recurrent mucocutaneous disease caused by Herpes simplex virus (HSV), a DNA virus that infects only humans. There are two serotypes, HSV 1 and HSV 2. HSV 1 is the primary agent in orofacial herpes and HSV 2 is involved in genital infections. Overlap does occur. After the primary mucocutaneous infection, the virus enters the sensory

ganglia and remains dormant until reactivation. Precipitating factors for recurrence include ultra violet radiation, menstruation, fever, common cold, and altered immune states.

Clinical features: *Primary infections* are preceded by a prodrome of local tenderness for a day or two. *Gingivostomatitis* is the most frequent manifestation and presents as vesicles, erosion and maceration over the entire buccal mucosa. There is marked erythema and edema of the gums. There is often severe pain and tender lymphadenopathy making it difficult to eat or drink. *Recurrent lesions (cold sores)* are usually preceded by a burning or tingling sensation for several hours. Multiple grouped vesicles on a normal or erythematous skin appear at the site of premonitory symptoms. The lesions heal within 7-10 days. The most common sites are the lips, perioral area, cheeks and nose, though it can occur anywhere. Intraoral lesions are extremely rare in recurrence, except in immunocompromised hosts.

Inoculation herpes occurs when secretions containing the virus come in contact with abraded skin anywhere on the body. In wrestlers and rugby and football players, transmission occurs during contact sports. This is known as *herpes gladiatorum*. Painful vesicles, erythema and edema associated with lymphadenopathy on the fingers and hands, called *herpetic whitlow* is commonly an occupational hazard in health care professionals especially dental personnel. This is uncommon after the universal precautions are followed.

Cutaneous HSV infection in immunodeficiency causes significant morbidity. Lesions may persist for months. Dissemination can lead to esophagitis, hepatitis and pneumonia. Pre-existing skin conditions such as atopic dermatitis predispose patients to develop widespread cutaneous disease called *eczema herpeticum* or *Kaposi's varicelliform eruption*. The infection spreads via the damaged skin surface and so complications from viremia are rare. It is associated with fever and lymphadenopathy. The eruption lasts for 2-6 weeks.

Neonatal HSV infection occurs when the mother has an acute primary genital herpes infection. If untreated, neonates have a risk of visceral and CNS involvement and a mortality rate of over 50%.

Genital herpes in a pregnant woman at the time of delivery is an indication for caesarean section, as neonatal infection can be fatal. Genital herpes is covered under the section sexually transmitted diseases.

Treatment

General measures: The area should be kept dry and clean. Secondary infection, if present should be treated.

Specific therapy: Acyclovir in a dose of 200 mg 5 times daily or 400 mg thrice daily for 10 days in primary

infections and for 5 days in recurrent infections is the preferred drug. To prevent frequent attacks, prophylactic treatment with 400 mg twice daily for many months or even years may be required. Except for transient renal dysfunction following rapid IV infusion, side effects are uncommon. Valacyclovir has greater bioavailability than acyclovir. Recommended doses are 1 g bid for 10 days for primary infection, 500 mg bid for 5 days for recurrent infection and 500 mg once daily for suppressive therapy. Famciclovir 250 mg tid for 5-7 days is an effective alternative.

Points to remember

- Type 1 HSV infection has usually orofacial lesions- childhood onset.
- Type 2 HSV infection occurs in genitalia- adult onset.
- Characterized by recurrent grouped vesicles that leave superficial erosions at the same site
- Acyclovir is effective.

HERPES ZOSTER

This is caused by varicella zoster virus which belongs to the Human Herpes Virus (HHV) group. Varicella zoster virus causes two distinct clinical entities, varicella (chicken pox) and herpes zoster (shingles). This is discussed in detail in chapters 53 and 184.

Herpes zoster begins with segmental pain and the rash appears 3-5 days later as grouped papules progressing to vesicles, pustules and crusts. The lesions appear first posteriorly and progresses to the anterior and peripheral distribution of the nerve involved. Mucous membrane within the dermatosis is also affected. Thoracic nerves are most commonly involved. The areas of distribution of the trigeminal and facial nerve are also commonly involved.

Differential diagnosis includes zosteriform herpes simplex, localized bacterial infection and phyto contact dermatitis. Pre-eruption neuralgia may be mistaken for other painful conditions. Once the eruption occurs, the diagnosis becomes evident. The most common complication of zoster is post herpetic neuralgia, defined as pain persisting after the cutaneous lesions have resolved. This is common in the elderly.

Treatment

General measures: Cool compresses and application of a drying agent like calamine lotion is soothing. Analgesics and systemic antibiotics (if secondary infection occurs) are required.

Specific measures: In elderly and immunosuppressed oral acyclovir 800 mg 5 times daily or valacyclovir 1 g bid or famciclovir 250-500 mg tid for 7-10 days is advised. Treatment should be started within 2-3 days of the onset of eruption.

Points to remember

- Reactivation of the virus in the posterior root ganglion leads to grouped vesicles in a dermatomal pattern.
- Thoracic and trigeminal areas are commonly involved.
- Post-herpetic neuralgia is common in elderly.
- Dissemination suggests underlying immunosuppression
- Oral acyclovir is the mainline of treatment.

Orf: This is primarily a disease of sheep. This virus can infect human beings by contamination. It manifests as painful purplish nodules on the exposed parts of the body like hands, arms, legs and face. It heals spontaneously in 4-6 weeks.

Milker's nodule: is caused by pseudo-cowpox or para pox virus which normally infect cattle (papular lesions occur on the oral cavity and on teats of cows) and only accidentally cause infection in humans. The manifestation is similar to Orf.

Cowpox: This is a zoonotic infection accidentally transferred to humans from cattle. Cowpox is caused by vaccinia virus (*cowpox virus*). In humans, lesions start as painful papules which evolve into vesicles and then to umbilicated pustules surrounded by erythema, finally developing in to an eschar or ulcer. Fever and local lymphadenopathy are common. Multiple lesions occur on the face or hands, which resolve in 3-4 weeks.

Fungal Infections

Dermatophytoses are caused by a group of filamentous fungi known as dermatophytes or ringworm fungi. There are three genera of dermatophytes. Trichophyton (T), Microsporum (M) and Epidermophyton (E). The dermatophytes are termed geophilic, zoophilic or anthropophilic depending upon whether their normal habitat is the soil, animal or man respectively.

Dermatophytosis is commonly classified depending upon the site of infection as tinea capitis (head), corporis (body), cruris (crural region), pedis (feet), manuum (hands), faciale (face), barbae (beard region) and tinea unguium (nails).

Tinea Capitis

Tinea capitis is the dermatophyte infection of the scalp hair and scalp skin. It is common in Asia, Africa and southern and eastern Europe. It is primarily a disease of the prepubertal children between 6-10 years of age and is more common in males. It spreads by direct contact from infected humans or animals such as dogs, cattle, horses, rodents and others. *M.audouinii*, *T. tonsurans* and *T. violaceum* are commonly associated with tinea capitis. There are four distinct clinical types.



Fig. 205.5: Inflammatory tinea capitis.
Note the inflammation and crusting



Fig. 205.6: Erythematous annular plaques of tinea corporis on the upper chest

1. *Grey patch type*: presents as circular scaly patches of alopecia. Hairs are broken off 2-3 mm above the scalp surface. The infected hairs show green fluorescence under Wood's light.
2. *Inflammatory type (kerion)*: presents as a painful inflammatory mass or a boggy swelling with crusting, oozing of pus and matting of adjacent hairs (Fig. 205.5). Hairs that remain are easily detachable. This is often caused by zoophilic species like *T. verrucosum* or *T. mentagrophytes*.
3. *Black dot type*: There are irregular scaly patches of alopecia with a black dot appearance due to the breaking of affected hairs at the scalp surface.
4. *Favus*: is uncommon. Yellowish crusts (scutula) around follicular openings with a foetid odor are characteristic.

Treatment

The recommended treatment in children is oral griseofulvin in a dose of 10-15 mg/kg/day for 6-8 weeks. Treatment is to be continued till hair re-grows. Alternative treatments include 1) Terbinafine in a dose of 62.5 mg/day for children < 20 kg, 125 mg/day for those of 20-40 kg and for those >40 kg, 250 mg/day is recommended for 4 weeks. 2) Itraconazole in a dose of 3-5 mg/kg for 4-6 weeks is also effective. Topical azole creams can be adjunctive to oral therapy, but not by themselves curative.

Prevention

1. Avoid sharing of combs and brushes.
2. Asymptomatic carriers should be traced and treated.
3. Family contacts should be screened.
4. Source of infection like pets should be identified and treated.



Fig. 205.7: Tinea faciale on the forehead

Tinea Corporis

Tinea corporis is the dermatophyte infection of the trunk, legs and arms. It presents as annular polycyclic lesions with erythematous raised vesicular and scaly border and a central clearing (Fig. 205.6). The frequent misuse of combination creams with steroids modifies this picture (Tinea incognito). Lesions on the face are called tinea faciale (Fig. 205.7).

Tinea barbae

Tinea barbae is the involvement of the beard hair. Clinical features are perifollicular pustules, papules, erythema, crusting and easy pluckability of hair.

Tinea cruris

Tinea cruris is the involvement of crural regions like axillae and groins and inframammary, abdominal and inter-gluteal folds which are warm and moist. Lesions are usually bilateral but asymmetrical. Prevention is by keeping the area dry and avoiding occlusive and synthetic

under garments. Other sites of infection should be identified and treated.

Tinea pedis

Tinea pedis presents as scaling, fissuring or maceration of the interdigital spaces of the feet, commonly the lateral two web spaces or as dry hyperkeratotic scaling of the soles and rarely as vesicular type involving the instep of soles. This is commonly acquired from communal bathing places and showers.

Prevention: Maintaining the feet dry, use of antifungal powders, cotton socks and avoidance of occlusive foot wear prevents recurrence.

Tinea unguium

Tinea unguium is the dermatophyte infection of the nails commonly due to *T. rubrum* and *T. mentagrophytes*. The nails become discoloured, thickened and friable. There is onycholysis (separation of nail plate from nail beds). Nail involvement usually starts from the distal end. *Onychomycosis* is a general term that includes infection of nails due to dermatophytes, non-dermatophytes and yeasts. Onychomycosis accounts for more than 50% of nail diseases.

Laboratory Diagnosis of Superficial Fungal Infections

Direct microscopic examination of fungal scrapings provides immediate confirmation of fungal infection. Scrape the active edge of a lesion with a scalpel and collect the scales on a glass slide. Add a drop of 10% potassium hydroxide and cover with a cover slip and heat gently, but not to boiling. Examine under low power of microscope (x10 magnification) after the slide cools. Dermatophytes appear as long septate and branched hyphal filaments without constriction at the branching points. Fungal species can be identified by culture in Sabouraud's medium.

Treatment

Dermatophyte infection of the skin usually responds to topical (1) Azoles like clotrimazole 1%, ketoconazole 2%, miconazole 2%, oxiconazole 1% or terconazole cream. (2) Allyl amines like terbinafine 1% and butenafine 1%. (3) Tolnaftate 1% or (4) Ciclopirox olamine 0.77%. Topical creams should be used at least 3 cm beyond the advancing margin of the lesion, twice daily for 2-4 weeks. Treatment should be continued for at least one week after the lesions have cleared.

Oral treatment is indicated for extensive lesions and for failure of response to topical therapy. Tinea capitis, tinea pedis and manuum requires oral treatment. The drug

of choice is terbinafine 250 mg/day for 2 weeks, and for scalp infection 4-6 weeks, for nail infection 3-4 months. Itraconazole 200 mg/day for 2 weeks and griseofulvin 250 mg bid for 4-6 weeks are also effective.

Points to remember

- Dermatophytes infect the body, groins, feet, hands, nails and scalp.
- Commonest pathogen is *Trichophyton rubrum*.
- Presents clinically as annular polycyclic lesions with raised scaly border and central clearing.
- Scalp infection is common in children.
- Topical imidazoles, tolnaftate and terbinafine are effective in mild infections.
- Oral terbinafine/griseofulvin are required for severe infections.

CANDIDIASIS

Superficial candidiasis is caused mostly by *Candida albicans*, though occasionally other species of *Candida* may be responsible. This organism is found as a commensal on the skin, oral cavity, and the gastrointestinal tract. Under favorable conditions of growth such as excessive moisture and maceration, immune deficiency, diabetes mellitus or treatment with tetracyclines or immunosuppressive drugs, this fungus multiplies and becomes invasive to cause disease. In its natural habitat the organism is found in the spore or yeast form but when it invades the skin or the mucous membrane, it grows to form pseudomycelium and the filaments can be demonstrated microscopically in skin scrapings. The source of infection is usually from the individual's own endogenous reservoir. In some cases person to person transmission can occur.

Candida affects the skin, mucous membranes of the mouth and genitalia, base of the nails, and the nail plates.

Oropharyngeal candidiasis can be classified into pseudomembranous (thrush), erythematous (atrophic), and hyperplastic.

Thrush is an acute infection and can be recurrent in immunocompromised patients. It is also seen in neonates and among terminally ill patients. It is characterized by white plaques often painless, on the surfaces of the buccal mucosa, tongue, hard and soft palate and tonsils (Fig. 205.8). The white pseudo membrane can be dislodged to reveal an eroded erythematous base. Involvement of the throat causes severe dysphagia. It is the most common form of candidiasis in patients with AIDS. In HIV infected individuals, the lesions are persistent and often spread to all parts of the mouth.

Erythematous (atrophic) type is often associated with broad spectrum antibiotic treatment, chronic corticosteroid use and HIV infection. It manifests as a flat red lesion, usually on the palate or dorsum of the tongue. The dorsum



Fig. 205.8: Oral thrush. White plaques on the hard palate

of the tongue is depapillated, shiny and smooth with restriction of tongue movement. The mouth is often tender.

Hyperplastic type (*candida leukoplakia*): This condition is important because 15-20% can undergo malignant transformation. It presents as dense opaque plaques, usually asymptomatic, on the inner side of the cheeks, or less commonly on the tongue. It is often associated with smoking or local trauma. The lesions cannot be rubbed from surface in contrast to the pseudomembranous type.

Chronic atrophic candidiasis (denture stomatitis) occurs in up to 60% of denture wearers. The characteristic presenting signs are chronic mucosal erythema and edema of the portion of the hard palate that comes in contact with the denture. It is often associated with angular cheilitis.

Angular cheilitis is most common in patients with moist, deep folds at the corners of the mouth. It has been reported in up to 20% of HIV infected persons. It presents as soreness, erythema and fissuring at the corners of the mouth.

Vulvovaginal candidiasis: The condition is often abrupt in onset, with intense pruritus and burning of the vulva and vagina with or without vaginal discharge. Vulval erythema and fissuring can spread to labia majora (Fig. 205.9). Perineal intertrigo with vesicopustular lesions may be present. The discharge is often thick and curdy, but may be thin or even purulent. Dyspareunia and dysuria are common.

Balanoposthitis: In men, genital candidiasis presents as soreness, edema, fissuring, papules and diffuse erythema of the glans penis and prepuce. Patients should be investigated for diabetes mellitus.

Cutaneous candidiasis: The lesions tend to occur in the folds of the skin, such as the groins and the inter gluteal folds, where the environment is warm and moist due to maceration and occlusion. Inter digital spaces can be



Fig. 205.9: Vulvovaginal candidiasis-whitish sodden appearance with erythema and fissuring



Fig. 205.10: Diaper dermatitis

involved. Predisposing factors include over weight and diabetes mellitus.

It presents as erythematous lesions with papules or vesicopustules and an irregular margin. The main lesion is surrounded by numerous small pustules called satellite lesions. Severe itching and burning sensation are common. Lesions on the interdigital spaces are seen as white fissures with surrounding erythema and maceration. It is common in individuals whose occupations necessitate frequent immersion of hands in water. This is often associated with paronychia of the same hand.

Diaper dermatitis in infants and chronically ill patients, is primarily an irritant dermatitis with super added candidal infection (Fig. 205.10).

Nail infection: Candidal infection accounts for 5-10% of all cases of onychomycosis. It is more common in women than men and in finger nails than in toe nails. Chronic paronychia usually begins in the proximal nail fold. Periungual skin is erythematous edematous and painful with absence of cuticle. Nails become discoloured. Bacterial super infection is common.

Diagnosis is confirmed by the microscopic demonstration in 10% potassium hydroxide mount, of oval thin-walled yeasts that bud on a narrow base and filaments which are either true hyphae or pseudohyphae.

Treatment

Oral candidiasis is treated with nystatin oral suspension 100 000 units/mL at 4-6 hours interval or clotrimazole mouth paints. The medication should be retained in the mouth for as long as possible. In HIV infected persons and other immunocompromised individuals, systemic drugs are preferred. Oral fluconazole 200 mg first dose, followed by 100 mg/day for 7-14 days is more effective than itraconazole or ketoconazole 200-400 mg/day for 14 days.

Vaginal candidiasis: Imidazole compounds like clotrimazole, miconazole or terconazole cream topically and intra vaginal clotrimazole pessaries daily for 6 nights are effective in vaginal candidiasis. Oral Fluconazole 150 mg as a single dose or Itraconazole 200 mg bid for one day is as effective as topical therapy. In recurrent candidiasis, ensure that the patient avoids the potential precipitating factors. Local treatment with clotrimazole (500 mg as a single dose) at 2-4 weeks interval, suppresses the symptoms. Oral Fluconazole 150 mg/week for 3-6 months is also effective. Penile and cutaneous candidiasis responds to topical imidazole creams like clotrimazole or ketoconazole, applied twice daily for 2-3 weeks.

Candidal paronychia responds to antifungal cream or lotion applied twice daily for 6 months. Nail damage should be managed with oral drugs. Itraconazole 200-400 mg/day for 6 weeks or pulse therapy (3 pulses of 400 mg/day for 1 week per month) is the treatment of choice. Terbinafine is less effective in candidal infections. Amorolfine nail lacquer applied once or twice weekly for 3-6 months is also useful.

Points to remember

- *Candida albicans* produces opportunistic infections of the body folds, oral and genital mucosa and nail folds.
- Commonly manifests as oral thrush which are painless white plaques. Common in HIV infection.
- Predisposing factors are humidity, obesity, diabetes and immunosuppression
- Topical imidazoles and oral fluconazole are effective.

PITYRIASIS VERSICOLOR

Pityriasis versicolor (syn; tinea versicolor) is a common, mild but often recurrent infection of the stratum corneum due to lipophilic yeasts of the genus *Malassezia*. These organisms can cause serious systemic infection in immuno-compromised and debilitated individuals. *Malassezia* species form part of the normal microbial flora of the human skin where it exists in the yeast form. Most



Fig. 205.11: Pityriasis versicolor on the upper limb. Note the classical wrinkled appearance

infections are endogenous in origin, but human to human transmission is possible. Pityriasis versicolor, pityrosporum folliculitis and seborrheic dermatitis are associated with *Malassezia* species. It is most prevalent in hot, humid tropical climates, where 30-40% of the adult population may be affected.

Clinical features: It presents as hypopigmented (Fig. 205.11) or fine brown scaly patches, particularly on the face, trunk, neck and upper arms. The lesions become confluent and have a polycyclic border. Different shades of lesions can be present in the same patient and so named as 'versicolor'. It is usually asymptomatic but some patients may have itching, especially on sweating. Pityrosporum folliculitis is characterized by multiple hypopigmented follicular macules, seen commonly on the trunk and arms.

Diagnosis: Scrapings for direct microscopic examination in 10% potassium hydroxide, shows a mixture of spherical thick walled yeast cells and a coarse mycelium fragmented to short filaments, having a classical 'spaghetti and meat balls' appearance. Their isolation in culture does not contribute to diagnosis because they form a part of normal cutaneous flora. The hyphae are diagnostic and demonstrated only in its pathogenic phase.

Differential diagnosis: Pityriasis versicolor is at times difficult to differentiate from Pityriasis alba. The borders are ill-defined, lesions are mostly on the face and the initial lesions may be erythematous in pityriasis alba. In pityriasis versicolor, the borders are usually distinct, the surface is wrinkled and scaly and the lesions may involve the chest and back.

Treatment: Selenium sulphide shampoo or ketoconazole shampoo applied to the affected areas for 10-15 minutes before bath for 1-2 weeks is effective. Topical imidazole creams such as clotrimazole, oxiconazole, miconazole and ketoconazole applied twice daily for 2-3 weeks are

effective. Topical terbinafine and butenafine are also useful. Oral terbinafine and griseofulvin are not effective in tinea versicolor. Oral therapy is reserved for patients with extensive lesions or recalcitrant infection unresponsive to topical therapy. Itraconazole and ketoconazole in

doses of 200 mg/day for one week and fluconazole 400 mg, two doses, 2 weeks apart are effective. It is very important to explain to the patient that the hypopigmentation may take a long time to clear and it is not necessary to continue the treatment till hypopigmentation clears.

206

Skin Infestations

Usha Vaidhyathan

Chapter Summary

Scabies 1357

Pediculosis 1358

Scabies

Scabies is an intensely pruritic disease of the skin caused by the ectoparasitic mite *Sarcoptes scabiei var hominis*. Transmission to a new host is by contact and through infested clothes and linen.

Pathogenesis: Infection of a new host is initiated by the pregnant female mite that burrows into the superficial layers of the skin to lay eggs. The pruritic lesions develop about four weeks after the initial infection.

Clinical features: The patient presents with pruritus that is worse at night, but in warm humid conditions it may occur throughout the day. Itching in the early states is confined to the sites of lesion, but it becomes generalized later on. The pathognomonic lesion is the burrow which is a curvilinear track made by the mite. Papules, pustules, vesicles and excoriations are seen in the webs of the fingers (Fig. 206.1), flexor aspects of the wrist, extensor aspects of the elbow, anterior axillary fold, nipple and areola in the female, umbilicus and periumbilical regions, genitalia, upper thighs, knees, and ankles. The lower part of the gluteal region is affected, but rest of the back is spared. In general the scalp, face, palms, and soles are spared. In children these areas can also be affected.

The lesions soon get secondarily infected with nephritogenic strains of group A streptococci and *Staph*

aureus and infection converts them into pustules. In some cases the lesions are crusted and scaly. This type is called **crusted scabies** or **Norwegian scabies**. In this type, in addition to classical areas of involvement, the scalp, face, ear lobes, and back may also be affected. Large number of organisms are present in these cases and it usually occurs in people with poor nutrition or immunosuppression.

When scabies affects infants and children, it tends to involve the scalp, palms, and soles as well. Vesiculation, secondary pyoderma, and eczematization are common. Whenever an infant presents with a suggestive lesion, examination of the mother is mandatory. The diagnosis of infantile scabies may be strengthened by the presence of lesions in the mother as well.

Persistent itchy nodular lesions (nodular scabies) on male genitalia, especially scrotum (Fig. 206.2) can be very troublesome.



Fig. 206.1: Classic scabies on the interdigital space



Fig. 206.2: Nodular scabies on the scrotum

Complications: Complications occur frequently. These include pyoderma, eczematization, and development of acute glomerulonephritis. One-third of the cases of acute glomerulonephritis in India, Africa, and many other tropical countries are attributable to infected scabies.

Diagnosis: is based on the classical clinical features like characteristic distribution, nocturnal aggravation of itching and a positive family history of similar disease. Diagnosis is confirmed by the demonstration of mite or its products, larva, egg or fecal matter (scybala). Scrapings are obtained from the burrows, and examined under low power of the microscope under a drop of mineral oil.

Treatment

General measures: It is mandatory to treat all family members and close contacts simultaneously. All clothes and bed linen are disinfected by laundering or hot ironing. Secondary infection should be treated with antibiotics before the initiation of topical antiscabietic treatment. Erythromycin 500 mg qid for 5 days or cephalixin 500 mg qid for 5 days or amoxicillin plus cloxacillin 250 mg each tid for 5 days are effective.

Specific treatment: Permethrin 5% cream is the drug of choice. Gamma benzene hexachloride 1% (GBHC) is also effective. Permethrin and GBHC are to be applied overnight over the entire body below the neck. In infants and pregnant women permethrin is safe. Benzyl benzoate 25% applied all over the body after a scrub bath, three applications 12 hour apart is an effective and freely available alternative. Ivermectin, a macrocyclic lactone, is a safe oral drug available for the treatment of scabies. 200 µg/kg body weight as a single dose on empty stomach is recommended in crusted scabies and in immuno-compromised hosts in addition to topical therapy. A second dose 7-10 days later gives better results. It is also effective in classical scabies. It is available as 3 mg and 6 mg tablets.

Points to remember

- Scabies is spread by direct contact.
- Intensely itchy papules in the classical sites- interdigital spaces of fingers, genitalia.
- Severe crusted lesions occur in immunosuppression.
- common predisposing factor for glomerulonephritis in India.
- Mites and its products can be demonstrated by microscopy on scraping the burrows.
- Overnight application of permethrin is the treatment of choice .

Pediculosis

Pediculosis or louse infestation is a worldwide problem. Poor living conditions and poor personal hygiene contribute to infestation. There are two species of blood sucking lice - *Pediculus humanus capitis* and *corporis* (head and body louse respectively) and *Phthirus pubis* (crab louse).

Pediculosis Capitis (Head Louse Infestation)

Adult head lice are 1-3 mm long, flattened dorso ventrally, have three pairs of legs that end in powerful claws. The female louse lives for about one month and lays up to 300 eggs (nits) during her life time. Eggs hatch in 6-10 days. Empty egg cases remain on hair shaft. Head louse is not a vector of infectious disease. The louse is transmitted through direct contact or through fomites. It commonly affects young girls with long hair. Itching is the main symptom. As the lice feed, they inject their digestive juices and fecal material into the skin and this causes severe pruritus. Secondary infection and occipital lymphadenopathy are common. Crawling lice or nits that are firmly attached to the hair can be seen with naked eyes.

Treatment: Permethrin 1% is applied for 10-15 minutes and then washed off. 1% GBHC applied for 5 minutes and malathion 0.5% applied for 8-12 hours are also effective pediculicides. Most of the pediculicides are not effective ovicides. A second application 7-10 days later is more effective. After treatment, the hair is wet combed with a fine toothed comb to remove nits.

Pediculosis Corporis

Body lice are present on the clothes of a person and causes severe itching, excoriations, and crusting when they come in contact with the body for a blood meal. Body louse transmits many infectious agents while feeding and spread diseases like epidemic typhus, louse borne relapsing fever and trench fever. Treatment includes maintaining good personal hygiene, application of insecticides to clothing and permethrin or GBHC to body hair.

Pediculosis Pubis

Crab louse spreads commonly by sexual contact. It is mainly seen attached to the pubic hair, but may spread to axillary hair, eyebrows and eyelashes. Patients will have severe itching and blue grey macules (*maculae cerulae*) on the lower abdomen and thighs. Secondary infection and regional lymphadenopathy are common. Oral Ivermectin 200 µg /kg body weight, 2 doses, 7-10 days apart is effective for all types of pediculosis.

Points to remember

- Head lice infestation is transmitted by direct contact especially between school children.
- Secondary infection is common.
- Body lice transmits diseases like epidemic typhus, trench fever and relapsing fever.
- Body lice are present on the clothes of the infected persons.
- Crab lice spread by sexual contact and are seen attached to the pubic hair.
- Topical permethrin 1% and oral ivermectin are effective.

207

Acne and Rosacea

Usha Vaidhyathan

Chapter Summary

Acne Vulgaris 1359

Rosacea 1360

ACNE VULGARIS

Acne vulgaris, a chronic inflammation of the pilosebaceous units, is an extremely common disorder, with peak prevalence during adolescence. Acne begins early in females, but is more severe in males. Acne usually persists until early 20's, although in a few patients, it may even continue into the fifth decade.

Aetiopathogenesis: Acne is multifactorial in origin. Major pathogenic factors include:

1. Defective keratinization of the follicular infundibulum, above the opening of the sebaceous duct initiates acne. Keratinocytes multiply and show enhanced cohesiveness thereby obstructing follicular channels. Cellular debris and sebum collect behind and forms a solid mass known as 'comedo'.
2. There is increased sebum production, which is primarily controlled by androgenic hormones. In some patients, elevated androgen levels have been documented. In others with normal androgen levels, the affected skin has increased sensitivity to androgenic stimulation.
3. Inflammation due to the proliferation of *Propionibacterium acnes* within the follicles.

Clinical features: The pathognomonic lesion is the comedo. Comedones are small papules that are either open with a dilated follicular ostium with black plugs of keratin (black head) or closed (white head). The comedones develop into inflammatory papules or pustules (Fig. 207.1) and sometimes nodules or cysts. Face is the commonest site of involvement, but back, shoulders and upper chest may also be involved. Lesions may leave behind post-inflammatory hyperpigmentation and scars. Severely inflamed lesions heal with small but deeper scars known as *ice-pick scars*.



Fig. 207.1: Acne vulgaris showing inflammatory papules and pustules

Variants of Acne

1. **Acne excoriée:** It is seen in depressed or obsessional young women who often squeeze the lesion. Picking and scratching the lesions lead to exacerbation of lesions.
2. **Infantile acne:** It is seen on the face of some infants, mostly males and disappears spontaneously.
3. Drugs like systemic/topical steroids and androgens induce acne.
4. **Acne conglobata:** It presents as severe acne with abscesses, burrowing sinuses and scarring.
5. **Occupational acne:** Exposure to cutting oils and lubricating oils cause acne due to occlusion at the site of contact. Oily cosmetics can also cause acne.

Management

General measures: Gentle washing of the face with soap and water without vigorous scrubbing is recommended. Cosmetics should be non-comedogenic. Diet has no effect on acne.

Specific therapy: In the early stages with comedones and papules, a topical retinoid such as tretinoin 0.025% to 0.1%, adapalene 0.1% or tazarotene 2.5% at night and benzoyl peroxide 5% in the morning would suffice. Topical retinoids cause dryness, scaling, redness and an initial flare of acne. Benzoyl peroxide (BPO) may produce a mild burning sensation for a short period of time. Topical retinoid and BPO should never be mixed. It may take a few weeks for the response to begin. The patients should be adequately warned, about these problems. Otherwise, the patient may discontinue treatment due to irritation and lack of response. Avoidance of sun exposure and use of sun block lotions diminish the side effects.

In the pustular stage, a topical antibiotic like clindamycin or erythromycin should be added. If no response, systemic antibiotics like tetracycline, doxycycline and minocycline for 2-3 months are very effective. Erythromycin is also useful. Long term treatment for at least 3 months is required. In severe recalcitrant cases, oral retinoids (isotretinoin) and hormonal therapy may be needed.

Management of Complications

Pigmentation and scarring can have profound psychological effects. Post acne pigmentation can be reduced to some extent by chemical peeling, e.g. 70% glycolic acid peels. Multiple sittings are needed.

Superficial scars improve with multiple sittings of microdermabrasion (Figs 207.2 and 207.3). Erythema and edema may develop immediately after dermabrasion. Aluminium oxide crystals are used to abrade the skin superficially. Many other cosmetic procedures like intralesional injection of triamcinolone into the cysts,



Fig. 207.2: Post-acne scars



Fig. 207.3: Superficial scars improved after 6 sittings of microdermabrasion

subcision, punch elevation and grafting and laser surgery are also useful.

Points to remember

- Peak prevalence in adolescence
- Abnormal keratinization of the follicular epithelium, increased sebum production and proliferation of *Propionibacterium acnes* are the main causes.
- Characterized by comedones, erythematous papules, pustules, cysts and scars on the face, chest and back
- Topical benzoyl peroxide, tretinoin, clindamycin and oral tetracycline, minocycline or erythromycin are used to control the lesions.
- Severe cases need oral antiandrogens or isotretinoin.

ROSACEA

Rosacea is a chronic inflammatory facial dermatosis characterized by erythema and pustules. The cause is unknown. Rosacea commonly affects middle aged females. The earliest symptoms are the intermittent episodes of flushing that resolve with increasingly permanent erythema and telangiectasia. Papules, pustules and occasionally lymphedema involve the cheeks, nose,

forehead and chin. Sunlight and topical steroids exacerbate the condition.

Rosacea is different from acne by the absence of comedones, occurrence in middle age group, presence of flushing and telangiectasia. Other differential diagnoses include seborrheic dermatitis, lupus erythematosus and photo sensitive dermatoses.

Complications include rhinophyma (hyperplasia of the sebaceous gland and connective tissue of the nose and ocular rosacea (blepharitis, conjunctivitis).

Treatment is with oral tetracycline 500 mg qid, or doxycycline/minocycline 100 mg once daily for 2-3 months. Topical metronidazole is helpful. Sun protection with sunscreens help to allay the condition.

208

Papulosquamous Disorders

Usha Vaidhyathan

Chapter Summary

Psoriasis 1361
Lichen Planus 1365
Pityriasis Rosea 1366
Reiter's Syndrome 1367
Exfoliative Dermatitis (Erythroderma) 1367

Psoriasis

Psoriasis is a chronic recurrent, papulosquamous disorder of the skin. It affects 2% of the world population. The sex incidence is equal. The disease can start at any age but the peak onset is in the second or third decades.

Etiopathogenesis*Genetics*

Psoriasis is a multifactorial genetic disease that requires both polygenic and environmental factors for its clinical expression. About 35% of patients have a family history. There are strong correlations with the HLA antigens Cw 6 and B 57.

Immunopathogenesis

Psoriasis has a T- cell mediated immunopathogenesis. There is an interaction between environmental, genetic and immunologic factors. Antigens may be environmental antigens, super antigens or auto antigens. These antigens

are taken up by the antigen presenting cells (APC) in the skin. These APC's migrate from the skin to the lymph nodes, where they encounter naïve T cells. These T cells become activated through a series of interactions with APC's. Once activated, T cells migrate back to the skin where they secrete pro-inflammatory cytokines such as interleukin 2 (IL 2) and interferon (IFN γ). This induces further production of cytokines including tumour necrosis factor (TNF α). These cytokines induce epidermal and vascular changes that lead to psoriatic plaques. TNF- α is involved in many important cellular functions such as proliferation, activation, migration and apoptosis. The actions of TNF- α initiate and maintain the inflammatory process.

Pathophysiology

Psoriasis is characterized by erythematous scaly plaques. The characteristic pathophysiological events that occur in lesional skin are:

1. Epidermal proliferation: There is an increase in the number of proliferating keratinocytes in the basal layer of the epidermis and there is loss of differentiation. This causes the thick silvery scale. The growth rate of psoriatic epidermis is up to 10 times that of normal epidermis.
2. Expansion of the dermal vasculature: The blood vessels in the upper dermis become dilated and hyper permeable and increased in number. This accounts for the erythema of the lesions.
3. Accumulation of inflammatory cells like neutrophils and T lymphocytes in the dermis and epidermis.

The lymphocytes play a key role in the disease process and epidermal changes are secondary and a consequence of the release of mediators from infiltrating lymphocytes.

Points to remember

- Affects 2% of the population.
- Peak onset in the second or third decades.
- Polygenic inheritance. 35% have a family history of psoriasis.
- Epidermal cell proliferation rate is increased.
- Mainly T-cell mediated immunopathogenesis.

Precipitating Factors

1. Physical trauma to the skin can precipitate psoriasis in the damaged skin. This is known as Koebner phenomenon. Rubbing and scratching stimulate the proliferative process.
2. Infection: Streptococcal infection precipitates guttate psoriasis.
3. Drugs: Beta blockers, lithium, antimalarials and withdrawal of systemic steroids aggravate psoriasis.
4. Exposure to sunlight can aggravate psoriasis in about 10% of patients, although in the majority, it has a beneficial effect.
5. Psychological stress can exacerbate psoriasis.

Pathology

The characteristic histologic picture of a fully developed skin lesion shows

1. Regular elongation of rete ridges with thickening in their lower portion.
2. Papillae are edematous with dilated capillaries.
3. Supra papillary thinning of stratum malpighii with the occasional spongiform pustule.
4. Absence of stratum granulosum.
5. Parakeratosis (nucleated stratum corneum cells).
6. Collection of neutrophils (*Munro micro abscess*) in the parakeratotic mounds.

Systemic involvement includes inflammation of joint structures leading to psoriatic arthropathy.

Clinical Features

Psoriasis widely varies in severity, appearance and behaviour. Presentation patterns of psoriasis are:

1. Psoriasis vulgaris
2. Guttate psoriasis
3. Flexural psoriasis
4. Localized forms
5. Pustular psoriasis
6. Erythrodermic psoriasis.

Psoriasis Vulgaris

Psoriasis vulgaris ('vulgaris' means common) is the



Fig. 208.1: Psoriasis vulgaris



Fig. 208.2: Multiple psoriatic lesions coalesced together

erythematous papules and plaques with silvery white scales (Fig. 208.1). On removal of the loosely attached scales, minute bleeding points are seen (*Auspitz' sign*). Papules and plaques coalesce to form polycyclic (Fig. 208.2) or serpiginous patterns. Sites of predilection of lesions are elbows, knees, scalp hair margin and sacrum. Lesions are bilateral and often symmetrical. Differential diagnosis includes seborrheic dermatitis, hypertrophic lichen planus, psoriasiform drug eruption (beta blockers, gold and methyl dopa), tinea corporis, secondary syphilis, lichen simplex chronicus and mycosis fungoides.

Guttate Psoriasis: (latin- gutta, 'drop')

Guttate psoriasis is an acute symmetrical eruption of a shower of small papular lesions usually on the trunk (Fig. 208.3). Adolescents or young adults are commonly affected. It often follows a streptococcal sore throat. It should be differentiated from pityriasis rosea, which has a classical morphology of oval papules with peripheral scaling and central wrinkling. The prognosis is good with spontaneous resolution but may evolve into chronic plaque psoriasis.



Fig. 208.3: Guttate psoriasis-drop like lesions

Flexural Psoriasis

Flexural psoriasis affects the axillae, groins, submammary areas and natal cleft. Due to the moist and warm environment in these regions, psoriatic plaques are usually not scaly, but erythematous and fissured. It is commonly seen in the elderly. The sharp demarcation permits distinction from intertrigo, candidiasis, contact dermatitis, seborrheic dermatitis and tinea cruris.

Localized Forms

Palmo-plantar psoriasis: Palms and soles may be the only areas involved. There is hyperkeratosis and scaling which is not easily removed. There may be painful fissures and bleeding (Fig. 208.4).

Scalp psoriasis: is characterized by sharply marginated pruritic plaques especially at the occiput with thick adherent scales. Lesions may be discrete or the entire scalp



Fig. 208.4: Plantar psoriasis

is involved. There is no hair loss. Scalp may be the only site involved or may be a part of generalized psoriasis. Scalp psoriasis has to be differentiated from seborrheic dermatitis. Seborrheic dermatitis is diffuse in distribution, whereas psoriatic lesions are patchy and have well defined edges. Silvery scales, if present are typical of psoriasis.

Psoriasis of the nails: Psoriasis affects the matrix or nail bed in up to 50% of cases. Thumb pitting is the commonest change, followed by onycholysis (separation of nail plate from the nail bed). Discoloration of the nail bed resembling an oil drop (**oil drop sign**) is seen adjacent to onycholysis. Subungual hyperkeratosis affects mainly the toe nails. Nail changes are frequently associated with psoriatic arthropathy. Treatment is often difficult, but the condition responds to oral methotrexate.

Pustular psoriasis: Pustular psoriasis is characterized by sterile pustules, not papules, arising on a normal or inflamed skin. It is classified into two types.

1. Localized pustular psoriasis
 - a. chronic palmo- plantar
 - b. acrodermatitis continua.
 2. Generalized pustular psoriasis (GPP)
 - a. acute GPP of von Zumbusch
 - b. GPP of pregnancy.
1. a. Chronic palmo-plantar pustular psoriasis is most common in females in the fifth or sixth decades. It presents as symmetrical well defined erythematous plaques studded with pustules. The lesions cause a burning sensation, and itching is variable. The thenar eminence of the palm, the instep, heel and borders of the feet are the common sites involved. Digital lesions are uncommon. It has a prolonged course and is refractory to treatment.
 - b. Acrodermatitis continua of Hallopeau is a chronic sterile, pustular form of psoriasis affecting the tips of fingers or toes, which tends to extend proximally. There is erythema, scaling and pustules. When the pustules dry up, they leave behind glazed, red and painful digits. The nails become dystrophic. It is common in children. It often evolves into GPP in elderly patients.
 2. a. Acute GPP of von Zumbusch (Fig. 208.5) is a serious life threatening form of psoriasis. It may develop from a pre-existing typical psoriasis, often after provocation by steroid withdrawal or other factors. It can begin later in life as an atypical acral or flexural psoriasis and rapidly progress to GPP. The eruption may begin with a sensation of burning with a dry tender skin and an abrupt onset of high fever and severe malaise. Generalized sheets of erythema and pustulation occur in crops and dries up into exfoliation. The configuration of lesions can be annular, circinate, plaques of erythema with pustular collarettes, isolated



Fig. 208.5: Generalized pustular psoriasis- pustules on an erythematous base on the chest and right arm

pustules, lakes of pus or erythroderma. Nails are dystrophic. Buccal mucosa and tongue may be involved (geographic tongue). Complications include hypoalbuminemia, hypocalcemia, renal and liver damage and deep vein thrombosis.

- b. GPP of pregnancy (*impetigo herpetiformis*) is very rare and it usually begins in the third trimester of pregnancy. Clinical features are similar to Von Zumbusch type of GPP. Constitutional symptoms are severe and may be fatal. Severe and long standing disease may cause placental insufficiency leading to still birth, neonatal death or fetal abnormalities. Fulminating disease is best treated with prednisolone. Methotrexate, retinoids or PUVA may be needed after delivery to wean off the steroid.

Erythrodermic Psoriasis

It is characterized by generalized (> 90% body surface area involved) erythema, scaling, and itching. It is a medical emergency requiring hospitalization (Refer erythroderma).

Psoriatic Arthropathy

Psoriatic arthropathy is a common sero-negative poly-arthritis. If not properly managed, the arthropathy progresses, leading to considerable morbidity. It is seen in about 5% of psoriatic patients. Four types are described. (1) Distal arthritis involving the distal interphalangeal joints (2) Rheumatoid like arthritis. (3) Ankylosing spondylitis or sacroilitis and (4) Mutilating arthritis (arthritis mutilans).

Course and Prognosis

The course is prolonged, but unpredictable. It may remain as discrete plaques or may become generalized. Relapse is the rule. Guttate psoriasis has a better prognosis.

Points to remember

- Extremes of presentation from a few lesions to erythroderma or generalized pustular psoriasis.
- Chronic plaques with silvery scales over the elbows, knees and scalp are the commonest lesions. Remissions and relapses are common.
- Nails show pitting, onycholysis and oil drop sign. Associated with psoriatic arthropathy.
- Pustular psoriasis is characterized by sterile pustules. It may affect the palms and soles or may be a generalized disease.

Management

Psoriatic lesions can be cleared considerably but recurrence is the rule. The need for long-term treatment and the non infectious nature of psoriasis should be explained. Treatment depends upon the type and extent of the disease, age, social factors and general health of the patient.

Topical therapy: Topical corticosteroids and bland emollients are the mainstay of treatment in localized psoriasis. The preparations include betamethasone dipropionate, flucinolone acetonide and clobetasol propionate for lesions on the limbs and trunk and fluticasone, mometasone or clobetasone for lesions on the face and flexures.

In chronic plaque psoriasis, coal tar preparations are useful singly or in combination with keratolytics such as salicylic acid. Salicylic acid and tar shampoos used daily and lotions containing betamethasone and salicylic acid are very effective in scalp psoriasis. Dithranol as a short contact therapy applied for 30 minutes daily and washed off is very effective. Topical calcipotriol (50 µg/g) and calcitriol (3 µg/g) are safe and effective vitamin D3 analogues. Topical tacrolimus 0.1% and tazarotene 0.05% and 0.1% are alternative treatments for psoriasis. Tazarotene is a topical retinoid that modulates abnormal

keratinization and proliferation. Start with 0.05% cream and increase the strength as tolerated. Apply at night. A topical steroid application in the morning decreases the irritation due to tazarotene.

Topical psoralen soaks and exposure to sunlight is very effective in chronic plaque psoriasis. Hands and feet are immersed in a solution of 8-methoxy psoralen (10 mg/L) of warm water for 15 minutes and then exposed to UVA phototherapy units. If these equipments are not available, exposure to direct sunlight for not more than 5 minutes would suffice.

Systemic therapy is indicated when psoriasis is life threatening as in GPP or erythroderma, extensive and not responding to topical treatment. The common drugs used are:

1. Methotrexate, a folate antagonist is a well established treatment for severe psoriasis. It is given orally once a week as a single dose (7.5-15 mg) or in 3 divided doses per week, 12 hours apart in succession. Blood counts, liver and renal function tests should be normal before starting methotrexate and should also be monitored during treatment. Improvement is seen within 2-4 weeks. The major side effects include hepatotoxicity, upper gastrointestinal symptoms, leucopenia, thrombocytopenia, megaloblastic anemia, oligospermia in men and teratogenesis.
2. Photochemo therapy (PUVA): 8-methoxy psoralen is given orally 2 hours prior to ultra violet exposure from PUVA chambers or natural sunlight (PUVA – SOL). Psoralen cross-links with cellular DNA inhibiting cell division. PUVA is usually given 2-3 times a week and there is progressive clearance in about 6 weeks. It is continued for 2 months after the skin lesions have resolved.
3. Narrow band UVB therapy (311 nm) is a safe and useful therapy in plaque psoriasis. Philips TL-01 fluorescent lamps emit a narrow UVB band at 311 nm. This is found to be superior to conventional broad-band UVB, producing longer remissions. UVB therapy 3 times/week is sufficient. This therapy is particularly useful in plaque psoriasis, guttate psoriasis, sebo psoriasis and psoriasis in a pregnant woman. It is not effective in erythroderma or generalized pustular psoriasis.
4. Retinoids are vitamin A derivatives, particularly useful in pustular psoriasis and plaque psoriasis. Etretinate and recently acitretin (25-50 mg/day) are useful either alone or in combination with PUVA (Re- PUVA). Acitretin is started in a daily dose of 25 mg and gradually increased to 50 mg for 3-4 months, depending on the response and side effects. After good clearance of lesions is achieved, the dose is gradually tapered and stopped.
5. Cyclosporine is an immunosuppressant used in doses of 3-5 mg/kg /day orally and it is highly effective. The

drug is continued till lesions resolve and the dose is slowly tapered. It can cause hypertension and renal toxicity and so monitoring is mandatory.

Recent Advances in the Treatment of Psoriasis

Biological response modifiers (biologics) are a new class of drugs and are likely to revolutionize the treatment of moderate to severe psoriasis. Biologics are proteins derived from recombinant DNA technology, hybridomas and blood and whole human cells. Three main types are used to treat psoriasis and other immune mediated diseases like rheumatoid arthritis or Crohn's disease. They are:

- recombinant cytokines
- monoclonal antibodies and
- fusion proteins

They interfere with T cell activation and effector function and prevent the inflammatory effects. Biologics are large molecules and administration is via injection or infusion. Biologics available to treat moderate to severe psoriasis or psoriatic arthritis are:

1. *Etanercept* is a fusion protein which blocks the TNF- α . It is given subcutaneously in a dose of 50 mg twice a week for 12 weeks and then tapered to 25 mg. Injection site reactions and multiple sclerosis like syndrome are the main side effects.
2. *Alefacept* is a fusion protein and acts by eliminating the pathogenic T cells. Dose is 7.5 mg IV or 15 mg IM weekly for 12 weeks. CD4 suppression is the main side effect and should be monitored.
3. *Efalizumab* is a monoclonal antibody that blocks the T cell activation, co-stimulation and migration. Dose is 1 mg/kg subcutaneously every week. Head ache, nausea and chills are the side effects noted.
4. *Infliximab* is a monoclonal antibody that blocks TNF- α . Side effects include infusion reactions and reactivation of tuberculosis. It is under trial.
5. *Adalimumab* and *oncept* are under trial.

Their major advantage is the low risk for end organ toxicity and drug-drug interactions. Some of these may offer long-term remissions. These are under regular use for only about 5 years. Long-term safety has yet to be determined.

Points to remember

- Topical corticosteroids, coal tar, salicylic acid, dithranol, tacrolimus and tazarotene are used for localized lesions.
- Generalized involvement necessitates systemic treatment with methotrexate, PUVA or retinoids.
- Newer biologics are now approved for the treatment of psoriasis.

Lichen planus

Lichen planus (LP) is an acute or chronic inflammatory dermatosis involving skin and / or mucous membrane. LP is most common between 30-60 years of age.

Etiology: It is idiopathic in most cases, but it is evident that cell mediated immunity (CMI) plays a major role. Majority of the infiltrate contains CD 8+ and CD 45 RO+ memory cells. Drugs such as beta blockers, antimalarials, thiazides, gold and mercury salts and infection with hepatitis C virus result in altered cell mediated immunity. All these have been implicated as triggering factors for LP.

Pathology is quite characteristic. There is epidermal hyperkeratosis, hyper granulosis, acanthosis, basal cell degeneration and a band like lymphohistiocytic infiltrate in the upper dermis.

Clinical Features

The onset is usually insidious with the classical violaceous, polygonal, flat topped extremely pruritic shiny papules (Fig. 208.6) distributed symmetrically over the flexor aspect of forearms, wrists, lower parts of legs and genitalia. The initial lesions may be erythematous. Some lesions show a white lacy network (*Wickham's striae*) on the surface. Koebner phenomenon (spread of lesions along the lines of trauma) is seen. In two thirds of cases, the buccal mucosa is involved.

Sometimes the onset may be acute and generalized. Scalp involvement leads to scarring alopecia. Nails become dystrophic with longitudinal splintering.

Several clinical variants may occur. These include **hypertrophic lichen planus** that presents as hyperkeratotic verrucous plaques especially on the lower parts of legs. **Annular** lesions occur commonly on the glans penis. **Linear** violaceous papules of lichen planus occur on the limbs and trunk and **follicular** lesions on the scalp. **Graham Little syndrome** is the occurrence of follicular lesions and scarring alopecia of scalp with classical LP. In **lichen planus actinicus**, the lesions are on the sites exposed to sunlight. **Ulcerative lesions** are common on the soles and are resistant to therapy.

Diagnosis: Diagnosis is usually clinical. It can be confirmed by histopathology.

Differential diagnosis includes pityriasis rosacea, psoriasis, cutaneous lupus erythematosus and contact dermatitis. Hypertrophic lichen planus should be differentiated from lichen simplex chronicus and prurigo nodularis.

Course: The lesions usually subside within 9-18 months. Remissions and relapses are common. Resolving plaques may leave a post inflammatory hyperpigmentation.

Treatment: Classic LP can be treated with potent topical steroids such as clobetasol propionate 0.05% twice daily for 2-3 weeks, if there are few lesions. Liquid paraffin or petroleum jelly should be applied 4-5 times daily in one direction, from above downwards on the limbs in order to avoid folliculitis. In acute generalized LP, oral corticosteroids such as prednisolone 30-40 mg/day tapered over 1-3 months halt the rapid progression. Intra lesional injection of 0.1 ml of triamcinolone (10 mg/ml) is effective in hypertrophic LP. Cyclosporine in a dose of 3-5 mg/kg orally for chronic LP induces long lasting remission.

Points to remember

- Characterized clinically by pruritic violaceous flat topped papules with flexor distribution. Resolves mostly within 18 months.
- Lichenoid reactions occur due to drugs like gold, chloroquine and chlorothiazides.
- Responds to topical steroids and emollients.

Pityriasis Rosea

Pityriasis Rosea (PR) is an acute self limiting disorder of unknown etiology, probably infective in origin, affecting mainly children and young adults. Recently Herpes virus type 7 has been incriminated to play a role in the pathogenesis.

Clinical features: PR is characterized by the onset of herald patch in 80% of patients. "*Herald patch*" is an oval plaque, 2-5 cm in size, erythematous, with fine collarette of scales at the periphery. The scales are attached at the periphery and free towards the center of the lesion. After an interval of 1-2 weeks, a generalized eruption appears in crops, mainly over the trunk and proximal limbs. The characteristic lesion is a small oval papule with a crinkly surface and a rim of fine scales (Fig. 208.7). The long axis of the lesions are oriented in the planes of cleavage, running parallel to the ribs and classically form a 'fir-tree' or 'christmas tree' like pattern. Pityriasis rosea is asymptomatic in 50% of patients. The others get pruritus of varying severity. Atypical presentations may occur. This includes (1) lesions occurring only on the face and neck (2) localized (3) unilateral (4) vesicular (5) inverse PR- (PR occurring in the flexures of the axillae and groins)



Fig. 208.6: Violaceous papules of lichen planus



Fig. 208.7: Herald patch and oval papules of pityriasis rosea on the abdomen

(6) erythroderma. The lesions undergo spontaneous remission in 6-12 weeks. Recurrence is uncommon.

Treatment is mainly symptomatic with oral antihistamines such as cetirizine 10 mg or levocetirizine 5 mg once at night for 2-3 weeks depending on the severity of itching. If asymptomatic, emollients like petrolatum alone would suffice. Topical steroid creams like fluticasone 0.05%, mometasone 0.1% or betamethasone dipropionate 0.05% applied once at night over severely pruritic lesions alleviate the itching. However topical steroids should not be applied over large areas. Oral erythromycin 250 mg qid for 2 weeks may allay the condition in 74% of patients.

Reiter's Syndrome

Reiter's syndrome consists of polyarthropathy, urethritis, iritis and a psoriasiform eruption. It invariably affects males and is preceded by genitourinary or gastrointestinal infection. There is a strong association with HLA- B 27.

The main skin lesions are keratoderma blennorrhagicum which are brownish red papules or macules sometimes with a central vesicle seen mainly on the palms and soles. Center of lesions become pustular or hyperkeratotic and crusted. Circinate balanitis is another classic feature of Reiter's and presents as shallow erosions with serpiginous micropustular borders on the glans, if uncircumcised. Only 30% develop the complete triad of arthritis, urethritis and conjunctivitis. Majority have a self limited course and resolves in 3-12 months. Treatment is similar to psoriasis. Methotrexate and retinoids are needed in severe cases (See chapter 111).

Exfoliative Dermatitis (Erythroderma)

Exfoliative dermatitis includes any inflammatory dermatosis which involves more than 90% of the body surface area. It is a dermatological emergency as the systemic side effects are potentially fatal. Exfoliative dermatitis is a

secondary process and represents the generalized spread of a dermatosis or a systemic disease.

Common causes are eczemas (atopic, contact, photo dermatitis), psoriasis, lymphoma or Sezary syndrome, drug eruption (sulfonamides, barbiturates, NSAIDs and phenytoin are the common drugs), pityriasis rubra pilaris and ichthyosis. In about 23% of cases the cause is unknown.

Clinical features: It is commonly seen in middle aged and elderly males. The onset is often acute. It is characterized by generalized erythema and scaling. Temperature regulation is altered. Large amounts of warm blood are present in the skin due to dilatation of capillaries and there is considerable heat dissipation through insensible fluid loss and by convection. So the patient shivers. Scalp and body hair is lost and nails may be thickened or shed. Generalized lymphadenopathy which is a secondary response to severe skin inflammation is common.

Complications: In exfoliative dermatitis, there is skin failure, and so all the normal functions of the skin are affected. Edema, cutaneous and respiratory infection, cardiac failure, hypo albuminemia due to protein loss through scales, dehydration and metabolic derangement, impaired temperature regulation and dermatopathic lymphadenopathy are the major complications.

Diagnosis: History, pathognomonic signs and symptoms of the pre-existing dermatosis, if present, help in the diagnosis.

Course and prognosis depends upon the underlying cause. In most patients, the problem subsides in weeks to months though recurrence is possible. Death rate ranges from 11-30%. Common causes of death are pneumonia, sepsis, high output cardiac failure and other cardiac complications and lymphoma.

Management: Patient needs to be hospitalized. A warm environment and good nursing care are needed. Pulse, blood pressure, temperature and fluid balance are monitored. Emollients and topical steroids are the mainstay of treatment. Adequate nutrition is maintained. The primary cause is treated. Cardiac failure and infections should be corrected.

Points to remember

- Exfoliative dermatitis is a dermatological emergency.
- Uncommon, but potentially fatal, often sudden in onset.
- Psoriasis and eczema are the common causes.
- Characterized by generalized erythema, edema and scaling
- Skin failure leads to complications such as cardiac failure, hypothermia, infection and lymphadenopathy.
- Inpatient management is needed to correct the nutrition, electrolyte imbalance, secondary infection and other complications.
- Treatment of the underlying cause and emollients are essential.

Chapter Summary

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General Considerations

Eczema is a polymorphic inflammatory reaction pattern of the skin involving the epidermis and dermis. The term ‘eczema’ literally means to ‘boil over’ (Greek). The terms eczema and dermatitis are used interchangeably. Dermatosi s is a general term which denotes any skin disorder.

The etiology of most eczema is not known. It is classified into endogenous (due to internal or constitutional factors) and exogenous (due to external agents). However, in clinical practice these distinctions are often blurred.

Depending on the morphology of the eruption, eczema can be divided into (1) Acute eczema characterized by pruritus, erythema, edema, vesiculation, oozing, crusting and scaling. (2) Chronic eczema characterized by pruritus, lichenification (thickened with prominent skin markings), excoriation and either hypo- or hyperpigmentation.

Microscopic changes in the early stages (acute eczema) show inter cellular and intracellular edema with resultant vesicle formation and associated dermal vasodilatation and infiltration with chronic inflammatory cells.

In chronic eczema, there is thickening of the epidermis (acanthosis, hyperkeratosis) and retention of nuclei by

some corneocytes (parakeratosis). Rete ridges are elongated, dermal vessels dilated and inflammatory mononuclear cells infiltrate the skin.

Eczema is classified into

Endogenous	Exogenous	Unclassified
1. Atopic dermatitis	1. Allergic contact dermatitis	1. Asteatotic eczema
2. Seborrheic dermatitis	2. Irritant contact dermatitis	2. Lichen simplex chronicus
3. Nummular eczema	3. Photodermatitis	
4. Stasis eczema		
5. Pompholyx		

General Principles in the Management of Eczema

1. Acute eczema is managed with wet dressings or compresses. Normal saline, 1 in 8000 dilution of potassium permanganate solution or 1% boric acid can be used. This removes the crusts, stops oozing and provides comfort.
2. Topical creams, particularly combination of glucocorticoid and antibiotic creams (e.g.)Fucidic acid and betamethasone/hydrocortisone, or mupirocin and fluticasone, are preferred.
3. Severe secondary infection needs treatment with systemic antibiotics. Erythromycin 250 mg qid for 5 days is cheap and effective.
4. Ointments should not be used over oozing eczema as it would cause occlusion and worsen the oozing.
5. Creams are preferred in the acute and sub acute stage and ointments in chronic stage.

Endogenous Eczemas

ATOPIC DERMATITIS

Atopic dermatitis (AD) is an acute, subacute or chronic relapsing skin disorder that usually begins within the first 6 months of life, though it can begin at any age. Approximately 70% of patients have a family history of atopy.

Etiopathogenesis

There is a complex interaction between skin barrier, genetic, environmental, pharmacologic and immunologic factors. Triggering factors include

1. Inhalants- dust mites, pollens
2. Microbial agents- exotoxins of *Staph aureus* act as super antigens and stimulate T cells and macrophages.
3. Autoallergens are released from damaged tissue.
4. Foods- eggs, milk, peanuts, fish, wheat.

These allergens are taken up by the antigen presenting cells in the skin and processed and presented to the CD 4 T cells along with class II MHC antigens. The activated T cells secrete many cytokines, especially Interleukin-4 (IL-4), (Th 2 type of response). There is a relative reduction in the number of CD 4 + T cells that secrete IL-2 and γ -interferon and also a decrease in CD8 + T cells. IL-4 activates the B lymphocyte to produce excess of IgE. IgE interacts with the antigen and sensitizes the mast cells and basophils, and causes degranulation. Inflammatory mediators are liberated and cause intense itching and eczema. The damaged skin provides a good environment for the *Staph aureus* population to grow and the exotoxins further worsen the eczema, by acting as super antigens.

Exacerbating Factors

1. Skin barrier function is disrupted causing dehydration. Xerosis of the skin is the most important aggravating factor.
2. Infection with *Staph aureus*.
3. Seasonal variation- atopic dermatitis usually improves in hot season and flares in the cold season.
4. Clothing- wool and fur aggravate the condition.
5. Emotional stress.

CLINICAL FEATURES

Pruritus is the main symptom. It is the itch that rashes rather than the rash that itches. The constant scratch leads to a vicious cycle of itch → scratch → rash → itch. Itching is severe and often interferes with sleep. The skin becomes very dry.

The clinical picture of eczema varies with age.

Infantile phase: Lesions of acute eczema first occur on the cheeks, forehead and scalp and later the trunk and extremities. When the infant begins to crawl, the extensor aspects of knees are involved (Fig. 209.1). Secondary infection with *Staph aureus* is common. In more than half the patients, the eczema resolves by 18 months.

Childhood phase: Papules, lichenified plaques, erosions and crusts are seen mainly on the ante cubital and popliteal fossa (Fig. 209.2), neck, wrists and ankles. There is erythema on the face with infra orbital folds. Periorbital pigmentation and loss of eyebrows on the lateral one third



Fig. 209.1: Atopic dermatitis in an infant



Fig. 209.2: Atopic dermatitis in a child

may occur due to rubbing. Palmar markings may be exaggerated (hyperlinearity of the palms).

Adult phase: Lichenification and excoriations in a flexor distribution is the characteristic feature in this phase. Irritant dermatitis of the hands is common.

Other features:

1. Stroking leads to blanching and not redness as in normal skin. This unique feature of AD is called **white dermographism**.
2. Chelitis, conjunctivitis, facial palor, ichthyosis and nipple eczema are the minor features of AD.
3. Extensive skin involvement may cause exfoliative dermatitis.

Diagnosis: Diagnosis is based on clinical findings such as onset in infancy, severe pruritus, typical distribution, morphology of lesions, personal or family history of atopic dermatitis, allergic rhinitis or asthma.

Differential diagnosis: Seborrheic dermatitis, irritant and allergic contact dermatitis, psoriasis, nummular eczema and dermatophytosis should be differentiated from atopic dermatitis.

Prognosis: Spontaneous and complete remission occurs during childhood. 30-50% of patients may develop asthma or hay fever later in life. Adult onset AD often runs a severe course.

Management

The patient is advised to avoid any predisposing factors like dust, infection or any particular food which aggravates the condition. Dry skin management is the most important. The child should be given a quick bath with luke warm water. Soap substitutes like cleansers containing cetyl and stearyl alcohol or super fatted soaps used for bathing, prevents drying of the skin. Moisturizers and emollients should be applied immediately after bath and repeated many times to prevent drying. Moisturizers should be applied along the direction of hair follicles to avoid folliculitis. Creams are preferred in an acute eczema and petrolatum for dry eczema. Wet compresses with saline or dilute potassium permanganate solution reduce the oozing associated with acute eczema. Oral and topical antibiotics to eliminate the *Staph aureus* infection promote healing. Cotton clothes are preferred. Cool and comfortable environment prevents itching. Antihistamines such as hydroxyzine should be used without hesitation because it is the 'itch that rashes'.

Topical steroids like fluticasone, desonide or mometasone applied once or twice daily till the lesions resolve reduces inflammation and itching. Tacrolimus (0.03%, 0.1%) and pimecrolimus creams are also widely used now. Severe and resistant forms are managed by phototherapy and systemic steroids like prednisolone 1 mg/kg body weight till the acute symptoms are controlled. Oral cyclosporine is very effective but the side effects and cost restricts its use.

Points to remember

- Usually begins in infancy
- Immunologically mediated, environmental factors also play a role
- Clinical features include acute eczema in infancy affecting face and hands, subacute eczema in childhood affecting antecubital fossa and popliteal fossa, neck, wrists and ankles and chronic lichenified eczema in flexor distribution in adults.
- Itch scratch cycle is predominant
- Infection, heat, wool, stress, inhalants (dust) and certain foods are the exacerbating factors. Treatment includes emollients, topical steroids, antihistamines and antibiotics.



Fig. 209.3: Seborrheic dermatitis of the scalp

more common in males and occurs after puberty and the incidence increases with age. Onset in infancy is also common (cradle cap). HIV infected individuals have an increased incidence of SD that is often severe and intractable.

Etiology: is unknown. *Malassezia furfur* is said to play a role. Abnormalities in sebaceous gland activity and zinc, niacin and pyridoxine deficiencies are also implicated.

Clinical features: The common clinical patterns are

1. Scalp and face involvement: greasy or dry scaling, erythematous macules and papules often cause a diffuse involvement of the scalp (Fig. 209.3). Other classical sites are eyebrows, eyelashes, beard, malar region, scalp hairline (corona seborrheica), naso labial folds, retroauricular and meatal region.
2. Petaloid: Lesions simulating pityriasis rosacea, occur over the presternal area.
3. Flexural: In the axillae, groins, anogenital and submammary areas, SD presents as diffuse, sharply marginated erythema with erosions and fissuring. Common in the elderly.
4. *Pityrosporum folliculitis*: is an erythematous follicular eruption with papules or pustules over the back.

Course and prognosis: Seborrheic dermatitis affects majority of individuals at sometime during life. Recurrences and remissions are common. Infantile and adolescent seborrheic dermatitis disappears with age.

Management: As the condition is chronic, initial therapy followed by long term maintenance therapy is required.

Scalp: Shampoos containing selenium sulphide (2.5%), zinc pyrithione (1-2%), ketoconazole 2%, flucinolone acetonide, applied twice a week (the frequency can be reduced later), are effective. Salicylic acid and coal tar shampoos are useful in reducing thick greasy scales.

Face and trunk: Topical glucocorticoid creams (1-2.5% hydrocortisone), ketoconazole 2% cream, tacrolimus 0.03%, pimecrolimus 1% are all effective.

Seborrheic dermatitis (SD) is a very common, chronic inflammatory dermatosis characterized by erythema and scaling in regions where the sebaceous glands are most active. Mild scalp SD causes flaking (dandruff). SD is



Fig. 209.4: Coin shaped lesions of nummular eczema on the leg

Cradle cap: Removal of crusts with warm oil (olive) compresses is needed, followed by creams or shampoos.

Nummular Eczema (Discoïd Eczema)

Nummular eczema is a chronic pruritic inflammatory dermatitis, typically affects middle aged or elderly, clinically characterized by coin shaped erythematous plaques with exudation and crusting (Fig. 209.4). It is severely pruritic, with excoriations. Sometimes dry scaly lichenified plaque may be seen. Lesions may be clustered on the lower parts of the legs or trunk in males and hands or fingers in females. It may be generalized and scattered. It has a chronic course from weeks to months and tends to recur. Secondary bacterial infection is common.

Management: Moderate to high potency topical steroid combined with antibiotics (fucidic acid and betamethasone), moisturizers and anti histamines like hydroxyzine or cetirizine are the mainstay of treatment. Systemic antibiotics may be needed if secondary infection is severe. Photochemotherapy (PUVA) or narrow band UVB (311 nm) are very effective in severe cases with extensive involvement.

Stasis Eczema

Chronic venous insufficiency leads to stasis eczema (varicose eczema) in the lower parts of the legs and feet.

Pathogenesis: Incompetence of the deep perforating veins increases the hydrostatic pressure in dermal capillaries. Pericapillary fibrin deposition leads to the pathological and clinical changes.

Clinical features: Inflammatory edema, papules, scaling, crusting, erosions, pigmentation stippled with recent and old hemorrhages and dermal sclerosis are the characteristic features. There may be concomitant irritant contact



Fig. 209.5: Pompholyx. Note the vesicles on the sides of fingers

dermatitis due to secretion from stasis ulcer and allergic contact dermatitis secondary to topical medications and bacterial colonization.

Management: Emollients and topical steroids are needed. Venous insufficiency should be managed.

Pompholyx

Pompholyx is an acute, chronic or recurrent dermatosis of the lateral aspects of the fingers, palms and soles characterized by symmetrical deep seated pruritic, clear vesicles (Fig. 209.5) and later by scaling, fissures, and lichenification. Spontaneous remissions can occur in 2-3 weeks. Recurrence is the rule. Secondary infection may occur. Hyper hidrosis is common.

Management: wet compresses with saline, topical steroids and in severe cases, a short course of systemic steroids are needed. Topical PUVA (as soaks) are also useful in severe cases.

Points to remember

- Seborrheic dermatitis affects the scalp and face. Treated with combination creams of steroids and antifungals.
- Nummular eczema presents as coin shaped lesions on the limbs of the elderly.
- Stasis eczema, associated with venous insufficiency is treated with emollients and low or moderate potency topical steroids.

Exogenous Eczema

CONTACT DERMATITIS

Contact dermatitis (CD) is a term applied to acute or chronic inflammatory reaction to substances that come in contact with the skin. There are two types of CD. Irritant contact dermatitis (ICD) caused by a chemical irritant and

allergic CD (ACD) caused by an allergen (antigen), which elicits a type IV hypersensitivity reaction.

Irritant Contact Dermatitis

ICD is caused by exposure of the skin to chemical or physical agents that are capable of producing cell damage, acutely or chronically. It is dependent on the concentration of the offending agent and occurs in all those who are exposed, depending on the penetrability and thickness of the stratum corneum. There is a threshold concentration for these substances above which they cause acute dermatitis and below which they do not.

ICD may occur minutes after exposure or may be delayed up to 24 hours. Acute ICD can occur due to strong irritants like acids, chloroform, methanol, phenol or propylene glycol and cause toxic reactions after a short exposure. The spectrum of changes ranges from erythema to vesiculation. Erosion, crusting and scaling follows. Papules are not seen. In chemical burns, necrosis of tissues leads to ulceration. Lesions are sharply demarcated to the site of contact with the irritant. Configuration is often bizarre.

Most cases however, are caused by cumulative exposure to one or more mild irritants like water, soaps and detergents. This causes a chronic disturbance of the barrier function that allows even subtoxic concentrations of the offending agents to penetrate into the skin and elicit a chronic inflammatory response. Hands are most commonly affected. There is dryness, chapping, erythema, scaling, fissuring, and crusting. Stinging and itching are the main symptoms.

Allergic Contact Dermatitis

Allergic contact dermatitis is dependent on sensitization and thus occurs only in sensitized individuals. Depending on the degree of sensitization, even minute amounts of allergen may elicit a reaction.

The eruption starts in a sensitized individual 48 hours or a few days after contact with the allergen. The eruption worsens on repeated exposures (crescendo reaction). There is intense pruritus. Lesions are initially confined to the area of contact with the allergen and later spread to the surrounding areas. Generalized involvement can also occur, if sensitization is strong. In the acute stage (Fig. 209.6) there is erythema, papules, vesicles, erosions, scaling and crusting and in the chronic stage (Fig. 209.7) there is lichenification, fissuring, scaling and crusting.

Patch test: In ACD, sensitization is present on all parts of the skin as it is immunologically mediated. Therefore, application of the allergen to any area of normal skin provokes an eczematous reaction. It should be performed



Fig. 209.6: Allergic contact dermatitis to diclofenac spray



Fig. 209.7: Allergic contact dermatitis to rubber



Fig. 209.8: Patch test allergens pasted on the back

on a previously uninvolved skin after the dermatitis has subsided (Fig. 209.8).

Management of Contact Dermatitis

1. Avoidance of irritants/allergens.
2. Wet dressings and topical steroids for acute reaction and if severe, systemic glucocorticoids are indicated.
3. In chronic CD, protective/lubricating creams and high potency topical steroids are necessary.

Points to remember

- ICD is more common than ACD. Atopics are more susceptible to irritants.
- Common irritants are water, abrasives, chemicals (alkalis) and detergents.
- Common allergens are nickel (jewellery, zips, instruments), chromates (cement, primer), cobalt (paint, ink), colophony (glue, adhesive tape), preservatives, perfumes and paraphenylenediamine (dye).
- * Avoidance of allergens and irritants are important in the prevention of CD.

Photosensitive Dermatitis

In normal persons pigmentation of the skin increases with exposure to sunlight, depending on its intensity, duration of exposure and type of skin. Photosensitivity is an abnormal response to sunlight and affects the sun exposed parts of the body like the forehead, malar region, nose, rim of ears, sides and back of neck, 'V' area of the chest and extensor aspect of distal extremities. Ultra violet A (UVA 320-400 nm) and ultra violet B (UVB 290-320 nm) are the primary inducers of most photosensitivity reactions. The photon energy is absorbed by molecules such as skin cells (chromophores) and then either dispersed harmlessly or results in clinical disease. The chromophore can be a) exogenous (topical or systemic), b) endogenous (DNA is the most important skin chromophore), c) endogenous or exogenous allergen causing an immune reaction activated by photo radiation.

Photo dermatosis is broadly classified into

1. Photo toxicity- sunburn, drug/chemical induced, plant induced (phyto photo dermatitis)
2. Photo allergy- drug/chemical, chronic actinic dermatitis, solar urticaria
3. Idiopathic- Polymorphous light eruption, actinic prurigo, hydroa vacciniforme
4. Miscellaneous- Metabolic, nutritional, genetic, photo aggravated dermatosis, chronic photo damage.

Sunburn is a transient inflammatory response of normal skin due to exposure to UVB rays. It is common in fair skinned individuals. There is uniform erythema, edema, vesicles and bullae strictly confined to the sun exposed areas. Erythema is visible 2-6 hours following exposure and reaches a maximum at 24-72 hours and fades in 3-5 days, followed by pigmentation.

Drug / chemical induced photo toxic reactions: In this condition interaction occurs between drugs /chemical with ultra violet rays in the skin and manifests like an ICD (e.g. dyes, coal tar derivatives, psoralens, tetracyclines, phenothiazines, thiazides, sulfonamides and others).

Photo allergic reactions: A photo allergen such as fragrances like musk ambrette, PABA, phenothiazines and

halogenated salicylanilides in deodorant soaps, formed in the skin initiates a type IV hypersensitivity reaction and manifests like an ACD.

Idiopathic- Polymorphous light eruption: Polymorphous light eruption (PMLE) is the most common photodermatosis. This is common in women. UVA and UVB can evoke PMLE, UVA being more common. Lesions are papular, papulovesicular or urticarial plaques that begin within 24 hours of exposure. In the individual patient, usually one type of lesion predominates. Recurrences are common. Spontaneous improvement occurs after years.

Management: Strict avoidance of sunlight is necessary. Sun block creams like zinc oxide or titanium dioxide, broad spectrum sunscreens, topical glucocorticoids and antihistamines are used in the treatment of PMLE. Severe eruption may necessitate systemic steroids.

Points to remember

- Sunlight can cause tanning, sun burn and photo ageing in normal skin.
- Important idiopathic photodermatoses are PMLE and chronic actinic dermatitis.
- Some conditions like lupus erythematosus, porphyria and rosacea are worsened by sunlight.
- Treatment includes avoidance of sun exposure, irritants and allergens, use of sun screens and topical steroids.

Asteatotic Eczema (Eczema Craquele)

Asteatotic eczema is a dry eczema with fissuring and cracking of the skin, often affecting the limbs in the elderly. The skin is dry, erythematous and itchy and shows a crazy-paving pattern of fissuring. Dry winter climate, over washing and hypothyroidism exacerbates the condition. Topical emollients and bath emollients should be used regularly. Sometimes a mild topical steroid is necessary.

Lichen Simplex Chronicus (LSC)

LSC is a localized form of lichenification due to rubbing or scratching as a habit or due to stress. The skin becomes highly sensitive and hyperexcitable in response to minimal external stimuli. LSC is common in elderly females. It usually occurs as a single plaque of lichenification with exaggerated skin markings and hyper pigmentation (Fig. 209.9), associated with paroxysms of pruritus. Common sites are the lower parts of the legs and back of the neck. Sometimes a nodular lichenification known as *prurigo nodularis* develops on the shins and forearms.

It should be explained to the patient that the rubbing and scratching must be stopped. Potent topical steroids, coal tar and intra lesional triamcinolone are effective.



Fig. 209.9: Lichenified plaques of lichen simplex chronicus



Fig. 209.10: Infective eczema-there is edema vesiculation oozing and crusting

Infective Eczema

Infectious eczematoid dermatitis (IED) or infective eczema is an eczema that occurs secondary to an infection in the skin. It can occur around discharging

wounds, sinuses or ulcers as an acute eczema (Fig. 209.10). This should be differentiated from infected eczema where a primary eczema is complicated by secondary bacterial infection.

210

Vesiculo Bullous Disorders

S. Pradeep Nair

Chapter Summary

- General Considerations 1374
- Pemphigus Vulgaris 1375
- Bullous Pemphigoid 1375
- Dermatitis Herpetiformis 1375
- Linear IgA Disease 1376

TABLE 210.1

Blistering disorders classification	
Genetic	Immunobullous
Epidermolysis bullosa	Pemphigus vulgaris Bullous pemphigoid Dermatitis herpetiformis Linear IgA disease

GENERAL CONSIDERATIONS

Blistering disorders are a heterogeneous group of diseases presenting with vesicles and bullae on the skin and mucous membrane. These groups of disorders cause great morbidity and even mortality in dermatological practice. The basic classification of blistering disorders is given in

Table 210.1. Blistering drug reactions are described in the section on drug reactions.

The genetically transmitted group of blistering disorders like epidermolysis bullosa are mechanobullous disorders where friction and trauma contribute to the formation of blisters. In immunobullous disorders, autoimmune mechanisms contribute to the formation of

blisters. Autoimmune blistering disorders account for 0.49% of the skin disorders in Kerala, pemphigus vulgaris being the commonest.

Pemphigus Vulgaris

The word pemphigus is derived from the Greek word “pemphix” meaning bubble. The usual age group is 40-60 years. Auto antibodies (IgG) are directed against cell surface glycoproteins called pemphigus antigens, especially desmoglein 3. This leads to a loss of the normal cell to cell adhesion in the epidermis (acantholysis). It is clinically characterized by multiple flaccid vesicles and bullae, arising on normal skin, distributed on the flexures, scalp and oral mucous membrane (Figs 210.1 and 210.2). A tangential pressure applied adjacent to a bulla or vesicle will cause the skin to peel away (*Nikolsky sign*), while vertical pressure on the bulla leads to lateral extension of the blister (*Asboe-Hansen or bulla spread sign*). The bulla on rupture leads to large, painful denuded areas which extend without healing. The oral mucosa shows erosions and ulcers. It is invariably fatal if not treated aggressively with immunosuppressive agents.



Fig. 210.1: Pemphigus vulgaris



Fig. 210.2: Flaccid vesicles of pemphigus on axilla



Fig. 210.3: Pemphigus vegetans: Note the vegetating plaques on the back over the erosions of pemphigus vulgaris

Variants

1. **Pemphigus vegetans** presents with granulomatous vegetative purulent plaques on the flexures, trunk and other areas (Fig. 210.3).
2. **Pemphigus foliaceus** presents with superficial pustules, erythema, scaling and crusting distributed on the face, scalp, upper chest and abdomen and may present as exfoliative dermatitis.
3. **Pemphigus erythematosus** (*Senear-Usher syndrome*) is a variant of foliaceus where there is erythema on the malar area and considerable overlap with SLE.

Bullous Pemphigoid

Bullous pemphigoid occurs after 60 years of age. Autoantibodies interact with bullous pemphigoid antigen in the hemidesmosomes of basal keratinocytes and there is complement activation and attraction of neutrophils and eosinophils. These inflammatory cells release various bioactive molecules causing bullous lesions.

Clinical features include multiple tense bullae and vesicles distributed on the lower abdomen, thighs and flexor aspect of forearms. The bulla heals after rupture with no peripheral extension. Nikolsky and bulla spread sign are negative. Oral lesions are rare.

Dermatitis Herpetiformis

The age of onset is 20-40 years. It is associated with gluten sensitive enteropathy and IgA deposits in the skin. Autoantibodies to epidermal transglutaminases probably cross react and bind to transglutaminases in the gut and



Fig. 210.4: Grouped vesicles of dermatitis herpetiformis

circulate as immune complexes and deposits in the skin. IgA activates complement leading to chemotaxis of neutrophils and produces tissue injury. The patient presents with severely pruritic multiple grouped vesicles, papules and urticarial plaques distributed on the upper shoulder, lower back and extremities (Fig. 210.4). Nikolsky sign and bulla spread sign are negative. Oral lesions are uncommon. 70% of the patients may give history of exacerbation of lesions and diarrhea while taking gluten containing food such as wheat, barley and oats.

Linear IgA Disease

Linear IgA disease presents with multiple pruritic tense subepidermal bullae on the extensor surfaces of elbows,



Fig. 210.5: Chronic bullous disease of childhood—annular lesions with peripheral vesicles give a string of pearl appearance

knees, buttocks and trunk. Oral erosions and ulceration are common. The similar disease occurring in children is known as *chronic bullous disease of childhood* (Fig. 210.5). Here the lesions are confined to the perineum, lower abdomen, eyelids and scalp. Annular lesions with vesicles along the edge give a “string of pearl” appearance. Homogenous linear deposits of IgA are present at the basement membrane zone.

Investigations and Treatment

Tzanck test, skin biopsy and immunofluorescence are the investigations done to diagnose vesiculo-bullous disorders. Tzanck test is a cytodiagnostics technique

TABLE 210.2

Investigatory findings and treatment of vesiculo bullous disorders			
Description	<i>Pemphigus vulgaris</i>	<i>Bullous pemphigoid</i>	<i>Dermatitis herpetiformis</i>
Tzanck test	Acantholytic cells ¹	Eosinophils	Neutrophils
Skin biopsy	Suprabasal intraepidermal bulla with acantholytic cells	Subepidermal bulla containing eosinophils	Subepidermal bulla containing neutrophils
Immunofluorescence	IgG against inter cellular cement substance	IgG against basement membrane zone	Granular IgA against upper papillary dermis
Electron microscopy	Antibody against desmoglein – 3	Antibody against bullous pemphigoid antigen in hemidesmosomes	Antibody against epidermal transglutaminases
Treatment	Steroids, dapsone, cyclophosphamide, gold therapy, DCP therapy ² , plasmapheresis	Steroids	Dapsone

1. Acantholytic cell is a rounded epidermal keratinocyte with hyperchromatic nuclei and perinuclear halo.
2. DCP – Dexamethasone cyclophosphamide pulse therapy.

where a smear is taken from the floor of a de-roofed bulla and stained with Geimsa or Leishman stain. Specific cells are seen in each condition (Table 210.2). Immunofluorescence is the gold standard for diagnosing these disorders.

Treatment consists of oral corticosteroids, dapsone, cyclophosphamide, dexamethasone cyclophosphamide pulse therapy (DCP therapy) in severe cases and also plasmapheresis in life threatening cases. The investigatory findings and treatment are summarized in Table 210.2.

211

Urticaria and Angioedema

S. Pradeep Nair

Chapter Summary

History and Definition 1377
Clinical Features 1377
Treatment 1378

History and Definition

Hippocrates first described urticarial pruritic lesions caused by nettles and mosquitoes which he named “*knidos*”. It was in 1769 that William Cullen coined the term ‘urticaria’. Urticaria (syn. wheals, hives) is defined as transient erythematous papules and plaques occurring in the skin due to plasma leakage. Angioedema (syn. angioneurotic edema) are transient erythematous swellings of the dermis, subcutaneous and submucosal layers. Angioedema usually affects eyelids, lips, larynx and rarely genital mucosa. Laryngeal edema can be life threatening. Urticaria and angioedema can co-exist and occur as part of immunological and inflammatory reactions on the skin. Urticaria of less than 6 weeks duration is acute urticaria and more than 6 weeks duration is called chronic urticaria. The classification and etiological factors for urticaria/angioedema are given in Table 211.1.

Clinical Features

Urticaria presents as severely pruritic, superficial, well defined, erythematous papules and plaques on any part of the skin (Fig. 211.1). The lesions can be round, oval, arciform, annular or serpiginous. These lesions are

TABLE 211.1

Classification and etiology of urticaria	
Classification	Etiology
Acute and chronic urticaria	Infection Infestation
Physical and cholinergic urticaria	Injections Ingestion (food, drugs)
Urticarial vasculitis	Inhalation (pollen grains, dust, smoke)
Contact urticaria	Insect bite (mosquitoes, wasp and bee stings) Implants (dental, orthopedic)

transient lasting not more than 24 hours and then fresh crops of lesions occur. Angioedema presents with ill-defined edema involving the dermis and subcutaneous tissue, commonly of the lips and eyelids. It may involve the upper respiratory tract and the patient may present with dyspnea and runs the risk of impending life-threatening laryngeal edema which is a medical emergency. Meticulous history taking is very important keeping the etiological factors in mind. Acute urticaria is commonly due to drugs or infections. In children, foci of infection especially dental caries, helminthiasis and food are important factors. In most cases of chronic urticaria the cause may be obscure (idiopathic).

Physical and Cholinergic Urticaria

Physical urticaria is caused by external stimuli. *Dermographism* is a type of physical urticaria where stroking the skin elicits the triple response.



Fig. 211.1: Urticaria due to insect bite

Cholinergic urticaria (heat urticaria) is characterized by the presence of wheals when the patient sweats or does exercise. The wheals are very small and sometimes perifollicular.

Cold urticaria: The lesions are confined to the sites exposed to cold and occur within minutes after rewarming.

Aquagenic urticaria occurs when the patient comes in contact with water, irrespective of its temperature.

Solar urticaria occurs on exposure to sun light (290-500 nm of the electromagnetic spectrum).

Urticarial Vasculitis

This type of urticaria is a Type III hypersensitivity reaction and occurs in autoimmune disorders. Here the wheals will

persist for more than 24 hours and may be painful. Bullous lesions may also occur and investigations have to be done to find out systemic disorders.

Contact Urticaria

Contact urticaria may be immune mediated or non-immune mediated. Immunologic contact urticaria occurs in individuals sensitized to contact with external allergens like latex rubber gloves. This is also commonly seen in atopic children. Non immunologic contact urticaria is due to the direct effects of exogenous urticants penetrating into the skin or blood vessels e.g. benzoic acid in eye solutions and foods, cinnamic aldehyde in cosmetics and serotonin in nettle stings. The wheals may occur within 2 hours of contact.

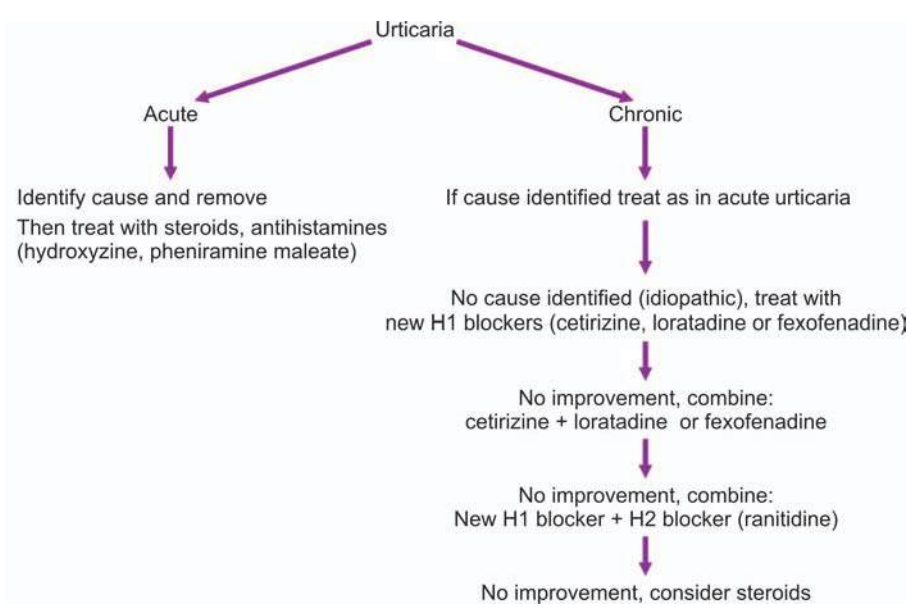
Treatment of Urticaria

In most cases, if the cause is identified and removed the urticaria subsides. The treatment protocol of urticaria is given in Flow chart 211.1.

Angioedema with impending laryngeal edema is a medical emergency as it is life threatening. The treatment protocol is given in Table 211.2.

TABLE 211.2
Treatment of angioedema
1. Inj. Adrenaline 0.5 mL SC or IM
2. Inj. Hydrocortisone 100 mg IV
3. Inj. Pheniramine maleate 22.75 mg IM
If no improvement:
Endotracheal intubation/tracheostomy

Flow chart 211.1: Treatment protocol of urticaria



Chapter Summary

Maculo-papular 1379
 Vesiculo-bullous 1379
 Erythema Multiforme 1379
 Stevens Johnson Syndrome 1380
 Toxic Epidermal Necrolysis 1380
 Exfoliative Drug Eruption 1380
 Urticarial Drug Reactions 1381
 Acneiform Eruptions 1381
 Lichenoid Eruptions 1381
 Photosensitive Drug Reaction 1381
 Hyperpigmentation 1381

A drug reaction is defined as an undesirable clinical manifestation resulting from the administration of a particular drug. Cutaneous drug reactions constitute 2.85% of the dermatological conditions seen in Kerala. The clinical manifestations of drug reactions are protean and can mimic many dermatoses. The classification of drug reactions is given in Table 212.1.

TABLE 212.1**Common drug eruptions**

Maculo-papular
Vesiculo-bullous
Exfoliative dermatitis
Fixed drug reaction
Urticarial
Acneiform
Lichenoid
Photosensitive
Hyperpigmentation

Maculo-papular

Maculo-papular reaction (syn. exanthematous drug reaction) is the commonest type of drug reaction. They are usually caused by penicillin and related antibiotics, allopurinol, gold salts and carbamazepine. Initial reaction usually occurs less than 14 days after drug intake. These

**Fig. 212.1:** Maculo-papular rash due to ampicillin

eruptions present with symmetrical, pruritic erythematous macules and papules on the trunk and limbs (Fig. 212.1). Buccal mucosa may be involved. The treatment is to stop the incriminated drug. Antihistamines and topical calamine lotion relieve the symptoms.

Vesiculo-bullous

Vesiculo-bullous drug reactions are commonly due to drugs like naproxyn, nalidixic acid, furosemide and piroxicam. They can mimic pemphigus, pemphigoid, porphyria or linear IgA disease.

Erythema Multiforme

This type of drug reaction presents with vesicles or bullae, papules, plaques, urticaria and the characteristic 'iris' or 'target' lesion. The iris lesion presents with a central area of vesicle or purpura, a mid zone of edema and an outer ring of erythema. The lesions are usually distributed on

TABLE 212.2

Drugs causing SJS and TEN

Carbamazepine
Phenytoin
Phenobarbitone
Penicillins
Sulphonamides
INH
Piroxicam
Allopurinol

the dorsum of the hands, palms and extensor aspect of extremities. The oral mucous membrane and the eyes can also be affected. Penicillins, sulphonamides, anti convulsants and NSAID'S are the usual culprits. Other than drugs, a wide variety of etiological factors can cause erythema multiforme, especially infections like herpes simplex and mycoplasma. Systemic steroids have to be given in severe drug reactions.

Stevens Johnson Syndrome (SJS)

This is a serious drug reaction characterized by constitutional symptoms like fever followed by maculo-papular rash, vesicles and bullae involving the trunk and limbs. The bullae rupture to form areas of extensive erosions. The eyes, oral cavity and genitals are invariably involved. The lips and oral cavity shows erosions and ulcers covered by hemorrhagic crusts (Fig. 212.2). The eyes may show purulent conjunctivitis and later corneal ulcers. The drugs commonly causing SJS in the state of Kerala is given in Table 212.2. Treatment is with high dose prednisolone (40-60 mg/day), antibiotics and antihistamines. Intravenous immunoglobulin (IVIG) in doses of 0.4 g/kg/day given for 3-4 days is life saving and therefore should be considered in severe cases. The care of the eye is very important. Frequent sterile saline irrigation for the eyes, topical eye antibiotics like tobramycin or quinolones, topical betamethasone or prednisolone eye drops are necessary. Eye should be managed by the ophthalmologists. Frequent rinsing of the oral cavity with chlorhexidine or dilute potassium permanganate mouth washes is essential.

Toxic Epidermal Necrolysis (TEN)

TEN is a dermatological emergency with a very high mortality. The drugs causing TEN in Kerala are given in Table 212.2. The patient first presents with high grade fever and severe toxemia followed by purpuric macules on the trunk and limbs with a 'charred' appearance involving more than 30% of the body area (Fig. 212.3).



Fig. 212.2: SJS-oral cavity shows ulceration and crusting



Fig. 212.3: Toxic epidermal necrolysis due to ampicillin carbamazepine

These lesions are soon followed by blistering and large areas of the skin sloughs off leading to extensive areas of erosions. There is severe oral, eye and genital mucosal involvement. Hepatitis and acute renal tubular necrosis are the systemic complications. Loss of large areas of skin leads to electrolyte imbalance, septicemia and temperature dysregulation which may lead to death. High dose systemic steroids, antibiotics and intravenous immunoglobulin have to be given. Barrier nursing and proper skin and eye care is essential for the patient.

Exfoliative Drug Eruption

Heavy metals like gold, phenytoin, INH, ayurvedic and homeopathic preparations are notorious to cause exfoliative type of drug reaction. Emollients like liquid



Fig. 212.4: Bullous lesion of FDE



Fig. 212.5: Fixed drug eruption due to sulphonamide—
Note the post-inflammatory hyperpigmentation

paraffin, systemic steroids and antihistamines have to be given (refer erythroderma).

Fixed Drug Eruption (FDE)

This is a localized type of drug reaction caused by paracetamol, sulphonamides, dapsone and tetracyclines. 30 minutes to 8 hours after taking the drug, the patient may develop sharply demarcated macules, initially erythematous, then dusky red to violaceous and then become oedemaous which may evolve to a bulla and erosion (Fig. 212.4). Common sites are the limbs, face or trunk. Sometimes there may be painful blisters and erosions on the oral or genital mucosa. The lesions heal by themselves with post inflammatory hyperpigmentation, but on subsequent exposure to the same drug the lesions recur at the same sites or other sites (Fig. 212.5).

Urticarial Drug Reactions

Urticaria and angioedema are usually caused by penicillins, cephalosporins and sulphonamides. Urticarial drug reactions can also occur as a part of anaphylaxis where the patient will have bronchospasm and vasomotor collapse. Adrenaline (0.5 mL SC), hydrocortisone (100 mg) and pheniramine maleate (10-20 mg) injections are life saving.

Acneiform Eruptions

Steroids, INH and phenytoin are the drugs causing acneiform eruptions. It is characterized by monomorphic, acne like lesions distributed on the face, limbs and trunk. Comedones are absent. Stopping the drug will clear the lesions.

Lichenoid Eruptions

It presents as pruritic violaceous papules resembling lichen planus on the trunk and upper limbs. Oral lesions are absent. Gold salts, captopril, antimalarials and beta-blockers may produce lichenoid eruption.

Photosensitive Drug Reaction

Photosensitising drugs like psoralens, sulphonamides, tetracyclines, retinoids, chlorpromazine and thiazide diuretics cause this type of reaction. Erythema, papules and sometimes vesiculation occurs on the face and extensor aspect of upper limbs (sun exposed areas).

Hyperpigmentation

Clofazimine, chlorpromazine, minocycline and antimalarials are the common drugs which cause diffuse hyperpigmentation of the face and trunk.

Chapter Summary

- Disorders of Blood Vessels 1382
- Vasculitis 1382
- Stasis Ulcer 1382
- Neuropathic Ulcers 1383
- Disorders of Lymphatics 1383
- Lymphedema 1383
- Lymphangioma Circumscriptum 1383

Disorders of Blood Vessels

Diseases of arteries and veins contribute to a large variety of dermatoses, leg ulcers being the most common. The common causes of leg ulcers in India are given in Table 213.1.

Vasculitis

Vasculitis is the inflammation of small and large blood vessels. The blood vessel is infiltrated by polymorpho-nuclear cells, lymphocytes or granulomas. It presents with well defined painful punched out ulcers on the lower aspect of the legs (Fig. 213.1). It can also be a manifes-



Fig. 213.1: Vasculitic ulcer
Note indolent ulcer—no sign of healing

tation of systemic disorders like SLE. *Pyoderma gangrenosum* is a type of vasculitis that presents with single or multiple well defined painful ulcers with undermined edges and a violaceous border on the trunk and lower extremities. It may be associated with systemic disorders, especially inflammatory bowel disease. Treatment of the primary cause leads to healing of ulcers.

TABLE 213.1 Common causes of leg ulcers	
1. Traumatic	
2. Arterial occlusion	Atherosclerosis Thromboembolism Thromboangitis obliterans
3. Vasculitis	SLE, Rheumatoid arthritis Pyoderma gangrenosum
4. Venous	Stasis ulcers
5. Infections	Fungal, Parasitic
6. Neuropathic	Leprosy Diabetes mellitus Tabes dorsalis
7. Malignancies	Squamous cell carcinoma Kaposi's sarcoma

Stasis Ulcer (Varicose Ulcer)

Chronic venous insufficiency of the deep veins of the legs leads to edema and later ulceration. It presents as chronic non-healing ulcers on the lower medial aspect of the legs along with stasis eczema. The lesions in the veins can be demonstrated by Doppler studies of the venous system. Foot end elevation, pressure stockings, and management of eczema by regular use of emollients and topical steroids and antibiotics are helpful in mild cases. Regular foot exercises help to allay progression of the lesion. Surgical treatment of the varicose veins may be required in intractable cases.



Fig. 213.2: Leprosy with neuropathic ulcer



Fig. 213.3: Maggots in the neuropathic ulcer

Neuropathic Ulcers

Neuropathic ulcers complicate sensory and autonomic neuropathy occurring in several diseases such as diabetes mellitus, leprosy and other forms of sensory neuropathies, syringomyelia and others. Leprosy is a very common cause for plantar ulcers in India (Fig. 213.2). Anesthesia, defective walking mechanism due to collapse of arches of feet and autonomic neuropathy leading to fissuring of soles contribute to the formation of the ulcers. Ball of the big toe, head of metatarsals and heel are the common sites for ulcers. The ulcers can also be complicated by infestation with maggots (Fig. 213.3). The patient should be advised bed rest. Antibiotics and potassium permanganate foot baths help to resolve the ulcers. Once

TABLE 213.2

Causes of lymphedema

Congenital	Milroy's disease-rare
Acquired	Filariasis
	Chronic cellulitis
	Lymphangitis
	Proximal lymphatic obstruction

the ulcer has become clean a plaster of Paris cast may be applied to help healing. Use of footwear with micro-cellular rubber (MCR) helps to prevent relapse. The primary condition should receive simultaneous treatment.

Disorders of Lymphatics

LYMPHEDEMA

Accumulation of lymph in the soft tissues due to obstruction leads to lymphedema. The common causes of lymphedema are given in Table 213.2.

Lymphedema presents with erythema and edema of the lower limbs, upper limbs or external genitals depending upon the cause. In chronic cases the edema becomes non-pitting. Recurrent fever with rigor and chills and streptococcal cellulitis complicates lymphedema caused by filariasis. Chronic lymphatic obstruction is common in malignant metastasis in the lymph nodes, in surgical removal and irradiation of the lymphatic system. Chronic lymphedema may be complicated by verrucous nodules and plaques on the skin surface known as *elephantiasis verrucosa nostra*. This may be rarely complicated by lymphangiosarcoma. There is no specific treatment. Cellulitis and lymphangitis should be treated with penicillin. Surgery may be required in some cases. See also Chapter 70.

LYMPHANGIOMA CIRCUMSCRIPTUM

This is a localized congenital lymphatic malformation characterized by confluent vesicles resembling “frog spawn”, distributed on the axillary folds, proximal part of limbs, perineum and tongue. Treatment is by surgical excision or ablation by CO₂ laser.

Chapter Summary

- Disorders of Hypermelanosis 1384
- Freckles 1384
- Lentigines 1384
- Melasma (Chloasma) 1384
- Incontinentia Pigmenti 1385
- Disorders of Hypomelanosis 1385
- Vitiligo 1385

Normal skin color is determined by the amount and distribution of melanin in the skin. Increase or decrease of melanin in the epidermis results in hyper or hypomelanosis respectively.

Disorders of Hypermelanosis

Dermatoses and systemic disorders that present with hypermelanosis are given in Table 214.1.

Freckles

Also known as ephelides, this autosomal dominant condition presents with hyperpigmented macules on the face and other sun exposed areas. This disorder is more common on the white caucasoid skin. Treatment is by applying sunblocks like zinc oxide or sunscreens containing avobenzones, oxybenzone, anthranilates, cinnamates or octyl salicylates, avoiding excessive

sunlight and cosmetic chemical peeling by phenol, solid CO₂ and glycolic acid.

Lentigines

Lentigines are hyperpigmented macules arising due to increased melanocytes at the dermo-epidermal junction. They may be single, segmental or multiple. Multiple lentigines can occur as part of syndromes like ‘LEOPARD’ syndrome consisting of L- lentigines, E- ECG abnormalities, O- ocular hypertelorism, P- pulmonary stenosis, A- abnormal genitalia (infantilism, cryptorchidism), R- retardation of growth, D- deafness. Lentigines can affect any area of the skin and mucous membrane. There is no specific treatment.

Melasma (Chloasma)

This disorder mainly affects women and presents with hyperpigmented macules and patches on the cheeks and forehead (Fig. 214.1). It results from exposure to sunlight. Pregnancy and use of oral contraceptives predispose to the condition, indicating a hormonal relationship. Treatment is by a combination of topical depigmenting agents like hydroquinone 2-4%, tretinoin 0.025-0.05% and hydrocortisone 1%. Chemical peeling with



Fig. 214.1: Hyperpigmented patches of melasma on the malar region

TABLE 214.1

Disorders of hypermelanosis	
Dermatoses	Systemic disorders
Freckles	Incontinentia pigmenti
Lentigines	Peutz-Jeghers syndrome
Melasma	Albright syndrome
Café-au-lait macules	Fanconi's anemia
	Endocrine disorders

trichloroacetic acid or glycolic acid is useful. Sunblock creams such as zinc oxide are essential in the prevention of melasma.

Incontinentia Pigmenti

This X-linked dominant genodermatoses presents with bullous lesions at birth evolving into warty plaques and later healing with hyperpigmented macules and patches with a bizarre pattern resembling “Chinese figures” distributed on the trunk and limbs. There may be associated ocular defects like cataracts, papillitis, congenital retinal folds and optic atrophy and dental defects like delayed dentition, impacted and missing teeth, pegged teeth and malformed crowns. There is no definite treatment. Genetic counselling is a must.

Peutz-Jeghers Syndrome

It is characterized by intestinal polyposis with periorificial lentigines. They are prone to develop intestinal malignancy.

Disorders of Hypomelanosis

Disorders presenting with hypopigmentation and depigmentation are given in Table 214.2.

Vitiligo

This is a primary autoimmune depigmentary disorder. Vitiligo accounts for 3.12% of the skin disorders in Kerala. Secondary post-inflammatory depigmentation is called leukoderma. In a vitiligo patch melanocytes are absent and hence no melanin production. Vitiligo presents with multiple depigmented macules and patches on any area of the skin including oral and genital mucosa (Fig. 214.2). They may be localized, segmental or generalized. Sometimes the hair on a vitiligo patch may also be depigmented known as leukotrichia. Vitiligo may be associated with other autoimmune disorders.

TABLE 214.2		
Disorders of hypomelanosis		
Genetic	Systemic disorders	Dermatoses
Albinism	Hypopituitarism	Leprosy
Piebaldism	Thyroid diseases	Pityriasis alba
Tuberous sclerosis	Pernicious anemia	Pityriasis versicolor
Vitiligo	Other autoimmune diseases	Syphilis
		Sarcoidosis



Fig. 214.2: Vitiligo-depigmented patches on the shin

Treatment: PUVA (Psoralens + UVA) is very effective. 8-methoxy psoralen is given in a dose of 0.03 mg/kg (20 mg for an adult) orally. Two hours later the lesions are exposed to ultraviolet light repeatedly for increasing duration till repigmentation, which usually occurs in 12-18 months. Alternatively sunlight can be employed as the source of ultraviolet light (PUVA- SOL) for 15-30 minutes. This procedure is done 2-3 times/week. Eye protection with UVA blocking glasses is necessary during and after treatment. Extensive and acutely occurring vitiligo responds satisfactorily to systemic steroids and these drugs have to be used with caution.

Chapter Summary

- Disorders of Hair 1386
- Alopecia Areata 1386
- Cicatricial Alopecia 1387
- Androgenic Alopecia 1387
- Hypertrichosis 1387
- Hirsutism 1387
- Canities 1387
- Diseases of Nails 1387
- Paronychia 1387
- Onychomycosis 1387
- Nail Psoriasis 1388
- Miscellaneous Conditions affecting the Nails 1388

Disorders of Hair

The hair is a skin appendage. It develops from the primary epithelial germ at the third month of gestation. The hair growth is cyclic. The growing phase of the hair is known as anagen, the involutionary stage catagen and the shedding stage is telogen. Hair disorders account for 1.89% of the skin disorders seen in Kerala. The common hair disorders encountered are given in Table 215.1.

ALOPECIA AREATA

This is an autoimmune disease characterized by localized reversible loss of hair usually involving the scalp, mustache and beard area, even though any hair bearing area can be affected. The involved area will resemble a



Fig. 215.1: Alopecia areata



Fig. 215.2: Alopecia universalis

TABLE 215.1

Hair disorders
Alopecia areata
Cicatricial alopecia
Androgenic alopecia
Hypertrichosis
Hirsutism
Canities

bald patch and at the periphery the typical “exclamatory” hairs can be seen (Fig. 215.1). Exclamation mark hairs are broken off stubby hairs where the distal ends are broader than the proximal ends. Alopecia totalis is denoted when the entire scalp hair is lost and alopecia universalis, when the entire body hair is lost (Fig. 215.2). Treatment is by topical irritants like salicylic acid, topical steroids

and intralesional steroids. The patient should be reassured of its benign nature and spontaneous recovery.

CICATRICIAL ALOPECIA

This is scarring alopecia and the hair does not regrow. Scarring alopecia is caused by trauma, infections, follicular lichen planus of scalp, discoid lupus erythematosus and malignancies. Hair transplantation or the use of artificial hair is indicated to relieve psychological distress and social disability.

ANDROGENIC ALOPECIA

This is male pattern baldness and is an androgen dependent condition with a strong familial background. The commonest type of clinical presentation is frontoparietal hair recession. Hamilton’s scale is used for grading the degree of hair loss. Treatment is with topical minoxidil 2-5% and/or systemic anti-androgen drugs like finasteride (1 mg/day). Female pattern alopecia may have to be treated with anti androgens like cyproterone acetate (100 mg/day), flutamide (250 mg/day) and spironolactone (200 mg/day). Unresponsive patients may require hair transplantation.

HYPERTRICHOSIS

Increased hair growth in areas of normal growth is called hypertrichosis. It can be congenital, acquired or iatrogenic. Congenital *hypertrichosis lanuginosa* is a condition where the infant’s skin is covered by lanugo hair. The hair will be silky and the entire body, excepting the palms and soles will be affected. Acquired hypertrichosis lanuginosa is paraneoplastic manifestation. Steroids, phenytoin, minoxidil and diazoxide are the drugs causing hypertrichosis.

HIRSUTISM

This is male pattern hair occurring in females. Terminal hairs develop on the androgen-dependent areas like the mustache and beard area in a female. Endocrine abnormalities may play a role. Polycystic ovary syndrome is an important cause for hirsutism. Medical treatment includes anti-androgens like finasteride, flutamide and spiranolactone. Electrolysis and laser epilation are the new modalities of therapy.

CANITIES

Graying of hair is known as canities and premature graying of hair is denoted when graying occurs below 20 years of age. Genetics may play a role in premature graying. Calcium pantothenate may be beneficial in some patients.

TABLE 215.2

Nail disorders
Paronychia
Onychomycosis
Nail psoriasis
Leuconychia
20 nail dystrophy
Beau's nail
Mee's nail
Terry's nail
Muerhcke's nail
Half and half nail

Diseases of Nails

The finger nails grow approximately 0.1 mm/day and toe nails one-third this rate. The nail lesions may at times reflect serious systemic disorders. The common nail disorders are given in Table 215.2.

PARONYCHIA

Acute paronychia is a staphylococcal infection of the nail folds. The patient presents with painful swelling and erythema of the nail folds. Compression helps to extrude pus. *Chronic paronychia* is seen in domestic workers, fish mongers and canteen workers who frequently come into contact with water. Chronic paronychia is caused by a combination of staphylococcus and candida albicans. There is separation of the cuticle from the nail plate and retraction of the proximal nail fold. It may be associated with swelling, redness and mild tenderness of the proximal nail fold.

Acute paronychia may need incision and drainage, and systemic antibiotics like cloxacillin or cephalosporins. Chronic paronychia is managed by topical anti fungal agents like clotrimazole lotion or a combination with topical steroids like betamethasone twice daily for 3-6 months. Topical amorolfine nail lacquer applied twice weekly is effective in localized distal nail infection. If proximal nail damage occurs, oral antifungal therapy with itraconazole 200-400 mg/day for 6 weeks or pulse therapy with 400 mg/day for 1 week/month, for 3 months, is required. Prevention is by stopping wet work and use of gloves to protect hands.

ONYCHOMYCOSIS

Fungal infection of the nails is called onychomycosis and is caused by dermatophyte species or by *Candida albicans* (Fig. 215.3). One or more nails may be affected. The nails will be discolored, brittle and sometimes total dystrophy



Fig. 215.3: Onychomycosis

may occur. The condition is generally resistant to treatment. Systemic therapy with griseofulvin (500 mg/day) for 3 months for finger nails and 6 months for toe nails is required. Pulsed doses of itraconazole, 200 mg bid for 7 days a month, repeated twice for finger nails and thrice for toe nails are effective. Terbinafine 250 mg/day for 6 weeks is the treatment for dermatophyte infections of the nails. Amorolfine, a nail lacquer applied once or twice a week is effective.

NAIL PSORIASIS

Psoriasis is the most common dermatosis affecting the nails. Fine pitting is the hall mark of psoriasis. Pitting of nail can also occur in alopecia areata. “Oil spot macule” is the most specific nail change seen as a yellowish brown macule on the nail plate. Subungual hyperkeratosis is thickening of the distal end of the nail with retained keratin underneath. Onycholysis is lateral or distal separation of the nail plate from the nail bed which can be seen in fungal infections and eczemas also. Sometimes dystrophy of all the nails can occur (Fig. 215.4).



Fig. 215.4: Nails show onychodystrophy, onycholysis and subungual hyperkeratosis with psoriasis of the adjacent skin

Miscellaneous Conditions affecting the Nails

Leuconychia is whitish discoloration of the nails as a consequence of hypoproteinemia and renal or hepatic disease.

Twenty nail dystrophy is considered to be a manifestation of lichen planus where all the 20 nails are dystrophic.

Beau’s nails are transverse grooves seen on the nail plate sometimes involving all the nails. They may follow severe systemic illnesses like pneumonia and is due to a temporary arrest of nail growth.

Mee’s nails are white transverse bands seen on the nail plate and may be a manifestation of chronic arsenic poisoning or chemotherapy.

The other nail disorders shown in the table are described in the cutaneous manifestations of systemic disorders.

216

Disorders of Elastin and Collagen Fibers

S. Pradeep Nair

Chapter Summary

- Cutis Laxa 1389
- Pseudoxanthoma Elasticum 1389
- Striae Distensae 1389
- Anectoderma (Macular Atrophy) 1389
- Ehlers-Danlos Syndrome 1390
- Keloid and Hypertrophic Scar 1390

The elastin and collagen fibers of the skin give strength and elasticity to the skin. The disorders affecting these fibers are given in Table 216.1.

TABLE 216.1

Disorders of elastin and collagen fibres	
Elastin	Collagen
• Cutis laxa	Ehlers-Danlos syndrome
• Pseudoxanthoma elasticum	Pachydermoperiostosis
• Striae distensae	Keloid/hypertrophic scars
• Anectoderma	
• Marfan's syndrome	

Cutis Laxa

Cutis laxa is a heterogenous group of elastic tissue disorders characterized by skin laxity and involvement of internal organs. It may be inherited or acquired, localized or generalized. Inherited cutis laxa may be autosomal dominant or recessive. Acquired cutis laxa is seen as a sequel of recurrent urticaria, angioedema and SLE in a few cases. Abnormalities of elastic fibers causes the skin to be lax and pendulous, hanging in folds especially on the face and axilla giving the patient a “blood hound” or “old man” facies (Fig. 216.1). The skin loses its elasticity. Pinching the skin causes slow recoiling. Plastic surgery procedures like “face lift” operations may benefit the patient.



Fig. 216.1: Acquired cutis laxa

Pseudoxanthoma Elasticum

This autosomal dominant disorder affects the elastic fibers of the skin, blood vessels and eyes. The skin is soft, lax and wrinkled involving the sides of neck, flexures and abdomen. The skin on the neck may have a “chicken skin” or “cobblestone” appearance. The patient may have cardiac and ocular defects. Angioid streaks of the retina are seen. There is no specific treatment.

Striae Distensae

These are linear scars occurring due to skin stretching in pregnancy, weight lifters and sometimes in Cushing’s syndrome. These present as linear hypopigmented or depigmented scars on the breast, axilla, lower abdomen and thighs. Prolonged topical therapy with potent corticosteroids may also cause striae (Fig. 216.2) in the area of application. Topical retinoids may help to resolve the condition in some patients.

Anectoderma (Macular atrophy)

This represents a localized area of slack skin due to elastic fiber damage. It may be primary, or secondary to syphilis, leprosy or SLE. They present as out pouchings of the skin on the trunk, upper arms and thighs. The surface of the



Fig. 216.2: Steroid induced striae on the right thigh

skin is wrinkled. A finger can be insinuated into the lesions. There is no effective treatment.

Ehlers-Danlos Syndrome

This is an inherited disorder of collagen fibers. There are 11 sub types of this syndrome. Abnormalities of collagen

fibers cause increased fragility of the skin and blood vessels. The skin is hyperextensible and rebounds quickly after pinching in contrast to cutis laxa. There is hypermobility of the joints resulting in joint damage. Ecchymosis is seen in Type V and ocular involvement in Type VI (See Chapter 94).

Keloid and Hypertrophic Scar

These are localized areas of excessive collagen tissue response following injury. Keloids may occur de novo or following injury or acne. It presents as firm skin coloured or hyperpigmented plaques with peripheral pseudopodia like extensions. The commonest site is over the sternum. Extensive keloids are seen following burns. Keloid has to be distinguished from hypertrophic scar. The latter is confined to the original site of injury unlike keloid and it usually undergoes resolution. Treatment is recommended for both conditions. Intralesional triamcinolone up to a maximum of 10 mg per sitting is helpful to favour resolution. Simultaneous use of cryotherapy with liquid nitrogen hastens resolution. Results are better for hypertrophic scars. CO₂ laser ablation therapy is helpful in resistant cases.

217

Cutaneous Manifestations of Systemic Disorders

S. Pradeep Nair

Chapter Summary

- Generalised Pruritus 1390
- Thyroid Disorders 1391
- Diabetes Mellitus 1391
- Liver and Kidney Disorders 1391
- Internal Malignancy 1392

Generalised Pruritus

This is a very common manifestation of systemic disorders. The systemic conditions causing generalized pruritus are given in Table 217.1.

Generalized pruritus associated with systemic disorders is worsened during night. In diabetes mellitus, hepatic disorders and chronic renal failure the dryness (xerosis) of the skin may worsen the pruritus.

Management: Emollients like liquid paraffin and antihistamines like hydroxyzine (10-25 mg thrice daily) alleviate the pruritus. The underlying systemic disorder should be treated appropriately.

Several systemic diseases produce cutaneous manifestations which may be the first indication of the disease. Skin is considered to be the mirror of the body.

TABLE 217.1

Systemic causes of pruritus
Diabetes mellitus
Liver disorders
Chronic renal failure
Hyperthyroidism
Iron deficiency anemia
Polycythemia
Chronic leukemias
Lymphomas

TABLE 217.2

Skin manifestations of thyroid disorders	
Hyperthyroidism	Hypothyroidism
Generalised pruritus	Xerosis
Warm skin	Cold skin
Palmar erythema	Palmoplantar keratoderma
Hyperpigmentation	Decreased sweating
Increased sweating	Edema of hands, face and eyelids
Pretibial myxoedema	Xanthomas
Chronic urticaria	Sparse and coarse hair

Thyroid Disorders

The skin manifestations of thyroid disorders are given in Table 217.2.

Thyroid disorders may also be associated with diabetes and vitiligo. Pretibial myxoedema presents with skin colored or yellowish waxy nodules and plaques on the anterolateral aspect of lower limbs. Treatment is with topical potent steroids or with intralesional triamcinolone. Treatment of the basic thyroid problem may alleviate some of the skin manifestations.

Diabetes Mellitus

Diabetes is associated with a large number of skin manifestations (Table 217.3). Some of the manifestations may be related to poor diabetic control. The autonomic neuropathy of diabetes leads to xeroderma and ichthyosis which in turn leads to generalized pruritus.

Granuloma annulare presents with multiple discrete annular plaques with peripheral pebbling. Treatment is with topical steroids.

Necrobiosis lipoidica is a very specific skin lesion associated with diabetes. The patient presents with erythematous plaques on the shin which later becomes yellowish brown and undergoes central atrophy. The lesions have a glazed appearance and may ulcerate and then heal with scarring. Local treatment consists of the application of a potent glucocorticoid like clobetasol propionate 0.05% ointment.

TABLE 217.3

Skin manifestations of diabetes
Generalised pruritus
Xeroderma/ichthyosis
Granuloma annulare
Necrobiosis lipoidica diabetorum
Infections – bacterial, fungal
Diabeticorum bullosum
Scleredema diabetorum
Eruptive xanthomas
Diabetic dermopathy
Acanthosis nigricans
Diabetic ulcers

Candidal intertrigo is a very common fungal infection seen in diabetes.

Diabeticorum bullosum is the presence of large hemorrhagic bullae on the lower limbs.

Scleredema presents with edema and sclerosis of the skin of the upper back.

Diabetic dermopathy (shin spots) presents with multiple hyperpigmented patches on the lower limbs.

Eruptive xanthomas: The hyperlipidemia seen in diabetes may cause eruptive xanthomas presenting with skin colored to yellow papules on extensor surfaces and buttocks.

Acanthosis nigricans presents as velvety plaques on the nape of the neck and flexures.

Diabetic ulcers: These are common complications of longstanding diabetes. See section on diabetes.

Liver and Kidney Disorders

Liver and kidney disorders present with a wide variety of skin manifestations (Table 217.4).

Liver disorders: Hepatitis B and C infection can present with chronic urticaria. Palmar erythema and spider

TABLE 217.4

Skin manifestations of liver and renal disorders	
Liver disorders	Renal disorders
Generalized pruritus	Generalized pruritus
Xeroderma	Xeroderma
Jaundice	Hyperpigmentation
Hyperpigmentation	Kyrle's disease
Palmar erythema	Half and half nail
Spider angiomas	Calcinosis cutis
Terry's nails, Muerhrcke's nails	



Fig. 217.1: Kyrle's disease

angiomas occur in liver failure. Spider angiomas are usually seen on the upper half of the body. Terry's nails present with proximal white color and distal pink color. They occur in cirrhosis liver. Muehrcke's nails present with white bands and may be due to hypoalbuminemia.

Chronic renal failure: The skin signs are seen in advanced cases and are of limited diagnostic value.

Half and half nail presents with proximal white color and distal pink, red or brown color and is seen in 10% of patients with chronic renal failure.

Kyrle's disease is a perforating collagenosis of the skin and is often associated with diabetic nephropathy and/or retinopathy. It presents with multiple discrete hyperpigmented keratotic papules on the limbs and trunks (Fig. 217.1). The lesions may even precede the renal failure.

Metastatic calcification in the form of *calcinosis cutis* over the joints and flexures may occur.



Fig. 217.2: Plaques and nodules due to Non-Hodgkin's lymphoma

Internal Malignancy

The skin manifestations of internal malignancy may be either in the form of secondaries or as paraneoplastic syndromes. The abdominal skin is the commonest site of cutaneous secondaries in intra abdominal malignancies and occur in the form of papules, plaques or nodules (Fig. 217.2), a classic example being 'Sister Joseph's nodules' which are periumbilical cutaneous secondaries. Secondaries may be seen on the trunk and scalp in lung cancers, and on the scalp or operative scars in hypernephroma. The skin manifestations of paraneoplastic syndromes are given in Table 217.5 (Fig. 217.3).

Malignant acanthosis nigricans presents with diffuse hyperpigmentation of face and flexures. The palms of the hands show increased rugosity and hyperkeratosis (tripe palms). The usual malignancy is carcinoma stomach.

Leser Trelat sign is the occurrence of multiple pruritic seborrheic keratoses in a short duration on the trunk.

TABLE 217.5

Skin manifestations of paraneoplastic syndromes	
Skin manifestation	Malignancy
Generalized pruritus	Leukemia, lymphomas
Exfoliative dermatitis	Leukemia, lymphoma, Ca. rectum, colon, prostate
Acquired ichthyosis	Leukemia, lymphomas
Bullous eruptions	Ca. GIT, breast, lung, thymoma, Castleman tumour
Acanthosis nigricans	Adenocarcinoma of GIT
Leser Trelat sign	Adenocarcinoma of GIT
Pityriasis rotunda	Hepatocellular carcinoma
Erythema gyratum repens	Ca. lungs
Erythema annulare centrifugam	Leukemia, lymphomas
Erythema multiforme	Leukemia, lymphomas
Erythema nodosum	Leukemia, lymphomas
Necrolytic migrating erythema	α - cell tumour of pancreas
Migrating thrombophlebitis	Ca. pancreas, stomach, lungs
Acquired hypertrichosis lanuginosa	Ca. colon, rectum, bladder



Fig. 217.3: Acquired ichthyosis due to Hodgkin's lymphoma



Fig. 217.4: Erythema gyratum repens
Note the concentric plaques with wood-grain appearance

Erythema gyratum repens (Fig. 217.4) is characterized by multiple confluent erythematous scaly concentric and whorled patches on the trunk resembling “wood grain” pattern. These patients have a high incidence of lung carcinoma.

Erythema annulare centrifugum presents with multiple erythematous annular patches on the trunk with peripheral extension.

Necrolytic migratory erythema (glucagonoma syndrome) presents with superficial eroding areas of erythema and

scaling distributed on the lower abdomen, buttocks and thighs.

Migrating thrombophlebitis (Trousseau’s sign) involves the veins of the upper limbs and trunk.

Acquired hypertrichosis lanuginosa presents with excess lanugo or vellus hairs on the face and ears and later other hair bearing areas. This cutaneous manifestation has a very strong relation with internal malignancy.

218

Skin Tumours

S. Pradeep Nair

Chapter Summary

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Premalignant Skin Conditions	1394

Benign Skin Tumours

This chapter deals with the benign skin tumours and the premalignant skin conditions. They account for 1.98% of

the skin conditions in Kerala. Benign skin tumours can arise from the epidermis, dermis or the skin appendages. They commonly present with asymptomatic papules or nodules. The common benign skin tumours are given in Table 218.1.

Seborrheic Keratoses

This is a pigmented benign skin tumor composed of epidermal keratinocytes. This presents with single or

TABLE 218.1

Benign skin tumors
Seborrheic keratoses
Acrochordon
Keratoacanthoma
Trichoepithelioma
Syringoma



Fig. 218.1: Seborrheic keratosis

multiple hyperpigmented flat papules or plaques on the face, neck and upper trunk with a ‘stuck-on’ appearance (Fig. 218.1). Dermatitis papulosa nigra is a clinical variant presenting with tiny pin head sized hyperpigmented papules on the face and neck. Electro-surgery and cryotherapy are the treatment modalities.

Acrochordon

They are also known as skin tags or Templeton’s tags and are soft skin colored pedunculated papules usually seen on the neck, axilla, back and chest. Histologically they are soft fibromas. Treatment is by electrosurgery or cryotherapy.

Keratoacanthoma

This is a benign tumour originating from the pilo-sebaceous unit containing keratinized squamous cells. It presents as skin colored dome shaped firm papules or nodules with a central crater filled with a keratin plug usually seen on the central part of the face (Fig. 218.2). This has to be differentiated from squamous cell carcinoma. Spontaneous resolution may occur. Surgical excision, electrocautery or topical 5-fluorouracil are the treatment modalities.

Trichoepithelioma

This is a benign skin tumour arising from hair structures. These may be solitary or multiple. Multiple trichoepithelioma may be an autosomal dominant disorder. It presents



Fig. 218.2: Keratoacanthoma of the forearm

with skin colored papules distributed on the face, especially on the eyelids, cheeks and naso-labial folds. Treatment is by excision.

Syringoma

This is a tumour arising from the ductal part of the eccrine sweat glands. It presents with skin colored papules with a crenated edge on the upper and lower eyelids and cheeks. Treatment is by electrosurgery.

Premalignant Skin Conditions

Some common premalignant skin conditions are given in Table 218.2. They usually lead to squamous cell carcinoma.

Actinic Keratoses

This occurs due to chronic exposure to sunlight. It is rare in India, but common in white races. It is characterized by skin coloured or hyperpigmented hyperkeratotic papules and plaques on the sun exposed areas like the face and dorsum of hands. They may lead to squamous cell carcinoma. Small and superficial lesions can be treated with liquid nitrogen cryotherapy and topical

TABLE 218.2

Premalignant conditions
Actinic keratoses
Arsenical keratoses
Bowenoid papulosis
Cutaneous horn
Erythroplasia of Queyrat

5-fluorouracil. Large indurated lesions must be excised and sent for biopsy. Prevention consists of avoidance of direct sunlight and regular use of sunscreens containing avobenzones, oxybenzones and cinnamates.

Arsenical Keratoses

This occurs in individuals who are exposed to chronic arsenic poisoning. It presents as multiple discrete punctate keratotic papules and plaques on the palms and soles. It may be associated with lung carcinoma. Treatment is difficult, but keratolytic agents can be tried.

Bowenoid Papulosis

This is caused by human papilloma virus, HPV-16 and presents with multiple discrete lichenoid papules usually on the shaft of the penis. They may progress to squamous cell carcinoma. Treatment is by electrosurgery, cryotherapy

and topical 5-fluorouracil. Topical immune response modifier, imiquimod is also effective.

Cutaneous Horn

This presents as hard yellowish brown horny plugs or outgrowths on the upper part of the face and ears. Treatment consists of excision. Underlying squamous cell carcinoma should be excluded by histopathology.

Erythroplasia of Queyrat

This presents as red velvety plaques with a moist appearance on the glans penis in people with intact prepuce. It is considered to be a form of squamous cell carcinoma in situ. Treatment is with topical 5 fluorouracil if there is no submucosal invasion. Moh's surgery is the treatment of choice if the condition is invasive.

Psychiatry

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GENERAL CONSIDERATIONS

What is Psychiatry? The German Dr. Johann Reil originated the term ‘Psychiatry’ from the Greek root ‘psyche’ (=mind) and *iartos* (=treatment). Psychiatry or psychological medicine can be defined as that branch of medicine concerned with the study, diagnosis, treatment and prevention of disorders of the mind. Psychiatric disorders are termed variously as *insanity*, *mental illness*, *mental disease*, *emotional disorders*, *behavioral disorders*, *functional disorders* and the like in the past. Psychiatry differs from Psychology. *Psychology* deals with scientific study of behavior of normal man and animal.

Evolution of psychiatry: Though in prehistoric times physical and psychological illnesses were treated with contempt, with the renaissance movement the attitude towards the victim of illness came to be one of compassion. The **moral treatment** of insane was initiated by Phillippe Pinel in France in the 18th Century by setting free the lunatics from chains.

Mental hospitals have a long history of evolution. Originally these were called *mad houses*, *lunatic asylums* or *mental asylums* and these were places where the aggressive and violent psychiatric patients could be admitted and kept in isolation under custody along with other criminals. Laws providing for the admission, detention and discharge of lunatics into such lunatic asylums were also formed and these were known as the *Lunacy Acts*. With the passage of time these institutions came to be known as mental hospitals. At present the mentally disordered person are kept in the community and

treated without isolating them into mental hospitals. The modern approach is to consider psychiatric patients also along with the general stream of other patients and to provide treatment facilities for them in general hospitals under especially trained personnel. The mental hospitals are giving way to general hospitals and community psychiatry centers especially with the advent of modern drugs. Custodial care is being discouraged and the family and society are brought more and more to take care of the mentally ill patient who is allowed to remain in the community itself as far as possible. This helps to minimize psychiatric morbidity, facilitate early recovery and remove the social stigma. This practice of community psychiatry is a modern concept.

SIGNS AND SYMPTOMS OF MENTAL DISORDERS

Most of the symptoms are subjective in nature. Often the patients are mocked at and alleged of simply imitating the symptoms. These symptoms are expressed as disturbances in the mental functions. They are best described as disturbances of mood, cognition, and psychomotor activity (conation).

Disturbance of Mood

Laughing, crying, anger and the like are expressions of emotion. Emotion is the subjectively experienced feeling tone of mind. It is commonly noted as affect and mood. Though both are used interchangeably in the clinical setting, there are subtle differences. *Affect* is a momentary accentuation of emotion and *mood* a more sustained emotional state. The normal mood of a person is congruent with the ideas, action and behavior and it is appropriate to the situation. It is stable and adequate in intensity.

Disturbance of Mood

- Pleasant mood states
 - Euphoria
 - Elation

Ecstasy

Exaltation

Unpleasant mood states

Anxiety

Depression

Irritability

Hatred

Other mood states

Apathy

Anhedonia

Blunting

Incongruous.

Disturbance of Thinking*Of Formal thought*

Loosening of association

Flight of ideas

Neologism

Perseveration

Of Stream

Thought block

Pressure of talk

Poverty of thinking

Circumstantiality

Of Abnormal content

Delusions

Obsessions

Phobias

Suicidal ideas

Of Possession

Thought deprivation

Thought insertion

Thought broadcast

The common disturbances of mood include incongruity, anxiety, depression, elation, euphoria, ecstasy, flattening (blunting), lability, apathy and anhedonia. When mood is not in harmony or congruent to the ideas or actions it is called *incongruous affect*. For example, the person may start smiling on hearing the tragic news about a dear one. *Anxiety* refers to an unpleasant fearful mood. *Depression* denotes sadness of mood. Anxiety, depression, irritability, hatred and others are *dysphoric (unpleasant) mood states*. *Elation*, *euphoria* and *ecstasy* are euphoric (pleasant) mood states. Elation is a well sustained cheerful mood. Euphoria is a happy mood with grandiosity and increased physical well-being. Ecstasy is the extreme degree of pleasure (rapture). In *labile affect*, the mood frequency changes without reason (*emotional incontinence*). In *affective blunting* (flattening) the degree of emotional expression is reduced much (constricted). Loss of emotional expression is called *apathy*. The inability to feel or share pleasure is referred as *anhedonia*.

Typically the mood is sad in depressive disorder, elated in manic disorder, anxious in anxiety disorder, incongruous or blunted in schizophrenia and labile in organic disorders.

Disturbance of cognition: Cognition refers to an individual's thoughts, knowledge, interpretation, understanding and ideas about himself and his environment.

Thought (thinking) is the goal directed arousal of symbols, ideas and associations leading to a reality-oriented conclusion. The thought comes to light through the verbalization (talk/speech), writing and gestures. Normally, thinking is coherent (fully understandable) and relevant to the context. It follows logic and contains only relevant matters as contents.

Disturbances in thinking may involve its formation, stream (flow), contents and ownership (possession). Loosening (looseness) of association, flight of ideas, neologism and perseveration, are formal thought disorders. In *loosening of association* the grammatical alliance of talk is lost and no meaningful relation occurs between the ideas. The talk lacks comprehension. Apparently it looks like a flight of ideas. In *flight of ideas* the talk jumps from topic to topic in quick succession, the ideas are related to each other and they are comprehensible. *Neologism* denotes the formation of new words which have no meaning to others (e.g. Hirschsprung, Heboobi). *Perseveration* is the involuntary repetition of the same thought (talk or activity) given in response to a stimulus when a subsequent stimulus is presented. Thought is said to be *irrelevant* when it is not to the context. It is *incoherent* when it is not meaningful. Thought block, pressure of talk, poverty of thinking, tangential thinking and circumstantiality are disturbances of the stream of talk. When the stream of the talk suddenly stops in the midst and fails to proceed further it is termed *thought block*. In *pressure of talk* ideas continue to rush out of the mind due to its richness. On the other hand, in *poverty of thinking* the talk is scanty and flow is slow. In *circumstantiality* the talk is prolonged by lengthy narration of unwanted details before coming to the right point finally. In *tangential thinking* the flow of talk deviates in different directions and a final goal (point) is not reached. The thought may be disturbed by abnormal contents like delusions, obsessions, phobias and suicidal ideas. A **delusion** is an abnormal belief not shared by other people. It is a false, fixed notion which cannot be corrected even by giving evidence to the contrary. Delusion can be corrected by treatment. *The various kinds of delusions are persecutory, paranoid, grandiose, poverty, guilt, nihilistic, infidelity, control, and hypochondriacal/somatic*. In *persecutory delusion*, the patient may have the wrong notion that attempts are being made to harm

or kill him. He believes that secret plots are made against him; he is poisoned, he is spied upon and so on. A news in the media, a gesture observed, and a conversation he heard may be construed as referring to him only, and that they are deliberately done by his enemies (*delusion of reference*). *Paranoid delusion* is synonymous with persecutory delusion though it actually includes grandiose delusions as well. In case of *grandiose delusion* the patient may retain the false notion that he is immensely rich, he is having close contact with people of high caliber, he is very powerful or that he is a big scholar or scientist. In *delusion of poverty* he holds that he is extremely poor having lost everything and he may even start begging. In *delusion of guilt*, the belief is that the patient is a sinner who has done sinful deeds in the past or in the previous birth and attributes guilt to himself. The wrong notion held in *nihilistic delusions* is that part of his body, he himself or the world itself is not existing. In *delusion of infidelity* (amorous delusions, jealous husband's or wife's syndrome, pathological jealousy) the wrong notion is that the spouse is having illicit sexual relations. In *delusions of love (erotomania)* it is wrongly believed that someone is in sincere love with him or her. In *delusions of control* (influence/ passivity feeling) the person's belief is that his thoughts, mood and actions are being controlled by people outside. In *hypochondriacal delusion* the patients may think that he suffers from some incurable illness.

Primary delusion (autochthonous delusion) is the sudden development of delusion without being preceded by any psychological event in the background.

Secondary delusion occurs as a consequence of some psychological events such as mood changes, hallucinations, delusions, or others.

Systematized delusions are a complex set of delusions built one upon another around a single theme or an event.

Obsession denotes recurrent intrusion of unwanted thoughts into mind in spite of the efforts made to stop it. *Phobias* denotes a kind of fear specific to an object or a situation which are normally harmless. *Suicidal* idea is another abnormal content.

The ownership ('my-ness') of thought may be changed. Thought deprivation, thought insertion and thought broadcasting are disturbances in possession of thought. In *thought deprivation* (withdrawal) the patient believes that ideas are stolen or taken away from his mind. In *thought insertion* the belief is that ideas are introduced into his mind from outside agencies. In *thought broadcast* the belief is that his thoughts (unexpressed) are known to others as soon as it occurs to him. He may believe that his actions and thought are being controlled.

Thought disturbance is frequent in schizophrenia. Cognitive decline is the hallmark of dementia. Sad gloomy thought pervades depression.

Clinical importance of delusions		
Types of delusion	Characteristic false belief of	Typical mental disorder
Paranoid		
Persecutory	Persecution – to kill or – to harm	Schizophrenia, Depression (when moved congruent)
Reference	Actions of others have special reference/meaning	-do-
Grandiose	Oneself being high, big, rich	Mania
Poverty	Poverty or loss	Depression
Guilt	Sinful action	Depression
Nihilistic	Non-existence of part or whole of self or the world itself	Depression
Somatic/hypochondriasis	Bodily disease	Depression
Jealousy	Illicit sexual relationship	Delusional disorder, Alcoholism
Love	Being loved	Delusional disorder
Primary		Schizophrenia
Secondary delusions		Mood disorder or any psychosis

Disturbance of perception: Perception is the cognitive process of becoming aware of the objects and the environment around us by way of the sense organs. The various kinds of perceptions include visual (seeing objects), auditory (hearing sounds), tactile or haptic (feeling touch), olfactory (smelling odours) and gustatory (feeling taste), and gustatory phenomena. Hallucinations, illusions, macropsia and micropsia are the common disturbances of perception. *Hallucination* is the vivid sensory (perceptive) experience occurring in the absence of the corresponding external object or stimulus. Thus there can be visual, auditory, tactile, olfactory, and gustatory hallucinations. In *auditory hallucinations* one may hear voices or noises in the absence of the corresponding external stimulus. In *visual hallucination* one may see objects in the absence of such external objects. In a similar way, the hallucination may be olfactory, tactile or gustatory. In *Liliputian hallucinations*, the hallucinatory objects especially the people appear much smaller. Auditory and haptic hallucinations are common in schizophrenia. Visual hallucinations are common in organic disorders. Visual illusions occur in delirium and auditory illusions are common in depression. Hallucinations and illusions are not always pathological. *Hypnagogic hallucinations* occurring as one falls to sleep and *hypnopompic hallucinations* occurring as one

awakens from sleep are common phenomena. This may be a normal phenomenon at times.

Type of hallucinations	Typical disorder
1 Auditory	
a. Third person-running commentary; discussion, arguing, conversation	Schizophrenia
b. Second person-blaming, accusing, prompting suicide	Major depression
c. Hearing one's own thought aloud.	Schizophrenia
2 Visual	
a. Insects-spiders, snakes, and the like	Organic-delirium
b. Lilliputian.	Temporal lobe epilepsy (TLE)
3 Olfactory	
a. Aura-burnt smell	Temporal lobe epilepsy (uncinate fit)
b. Foul odor emanating from the body	Major depression
c. Poisonous, foul smelling gas applied from outside.	Schizophrenia
4 Tactile	
a. Cocaine 'bug'	Cocaine psychosis
b. Bizarre sensation such as radiation, electromagnetic waves, cosmic rays all caused by enemies outside.	Schizophrenia

Illusion: This refers to misrecognition of objects. A rope may be perceived as a snake or a shadow of a tree may be viewed as a ghost. The illusion can be corrected by verifying the truth by closer examination.

Micropsia: In micropsia the real object or figure appear smaller than what they actually are, and in **macropsia** it is the reverse. They are found in temporal lobe epilepsy (TLE).

Disturbance of memory: The function of memory includes *registration*, *retention* and *recollection* of past events and information. Events once registered are retained and stored in the memory centers, and are recalled later according to need. Recollection with the help of a cue is recognition.

The common disturbance of memory is amnesia, which denotes loss of memory. Amnesia may be global and progressive or selective for certain events only. The memory loss may be for immediate events (loss of retention) or for recent or remote events. The gap in memory may be filled up by fabricated and irrelevant events and information. This phenomenon is called **confabulation**.

Disturbance of intelligence: Intelligence is the global capacity of an individual to think rationally, to act swiftly and to adjust adequately to the surroundings. Intelligence grows and develops with physical growth and maturation.

Intelligence is expressed in terms of **Intelligence Quotient (IQ)**. The average IQ is 100 ± 16 . When the intelligence is not proportionately grown and developed **mental retardation** results. In **dementia**, on the other hand the normally acquired intelligence deteriorates. Dementia is an acquired disorder and mental retardation is developmental disorder.

Disturbance of consciousness: These affect the clarity of the sensorium. The disorder of consciousness includes **clouding, confusion, stupor and coma**. Functional psychiatric symptoms develop in a clear conscious setting. On the other hand if the symptoms are found to supervene on an impaired state of consciousness, an organic illness has to be considered. In hysterical fainting there is no real loss of consciousness, and they will be aware of the surroundings.

Disturbance of orientation: Orientation is the appreciations of one's own temporal, personal, and spatial relations at a given moment. **Disorientation** is the disturbance of orientation. Disorientation may pertain to time, place or persons. It may occur in delirium.

Disturbance of attention and concentration: Distractibility is the disorder in which the attention is impaired. Fluctuating levels of attention are found in organic brain syndromes, e.g. delirium. Lack of concentration is seen in depression, schizophrenia, dementia and delirium.

Disturbance of insight: This denotes the abnormalities in the state of awareness of physical or mental health. Psychotic patients believe that they have no illness and so refuse treatment, whereas neurotic patients admit their illness but generally refuse to admit that their illnesses are psychological. They prefer treatment from doctors other than psychiatrists.

Disturbance of conation (motor activity): *Conation* represents the will to carryout an activity. It can be expressed as psychomotor or motor activity. It is different from neurological motor function. The disorder of motor activity may include decreased, increased and repetitive activity and disturbance of posture. The condition is called **psychomotor retardation** when the motor activity is decreased. In **psychological stupor** the motor activity is reduced to a minimum and the patient is fully conscious, unlike as in organic stupor. When motor activity is increased it is termed as **psychomotor overactivity**. Motor activity is increased to a very high degree in states of psychotic excitement. Repetitive motor activity includes stereotypy, mannerism, perseveration, echopraxia and echolalia.

Stereotypy: This term refers to monotonous, purposeless, repetition of an activity. **Mannerism** also is a repetitive

activity but is not monotonously repeated and often goes with normal personality. The repetition of a previous activity in spite of the patient's effort to move on to a new activity is called **perseveration** of activity. **Echopraxia** denotes involuntary repetition or imitation of an activity just seen. **Echolalia** denotes involuntary repetition or imitation of words just heard.

Catatonia: This term refers to widespread rigidity which may manifest as waxy flexibility posturing, negativism and excitement. **Waxy flexibility (flexibilitas cerea/catalepsy)** In this disorder limb can be positioned in any awkward posture for any length of time. **Posturing** refers to maintenance of imposed postures, which may be even bizarre and uncomfortable for long periods of time, however, awkward they may be.

Negativism: This term refers to the resistance to perform an activity, or doing opposite to what is expected for a given stimulus.

Disturbance of behavior: Behavior is a general term. It is any activity either physical or mental, like walking, crying, speaking, eating, writing and the like. This term is broadly used to describe mental function.

Somatic symptoms: Physical symptoms pertaining to any bodily system may be associated with psychiatric disorders and occasionally be the presenting symptom of such disorders.

Clinical Examination of a Psychiatric Patient

Examination of a psychiatric patient in general is similar to that of a medical case. The first part consists of history taking and the next consists of the mental state examination. In addition, a full physical examination is required for all cases. An informant to whom the patient is closely known should be selected for eliciting the history, especially in the case of psychosis and mental retardation. It is important to establish an understanding relationship (rapport) with the patient. A scheme followed in psychiatric examination is given below:

- A. *History*
 - a. Bio-data
 - b. Presenting complaints
 - c. History of the present illness
 - d. History of past medical and psychiatric illness
 - e. Family history
 - f. Personal history
 - g. Premorbid personality
- B. *Mental status examinations*
 - a. Appearance and general behavior
 - b. Motor activity
 - c. Mood (affect)

- d. Thinking
- e. Perception
- f. Consciousness
- g. Orientation
- h. Attention and concentration
- i. Memory
- j. Intelligence
- k. Judgment
- l. Insight
- C. *Physical examination*
 - a. General
 - b. Systemic
- D. *Provisional diagnosis*
- E. *Investigations - biological and psychological*
- F. *Final diagnosis.*

History

Bio-data: The name, address, age, sex, income, education, occupation and marital status are noted.

Presenting complaints: The common presenting complaints include aggression, violence, excessive talk, retarded motor activity, suicidal behavior, insomnia, loss of appetite, body aches and pains, paralysis, loss of memory, poor intelligence, habituation to drugs and intoxicants, and sexual disorders. The presenting complaints are recorded in sequential order.

History of present illness: All details of the illness from its onset to the present state should be vividly described. Precipitating and aggravating factors and daily variation of symptoms are enquired into. Details of treatment have to be recorded. Leading questions may be required to bring out features such as suicidal tendencies, substance abuse, sexual disturbances, obsessions, delusions or hallucinations.

History of past illness: This should include all the past psychiatric problems, medical illness, physical trauma and accidents. Important events from birth (including birth injuries) and milestones of development have to be obtained.

Family history: All details of the family members, their inter-relationship, the family structure, the attitude of other family members towards the patient and the occurrence of psychiatric illness in family have to be elicited. It is always desirable to construct a family tree.

Personal history: All details regarding occupation, work, socio-economic status, sexual activity, addictions, marriage and marital adjustments and details of the children should be recorded. A biographic scheme is to be derived. Intrauterine history; details of delivery, diseases, trauma during childhood, administration of drugs, poor group relations and details of education are

taken. History of physical torture and sexual assault during childhood should also be elicited.

Premorbid personality: This refers to the personality of the individual before developing the illness. This should include the general behavioral pattern, his hobbies, likes and dislikes, character trait, habits, attitude, social relations and others. The patient comes back to premorbid personality level, once he recovers from the mental illness.

Mental Status Examination

General appearance and behavior: The look of the patient, his dressing, hair style, level of co-operation, communication skills and level of activity, are noted.

Psychomotor activity: Note whether the activity is normal, decreased or increased and then look for specific disturbances of motor activity such as stereotypy, stupor, mannerism, negativism and others.

Affect and mood: The mood is assessed objectively and subjectively. The patient is asked to tell about his mood which gives the subjective mood state. Objectively the mood may be assessed by the interviewer. Normally, both subjective and objective mood should be the same (congruent). Abnormalities of mood, if any, are determined.

Thinking: This is brought out by noting the talk, writing and gestures of the patient. Disturbance of thinking manifests as disturbance of the form, stream, content and possession of the thought. Suicidal tendencies, obsessions and sexual matters have to be brought out by specific interrogation. When the patient is mute, gesture or written language is taken for analysis.

Perception: Spontaneous gestures and self-conversation may give clue to hallucinations. Symptoms such as hearing voices or other sensory experiences, in the absence of any real source should suggest hallucinations. In the presence of hallucination, its content, the person (whether first, second or third) and the related mood should be elicited.

Consciousness: The level of consciousness has to be carefully recorded through inspection and interrogation.

Orientation: Orientation in time (day, date, week and year) place and persons should be assessed.

Attention and concentration: Attention can be assessed during interrogation. Normally, attention is prompt and sustained as long as the stimulus continues. Attention and concentration can be tested by:

- *Forward and backward counting test:* The patient is made to count 1 to 20 forwards and then backwards.
- *Serial deduction test:* To deduct serially 3s from 40 or 9s from 100. *The rate of performance and the*

errors committed will give an idea of the state of attention and concentration. These factors also depend to great deal on the level of his education.

- *Digit span test:* In the digit forward test the patient is asked to repeat digits given by the interviewer containing three, four, five, six, seven or eight digits (e.g.: 729, 3194, 27106....). In the backward digit test, the digits given by the examiner have to be repeated in the reverse order (i.e. 8139 as 9318). *7 digits forward and 5 digits backward constitute, normal ability.* It is lowered when the attention or immediate memory is impaired.

Memory: Immediate memory (power of retention), recent memory and remote memory have to be separately assessed.

- *Intelligence:* This can be assessed clinically by knowing his adaptive skills, general knowledge, occupational adjustments, educational achievement, motor skills, management of finance, household and others, during the interview. Intelligence can also be measured by scales of intelligence.

Judgment: This can be assessed by making the patient take decisions when confronted with specific situations. For example, the patient is asked “*what will you do when you see a house on fire?*”, “*What will you do when you get a wound on your finger?*” Answers to these types of questions help to reveal impairment in judgment.

Insight: This is the appreciation of one’s own physical and mental state. To assess the level of insight the patient is just asked whether he is sick or he needs any treatment. Patients who have no insight often answer that they are not ill and that they do not require any treatment in spite of severe symptoms.

Physical Examination

No mental examination is complete without a thorough physical examination.

At the end of the psychiatric and physical examinations, a provisional diagnosis can be arrived at in most cases.

Psychological testing: **Psychometry** is the method of measuring psychological processes, and states. These tests are ancillary to clinical assessment. They measure specific aspects of intelligence, personality and thinking. Neuropsychological tests help to quantify and localize the brain damage.

Intelligence test: The common scales of intelligence are:

- Wechsler Intelligence Scale for adults and for children
- Raven’s progressive matrices test
- Bhatia’s battery of intelligence scale
- Binnet Simon scale of intelligence.

Personality tests: These assess the type of personality, its change or deterioration, if any .The usual tests are:

- Minnesota Multiphasic Personality Inventory(MMPI)
- Rorschach Test by Hermann Rorschach
- Bender Visual Motor Gestalt Test (BVMG).

Memory tests: These quantify the loss of memory, e.g.

- Boston Memory scale
- Wechsler Memory scale
- Bender Visual Motor Gestalt test (BVMG).

Rating scales: These are questionnaires, interviews and checklists that help to quantify behavior, thought and mood. For example:

- Brief psychiatric rating scale (BPRS)
- Hamilton’s rating scales for depression
- Hamilton’s rating scales for anxiety
- Abnormal involuntary movements scales (AIMS).

Classification of Mental Disorders

The terms ‘psychiatric’ and ‘mental’ which are used synonymously, denote disorders pertaining to the mind. A major impediment in the classification of mental disorders is the absence of a specific etiological factor. So, the term disorder is preferred in place of disease or illness. For the same reason an etiological classification may not always be possible. The psychiatric disorders are therefore categorised into diagnostic entities based on sets of symptom patterns having a separate course (categorical classification). The American Psychiatric Association has made a system of classification known as *Diagnostic and Statistical Manual of Mental Disorders* (DSM).The World Health Organisation has made its own system known as *International Classification of Diseases and Related Health Problems(ICD)*. The DSM 1V and ICD –10 are currently in vogue.

ICD –10 is widely followed. The diagnostic categories are give under chapter V(F). Each diagnostic category is given an alphabetic letter code (F) followed by a number code (alpha numerical coding). The disorders range from F-00 to F-99.

Features of psychoses and neuroses are given in Table 219.1.

TABLE 219.1
Features of psychoses and neuroses

Major psychological disturbance with	Minor psychological disturbance with
Loss of contact with reality	No loss of contact with reality
Loss of insight	No loss of insight
Disintegration of personality	No disintegration of personality
Presence of delusions	No delusions
Presence of hallucination e.g. schizophrenia, delirium	Typically no hallucination, except rarely, e.g. anxiety neurosis, hysterical neurosis

A simplified version of the main category of mental disorders

- F00—F09 Organic mental disorders
- F10—F19 Mental disorders due to psychoactive substance use
- F20—F29 Schizophrenia and delusional disorders
- F30—F39 Mood (affective) disorders
- F40—F49 Neurotic stress-related and somatoform disorders
- F50—F59 Behavioral syndromes associated with physiological disturbance
- F60—F69 Personality disorders
- F70—F79 Mental retardation
- F80—F89 Psychological developmental disorders
- F90—F98 Childhood emotional disorders
- F99 Unspecified mental disorders.

The terms such as *psychosis*, *neurosis* and *functional* disorders are not in common use at present. By tradition, a disorder or symptom is said to be functional when there is no demonstrable physical abnormality in any organ system.

Chapter Summary

Delirium 1405

Dementia 1405

Amnesic Disorders 1406

These are a group of psychiatric disorders resulting from diagnosable physical disease. Though there are a large number of physical diseases, the psychiatric manifestations mainly occur as three syndromes. They are *delirium*, *dementia* and *organic amnesic syndromes*.

DELIRIUM

Synonyms: *Acute psycho-organic syndrome*, *acute brain disorder*, *toxic metabolic encephalopathy* and *acute confusional state*.

Delirium is a syndrome and not a disease.

Clinical Features

The clinical features of delirium depend on the degree of severity. It may vary from mild to severe abnormality. Symptoms are rapid in onset, transient in duration and reversible in outcome. These often fluctuate with brief spells of symptom-free intervals (lucidity). Children and old people are more vulnerable. Widespread psychological (cognitive) disturbance is seen. The cardinal feature is impairment of the level of consciousness. The clarity of awareness of sensorium is reduced. It leads to clouding, confusion, stupor or even coma. Orientation in time is lost early, and later to place and even to persons. Attention is fleeting with distractibility. Concentration is poor. Immediate and recent memory is impaired, affecting comprehension and learning. Visual hallucination of insects, reptiles and small objects and visual illusions are characteristic. Disturbed thinking results in irrelevant and incoherent talk and persecutory delusions. Mood becomes irritable, anxious and apprehensive. It may be perplexed, labile or even depressed. Disturbance in motor function produces severe restlessness, excitement or violent and

aggressive behavior. It brings danger to self and to others. Sometimes under-activity is seen. Insomnia is one of the earliest features of delirium. It is typically associated with day time somnolence. Sleep-wake cycle is altered. Insight and judgment are lost. These mental symptoms are accompanied by physical symptoms such as dehydration, tremors, incoordination, aphasia and incontinence. The EEG may show generalised slowing of activity, but in delirium tremens due to alcohol withdrawal, overactivity is more common in the EEG.

Delirium is due to generalised metabolic disturbances. The major neurotransmitter implicated is acetylcholine. Reticular activating system (RAS) is the main seat of pathogenesis. Delirium occurs in a large number of physical conditions as listed in Table 220.1.

- **Diagnosis and management:** Delirium is an emergency. The diagnosis is made from the clinical features and relevant investigations. The identification of the primary medical condition and its management are the goals. Good supporting environment and nursing care play the key role. Mild delirium may clear up with supportive care. In other cases appropriate drugs are needed. These include injection diazepam (5-10 mg) IV or lorazepam 2 mg oral may help to relieve restlessness and anxiety. Injection of haloperidol 2-5 mg IM reduces psychotic features such as delusions, violence and excitement. The drugs may have to be repeated and later changed to oral route and gradually withdrawn.

DEMENTIA

This is a syndrome, not a particular disease. The word dementia in Latin means general mental deterioration. It is a neuro-psychiatric syndrome produced by organic brain diseases. Dementia is characterised by decline of cognition, memory, thinking, intellect and personality. Associated symptoms may develop. The level of consciousness is not altered. Dementia is of insidious onset, and runs a chronic progressive course. Primary dementia is generally irreversible in nature (See Chapter 189).

TABLE 220.1

Common causes of delirium

Metabolic disturbances	Vascular causes
Electrolyte disturbances	Cerebrovascular disorders
Acidosis/alkalosis	Cardiac failure
Hypo/hyperglycemia	Acute myocardial infarction
Hepatic failure	Cerebral edema
Uremia	Hypertensive encephalopathy
Endocrine disturbances	Eclampsia
Hypo/hyperthyroidism	Drugs
Hypo/hyperparathyroidism	Consumption/withdrawal of:
Adrenal dysfunction	alcohol
Pituitary dysfunction	Barbiturates
CNS infections	Anticholinergics
Meningitis	Antipsychotics
Encephalitis	Nutritional Deficiency of
Cerebral abscess	Thiamine, niacin,
Systemic infections	Vitamin B ₁₂ and folates
Pneumonias	Others Epilepsy
Enteric fever	Head trauma
Viral fevers	
Septicemia	

- **The clinical features** of dementia depend on the stage of the disorder. Loss of recent and immediate memory is noted early. It interferes with day-to-day functions. Remote memory is affected only gradually and it leads to disorientation. The gap in memory is filled by irrelevant events and information (confabulation). Other cognitive areas such as thinking, attention, concentration, intelligence, perception and judgment also show decline. Thinking is slow with low word output. Grandiose and persecutory delusions may occur. Attention and concentration are impaired, but the level of consciousness is unaffected. Visual hallucinations, loss of judgment and loss of insight occur. Personality changes are obvious. Lack of personal care, filthy habits, sexual disinhibition, stealing, lying and drug abuse may be there. Mood deteriorates to one of depression, elation or lability. Changes in the motor activity lead to restlessness and wandering, which predispose to accidents. Suicidal thoughts and attempts are not rare. When the patient fails to cope-up with the stress, temper outbursts occur (catastrophic reaction). The patient follows a rigid, stereotyped routine (organic orderliness). Insomnia is common. Aphasia, agnosia, apraxia, tremors, myoclonus, peripheral neuropathy and other neurological signs may appear. All symptoms worsen as the disease progresses. Several diseases may give rise to dementia. These are described in Section: 17 Chapter 189.

Diagnosis and treatment: The typical clinical features and investigations help to identify the condition and detect the cause. Dementia is differentiated from mental retardation which is a developmental disorder, delirium and pseudodementia, which is depression with cognitive impairment. The major aim of treatment is to remove the cause whenever possible, in order to reverse dementia or atleast to arrest its progress. Attention to general health is important. Regular physical exercise, proper nutrition and prevention of accidents are essential. Counselling to the patient and the family is needed. The involvement of community and social agencies can help to reduce the burden of management.

Unmanageable cases need institutional care. Any common psychotropic drug can be used symptomatically to reduce restlessness, wandering, insomnia, delusions and hallucination and depression.

Drugs with minimum anticholinergic side effects are preferred, and they should be given in minimal effective doses.

Lorazepam – 0.5-1 mg (anti-anxiety and hypnotic)
Risperidone drops/tablet – 0.5-1 mg (anti-psychotic)
Olanzapine tab – 2.5-5 mg (anti-psychotic)
Quetiapine – 12.5-25 mg (antipsychotic)
Mirtazapine – 7.5-15 mg (antidepressant)
Citalopram – 5-10 mg (antidepressant)
Fluoxetine – 10-20 mg (antidepressant)

Cognitive enhancers: These are newer drugs tried in Alzheimer's diseases, but they are still experimental.

- a. Memantine—5-15 mg. This drug is a NMDA receptor blocker
- b. Donepesil (5-15 mg)-Acetylcholineesterase inhibitor
- c. Cortisol, oestrogen, vit E, and plant products like *Ginko biloba* are other agents tried from time to time.

Since there is no specific drug for dementia the emphasis should be on prevention.

AMNESTIC DISORDERS

These disorders are characterised by profound impairment in recent memory with minimal impairment of other cognitive functions. Ability to learn new informations (anterograde amnesia) and ability to recall previously learned informations are impaired. Orientation to time and place may be lost, but orientation to person is retained. Visuo-spatial and geographical memory are unaffected. The amnesic gap may be filled by unrelated informations (*confabulation*). Full insight is retained. Lesions are demonstrable in the hippocampus, amygdala, fornix and midline structures like the mamillary bodies and dorso-medial thalamus.

Course: The disorder may be of gradual or sudden onset. It may recover fully or run a chronic course.

The common amnesic disorders include transient global amnesia, alcoholic black out, **Korsakoff's**

syndrome, multiple sclerosis, cerebrovascular diseases and such other conditions.

Treatment: Treatment is directed to the cause. In addition to the supportive psychotherapy, drugs can be used to allay the anxiety.

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Schizophrenia and Delusional Disorders

N. Krishnan Kutty

Chapter Summary**Schizophrenia** 1407

General Considerations 1407

Clinical Features 1408

Treatment 1409

Persistent Delusional Disorders 1410**Schizophrenia****GENERAL CONSIDERATIONS**

A precise definition of schizophrenia is lacking. It is a mental disorder characterized by specific psychological symptoms which interfere with the thinking, emotion, conation and motor behavior of the patient. Often the disorder runs a chronic deteriorating course. Whether schizophrenia is a single disorder or a group of many disorders is an unsettled riddle. Schizophrenia is a serious psychiatric disorder. The concept of schizophrenia was initially introduced by **Emil Kraepelin** and termed it *dementia praecox* (dementia = intellectual deterioration, praecox = early onset). To him it was an illness among adolescents and young adults which gradually lead to intellectual deterioration. Later, **Eugene Bluler** showed that splitting of emotion, thought and behavior was the essential feature of schizophrenia. Hence, he coined the term **schizophrenia** (Schizo=split; phrenum=mind).

Etiology: The exact etiology is not clear, but several factors play their roles.

- **Heredity:** Genetic factors play a major role in the etiology. The incidence of schizophrenia is about 1%

in the general population. There is higher incidence of the disorder in the family members of schizophrenic patients. About 5% of the parents, 8% of the siblings and 12% of the children of schizophrenics are seen to be affected by the disorder. In twin studies, the concordance rate is 57% in monozygotic twins whereas it is only 12% for dizygotic twins. The mode of transmission may be monogenic or polygenic and the gene may be dominant or recessive. Defects in the long arms of chromosomes 7, 11 and 18 and the short arms of chromosomes 19 and X have been shown in linkage studies.

- **Personality:** Many schizophrenic patients show schizoid personality trait. These individuals are very shy, sensitive and are largely unsocial.

Family background: In many instances there may be disturbances of family background. These include faulty parental attitudes, irrational and incoherent family atmosphere, defects in family communication, broken homes and the like. Emotional instability is found in many families.

- **Social factors:** Schizophrenia is more common in the lower socioeconomic groups. Urbanisation and industrialization are other significant contributory factors.
- **Biochemical:** Dopamine hypothesis—It is hypothesized that schizophrenia is the result of *dopaminergic hyperactivity* in the CNS, especially of D-2 receptor. Hyperactivity of other amines such as serotonin (5HT) and *nor-epinephrine* are also probable. But these findings are not specific to schizophrenia. The GABAergic neuronal loss observed in the hippo-

campus suggests a role for GABA. The role of the excitatory amino acid, glutamine has also been implicated.

- **Neuropathology:** Pathological changes are noted in the frontal lobe, hippocampus and basal ganglia. The size of the hippocampus, para hippocampus and amygdala is reduced on postmortem studies. Cell loss is also seen in the putamen and globus pallidus. Neurodevelopmental disturbance and neurodegenerative changes have also been attributed.
- **Stress:** Schizophrenia may be precipitated by physical stress like infection, injury, general debility, childbirth or several forms of psychological stress. Life events too are important factors.

CLINICAL FEATURES

Schizophrenia is a disease with protean manifestations. The symptoms of the illness include disturbances in thinking, mood, perception and motor behavior. These symptoms occur in a clear conscious setting of the mind.

- **Disturbance in thinking:** Thought disorder is a prominent symptom of schizophrenia. There is loss of meaningful connection in the sequential pattern of ideas (*loosening of associations*) which is a formal thought disorder. So the talk becomes incoherent. The stream of thought is affected. Circumstantiality, stereotypy and perseveration may be observed. New words or phrases may be invented which may not make any sense to others (*neologism*). The patient may detach from reality and live in his own inner world of phantasy (*autism*). Occasionally, the patient may be mute. At times there may be excessive, incoherent and irrelevant talk and activity at a high rate (excitement). They may fail to catch the wider implied meaning of proverbs which are interpreted in a purely literal sense (*concrete thinking*). This is due to the *loss of abstract* thinking. It may be their experience that the feelings, thoughts or activities are being carried out under external control (*passivity*).
- **Delusions** are common. They may arise without an attributable cause. Such primary delusions are characteristic of schizophrenia. It may be of persecutory, grandiose, somatic or religious themes. Secondary delusions also exists. The thoughts may be alienated, i.e. the patient experiences that thoughts are being taken away from his mind (*thought withdrawal*); or that thoughts are being introduced into his mind (*thought insertion*). Another phenomenon is the feeling that thoughts are being known to others as soon as it occurs in their mind (*thought broadcasting*).
- **Disturbances of affect:** All forms of affective changes may be seen in schizophrenia. In the early stages loss of emotional feelings (*anhedonia*) may be present. Usually, the patients show an incongruous or

Schizophrenic thought disorder

Loosening of association
Thought blocking
Neologism
Autism
Loss of abstract
Thinking
Primary delusions
Thought insertion
Thought withdrawal
Thought broadcasting
Passivity

blunted affect. In some cases lability, depression, elation, anxiety or exaltation may be the affective changes.

- **Disturbances of perception:** The most common abnormality is auditory hallucination which occurs in a clear, conscious setting. Hallucinatory voices may pass comments or give orders or pass simple statements about the patient (third person auditory hallucination). Voices may be threatening, accusatory and obscene. Tactile hallucinations in the form of electromagnetic waves, electricity, vibrations or cosmic rays may be experienced. Visual hallucinations are uncommon and other kinds of hallucinations are rare.
- **Motor disturbances:** The patient lacks energy, initiative and drive. The motor activity may be completely blocked-up at times (catatonic stupor). The patient may carry-out all given instructions without any resistance, even if they are harmful (*automatic obedience*). The patient's limbs shows spasm and can be passively moulded to any awkward posture for any length of time (*waxy flexibility /catalepsy*).They may actively resist instructions or may do just the opposite of what is expected normally(negativism). Negativism also causes retention of saliva/urine. Other motor disturbances like repetition of activities such as stereotypy, mannerisms, perseveration or echopraxia are also found. At times they exhibit spells of senseless excitement or states of complete withdrawal from the surroundings. Impulsive, suicidal, and homicidal behavior may occur. These may be in response to delusion or hallucination.
- **Cognitive disturbances:** Attention, concentration and vigilance are impaired in schizophrenia. This adversely affects the immediate memory. In chronic cases intellectual deterioration is also seen.
- **Other clinical features:** Mental functions such as consciousness, orientation, memory and intelligence are fully preserved but reasoning, judgment and insight are impaired.
- **Soft neurological signs:** Certain non-localising neurological signs (soft signs) have been reported in

schizophrenia. They include tics, stereotypies, grimacing, abnormal motor tone, abnormal movements, dysdiadokokinesis, astereognosis, diminished dexterity and the like.

- **Eye signs:** The blink rate may be increased. The patient does not make eye-to-eye contact with others.
- **Fundamental symptoms:** *Eugene Bleuler* classified the clinical features into fundamental symptoms and accessory symptoms. Autism, ambivalence and disturbances in affect and associations (4 A's) are the *fundamental symptoms*. All the other symptoms like delusions hallucinations, etc. are included under *accessory symptoms*. The fundamental symptoms are diagnostic of schizophrenia.
- **Positive and negative symptoms:** All the symptoms of schizophrenia can be grouped into two sets: (i) positive symptoms, and (ii) negative symptoms.

Positive symptoms	Negative symptoms
More acute	More chronic
Productive symptoms	Deficit symptoms
More in acute disease	More in chronic disease
Formal thought disorders	Anhedonia, lack of initiative and poverty of thinking.
Delusions	Incongruity and flattened affect
Hallucinations	Social withdrawal
Inappropriate affect	Impaired attention and concentration
Disturbance in motor activity	
Increase in dopamine in subcortical tissues	Decrease in dopamine in prefrontal cortex

Classification of Schizophrenia

Classically, schizophrenia is divided into four types. These are the *catatonic*, *paranoid hebephrenic* and *simple schizophrenias*. This classification is made on the basis of the dominant clinical features

Schizophrenia-Types (Eugene Bleuler)
Catatonic schizophrenia Paranoid schizophrenia Hebephrenic schizophrenia Simple schizophrenia

In *catatonic* schizophrenia, motor disturbances are very prominent.

In the *paranoid* form, delusions and hallucinations are the prominent features.

In *hebephrenia*, florid thinking disturbances and marked mood changes are predominant.

In *simple* schizophrenia, an insidious onset, lack of interest, and initiative and gradual social withdrawal are the characteristic features.

In addition to these classic forms, many other special varieties have been described.

Drugs used in Schizophrenia
Conventional anti-psychotics Chlorpromazine Trifluoperazine Thioridazine Haloperidol
Atypical anti-psychotics Risperidone Clozapine Olanzapine Quetiapine Aripiprazole
Depot preparations Inj fluphenazine decanoate Inj haloperidol decanoate

Diagnosis

Schizophrenia is diagnosed on the basis of clinical features. The symptoms should be present atleast for a period of one month. Psychometric tests may be helpful. Schizophrenia has to be differentiated from physical disorders like uremia and other organic mental disorders and also from masked depression, mania, hysteria and others.

Course

Some cases of schizophrenia may recover fully. Others show remissions and exacerbations. A few deteriorate gradually and progressively. The prognosis depends on many factors.

TREATMENT

Schizophrenia poses the threat of chronic handicap and therefore treatment should be instituted early. Mainly three modalities of treatment are at hand. These include anti-psychotic drugs, electroconvulsive therapy (ECT) and psychosocial therapy.

Anti-psychotic drugs: Both conventional antipsychotics such as phenothiazines and haloperidol, and newer atypical anti-psychotics such as: Risperidone, clozapine , olanzapine, quetiapine and aripiprazole are currently in use (See Chapter 234).

A suitable drug is to be selected depending upon the efficacy, availability, affordability, side effects, drug compliance and general health of the patient. The starting dose should be small and the dose is increased to the effective range and maintained for symptom control. Drug therapy may have to be continued for at least for 24 to 36 months.

Depot preparations like injections of fluphenazine decanoate 25 mg IM once in 2-4 weeks and inj of haloperidol decanoate are more advantageous than oral preparations in the maintenance phase.

Electroconvulsive Therapy (ECT)

ECT is beneficial in catatonic schizophrenia, acute schizophrenic episodes, and in schizophrenic excitement.

Psychosocial treatment: Steps are taken to keep the patients socialized by means of psychosocial education, close personal contact, group therapy, recreational therapy and occupational therapy so that the patient can readily come back to the social milieu after the treatment. The relatives are counselled regarding the nature of the disorder and the role they have to adopt. Chronically handicapped persons need rehabilitation.

Persistent Delusional Disorders

These are a group of disorders characterised essentially by a single type of long-standing delusion. It was known previously as *paranoia*,

The symptoms do not fit into any other type of mental disorders such as schizophrenia, mood disorders or organic psychosis. The delusions may be of several types:

1. Some important person is strongly in love with the person—*delusion of love (Larabault's syndrome, erotomania)*.
2. The spouse has extramarital relationship (*morbid jealousy, jealous husband/ wife syndrome, delusion of infidelity, Othello syndrome*).
3. Infestation by a parasite or venereal disease or cancer (*paracito-phobia/venereo-phobia , cancer-phobia*).
4. Mis-shapening of body parts such as nose or face (*dysmorphophobia*), or
5. Emanation of foul order from body parts.

The delusion is treated by anti-psychotics and psychosocial therapy.

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Mood Disorders: Mania, Depression, Dysthymia

N. Krishnan Kutty

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- Mania 1411
- Depression 1411
- Dysthymic Disorders 1412

GENERAL CONSIDERATIONS

What was originally described as manic depressive psychosis (MDP) by Emil Kraepelin is presently known as *Mood disorders* (MD). A persistent change in mood is the basic abnormality in this disorder. When the mood remains sad (depressed) the resulting clinical condition is called *depression*. It is called *mania* when the mood remains elevated and cheerful. The disorder usually runs an episodic course with recovery and recurrence. In between, lucid intervals occur in which the patient is

normal. Mood disorders may be unipolar depression, or bipolar mood disorders (BPMD). In unipolar depression only depressive episodes occur but they occur consecutively atleast thrice. In BPMD both depressive and manic episodes occur.

Etiology

The etiological factors for mood disorders fall under two broad groups-biological and psychosocial. The important biological factors may be genetic, biochemical, endocrine or neuro-anatomical.

Genetic factors: The incidence of mood disorders is high among the close relatives of the patients. Children born to affected parents develop the disorders even when the environment is different. In monozygotic twins the prevalence rate is 69% compared to the general population. Non-biological children and dizygotic twins have prevalence rates of only 19%.

- **The central monoamines**, residual sodium and melatonin are the more important biochemical factors implicated. *Norepinephrine*, *serotonin* and *dopamine* are the brain neurotransmitters involved. The concentration, turnover and postsynaptic receptor sensitivity of these neurotransmitters are diminished in depression. The converse is true in mania. Reserpine, which depletes serotonin from its stores, causes depression. *The residual sodium*, both intracellular and bone marrow sodium is increased upto 50% in depression and 200% in mania.
- **Endocrine** disorders such as Cushing's syndrome, hypothyroidism and hyperparathyroidism are known to produce depression. The secretion of cortisol is high in depression due to hyperactivity of the hypothalamic-pituitary-adrenal axis. This secretion is not suppressed by exogenous dexamethasone as occurring in normal persons.
- **Organic disorders** like cerebral atherosclerosis, neurosyphilis, AIDS, Parkinson's disease and frontal lobe injuries may produce depression. PET and SPECT studies have demonstrated reduced cerebral blood flow and reduced oxygen and glucose consumption in the frontal cortex among such patients- (*hypofrontality*). The hypothalamus, the basal ganglia and limbic cortex are probably the anatomical sites affected in depression.

Psychological and social factors are closely linked. The prominent psychosocial factors are recent stressful life events, obsessive and cyclothymic (mood swings) personality traits, loss of maternal affection during childhood, loss of loved objects, loneliness, helplessness, and cognitive distortions. In simple terms cognition simply means thinking. **The cognitive theory** proposes that depression results primarily due to negative cognition, negative view of the self, of the world and of the future. The mood change is secondary.

Mania

CLINICAL FEATURES

- **Elation of mood** is the characteristic disturbance in mania. It is expansive. Generally, the manic patient appears well dressed, often in colorful clothing and is cheerful. He is entertaining and often highly interfering. He forms the focus of attention by his talk and jocularity. In the case of hypomania, the mood is one of euphoria with a generalized feeling of increased well-being. In the case of manic excitement the mood is one of excitement. Occasionally, the mood may be irritable.
- **Thought/talk:** The patient talks excessively and he is rich in ideas. The talk is often coherent, but may

not be relevant. Since the rate of talk is high, too many ideas may be crowded into the mind, giving rise to pressure of talk. Often, the ideas shift from topic to topic giving rise to "*flight of ideas*". The talk may contain typically grandiose delusions or persecutory delusions. The talk is jocular.

- **Disorders of perception** such as illusions may be present during manic excitement. Hallucinations are rare in mania.
- **Motor activity:** Mania is associated with exuberant energy and overactivity. He may get-up very early in the morning and engage himself in various kinds of unwanted activities. The actions are left incomplete. He unnecessarily interferes in the affairs of other people when he is hyperactive, and picks up quarrels. In states of excitement he may turn violent, aggressive, destructive and uncontrollable.
- **Other symptoms:** These include increased sexual urge, extravagance, drug abuse and intoxication. Intelligence is well preserved. There is apparent impairment of memory on account of rapid flight of attention. Insight and judgment are impaired. Insomnia is a regular feature.

Diagnosis: The diagnosis is based on the clinical features. Mania is to be differentiated from schizophrenia, general paralysis of the insane (GPI), alcoholic excitement and delirium.

Features of mania
Elated, expansive mood High motor activity Richness of ideas Flight of ideas Jocularity Grandiose delusions

Treatment: Pharmacotherapy and electroconvulsive therapy (ECT) are employed in the treatment of mania. Antipsychotics and mood stabilisers are the drugs of choice for acute manic symptoms. Excited and violent patients have to be sedated with parental drugs. In some cases mechanical restraint may be needed.

ECT may be necessary to bring down violent excitement rapidly.

Depression (Major Depression)

Depression may be a symptom, a syndrome or a disease entity (depressive illness). Several terms such as *psychotic depression*, *endogenous depression*, *MDP depression*, *agitated depression*, *involutional melancholia* or *masked depression* are used to designate depressive disorder. The symptoms of depression are subject to diurnal variation,

being worse in the morning. Depressive episodes may be mild, moderate or severe.

CLINICAL FEATURES

- **Mood:** The symptoms of depression are centered around the disturbance in mood. The mood is sad. The face appears gloomy with wrinkled forehead, drooping of the eyelids and sagging of the angles of the mouth. They show no interest in pleasurable activities (*anhedonia*). Sometimes the mood is one of irritability and anxiety.
- **Thought and speech:** The speech is slow, and the voice is low. Poverty of thinking and loss of self-confidence are prominent symptoms. They are pessimistic and they lack self-confidence. They may retain ideas or delusions of guilt, worthlessness and hopelessness. Out of such thoughts may spring-up suicidal ideas and attempts. Eighty-percent of suicides are attributable to depression. In most cases of suicide the attempts are well-planned and secretly executed. Nihilistic and hypochondriacal delusions are not uncommon. In severe cases they may remain mute (*depressive mutism*).
- **Disorders of perception:** Auditory hallucinations of accusatory nature may occur.

Features of depression
Sadness of mood Retarded motor activity Poverty of thinking Delusion of guilt Hopelessness Worthlessness Suicidal ideas and attempts Loss of appetite Loss of weight Loss of libido Insomnia Other somatic symptoms

Motor activity is retarded. The movements are slow. The patient tends to stoop while walking or sitting. Depressed patients become self-centered and prefer to be left undisturbed. The routine work may be avoided due to the feeling of general weakness. In the extreme form the patient may develop *depressive stupor* where all the activities are minimal with least response to external stimuli.

- *Their attention* and concentration are impaired.
- *The insight and judgment* may be impaired.

- *Pseudodementia* The sluggishness of mental activity and impairment of attention and concentration may give an apparent impression of dementia.
- *Somatic symptoms:* Loss of appetite, loss of weight, constipation, loss of libido and late insomnia are vital symptoms of depression .Other bodily symptoms such as headache, giddiness, chest pain, backache and amenorrhea are common. Many give history of depressive symptoms preceding myocardial infarction.

Diagnosis: Diagnosis of depression is made on the basis of clinical features. Depression has to be differentiated from organic disorders, schizophrenia, endocrine disorders and substance use disorders.

Course: The symptoms of depression may recover fully but the risk of recurrence is present either as depression or as mania.

Treatment: Pharmacotherapy, psychotherapy and electro-convulsive therapy are effective. Combination therapy brings about more rapid recovery.

- **Inpatient care:** Patients in depressive stupor and those with suicidal ideas require hospitalization.
- **Drugs:** Antidepressants are the drugs of choice. Tricyclic antidepressants (TCA), selective serotonin re-uptake inhibitors (SSRIs), and other atypical antidepressants are in common use. The treatment is initiated with smaller doses and worked upto the optimum level. The drug is maintained for three to six months after recovery and then it is gradually tapered off. Hypnotics, anti-anxiety drugs and other supportive therapy are also indicated.
- **ECT** is indicated in cases of depressive stupor, suicidal ideas and suicidal attempts.
- **Psychotherapy:** Cognitive behavior therapy and supportive psychotherapy are beneficial.

Dysthymic Disorders

This used to be known as neurotic or reactive depression. This is considered as a variant of depression, mild in intensity, chronic in duration and without delusions or hallucinations. Somatic symptoms such as loss of weight, loss of appetite and loss of libido are not marked. Insomnia is early and sleep is fretful. The symptoms are worse in the evenings unlike as in the case of mood disorders.

Treatment: This includes counselling, psychosocial therapy, and pharmacotherapy with antidepressants.

Chapter Summary

Generalised Anxiety Disorders (GAD) 1413
Phobic Anxiety Disorder 1414
Panic Disorder 1414

Anxiety is a subjective unpleasant feeling of fear, tension, impending danger and panic. In normal persons fear or anxiety develops as a result of some known external reasons. Anxiety disorders are a group of conditions characterised by severe anxiety. The fear is usually accompanied by autonomic disturbances. There is no obvious external cause.

Three types of anxiety disorders are seen. These are:

- Generalised anxiety disorder
- Phobic anxiety disorder, and
- Panic disorder

Generalised Anxiety Disorders (GAD)
(Anxiety Neurosis)

In this disorder the anxiety is free floating and the symptoms are experienced all the time. It was previously known as anxiety neurosis.

Etiology: The important causative factors include hereditary predisposition, morbid environment and constitutional defects. Physical factors such as infection, exhaustion and others may precipitate anxiety reaction. According to Sigmund Freud anxiety develops as a result of the conflict in the unconscious mind. The conflict occurs when there is rivalry between the reality and the needs/wish of the individual, sexual or otherwise. The conflict is unpleasant. So it gets repressed into the unconscious part of the mind. When mental energy is diminished, repressed conflict tends to enter into the conscious mind. It is experienced as anxiety. Mental defense mechanisms do not come into play.

Overactivity of the neurotransmitters such as norepinephrine, serotonin and gamma-aminobutyric acid

Features of GAD
Mental Symptoms Severe anxiety Irritability Lack of attention and concentration Worry
Physical Symptoms Motor Restlessness Tremors Tension CNS Headache Dizziness Insomnia CVS Palpitation Tachycardia Preordial pain High systolic BP Respiratory Tachypnea Breathlessness Hyperventilation GIT-dysphagia Dry mouth Diarrhea GU tract Frequency of micturition Menstrual irregularities Sexual dysfunctions Skin Cold and clammy

(GABA) are seen in this disorder. Main pathological lesions are seen in the locus coeruleus.

Clinical Features

The symptomatology can be classified as: (a) mental, and (b) physical.

- **Mental symptoms:** Anxiety is the main symptom. It is generalized and present throughout. It hampers the activities of the individual. Anxiety interferes with the functions of attention and concentration and thereby,

the memory. Anxiety is the common cause of amnesia in students. The person is preoccupied by ‘worries’ and may have many kinds of anxious thoughts and feelings.

- *Physical symptoms:* General features are motor restlessness, fine tremors and generalised muscular tension. This causes aches and pains, especially frontal headache and backache. The pupils are dilated. The mouth is dry due to decreased salivation.
- *Cardiovascular manifestations:* Tachycardia, rise in systolic blood pressure, precordial pain and palpitation are common.
- *Respiratory symptoms:* Patients with GAD complain of breathlessness and tachypnea. Hyperventilation may lead to alkalotic tetany.
- *Gastrointestinal symptoms:* These include dryness of mouth, dysphagia, diarrhea, constipation, vomiting abdominal pain, ‘gas’ and others.
- *Genitourinary symptoms:* Anxiety disorder is associated with increased frequency of micturition. Sexual drive (libido) is often diminished. Menstrual irregularities are found in women.
- *Central nervous symptoms:* Headache is experienced as a tight band around the head. The patient experiences difficulty in getting into sleep. The sleep is light and fretful. The skin is cold and clammy.

Diagnosis: Clinical diagnosis can be made based on the somatic and psychic features. Persistent anxiety with somatic symptoms is the important feature. Careful search to exclude organic disorders such as endocrine abnormalities, ischemic heart disease, asthma and malignancy is absolutely essential. Other psychiatric conditions such as delirium, schizophrenia and agitated depression have also to be differentiated.

Treatment

- *Psychotherapy* is the principal form of treatment. Cases of recent onset may improve with counselling, by giving reassurance and encouragement to make adequate adjustment with the environment. In other cases relaxation therapy and cognitive therapy may be provided.
- *Drug therapy:* Antianxiety drugs are good to give rapid relief. For long term therapy any of the anti-depressants may be preferred.
See Table 223.1.

Phobic Anxiety Disorders

This disorder is characterized by the presence of ‘phobia’. Phobia denotes fear which is specific to an object or situation. The fear is unreasonable and out of proportion to the demand of the situation. The subject avoids the object or situation which evokes the phobia.

TABLE 223.1
Common anti anxiety drugs

<i>Benzodiazepines</i>
Alprazolam
Diazepam
Chlordiazepoxide
Clonazepam
<i>Beta blockers</i>
Propranolol
<i>Azaspirone</i>
Buspirona

Clinical features: The symptoms of phobia are very similar to those of generalised anxiety disorder but these symptoms occur only in the presence of the stimuli which evoke the phobia, either under imagination or in real situation. The patient is symptom-free at other times.

- In *simple phobia*, the fear is usually for harmless objects like pen, match box, spider and the like.
- In *social phobia* the fear is for social situations.
- In *agoraphobia* the fear is experienced on getting away from house or being in situations from which escape seem to be difficult.

Diagnosis: Diagnosis of phobia is based on the clinical features in relation to the phobic stimulus. Phobic disorder should be differentiated from generalized anxiety disorder, schizophrenia, obsessive compulsive disorder, epilepsy and depression.

Treatment: The acute symptom can be managed with anti-anxiety drugs. Behavior therapy which is intended to desensitise the patient to the phobic stimulus, is the treatment of choice. Systematic desensitization, implosion and flooding are the techniques used (See Chapter 235).

Panic Disorder

The characteristic feature is sudden, unexpected episodes of intense anxiety. It is marked by chest pain, breathlessness, palpitation, sweating and a feeling of imminent death or turning mad. The patient may run for help. It may be mistaken for acute myocardial pain. Sometimes it is associated with agoraphobia. Diagnosis is made from the typical features.

Lactate infusion test: Intravenous infusion of sodium lactate precipitates panic reaction and this test can be used for diagnosis.

Treatment: Panic disorder responds well to drugs such as alprazolam, diazepam, SSRIs, tricyclic antidepressants, valproate and cognitive and supportive psychotherapies. (see Chapter 235).

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Clinical Features 1415

Diagnosis 1415

Treatment 1415

GENERAL CONSIDERATIONS

This disorder is characterised by obsessions and compulsions. Obsessions are unwanted thoughts repeatedly coming to the mind in spite of a strong will to get rid of them. There is the subjective compulsion to act accordingly. Though the patient is fully aware of this absurdity, he is helpless. He is unable to resist this action.

Etiology: Obsessions usually occur among obsessive personalities. Such individuals are usually very meticulous and methodical, and are very particular about cleanliness and orderliness in everything. Many give a family history of obsessive disorder. Obsession may also result as a sequel of head injury and intracranial infections. Neuroimaging studies have revealed bilateral reduction in the size of the caudate nuclei. There is increased activity in the frontal lobe, basal ganglia and cingulum and dysregulation of central serotonin.

CLINICAL FEATURES

The obsessions may take the form of ideas, doubts, phobias, impulses, slowness and rumination. The idea may be of any form. Obsessive doubts may be for an activity that has been just carried out. For example, the patient may go to bed after bolting the door. He may get-up the next moment in doubt whether he had bolted the door or not. This may be continued indefinitely.

- Obsessive phobia is the fear that one may do a harmful thing. For example, a patient may have the fear that he may add poison in the medicine supplied.
- Obsessive compulsions are motor activities which are repeated (*obsessive rituals*). The patient may wash the hand repeatedly, being unsatisfied with the cleanliness. The washing may be continued even to the point of peeling off the skin.
- An impulse may arise to howl or utter obscene words in the church when the mass is on. Obsession may be associated with anxiety or depressive features.

DIAGNOSIS

The premorbid personality, the family history and clinical features help to make a diagnosis. Obsessive compulsive disorder has to be differentiated from schizophrenia, psychotic depression and dementia.

Course: In many cases the illness may recover gradually by itself. In some, the recovery may be sudden even during the early part of the illness. Often wilful efforts to suppress the obsession may tend to aggravate the condition.

TREATMENT

OCD responds well to treatment. A combination of pharmacotherapy and behavioral therapy is most suitable. Clomipramine and SSRIs are the drugs of choice. They are to be given at the higher dose for 2 to 3 weeks.

Exposure and response prevention are the behavioral therapy techniques employed. This itself may be curative. In addition, supportive therapy and counselling to the family are also indicated.

Psychosurgery like cingulotomy may have to be done in intractable cases.

Conversion Disorders, Dissociative Disorders, Somatoform Disorders, Cultural Bond Syndromes, Reaction to Stress and Adjustment Disorders

N. Krishnan Kutty

Chapter Summary

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 Somatoform Disorders 1417
 Cultural Bond Syndromes 1418
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 Acute and Post-traumatic Stress Disorders 1418
 Adjustment Disorders 1418

GENERAL CONSIDERATIONS

For a long time this disorder was known as *hysteria*, the term coined by *Hippocrates*. Later it was known as *hysterical neurosis* manifested as a conversion reaction and dissociative reaction. The disorder is characterised by psychogenic loss or disorder of function. When the symptoms are confined to the sensory, motor or visceral functions it is called conversion disorder. It is called dissociative disorder when the symptoms are psychic in nature.

Etiology: This disorder develops as a result of environmental stress in subjects who possess defective personalities such as hysterical personality. Such individuals are often emotionally immature. They are defensive, dramatic in behavior, demonstrative and demanding. They show tendency to be untruthful. They are seductive and easily suggestible.

Psychogenesis

- Sigmund Freud, the father of psychoanalysis found that hysterical symptom could be produced by suggestion and abolished by persuasion. He stated in his psychodynamic theory that hysterical symptoms develop as a result of psychic (emotional) conflict in the conscious mind. The conflict is repressed into unconscious part of the mind to be forgotten. Later

in life the repressed emotional conflicts try to enter the conscious mind. This produces anxiety which is very unpleasant. The anxiety is made innocuous by the mental defense mechanisms of *conversion* into bodily symptoms and *dissociation* into psychic symptoms.

- **Pathophysiology:** Hypometabolism in the dominant hemisphere, hypermetabolism in the non-dominant hemisphere, and defect in interhemispheric communications have been described.

The relief from anxiety is the *primary gain* in the disorder. The symptoms provide material advantage to the patients. This is the *secondary gain*. The patients are unconcerned about their disability (*La bella indifferenza*). In conversion disorders the emotional abnormality produces physical symptoms pertaining to motor, sensory and visceral systems. It may mimic any disease.

CONVERSION DISORDERS

Syn. Hysterical neurosis

Clinical Features

- **Motor symptoms:** Various types of paresis and paralysis like hemiplegia, monoplegia and paraplegia, bizarre gait, tremors and mutism are common. It is usually a function like movement and not a group of muscles on any nerve distribution that is affected. The proximal parts of the limbs are more affected than the distal parts. The left side is more affected than the right. The paralysed muscles may be used in one movement but not in others. Efforts to produce a particular movement in a paralyzed limb may produce spasm in the opposite group of muscles. Examination reveals generalized muscular rigidity with increased tendon reflexes and flexor plantar response. Disuse atrophy may rarely supervene in long-standing cases.
- **Tremors:** Coarse tremors occurring at rest and exaggerated when attention is drawn to them is suggestive of conversion disorder.
- **Seizures:** The seizures (fits) occur in emotionally charged situations in the presence of onlookers. Fits do not occur when the patient is alone. Consciousness

is not lost during the fits and the sequence of events is bizarre. The movements also are bizarre. They may resemble arching or such other acts. Serious injuries do not occur during these episodes. These features help to distinguish hysterical reactions from epileptic seizures.

- **Sensory symptoms:** These include anesthesia, paresthesia, and hyperesthesia. These sensory disturbances do not correspond to any anatomical pattern. Unlike as in neurological lesions the boundaries are sharply demarcated and the extent changes widely with repeated testing. Symmetrical anesthesia affecting the extremities such as gloves and stockings type may occur.
- **Special senses:** Blindness and deafness may occur. The patient can avoid obstacles in her path even when there is 'total blindness'. Many patients complain of diplopia as well. Diplopia can be complained of even when one eye is shielded.
- **Visceral symptoms:** Common symptoms are vomiting, retention of urine, constipation, loss of appetite and others.

DISSOCIATIVE DISORDERS

Clinical features : In dissociative disorder the symptoms are confined to the psychic field. Amnesia, fugue, somnambulism, multiple personality, and hysterical trance are the common manifestations.

- **Amnesia:** In dissociative amnesia, the loss of memory is confined to a circumscribed event or connected events which are normally tolerable but producing agony to the patient. The amnesia occurs in situations of intolerable stress. The intellectual functions are unaffected, unlike as in dementia.
- **Fugue:** In dissociated fugue the person may wander in the amnesic state with loss of identity. A new identity may be assumed and he may engage in a work quite dissimilar to the previous job. The original identity can be regained under hypnosis, or even spontaneously.
- **Somnambulism:** It is a dissociative state where the individual walks around in sleep. He avoids obstacles on his way. This symptom may also occur in depression and epilepsy.
- **Dual or multiple personality (identity disorder):** The patient is possessed by a different personality, usually by a 'spirit'- good or evil. In dual personality, the second personality may dominate the activities of the patient and he may not be aware of his real personality.
- **Dissociate trance (twilight state or stupor):** In this disorder the patient gets detached from reality and may become almost immobile and immersed in his own self or in some other divine power.

Diagnosis The diagnosis of dissociative disorder (conversion) is made from the clinical picture. Personality tests may be helpful in establishing the diagnosis.

- **Differential diagnosis:** The somatic symptoms may resemble those of physical diseases. Psychiatric disorders like schizophrenia, depression, dementia and mania have to be differentiated.

Treatment: Reassurance and suggestion are the usual modes of treatment adopted. The success depends on identification and removal of the secondary gain and resolution of the emotional conflict. Abreaction, psychotherapy and behavior therapy may be employed. Anti-anxiety drugs have their role to reduce the internal anxiety. It is not uncommon to find fresh symptoms cropping up when the existing symptom is removed by mere suggestions without resolving the conflict.

SOMATOFORM DISORDERS (SFD)

This includes a set of psychiatric disorders presenting with symptoms of a physical illness but with no physical finding either on examination or repeated investigations. *Somatisation disorder*, *hypochondriacal disorder* and *somatoform pain disorders* are the common types of SFDs.

In *somatisation disorder* multiple and often changing symptoms are present. The patient fails to get relief from several doctors. They are eager to get medicines for relief.

In *hypochondriacal disorders* the patients are pre-occupied with physical illness. They demand all kinds of investigations to prove their illness. At the same time they are afraid to take drugs.

Somatoform pain disorder (psychogenic pain disorder) Chronic pain such as headache, low backache, pelvic pain and chest pain are common symptoms. The pain may be symbolic of guilt, demand for affection, suppressed aggression or atonement for perceived sin. It may be rewarding to the patients in that they gain attention and care, and escape from job or unpleasant task. It may also be the manifestation of other psychiatric disorders such as anxiety, depression or schizophrenia.

Factitious disorder: In this disorder the symptoms of mental or physical illness are purposefully adopted in order to remain in the sick role and avoid specific situations. There is no external gain. Dermatitis artefacta, bruising, brittle diabetes, pyrexia of unknown origin, purgation of unknown origin, chronic wounds and self-medication are examples.

Malingering: In this condition symptoms of mental disorder or physical illness may be feigned by the person to get some external gain. The gain may be to get exemption from strenuous work, financial compensation

in accident, to get relieved from police action and the like. The symptoms may be vague and they may not suggest any typical disorder. They resist detailed evaluation and give evasive answers. Investigations give negative result. Constant observation and evaluation may bring-out the truth. It should be tactfully conveyed to the person.

CULTURAL BOND SYNDROMES

Some psychiatric syndromes are specific to different countries and cultures. 'Possession state' and 'Dhatt' syndromes are important members in this group.

Possession states: Individuals are seen talking and acting, not in their own self, but in the role of others, being possessed by phenomena such as the spirit of (a) a dead relative or friend or a person who met with an unnatural death, (b) a god or goddess and (c) a devil.

They bring-out various demands, wishes, orders or warning during the state of possession. These syndromes are more prevalent among young girls especially in rural India. Invocation of the fond deity in trance state is a common religious ritual.

Basically, the syndrome is a dissociative disorder. Major depression, schizophrenia or epilepsy also may appear as possession states. Usually no treatment is required. Counselling and supportive psychotherapy may help to remove the stress which may precipitate the syndrome. Other cases require appropriate pharmacological agents.

Dhatt syndrome: The syndrome is common among young males mostly prevalent in the northern part of India. They complain of losing semen before and after passing urine. This gives rise to mixed picture of anxiety and depression. Muscular weakness, lack of interest and energy, lack of concentration, palpitation, body aches and visual blurring are complained of. The wrong concept behind this syndrome is that semen (dhathu) is a vital bodily element for vigor and health, and its loss is harmful to health. It is to be treated by counselling and anti-anxiety drugs.

REACTION TO STRESS AND ADJUSTMENT DISORDERS

Acute and Post-traumatic Stress Disorders

Severe stress precipitates many kinds of mental disturbances, but stress reaction (disorder) stands out different from others. An exceptionally severe stress may produce characteristic symptoms known as **stress reaction** or disorder in a person with no previous history of mental illness. Such a stressor may be a major road traffic accident, death caused by lightning, earthquake, flood, bomb explosion, murder, rape, assault and similar situations. If the stressor is of a threatening nature the symptoms are more like those of an anxiety disorder.

When the stressor is one of loss or defeat the symptoms are more like those of a depressive disorder. Stress disorders may be acute or late post-traumatic.

Acute Stress Disorder

In *acute stress* disorder (ASD) the symptoms follow within minutes or hours of the trauma. It may last for 2-3 days and recover spontaneously. The main symptoms are a dazed feeling, numbness, inability to understand what is said and answer to questions. Autonomic arousal such as anxiety, restlessness, tachycardia, sweating and insomnia may be seen. Symptoms of dissociation, flash back memory of the traumatic event and nightmares are common. Medical help from a general practitioner may be warranted at times. Anti-anxiety and antidepressant drugs, counselling and other supportive measures offer relief.

Post-traumatic Stress Disorder

In *post-traumatic* stress disorder, (PTSD) the symptoms appear after a latent period ranging from a few weeks to six months. Psychiatric intervention is necessary for relief. The main symptoms are hyper-arousal, painful re-experiencing of the traumatic event, emotional numbness, guilt feeling, rejection, humiliation and a pattern of avoidance behavior. Illusions, hallucinations, dissociative state or panic state may manifest. At times aggression, violence and poor impulse control are also seen. The *treatment* is symptomatic. Counselling, catharsis, direct advice, education to build-up healthy coping skills, cognitive behavior therapy or hypnosis are essential.

Drugs such as tricyclic antidepressants, beta adrenergic blockers, and other antianxiety drugs are indicated.

Adjustment Disorders

Syn: Grief reaction

Psychological disturbances may be precipitated by life changes which may turn-out to be stressful. Bereavement, migration, divorce, detection of a serious illness, retirement, desertion and financial liabilities are but a few examples. It develops within one month to six months, usually not later than six months. The disturbances would not have developed in the absence of the stress. Worrying, poor concentration, anxiety, depression, irritability, nonspecific aches and pains and palpitation are the usual manifestations. Rarely, aggressive behavior, deliberate self harm and abuse of drugs and alcohol may occur. In children it manifests as regressive behavior such as thumb sucking, nail biting, babbling or enuresis.

The treatment is directed to resolve the stressful problem. Counselling is the best method to encourage them to talk-out and discuss their problems. Drugs such as anti-anxiety and antidepressant drugs, and hypnotic may also be used.

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GENERAL CONSIDERATIONS

Torture is the intentional infliction of brutal pain, both physical and mental on a victim with a view to procure information or confession or punishing for committed or suspected crime, or ruining a rival.

Torture is common in several situations in life. It may be present in the family, or inflicted by other agencies or persons including governmental establishments, especially during war or post-war situations, for eliciting evidence in crimes and as part of terrorism. Excluded is the pain or suffering arising only inherent in/or incidental to lawful punishment. Torture scenes occur in military set-up, police custody, refugee camps, dictator governments, the spread of social violence, and also at home (domestic violence). The methods of torture involves all sorts of physical violence such as kicking, beating, crushing, burning, mutilating, application of irritant chemicals, and mental inflictions such as isolating, humiliating, abusing, accusing, horrifying, guilt-inducing, providing false tragic news of dear persons, giving psychoactive chemicals and forcing to utter slogans opposite to their principles, morals and ethics, and sexual violence, especially against women including unwanted pregnancy. There is no intention to murder. As a result the torture victim is totally ruined, physically, mentally, morally and spiritually. His personality gets disintegrated. Doctors and psychologists are often called in to assist the torturers, especially by governmental agencies in many countries.

CLINICAL FEATURES

The symptoms are related to post-traumatic stress disorder (PTSD). Torture-victims present a spectrum of physical

and mental symptoms. These may be akin to post-traumatic stress disorders (PTSD), but the picture varies depending on the measures used to inflict torture. Prominent ones are the symptoms pertaining to musculoskeletal system, though all systems may be affected. Insomnia, nightmare and lability of mood, lack of concentration, loss of memory, social withdrawal, guilt feeling, insecurity and helplessness are the usual mental symptoms. Other symptoms are fears, apprehension, irritability, anxiety, depression, suicidal ideas and change of personality.

TREATMENT

Torture-victims are to be treated and rehabilitated. A holistic approach involving physical, mental, spiritual, legal and cultural measures has to be adopted to give better outcome. The victim is given respect as a human being, his trust and confidence is established. Drugs and psychosocial therapies are given appropriately to relieve symptoms and to rebuild his personality.

PREVENTION

Torture is an inhuman act and unacceptable to democratic principles. The UN convention prohibits the act of torturing and such inhuman acts, since it is a violation of human rights. *The International Rehabilitation Council for Torture Victims* (IRCT) and many such international organizations are active in its prevention and rehabilitation of the victims. Medical profession is often drawn to assist the torturers. Doctors are forced to stay to prevent death of the victim and they may be forced to issue false medical certificates of tissue damage. They have to treat and rehabilitate the victims, once they are freed. The World Medical Association looks down upon torture and makes plea to governments and doctors not to encourage this heinous act.

Disorders of Adult Personality

N. Krishnan Kutty

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GENERAL CONSIDERATIONS

The term, personality is derived from the Greek word *Persona* = *mask*. Personality is the total characteristic of an individual, i.e. everything that a person is made up of. It includes the physical makeup; behavior in relation to others, the thinking and feeling. The personality is stable, predictable and measurable. It is in harmony with the socio-cultural standards. When the character traits becomes rigid and maladaptable it results in personality disorders. It produces subjective distress to the person as well as to others in the society.

Etiology

Genetic factors, constitutional factors, and disturbance in family environment during childhood have been implicated. Some psychopaths show an extra 'Y' chromosome (XYY) syndrome. Some criminal psychopaths may show abnormal EEG patterns.

This disorder develops from early childhood without any clear-cut onset of time. Personality can be assessed by clinical interview and by psychological test such as Minnesota Multiphasic Personality Inventory (MMPI), Rorschach's test, Thematic Apperception Test (TAT), Personality Assessment Schedule (PAS) and others.

CLINICAL FEATURES

Personality disorder differs from personality changes. Personality changes are the deterioration of personality due to brain damage, chronic alcoholism, chronic schizophrenia, chronic distress or chronic epilepsy. On the other hand personality disorders develop as primary phenomena from early life. Many types of personality disorders are known. Some common types are given below:

Schizoid Personality Disorder

These individuals are shy, over-sensitive, and seclusive, often with autistic (phantasy) thinking and poor emotional relationship with others.

Obsessive Compulsive Personality Disorder (Anankastic Personality)

These subjects show excessive concern with conformity and adherence to standards of behavior. They are rigid, overinhibited, overcautious, and overdutiful and less adaptive.

Anxious (Avoident) Personality Disorder

Persistent feeling of tension and apprehension, avoidance of social interaction and criticism, and extreme sensitivity to rejection are the usual features.

Histrionic (Hysterical) Personality Disorder

It is marked by self suggestibility, attention seeking behavior, shallow or labile affect, self dramatisation, seductiveness, defensiveness and dependency.

Paranoid Personality

They are always suspicious and sensitive. They are stubborn and argumentative. They are pre-occupied with groundless conspirational explanations of events.

Dissocial (Antisocial) Personality Disorders (Asocial, Psychopathic, Sociopathic Personality)

These personalities are characterised by impulsive behavior, lack of guilt, failure to keep sustained affectionate relationship and failure to learn from past experience. They are labelled as heartless, callous, self-centered persons. They are in the habit of making crimes and offences of all sorts including substance abuse.

Treatment

Since these are life-pattern disturbances, treatment modalities are less effective. Individual and group psychotherapy are the method of choice, psychotropic drugs may help during periods of crisis.

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Psychoactive Substance Use Disorders and Alcohol-related Disorders

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These are disorders due to the self-administration of chemical substances for pleasure. These substances have their effect on the mind. They alter the mood, thought, level of consciousness and behavior.

PSYCHOACTIVE SUBSTANCE USE DISORDERS

Drug dependence, drug addiction and habituation were the terms used in the past to denote the same condition. The psychoactive substances (drugs) are of different kinds:

- Alcohol
- Amphetamine and other stimulants
- Cannabis—ganja, charas, bhang, hashish
- Cocaine
- Caffeine—coffee and tea
- Hallucinogens like LSD, mescaline
- Volatile solutions such as petrol, ether, benzene
- Nitrite, nitrous oxide
- Tobacco (nicotine)
- Opioids—morphine, codeine, heroin, pethidine and methadone, pentazocine
- Sedatives and hypnotics – benzodiazepines, e.g. diazepam, lorazepam, and others.
- Tranquilizers—alprazolam, librium and others.

Administration of, or self-medication by these drugs produces several phenomena referable to psychological functions. Most of such drugs lead to drug dependence on repeated administration. Ultimately they lead to changes in personality and behavior. Several syndromes may be produced by such psycho-active drugs.

Etiology: The three major factors involved in substance use disorders include: (1) The personality, (2) The substance and (3) The environment.

They form a closed chain. The personality has to be vulnerable, the drug should be readily available and the social environment has to be favorable.

- **Personality factors:** Family disturbances in early childhood and parental disharmony are important factors. Anxious and depressive personalities get their symptoms apparently relieved by the substance and they continue the abuse. Delinquency and antisocial personality disorders are other common causes. Challenges of day-to-day life and intra and inter personality problems are contributory to drug abuse.
- **Drug availability:** The drug used may be of medicinal nature such as diazepam, pethidine or mood elevators. Drug trafficking is a major and active menace when there is legal restriction. Substances such as tobacco and alcohol are freely available without restriction.
- **Social environment:** Many social factors such as unemployment, peer group relationship and social deprivation play a part. Disturbed family circumstances working environments, marital disharmony, poverty and consumerism are the major social factors.
- **Physiological reward theory:** Release of dopamine in large amounts is noted in the nucleus accumbens in drug dependent individuals. The nucleus gets its innervation from the ventral tegmentum. The dopaminergic response is rewarding since it is associated with the sensation of pleasure, (positive reinforcement).
- **Behavior theory:** The pharmacological effect brings on euphoria and relief. This positively reinforces the behavior to repeat the act of substance abuse. When the effect becomes one of flushing, nausea or tachycardia which is unpleasant, it negatively reinforces the behavior and drug consumption is given up.
- **Acute intoxication:** When the drug use is transient, a picture of acute intoxication results. Abnormal psychic and physical symptoms appear. Symptoms depend upon the drug used. They disappear as the drug is discontinued.
- **Harmful use (abuse):** Heavy substance use may lead to damage to physical health (e.g. alcoholic hepatitis) social health (e.g. disapproval and criticism) and mental health (e.g. depression).
- **Dependence syndrome:** These are altered physiological and mental states, (alteration of mood, behavior

and cognition) due to prolonged use of the drug. Withdrawal symptoms occur when the substance is abruptly discontinued. There is overwhelming desire (compulsion) to continue the drug in order to overcome the unpleasant effects.

- **Tolerance** is another feature. Effect of the drug diminishes with repeated use of the same dose. The dose has to be increased progressively to get the same effect. Interest and pleasure in other useful activities diminish.
- **Withdrawal state:** This develops once the drug is discontinued after prolonged use. Physical symptoms and psychological symptoms are seen.
- **Amnesic syndrome:** Constant impairment in recent memory is the prominent symptom. Events and time sense are confused (confabulation).

Diagnosis: is made from the history, physical examination and laboratory findings.

TREATMENT

- **Detoxification**, psychosocial therapy and rehabilitation are the methods of treatment.

The treatment of substance abuse is not easy. The first step is the motivation of the patient to accept the treatment. The substance is then totally withdrawn. The withdrawal symptoms which may result are treated medically. The abstinence is maintained by psychosocial therapy. Counselling and group therapy may help to resolve personal and interpersonal problems.

- **Rehabilitation** to re-establish their social and economic position is important to prevent relapse. Financial support and social guidance are helpful steps to bring the victim to mainstream life style.

Prevention: Substance abuse can be prevented through mass education, banning the production and distribution of drugs and giving moral education to build up psychic immunity. Since drug addiction starts early in life, the younger population is at risk and therefore the college and school students are to be specially targeted.

ALCOHOL-RELATED DISORDERS

These disorders result from the consumption of ethyl alcohol-containing beverages in quantities large enough to damage the physical, mental and social health of an individual. Wine, beer, toddy, brandy, whisky, rum and arrack are the usual beverages.

Etiology: The role played by genetic factor is important since persons show a genetic and familial predisposition to acquire the habit. Both psychological and environmental factors contribute to the development of alcoholism. Social and family maladjustment, economic

factors and vulnerable personality together promote the dependence on alcohol. Anxious and depressed persons find solace in alcohol to get-over their problems. Anti-social personalities find pleasure in alcohol, especially during periods of crisis.

Alcohol induces euphoria and relief from anxiety. These serve as positive incentives to repeat the consumption of alcohol. This positive reinforcing effect is associated with a high amount of dopamine release in the nucleus accumbens. In some oriental population such as the Japanese a variant of the isoenzyme *aldehyde dehydrogenase* provides them partial immunity to alcohol. They get negatively reinforced by the production of nausea, flushing and tachycardia on consuming alcohol. Several physical and psychological abnormalities can be caused by alcohol depending upon the amount of consumption, its frequency, type of beverage consumed, co-existent physical and psychiatric illnesses and the nutritional status (see Chapter 23).

CLINICAL FEATURES

Alcohol is a cerebral disinhibitant. Acute intoxication causes euphoria or elation, slurred speech, incoordination and gait disturbances. During periods of excitement, irrelevant talk, aggressive and violent activity, illusions and persecutory delusions may be observed. In cases of *chronic alcoholism* many other neuropsychiatric complications may be noted. These include continuous auditory hallucinations (*alcoholic hallucinosis*) and delirium tremens on withdrawal of alcohol. Other manifestations include delusion of infidelity (*alcoholic paranoia*), loss of recent memory with personality change (*amnesic syndrome /Korsakoff's Psychosis*) and intellectual deterioration (alcoholic dementia). Depression, schizophrenia and sexual dysfunction may be aggravated by chronic alcoholism. It is a major cause of suicide. Chronic alcoholism causes damage to several organs such as the stomach, liver, peripheral and central nervous system, heart and others. Consumption of alcohol by drivers is a major contributory factor for road accidents.

Diagnosis of alcoholism is based on the history and clinical features. The severity of intoxication generally correlates with the blood levels of alcohol though there are several exceptions. Blood level can be easily determined, so also the severity of consumption can be rapidly determined by breath tests.

TREATMENT

The treatment of alcoholism includes (i) *the treatment of the dependence*, (ii) *the psychiatric complications*, and (iii) *the physical complications*. Motivation may be required in most of the cases. The patient is initially detoxified. Alcohol is withdrawn. The resulting

withdrawal reaction—delirium tremens is medically managed. The patient is quietened with chlordiazepoxide. Electrolyte imbalance and dehydration are corrected. Anticonvulsants and antipsychotics may be needed. After the detoxification process psychotherapeutic measures are employed. The goal is to improve the environment and personality to maintain sobriety.

Prevention of relapse may be achieved through *behavioral therapy technique* or by *chemical aversion*. For chemical aversion disulfiram (*antabuse*) is chosen. Initially a dose of 0.5 g twice daily for the first day, 0.75g on the second day followed by 0.5 g on the third day and

0.25g on the fourth day onwards. The patient is advised not to take alcohol containing liquids, since they lead to intense discomfort and even life-threatening consequences when receiving antabuse. Relapse can also be prevented by anti-craving drugs such as *acamprosate* (calcium acetyl homotaurinate) a GABA analogue which inhibits the craving for alcohol. It is given in doses of 333 mg-666 mg thrice daily. Naltrexone is an antagonist of endogenous endorphin. This drug is given in the doses of 50 mg. once a day after stopping alcohol for 12 weeks. It helps to maintain abstinence. The neuropsychiatric complications and physical complications are medically managed.

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Behavioral Syndromes Associated with Physiological Disturbances and Physical Factors

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EATING DISORDERS

Eating disorders include anorexia nervosa and bulimia nervosa.

ANOREXIA NERVOSA

This disorder is common in young women. It is a condition characterised by severe resistance to eat or drink articles of food for prolonged periods leading to severe loss of body weight (below 15% of the standard weight). Any attempt to force them to feed may result in vomiting. Vomiting and diarrhea may be deliberately induced for losing weight. Though common among prepubertal

females, males are not exempt. Body image disturbance is the main cause. The fear of becoming obese is the triggering factor. The wish to become a 'lean beauty' is also a factor. Amenorrhea, intolerance to cold, growth of lanugo hair, dry skin and cardiac arrhythmias are the common features in this disorder. Symptoms of depression, obsessive compulsive disorder and sexual maladjustment are associated features. In severe cases cachexia supervenes. The condition is fatal, if untreated.

Treatment: is mainly supportive. Inpatient care may be required. The patient and family members are educated about the disease and better interpersonal relationship should be promoted. The patient is encouraged to bring up body weight by eating and helped by counselling, and drug therapy. At least 1,200-1,500 calories should be supplied per day and gradually increased upto 3,000-4,000 calories. Rarely parenteral feeding may have to be given. In 6% of cases *re-feeding syndrome* may develop. This may give rise to transient pedal edema. Emergency complications include prolongation of Q-T interval in the ECG, hypophosphatemia, weakness, confusion and neuromuscular dysfunction.

No drug is specific for anorexia nervosa. Cyproheptadine, chlorpromazine and pimozide are found to be useful. Modified insulin treatment can be used to bring up weight. Some cases may improve with electroconvulsive therapy.

BULIMIA NERVOSA

This is characterised by episodes of irresistible urge to overeat (binges). Surprisingly, the body weight remains normal. This is usually achieved by the self-induction of vomiting, use of laxatives or diuretics, or strenuous exercise. It is seen more commonly in women. Amenorrhea is not a feature. Stress encourages overeating. Cognitive behavior therapy and other forms of psychotherapy may help to reduce stress and stop this disorder. Drugs such as SSRIs are helpful adjuncts. Complications may develop on account of repeated vomiting or due to side effects of self-administered drugs.

SLEEP DISORDERS

Insomnia, hypersomnia and parasomnias are included under this term.

Insomnia

It is the most common sleep disorder. It may be primary or secondary. The secondary causes are medical and psychiatric. Physical pain, asthma, arthritis, hyperthyroidism, excessive use of caffeine, hunger, use of drugs such as aminophylline and steroids are the common medical causes. Depression, anxiety, mania, obsessive compulsive disorder, dementia and withdrawal from alcohol or drugs are the common psychiatric causes. The treatment depends on alleviation of the primary cause. Hypnotics can be used temporarily.

In primary insomnia no specific cause can be found. It is uncommon. There is difficulty in falling asleep or the patient wakes up frequently. The treatment modalities are conditioning of sleep, adoption of sleep hygiene using the bedroom only for sleeping, change of bedroom, and relaxation techniques and use of hypnotic on a short-term basis.

Hypersomnia

In this condition there is excessive sleep, Narcolepsy is the most common manifestation.

Narcolepsy

Narcolepsy is a disabling sleep disorder characterized by excessive day time sleepiness and abnormal rapid eye movement (REM) sleep. Other associated phenomena include **cataplexy** which is sudden loss of muscle tone triggered by strong emotions, sleep paralysis, and hypnagogic (at the onset of sleep) hallucinations and sleep paralysis. The prevalence in the general population is about 0.05%. The condition shows genetic predisposition strongly associated with a HLA allele. **Sleep paralysis** is the occurrence of inability to move the limbs or the head or to speak and breathe normally either at sleep onset or on waking up mainly from REM sleep, despite being mentally awake. The biochemical basis is the deficiency of *hypocretin-1* peptides which are produced in the

hypothalamus. The level of *hypocretin* in CSF are low. Values of CSF *hypocretin* lower than 110 ng/L or 30% or normal values are highly suggestive of narcolepsy.

Clinical features: Daytime sleepiness is the first symptom to appear. The sleep episodes are irresistible, often short, often associated with dreaming and followed by normal wakefulness lasting for several hours.

Cataplexy which is specific to narcolepsy is a diagnostic marker. It is characterized by sudden drop of muscle tone, often precipitated by positive emotions such as laughter. In most cases all the striated muscles except the diaphragm lose tone and the person collapses. Sometimes the involvement of the muscles may be partial. The attack may last for a few seconds to several minutes. Others associated features are sleep paralysis and automatic behavior.

Diagnostic criteria:

1. Excessive daytime sleep occurring almost daily for at least 3 months, not attributable to other causes
2. Associated cataplexy
3. Diagnostic features on polysomnography
4. Levels of CSF hypocretin—1 below 110 ng/L or less than 30% of normal values are highly suggestive with high sensitivity and moderate specificity.

Treatment: Narcolepsy has no cure and therefore the management is symptomatic. The medications include (1) dopaminergic stimulants for daytime sleepiness and sleep attacks (2) antidepressants (mostly noradrenergic) for cataplexy and (3) hypnotics for disturbed night-time sleep.

Modafinil is a wakefulness promoting agent, given in a dose of 100-200 mg in the morning, repeated after lunch if needed. Methylphenidate and amphetamines are commonly used in doses below 60 mg/day. Other stimulants include sodium oxybate, mazindol, pemoline and selegiline.

Dose of mazindol is 2-3 mg/day.

Sodium oxybate is the approved drug for cataplexy given in doses of 3-9 g at night. It reduces day time sleepiness, narcolepsy, sleep paralysis and hypnagogic hallucinations. Adverse side effects include dizziness, headache, nausea, and less frequently, pain, depressive mood, enuresis and sleepwalking. Antidepressant drugs (especially SSRIs) are effective in treatment of narcolepsy and cataplexy—especially clomipramine in doses of 10-25 mg.

Further reading: Yues Dauvilliers, et al. The Narcolepsy with cataplexy. The Lancet 2007;369:499-511.

Parasomnias: These are abnormal events occurring while asleep. They may be nightmares, night terror, somnambulism (sleep walking) somnolology (sleep talking), bruxism (teeth grinding) and enuresis (bed wetting). These are common in children.

- **Nightmare:** It occurs during rapid eye movement (REM) sleep. The person may get up from sleep with

frightening dreams. Sleep may proceed after it. The content of the dream is recollected the next day. It is always non-pathological. But it is common after a stress experience. Usually no treatment is required. Measures to reduce stress, tricyclic antidepressants to reduce REM sleep and diazepam are the modalities of treatment.

- **Night terror:** The person (often a child) gets up from sleep frightened, terrified, confused, disoriented, screaming aloud, clinging to others around or running for help. After this episode the person falls asleep again. The episode is not remembered the next morning. It occurs during NREM sleep. It can be a manifestation of temporal lobe epilepsy. Treatment is seldom required. Diazepam or antiepileptic drugs may be required if a seizure disorder is diagnosed.
- **Sleep walking:** This occurs during non-rapid eye movement (NREM) sleep. It may be associated with sleep talking. The person may get up while asleep and perform various activities like taking bath, getting dressed up and even going for a walk and returning. He may meet with accidents during this phase. The activity can be terminated by waking him up. The events are not recollected when awake.

SEXUAL DYSFUNCTION

Sexual response is a psychosomatic process. The natural sexual activity in humans is the coital union of man and woman culminating in orgasm in both the partners. Seminal discharge occurs in the male during this state. The causes of sexual disturbances may be physical, psychological or both.

The different disorders include:

1. Reduction or loss of sexual desire and lack of sexual enjoyment.
2. Lack of genital response, which includes impotence in men and absence of sexual arousal in women.
3. Orgasmic dysfunction which includes premature or retarded ejaculation in man and orgasmic failure in women.
4. Vaginismus and dyspareunia in women and painful ejaculation in men.

Erectile Disorder

Impotence: *Impotence* is the inability to get or sustain erection sufficient enough for satisfactory coitus. Impotence may be due to organic diseases or may be due to psychological causes. If erection occurs in the presence of another partner, or during masturbation, it indicates a psychological cause. Presence of spontaneous early morning erection also points to a psychological cause. Psychological causes leading to impotence include venereophobia, lack of privacy, inertia on the part of the partner, fear of castration, and incestuous feelings.

Diseases such as depression, conversion disorders, anxiety disorder are associated with impotence. Many psychotropic drugs impair erection and delay ejaculation on account of autonomic side effects. Drugs such as bromocriptine, yohimbine and cyproheptadine may be useful in such cases.

Phosphodiesterase type-5 inhibitor such as sildenafil, tadalafil, and vardenafil are found very effective. **Sildenafil** is very effective to induce strong erection when given in doses of 25-100 mg. SOS to be taken one-hour before expected intercourse. Only one dose should be taken within 24 hours. Cooperation from the partner is essential for success.

Side effects include vomiting, headache, flushing, dizziness, visual disturbances, raised intraocular pressure, nasal congestion and hypersensitivity reactions. Contraindications include the concurrent use of nitrates, and vasodilators; hypertension, recent stroke, unstable angina, myocardial infarction and hepatic damage.

Premature Ejaculation

This is the occurrence of ejaculation early during the sexual intercourse before penetration or soon after that. This leads to a sense of frustration in the male and the female partner does not get orgasm. Physical methods such as the 'stop and start technique' and 'squeeze technique' in which the glans penis is squeezed when ejaculation is imminent, may succeed in some cases. Drugs such as fluoxetine and tricyclic antidepressants are helpful to delay ejaculation.

- **Female orgasmic disorder:** Many women may fail to get orgasm or it may be obtained only after undue delay.

Abnormalities of Sexual Preference Syn. Paraphilias

- *Fetishism, transvestic fetishism, pedophilia, exhibitionism, sexual sadism, sexual masochism and voyeurism* are some of the important disorders.
- **Fetishism:** Libido gratification from contact with articles such as dress, hair and others of the opposite sex.
- **Pedophilia:** An unnatural urge and desire to have sexual relationship with children of pre-pubertal age
- **Exhibitionism:** Tendency to exhibit his/her genitals to members of the opposite sex in public for sexual pleasure.
- **Sexual sadism:** Sexual pleasure derived from inflicting mental or physical pain on the sexual partner.
- **Sexual masochism:** Sexual pleasure derived by being abused or being acted cruelly by the opposite partner.
- **Voyeurism:** This is the phenomenon in which a person derives sexual pleasure by observing sexual activity of others.

- *Scopophilia*: This is sexual pleasure uptake from visual sources such as nudity in the opposite sex and obscene pictures.

**POSTPARTUM PSYCHIATRIC DISORDERS
(PUERPERAL PSYCHOSIS)**

These are the psychiatric disturbances which are precipitated by the stress of child birth.

- **“Postpartum Blues”** “(Maternity Blues)” is a mild disturbance of short duration. The main symptoms are irritability, crying spells, labile mood, agitation and confusion. It may disappear by itself within 2-3

days. To hasten recovery anti-anxiety drugs may be used.

- **Postpartum Psychosis** is a severe kind of disturbance. The symptoms in the majority of cases are those of mood disorders - either of mania or depression with agitation. Schizophrenia and delirium-like picture do occur at times. The life of the infant is always at risk, because of the delusions involving the baby. So the baby has to be protected.

The diagnosis is to be made after exclusion of any intracranial pathology. The treatment depends upon the clinical presentations. Antidepressants, antipsychotics, anti-anxiety and hypnotic drugs may be selected.

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**Psychological Factors
Affecting Systemic
Medical Disorders**

N. Krishnan Kutty

Chapter Summary

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PSYCHOSOMATIC DISORDERS

The body and mind interact both in health and illness. The mind plays a major role in many physical illnesses. A physical illness may be precipitated, aggravated or prolonged by psychological factors. This paved the way for the concept of psychosomatic disorders. This term has now been replaced by the new terminology “Psychological factors affecting medical conditions”.

The psychological factors are many:

1. It may be a primary mental disorder which affects the course of a medical disease, e.g. major depression delays recovery from stroke; myocardial infarction.
2. It can also be a psychological symptom that adversely affects the disease, e.g. anxiety worsens bronchial asthma. Depressive symptoms delay recovery from surgery.

3. It may be a personality factor that precipitates a disease, e.g. Type A personality in coronary artery disease.
4. It may be severe stress.

There are many physical disorders where psychological factors play a major role. The common physical disorders are:

Respiratory disorders: Bronchial asthma, hay fever vasomotor rhinitis.

Gastrointestinal disorders: Peptic ulcer, irritable, bowel syndrome, ulcerative colitis, anorexia nervosa.

Cardiovascular disorders: Hypertension, paroxysmal tachycardia, coronary artery disease.

Nervous system: Migraine, headaches.

Endocrine and metabolic disorders: Hyperthyroidism, diabetes mellitus, menstrual disturbances, obesity.

Dermatologic disorders: Eczema, psoriasis, neurodermatitis.

Bones and joints: Rheumatoid arthritis, backache.

Maladaptive health behavior affecting a general medical condition, e.g. avoidance of physical exercise, over-eating, unsafe sex practices and others.

TABLE 230.1

List of important medical conditions which give rise to mental symptoms	
General medical conditions	Psychiatric symptoms/syndromes
Endocrine disorders Hyperthyroidism Hypothyroidism Hyperparathyroidism Cushing's disease Addison's disease Pheochromocytoma	Psychotic symptoms Delusions, hallucinations, agitation, insomnia
Metabolic Conditions Hypoglycemia	Mood symptoms Depression – persistent sadness, gloomy thought, motor retardation, suicidal intent, ideas and attempts
Hepatic encephalopathy Uremia	Mania-elated, expansive mood, hyperactivity, persecutory/ grandiose delusions, muscular rigidity, immobility, catatonic posturing, negativism, mutism, echolalia and echopraxia
CNS Conditions Encephalitis sequelae, GPI, post-stroke, post-traumatic, Alzheimer's disease, Huntington's chorea, Wilson's disease, tuberous sclerosis, parkinsonism, frontal and temporal lobe tumours	Anxiety symptoms Generalized anxiety, restlessness panic episodes, obsessive compulsive symptoms, amnesia, dementia
Drugs Propranolol, anti-psychotics, steriods sympathomimetics, ranitidine, L-dopa, oral contraceptives	Personality Change A persistant change in behavior from the previous state and character trait
Other conditions Vitamin B ₁₂ deficiency, pellagra, leukemia Systemic lupus erythematosus (SLE)	————Do————
Note: All the psychiatric symptoms may develop in any of the general medical conditions, nonspecifically.	

- **Management:** Medical treatment is the more important modality of management. It should be supplemented with measures to allay and counteract the psychological impacts caused by the underlying disease. Psychotherapeutic measures include counselling, general behavior therapy techniques such as muscle relaxation, biofeedback, controlled breathing exercises as practiced in yoga and other measures such as hypnosis.

Psychiatric Disorders Caused by General Medical Disorders

Several primary psychiatric disorders are accompanied by somatic manifestations. Similarly psychiatric symptoms

develop in several medical conditions such as cerebral infarction, encephalitis, drug toxicities and others. These are evident from the history, physical examination and laboratory findings. The Psychiatric symptoms are not specific or any particular medical disorder and vice versa. They are not reactions or sequelae of primary medical conditions. There are several medical and surgical conditions which give rise to psychiatric manifestations as part of the disease process. The psychiatric abnormality also clears up when the underlying condition is treated. These are described along with such disorders in the different sections.

The Table 230.1 gives a list of important medical conditions which give rise to mental symptoms.

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Down's Syndrome 1428

General Considerations

Syn:Mental subnormality /mental handicap/ idiocy/amentia/mentally challenged/ oligophrenia

Mental retardation (MR) is a state of sub-average intellectual functioning resulting in or associated with impairment in adaptive behavior and manifested during the developmental period before the age of eighteen years. Normal persons adapt sufficiently to various needs of the society and the environment. Adaptive behavior can be measured using *Vineland Adaptive Behavior Scale* (VABS). The retardation is graded on the basis of *intelligence quotient* (IQ) into four grades.

Causes of mental retardation: Mental retardation can occur with or without any obvious mental or physical disorder. Several etiological factors are known. A few of them include:

Grades of MR				
Grade of MR	IQ range	Mental age	Occurrence rate	Most common cause
Mild/moron or feeble mindedness	50-69	under 9	85%	Psychosocial
Moderate-(Imbecility)	35-49	under 6	10%	Down's syndrome, fragile X syndrome, Phenylketonuria
Severe	20-34	> 3< 6	3-4%	Microcephaly, cretinism, cerebralpalsy
Profound-Idiocy	below 20	below 3	1-2%	-Do-

Chromosome abnormality—For example, Down's syndrome, fragile X-syndrome, Inborn errors of metabolism, e.g. phenylketonuria.

Congenital brain abnormalities—For example, microcephaly hydrocephalus, tuberous sclerosis, cretinism, cerebral palsy.

Prenatal causes—For example, maternal rubella, syphilis, lead poisoning, alcohol.

Perinatal—For example, birth asphyxia, kernicterus.

Postnatal—For example, hypothyroidism, injury, intoxication with lead and mercury, autism, encephalitis, meningitis.

Down's Syndrome (Mongolism)

This condition is the most common chromosomal abnormality causing mental retardation (MR). It was described by **Landon Down** in 1886. The incidence is one in thirty live births occurring in children born to mothers aged 45 and above. The risk in the second child is 1 in 100.

Pathology: The 21st chromosome occurs as triple (trisomy) instead of the normal two alleles. About 95% of *trisomy* is due to non-disjunction which happens during meiosis. The rest 5% is due to translocation and *mosaicism*. In mosaicism the non-disjunction occurs during cell division after fertilization.

Clinical Features: Clinical features are characteristic. The face is round with small mouth and pegged teeth, furrowed protruding tongue and high arched palate. The eyes show oblique palpebral fissures and epicanthic folds. The occiput is flat. The hand is short and broad with a single palmar crease and short curved little finger. Hypotonia and hypermobility of joints may occur. Other less common features are congenital heart disease, especially septal defects, duodenal obstruction, impaired immune responses, higher incidence of leukemia, hypothyroidism and atlanto-axial dislocation.

Diagnosis: Is by the clinical findings and IQ measurement. IQ below 70 favors M.R. Mental retardation can be

predicted during infancy by the presence of clinical features such as microcephaly, mongoloid features, cerebral palsy and others. During early childhood, delay in the developmental milestones, academic backwardness, peer group maladjustment, and absenting from school or house may suggest mental retardation. Later in life such cases present as inability to bear responsibilities and failure in adaptation to life situations. Some of them require supervision even in routine work.

Management and care of mental retardation: The main objectives are provision of educational and psycho-social care. It depends on the age of the retarded person and type of retardation. Fostering, boarding, schooling in special schools and accommodation are their social needs. A team

approach including doctors, nurses, occupational therapists, psychologists, physiotherapists and speech therapists, is most rewarding. Persons with mild handicap can live independently though supervision may be needed in special situations.

Normalization is the modern concept, widely practiced in the USA. The mentally retarded person is made to live in the community and given the chance to experience and participate in social activities. Retarded children are preferably brought up in their own homes. Training and accommodation are provided in the proximity of the family. As in the case of normal persons, the mentally retarded are also prone to develop various psychiatric disorders. Drugs and behaviour therapy are given accordingly.

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Behavioral and Emotional Disorders Occurring in Childhood and Adolescence

(Syn. Psychiatric Disorders in Childhood and Adolescence)

N. Krishnan Kutty

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Disorders of Psychological Development 1429
Pervasive Developmental Disorders 1429
Childhood Autism 1429
Attention Deficit Hyperactivity Disorder 1430
Conduct Disorders 1430
Enuresis 1430

Children also suffer from common psychiatric disorders as other age groups. Some of the disorders are seen exclusively in children. The important ones are described below.

Disorders of Psychological Development

Children may lag behind in the development of learning of certain psychological skills specifically.

Examples:

- Specific reading disorders.
- Specific spelling disorders.

- Specific mathematics disorders.
- Understanding and articulation of spoken language.
- Impairment of motor coordination.

Lack of self-esteem and delay in brain maturation may be the cause in many. The disorders may disappear as the child grows. Emotional support and instilling confidence may enhance recovery.

Pervasive Developmental Disorders

The symptoms of these disorders are pervasive impairment of social skills, communication skills and behaviors. Childhood autism and Attention Deficit Hyperactivity Disorders (hyperkinetic syndrome) are the common disorders.

CHILDHOOD AUTISM (INFANTILE AUTISM)

The term autism denotes a state of absorption into ones own world of phantasy with loss of contact with the reality. Reported incidence of childhood autism is 2-5/10,000 live births.

Childhood autism was originally described by **Leo Kanner** in 1943 as Early Infantile Autism. Autistic

aloneness, language abnormality and restricted and compulsive behavior are the main three features of this disorder. Boys are more affected than girls. The disorder is unmasked by the third year of life. The child is abnormally quiet, lacks the usual emotional warmth and likes to be left alone. Eye-to-eye contact is avoided. He does not communicate through conversation. Pronouns are reversed. 'You' is used to mean 'I' Echolalia is common. Words and behavior are stereotypic. The child is fond of sameness in everything. Bizarre behavior such as rocking, whirling the head and flapping of hand may be present. Impulsive violence is common. The arithmetic skill is relatively high. IQ may be around 70 in most cases. Some have normal IQ. Many cases may be attributable to birth trauma. Autism is strongly a genetic disorder, and probably arises from multiple genetic defects. Recurrence within families with one affected child is high.

There is no specific treatment. Antipsychotics are given to control violence and hyperactivity. Behavior therapy may be helpful. Parents are to be counselled regarding management of the child at home. Many improve spontaneously and may be able to attend normal school. A few may require training in special schools. Some require special residential care.

Attention Deficit Hyperactivity Disorder-ADHD (Hyperkinetic syndrome)

This disorder is more common in boys. Persistent inattention, hyperactivity and impulsivity are the cardinal features. These affect their scholastic performance. Impulsive and reckless behavior are common. Brain damage due to birth trauma, allergy to food containing tartrazine, toxicity to lead and overactivity of peripheral adrenergic system are some of the recognized causes.

Treatment: Stimulant drugs such as dextroamphetamine 2.5-5 mg twice a day, clonidine, tricyclic antidepressants and monoamine oxidase inhibitors are beneficial. Many children become normal as they reach adolescence. Atomoxetine HCl is a recently introduced drug for this condition.

CONDUCT DISORDERS

These are the most common disorders of childhood. Persistent dis-social, aggressive, or defiant behavior are the presenting features. It is manifested as quarrelsomeness, disobedience, lying, cruelty to people and animals, destructiveness, stealing, absenting from school, fire setting, temper tantrums, running away from home and the like. The disorder may be the outcome of unsatisfactory family environment, poor academic performance and such other psychosocial adversities.

Treatment: Some may improve spontaneously. Drugs are of little value. Psychosocial therapy is important. The child is given insight-oriented psychotherapy to bring up problem solving skills. Adverse domestic factors are identified and removed. The child's behavior is rectified through rewards, praise and approval (*contingency management*).

Drugs: In selected cases anti-psychotics, SSRIs, mood stabilizers and anxiolytics may be helpful.

ENURESIS (BED WETTING)

Almost all children get bladder control by the age of five years. Enuresis is the voiding of urine during sleep persisting after the age of five years. In primary enuresis the child has never attained bladder control after birth. In secondary enuresis the child has attained bladder control which is subsequently lost. Delay in brain maturation, emotional factors such as school problems, birth of a younger child, loss of parental affection and other stressful factors may be the underlying causes. Local causes include low volume capacity of the urinary bladder, urinary tract infection, congenital abnormalities of the lower urinary tract and others.

Treatment: Behavior therapy techniques using *mattress alarm (bell or buzzer and pad)*, bladder training exercises and reassurance are the therapeutic modalities. Drugs such as imipramine 25-50 mg at night are useful. Intranasal administration of synthetic antidiuretic hormone is effective.

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Suicide, Attempted Suicide and Deliberate Self-harm 1431

Violent and Aggressive Behavior 1432

Acute Anxiety and Panic Episode 1432

Stupor 1432

Acute Psychological Reactions to Physical Diseases 1432

A psychiatric emergency can be defined as a sudden disturbance in behavior, thoughts or feelings for which immediate intervention is necessary to avoid danger to the patient, other people or both. The common psychiatric emergencies are:

1. Suicide and attempted suicide
2. Violent or aggressive behavior
3. Acute anxiety and panic episode
4. Stupor
5. Acute psychological reactions to physical illness
6. Abnormal reaction to drugs.

Suicide, Attempted Suicide and Deliberate Self-harm

‘Suicide is an expression of personal agony’. It is a deliberate act or an attempt to kill by oneself (*sui*=self, *cide*=murder). Some of these persons may not be actually bent upon causing death but may only be trying to seek attention or help when they are in distress through *self injurious behavior*. Hence, the term ‘*deliberate self harm (DSH)*’ is commonly used at present to denote such self-destructive actions including suicide.

Suicide can be due to many causes

- **Psychiatric disorders:** Major depression is the most common condition leading to suicide. It can also occur in schizophrenia, personality disorders, alcoholism, and drug addiction. Less serious suicidal attempts may be made by patients with dissociation/conversion

disorders, immature personality and antisocial tendencies.

- **Physical diseases:** Chronic or serious physical illness like malignancies and degenerative or disfiguring diseases or surgery may lead to a feeling of hopelessness and some may attempt or commit suicide.
- **Social factors:** Suicidal behavior is high among socially isolated individuals as shown by the French sociologist Emil Durkheim. Persons with broken families, disturbed marriages and stressful occupations are more vulnerable. Though both sexes make suicidal attempts more serious ones are made by males. Similarly, suicidal behavior is more common among adolescents and elderly subjects.
- **Psychological factors:** Acute psychological stresses of a severe degree may often lead to suicidal behavior. Loss of job, financial crisis, marital stresses, interpersonal problems in the family, death or serious illness of beloved ones, accidents, failure in examinations, humiliating or painful experiences and other similar factors may predispose to suicidal behavior.

Management: In attempted suicide emergency medical management is required to prevent deterioration and death. The modalities depend on the type of attempt and substances used as poisons. These are described in Section-4. Once the emergency is tided over, the next step is to identify the pre-disposing factors and arrange suitable measures to prevent recurrence. In suicidal risk the first step is to arrange a safe environment where they can be closely observed. The seriousness of suicidal risk is to be evaluated by taking all relevant factors into consideration. The presence of depression, previous history of suicidal attempts, young age, history of alcohol and drug addiction, presence of serious physical diseases, severe psychological stresses, social isolation and an immature maladjusted personality contribute to increase the suicidal risk. Such patients require psychological support in the form of counselling and psychotherapy. Drugs are needed to relieve depression, anxiety or psychosis, if they are present. Hospitalization is better when the risk is high.

Violent and Aggressive Behavior

This may result from psychoses like schizophrenia, mania, delirium and intoxication with drugs and alcohol. The patients are briefly evaluated. They should be kept in safe custody to avoid danger to themselves and others. Some of these patients may respond to supportive environment and reassurance. Physical restraints may be necessary in others. Injections of diazepam 10-20 mg IV slowly, Lorazepam 2 mg IM or haloperidol 5 mg IM can be given to quieten the patient. The basic disorder is to be identified and managed subsequently.

Acute Anxiety and Panic Episode

This may be secondary to unidentifiable stresses. The patient comes in severe tension, restlessness and with impending feeling of death or disaster accompanied by marked autonomic arousal. After proper evaluation, provision of supportive environment, reassurance and parenteral administration of anti-anxiety drugs serve to overcome the anxiety. The causative factors need exploration and further management.

Stupor

Stupor is a state of minimal psychomotor activity. These patients may refuse to eat and may not cooperate in maintaining proper hygiene. The causes of stupor include

catatonic schizophrenia, depressive illness and organic conditions. The general management is similar to that of a comatose patient. Further treatment depends on the underlying cause.

Acute Psychological Reactions to Physical Disease

Commonly in the medical and surgical wards, one encounters patients who present with acute anxiety, tension, depression, fear, agitation or even aggression occurring during acute physical disorders such as ischemic heart disease, stroke, accidents, burns, malignancy and postoperative pain. These manifestations are secondary to their anxiety and emotional stress. Such patients need sympathetic communication, education, reassurance and encouragement. Drugs may be used to control anxiety and depression. *The attending physician should extend psychological help as well as appropriate treatment for the basic physical condition.* Other situations where acute psychological stress occurs include the following:

- 1. When breaking the news of a serious illness such as AIDS, cancer or leukemia in the patient and
- 2. When giving the first information of death of a close relative.

In such cases proper empathy from the physician and a supportive attitude towards the persons help to ease the situation.

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General Principles of Management of Psychiatric Disorders

N. Krishnan Kutty

Chapter Summary

- Electroconvulsive Therapy 1433
- Pharmacological Methods 1433
- Anti-psychotic Drugs 1433
- Antidepressants 1435
- Anti-anxiety Drugs 1436
- Antiparkinsonism Drugs 1437

Therapeutic modalities in psychiatric medicine fall into three major groups.

These are:

- 1. Physical methods
- 2. Pharmacological methods and
- 3. Psychological methods

Psychiatric cases can be managed in the regular outpatients department, but inpatient care is

needed in cases of violence, stupor, suicidal threat, delirium and feeding problem.

Combination of therapies is much better than a single mode.

PHYSICAL METHODS OF TREATMENT

These are electroconvulsive therapy (ECT) and psychosurgery.

ELECTROCONVULSIVE THERAPY (ECT)

Convulsive Therapy was introduced by **Von Meduna** in 1934 as a treatment for schizophrenia. He observed that schizophrenia and epilepsy seldom occurred together. So his idea was to produce convulsions to drive away schizophrenia. First he used injection of camphor oil and later injections of leptazol to induce the convulsions. In 1938 **Cerletti** and **Bini** in Italy found that electricity could produce convulsions and they devised a machine. Thus, electro-shock treatment (EST) came into being and later used the terminology, electro-convulsive therapy (ECT). ECT became very popular because of its efficacy in the management of depression, mania and schizophrenia.

- **ECT technique:** In ECT an electric current is applied over the brain in the temporal regions, so as to induce a seizure. The seizure so produced, resembles a typical grand mal epilepsy. Two types of techniques are followed - direct ECT and modified ECT. At present modified ECT is the method of choice.
- **Modified ECT:** ECT is administered after giving a muscle relaxant in order to minimize the muscular convulsion. For practical purposes the ECT is comparable to a major surgical procedure. Informed consent should be obtained and the procedure should be undertaken by a specialist, only in places with facilities for emergency care.
- **Indications of ECT:** ECT is still considered as a very effective therapeutic procedure for the following conditions.
 1. Major depression with suicidal intent.
 2. Depressive stupor
 3. Resistant depression
 4. Catatonic schizophrenia
 5. Acute schizophrenic excitement
 6. Manic excitement
 7. Schizo-affective disorder.
- **Contraindications:** There is no absolute contraindication except for the anesthesia. The contraindications include acute coronary heart disease, acute febrile illnesses, hypertension, acute respiratory illness and intracranial space occupying lesions. Pregnancy is not a contraindication.
- **Complications:** Mortality is 3 to 4 per 100,000. It parallels the risk of anesthesia. The other complications include injuries to tongue, skeletal muscles,

ligaments and bones, aspiration pneumonia, cardiac arrest, respiratory arrest and post-ictal anterograde and retrograde amnesia. The amnesia disappears within 1 to 4 weeks.

Psychosurgery

It was introduced by **Egas Moniz**. These are neurosurgical operations to control intractable mental disorders. Nerve tracts or nuclei concerned with mental functions are severed or destroyed. Proton beams, radioactive implants such as yttrium-90, ultrasonic beams and electrical coagulation are employed for this operation. *Stereotactic tractomy* severs the connection between the orbital part of the frontal lobe and the limbic area. *Stereotactic limbic leucotomy* interrupts the frontal lobe pathways and cingulate gyrus and amygdala.

Indications for surgery include intractable conditions not responding to medical treatment such as:

- Obsessive compulsive disorder
- Anxiety disorders
- Depression
- Paranoid schizophrenia, and
- Pain disorders.

The outcome is unpredictable. Some may improve remarkably and others deteriorate, even to the level of vegetative existence.

PHARMACOLOGICAL METHODS (DRUG THERAPY)

The discovery of drugs that can rectify disturbed mental function was a major revolution in psychiatry. These drugs which have affinity towards the mind are collectively called *psychotropic* drugs. Such drugs are generally used in the treatment of mental disorders. They can be classified into:

- i. *Anti-psychotics*
- ii. *Antidepressants*
- iii. *Mood stabilizers*
- iv. *Anti-anxiety drugs*
- v. *Hypnotics*
- vi. *Psychostimulants*
- vii. *Cognitive enhancers*
- viii. *Antiparkinsonism drugs*

ANTI-PSYCHOTIC DRUGS (NEUROLEPTICS / MAJOR TRANQUILIZERS)

These drugs are capable of eliminating psychotic symptoms such as delusions, hallucinations, psychomotor excitement and the associated symptoms. Most of these drugs act by blocking dopamine receptors (D_2) or the serotonin ($5HT_2$) receptors in the CNS at the mesocortical and mesolimbic tracts. In addition they also block the histaminic (H_1) cholinergic and adrenergic receptors and

TABLE 234.1

Showing the common anti-psychotic drugs

Kind of drugs	Starting dose (mg) oral	Max. daily dose (mg)	Prominent side effect
<i>Conventional anti-psychotics</i>	<i>Common S/E</i>		
Phenothiazines			
Chlorpromazine	50-100 tid 50-100	1500 IM	Sedation Hypotension
Thioridazine	50-100 tid	800	extrapyramidal
Trifluoperazine	5 tid	60	symptoms (EPS) and others
Fluphenazine decanoate	12.5-50 once in 2-4 weeks	IM	EPS
Butyrophenones			
Haloperidol	5-20 mg tid oral 5-10 IM	100	Severe EPS; non-cardiotoxic
Haloperidol decanote	25-250 once in 2-4 weeks	IM	EPS
Diphenyl butyl piperidine			
Pimozide	2-4 mg od	20	EPS
<i>Atypical anti-psychotics</i>			
Benzisoxazoles			
Risperidone	1-2 mg bd oral	16	Sedation EPS
Dibenzodiazapines			
Clozapine	25-50 mg bd	900	Convulsion leucopenia sedation
Thienobenzodiazemine			
Olazepine	5-10 mg od HS	20	Sedation weight gain
Dibenzothiazepine			
Quetiapine	25-50 mg tid	500	Sedation
Aripiprazol	10-15 od	30	Insomnia

these account for their side effects. These drugs are readily absorbed from the gut and are bound to plasma proteins. They are metabolized mostly by hepatic microsomal oxidase system (Table 234.1).

• **Conventional Vs. atypical anti-psychotics**

Phenothiazines are the first group of antipsychotics that came into popular use. Butyrophenone came later. These drugs produced extrapyramidal side effects (EPS) which were very troublesome. The search for EPS-free drugs lead to the discovery of newer antipsychotics. These newer antipsychotics are relatively free of EPS and are called *atypical anti-psychotics* (second generation anti-psychotics). The original group of drugs, (first generation anti-psychotics) are also known as *conventional anti-psychotics*.

• **Indications**

These drugs are used to control psychotic behavior in disorders like schizophrenia, mania, delirium, depression with agitation, aggressive and violent behavior, delusions, hallucinations and others.

• **Dosage and administration**

Anti-psychotics have a wide dosage range with individual variations. Treatment is initiated with small doses. The optimum dose is built up to get symptom control. Maintenance dose is required in disorders like schizophrenia and manic disorders. Drugs which have long half-life need to be administered once daily and those with shorter half-life are given more frequently.

• **Side effects of anti-psychotics**

Extra pyramidal symptoms (EPS)

These result from antidopaminergic activity at the basal ganglia.

Drug induced parkinsonism - Tremor, rigidity, akinesia, dysarthria and 'mask like face'. These respond well to trihexyl phenedyl HCl, promethazine, diazepam and other antiparkinsonian agents. *Acute dystonia*: Acute spasms of muscles of neck, tongue, face, glottis and other parts—These respond well to antiparkinsonism agents.

Akathisia - Motor restlessness and a drive to move, which is not due to anxiety or agitation. The treatment is by reducing the dose and using drugs like diazepam or propranolol.

Tardive dyskinesia: (perioral tremors/oro-facial dyskinesia/rabbit syndrome), wide spread choreoathetosis and dystonia. Prevention is better, since it is not easy to treat. Diazepam, propranolol and antiparkinsonism agents are effective.

Anticholinergic (antimuscarinic) symptoms: Blurred vision, dry mouth, hesitancy of micturition, urinary retention, constipation, precipitation or aggravation of glaucoma.

Antihistaminic symptoms: Sedation and weight gain which are due to H₁ receptor blockade.

Antiadrenergic symptoms: Posturalhypotension, tachycardia, erectile dysfunction.

ECG changes: Prolongation of Q-T interval and T wave changes.

Malignant neuroleptic syndrome (MNS): It is a rare but very serious side effect mostly seen with high potency drugs. It is characterised by generalized muscular rigidity (catatonia), hyperpyrexia, unstable blood pressure, tachycardia, excessive sweating, myoglobinuria, urinary incontinence and impaired sensorium. Serum creatine phosphokinase (CPK) is elevated to very high levels. The treatment is symptomatic. The anti-psychotic is stopped immediately. Drugs like diazepam, dantrolene, bromocriptine, amantadine and L-dopa help to relieve symptoms. MNS is a medical emergency.

Endocrine side effects: Elevation of prolactin level leading to gynecomastia, galactorrhea, amenorrhea and weight gain.

Hematological: Agranulocytosis.

Allergic: Photosensitivity, skin rashes, itching, exfoliation of skin.

Gastrointestinal: Gastritis, hepatitis, constipation.

Antidepressant Drugs

Syn: Mood elevators / Thymoleptics

These are drugs which elevate the depressed mood by increasing the neurotransmitter levels of norepinephrine and serotonin at CNS synapses. The common antidepressant drugs are given in Table 234.2.

Tricyclic Antidepressants (TCAs)

- **TCAs** are the first group of drugs which became popular because of their proven efficacy. These are absorbed well from the GIT and are highly protein bound. They are metabolised in the liver.

Dosage is 25 mg bd or tds and raised to 50 mg tds. It is maintained for 3-6 months and gradually tapered off. Weight gain and cardiac toxicity are major disadvantages. ECG changes include prolongation of PR and QT intervals, ST segment depression, blunting of T wave and arrhythmias.

Selective Serotonin Re-uptake Inhibitors (SSRIs)

- **SSRIs** have recently become more popular because of their ease of administration and lack of cardiotoxicity. They produce GIT disturbances like nausea, and bloating sensations, diarrhea and CNS disturbances like day time sleepiness, headache, agitation, irritability, seizure and some times, EPS. Allergic reaction may occur giving rise to skin rashes.

Monoamine Oxidase Inhibitors (MAOIs)

- **MAOIs** were the first antidepressants discovered which lead to the discovery of TCAs. These drugs are rarely prescribed, because of lack of potency and serious side effects like 'cheese reaction', i.e. a patient on MAOIs goes into a state of fatal hypertensive crisis on consumption of tyramine containing foods like cheese.

Mood Stabilizers

These drugs are primarily meant for the prophylaxis of bipolar mood disorders (BPMD), but they are also effective in the treatment of acute mania. The common mood stabilizers are lithium, carbamazepine, oxcarbazepine, valproate, lamotrigine, topiramate and gabapentine.

- **Lithium**: The anti-manic effect of lithium was discovered by **Cade** in 1949. The carbonate and citrate salts are used.

Dosage: Lithium is given orally. It is absorbed well and excreted through the kidneys. 600-800 mg is given daily in 2-3 divided doses to obtain a serum lithium level of 0.8 to 1.2mEq/ L for treatment of acute mania. For prophylaxis the level can be 0.4 - 7 mEq/ L and this may be continued for 3 to 5 years. The level is adjusted by periodic estimation of the level of lithium after a 12-hour fast.

Side effects: 1) Diuresis, tremors, weightgain, hypothyroidism, GI-disturbances, widening of QRS complex in ECG, teratogenicity and others.

Serum levels above 1.4 mEq/ L produce toxicity, which includes nausea, vomiting, slurred speech, toxic tremors, seizures, and confusion. If, untreated this may end fatally.

- **Carbamazepine**: It is basically an anticonvulsant. **Dose**- 400-1600 mg given orally in two divided doses. For prophylaxis it is continued for 3-5 years, though

TABLE 234.2

Common antidepressant drugs				
Name	Starting dose mgs	Max. daily dose	Amine effect	Usual side effect (SE)
Tricyclic Antidepressant Drugs (TCA)				
Amitriptyline	25 tds od or bd	150	Norepinephrine (NE) 5 Hydroxytryptamine	Sedation anticholinergic action, sexual dysfunction, cardiac toxicity, Hypotension
Imipramine	25 tds	200	NE, 5HT	Same as above
Clomipramine	25 tds	300	NE, 5HT	Same as above
Selective serotonin reuptake inhibitors (SSRIs)				
Fluoxetine	20 OD	80	5HT	GI disturbances nausea, vomiting, anorexia, dry mouth
Sertraline	25 OD	200	5HT	Sexual dysfunction - delayed orgasm, anorgasmia,
Paroxetine	10-20 OD	60	5HT	CNS disturbances
Citalopram	10-20 OD	60	5HT	headache, somnolence
Escitalopram	10-20 OD	60	5HT	insomnia, agitation EPS, mania
Venlafaxine	37.5 bd	375	5HT, NE	
Monoamine oxidase inhibitors (MAOIs)				
Phenelzine	15	90		Cheese reaction
Tranylcypromine	30	60		CNS - confusion insomnia, headache
Isocarboxazid	10	30		ANS - Blurred vision, drymouth
Moclobemide	150 bd	600		Other S/E - hypotension, sexual disturbance (No cheese reaction with Moclobemide)
Atypical antidepressants				
Bupropion	100 bd	450	Dopamine (DA) NE	Agitation, headache insomnia hypotension
Trazadon	50 bd	600	5HT	Sedation, dry mouth constipation,
Mirtazapine	15 od Bed Time	45	5HT, NE	increased appetite sedation weight gain
* OD - Once daily, bd - twice a day, tds - thrice a day				

in smaller doses. It induces hepatic micro-somal enzymes.

Side effects: Diplopia, drowsiness, agranulocytosis, fatal skin reactions such as exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis. The drug is teratogenic.

- **Oxcarbazepine:** It is an analogue of carbamazepine. Dose 150-300 mg bd.
- **Valproate** - It is also basically an anticonvulsant. *Dose* - This drug is started with a dose of 400-600 mg in divided doses and increased to a maximum of 1-2 g daily. Serum levels of 50-100 µg/L are optimal. The drug is teratogenic. *Side effects:* GI disturbances, leucopenia and weight gain. Acute pancreatitis and hepatotoxicity are rare serious complications which could be fatal.

Lamotrigene, Topiramate and Gabapentin are being used recently as adjuncts; but they have not come into common use.

**Anti-anxiety Drugs
(Anxiolytics / Minor Tranquillizers)**

These are drugs which relieve anxiety symptoms and therefore, used in anxiety disorders. The common anti anxiety drugs are the following:

The Benzodiazepines are the most commonly used drugs. They can be given orally or parenterally, especially IV. They bind to the GABA receptors and thereby enhance GABA activity. Sedation, ataxia, confusion drug dependence and withdrawal syndrome are the common adverse effects.

General Principles of Management of Psychiatric Disorders

Drugs	Dose- oral and parenteral	Remarks
Benzodiazepines		
Lorazepam	1-2 mg once or twice daily 2 mg IM/IV	Short acting
Oxazepam	15-30 mg thrice daily	Short acting
Alprazolam	0.25 to 0.5 mg 2-3 times daily	Potent drug, long acting
Diazepam	5 mg twice daily 5-10 mg IV	Poorly absorbed when given IM- hence IV dose is preferred Long acting
Chlordiazepoxide	10-20 mg two to three times daily	
Clonazepam	0.5 to 2 mg once or twice daily	Long acting
Nitrazepam	5-10 mg at bed time	Hypnotic
Flurazepam	5-10 mg at bed time	Hypnotics
B-Adrenoreceptor blocker		
Propranolol	10-40 mg twice or thrice daily	Effective against peripheral manifestations of anxiety
Azapiron		
Buspiron	5-10 mg, twice or thrice daily	No sedation No dependence

Flumazenil is a Beta 2 receptor antagonist which antagonises the action of benzodiazepine and can be used as an antidote to treat acute toxicity of benzodiazepine.

Hypnotics: These are sleep promoting agents. The drugs in common use are listed below:

Benzodiazepines	Oral dose
Nitrazepam	5-30 mg bed time
Clonazepam	2-4 mg bed time
Lorazepam	2 mg bed time
Flurazepam	30-60 mg bed time
Oxazepam	15-30 mg bed time
Non-benzodiazepines	
Zolpidem	5-20 mg bed time
Zopiclone	3.75-7.5 mg bed time

Psycho-stimulant drugs: These include amphetamine, methyl phenidate, cocaine and caffeine. These drugs

release dopamine and prevent its re-uptake. They may lead to drug dependence and development of psychosis.

Amphetamine is used in the treatment of narcolepsy.

Methyl phenidate is used in the treatment of attention deficit hyper activity disorders.

Cocaine is used as a local anesthetic to mucus membranes. Recently it is being tried for therapeutic purposes as well. Being highly habit forming, this drug has to be used with caution.

Cognitive enhancers: Recently a few drugs have been introduced to improve memory and other cognitive functions in cases of dementia, especially in Alzheimer's disease. These drugs are:

Drugs	Dosage	Remarks
Choline esterase inhibitors		
Tacrine	30-40 mg qid	Treatment is initiated with small doses and gradually increased to the optimum level.
Donepezil	5-10 mg qid	
Rivastigmine	3-6 mg tid	GI disturbances may develop
Galantamine	8-12 mg bid	
NMDA antagonist		
Memantine	5-10 mg bid	
MAOIs (beta)		
Selegiline	5-10 mg bd	
Other nonspecific drugs		
Vitamin-E, calcium channel blockers		May be useful in some situations, especially as adjuvant drugs.
Ginkgo biloba, estrogens		

Antiparkinsonism Drugs: These drugs are very useful in the management of drug induced extra pyramidal symptoms. Commonly used drugs are:

Drug	Dosage
1. Trihexyphenedyl HCL	1-2 mg bid or tid
2. Procyclidine HCL	2.5-5 mg bid or tid 2.5-5 mg IM
3. Promethazine HCL	10-25 mg bid or tid 25-50 mg IM
4. Diazepam	2-5 mg bid or tid 10-20 mg IV slowly
5. L-Dopa is not recommended as it worsens or induces psychosis.	

Psychological Methods of Treatment (Psychotherapy)

N. Krishnan Kutty

Chapter summary

Psychoanalytic Psychotherapy 1438

Narcoanalysis 1439

Abreaction 1439

Supportive Psychotherapy 1439

Group Psychotherapy 1439

Behavior Therapy 1439

PSYCHOANALYTIC PSYCHOTHERAPY

Psychotherapy is also known as ‘*talking cure*’. It is based on the communication taking place between the therapist and the patient. The therapist is a trained person. Removing or modifying symptoms or promoting positive personality growth is the goal of the therapy. Over hundred types of psychotherapies are in vogue. All of them follow a few fundamental principles.

The therapist should be a trained person. He should establish therapeutic relationship with the patient. Listening and talking takes place between them.

This results in release of pent up emotions in the patient. The patient is given information and explanations of symptoms, guidance, suggestions and advice to restore his lost morale.

What is Psychoanalysis

- *Psychoanalysis* is not merely a form of psychotherapy. It also refers to the process of exploring (analysing) the mind **Sigmund Freud** (1856-1939) is the father of psychoanalysis. He was a Viennese physician. In his classic work “The Interpretation of Dreams”, he gave a model of the mind called the ‘*Topographical Theory*’ of the mind. The mind is formed of three regions—the unconscious, pre conscious and conscious regions.
- *The unconscious* part of the mind contains all the repressed (forgotten) ideas and affects. It is the seat of neurotic conflict and influences the conscious mind.

- *The preconscious* part is the region which is in between the conscious and unconscious regions and it can access both these parts. It contains the events and processes that can be brought to the conscious part, at will.

- *The conscious* mind is that part which becomes aware of the external and internal world through the senses.

In later years Freud proposed another model of the mind called the ‘*Structural Theory*’ of the mind. The mind is formed of three provinces—the id, ego and super ego.

- *The Id* – This is present at birth. It is unconscious and is the reservoir of basic drives and instinct for sex aggression and survival.
- *The Ego* - It is the conscious part. It is the organized portion of the id and includes perception, voluntary movement, memory, judgment, and adaptation to reality. It registers sensations from the outside world and internal sources. It is the organ that reconciliates between id and super ego.
- *The Super Ego* – It is formed from id and ego. It consists of ethical values, and moral principles. It imposes restrictions and prohibitions. It invokes guilt and self punishment.

The psychotherapy introduced by Sigmund Freud is called *psychoanalytic psychotherapy*. *Supportive psychotherapy*, group psychotherapy, suggestions, hypnosis, narcoanalysis, abreaction, exposure and response prevention and thought stopping, are some of the other common methodologies of psychotherapy employed.

The classical psychotherapy introduced by **Sigmund Freud** is psychoanalysis. He devised a technique known as ‘*free association*’. The patient is made to rest comfortably on a couch. He is allowed to talk freely, uninhibited, whatever comes to his mind, in sessions lasting for about 45 minutes. Repeated sessions are required. Block in the flow of talk may occur during the sessions. This indicates *resistance*. Resistance is indicative of unconscious painful experiences (conflict). As the psychotherapy proceeds the patient may develop an

emotional relationship (love, liking, hatred) with the therapist. This phenomenon is called *transference*. As a result, neurotic manifestations may develop in the treatment setting. This is known as *transference neurosis*.

The actual neurotic conflict is reflected in this transference neurosis, during the therapeutic sessions. This neurosis is *analyzed and interpreted*. It will help to resolve the neurotic conflict and thereby eliminate the symptoms. The patients also regain insight. The main idea of psychoanalytic psychotherapy is uncovering of the unconscious to resolve the neurotic conflict, the root of neurotic disorder.

Indications

Psychoanalytic psychotherapy is indicated in anxiety disorders, phobic disorders, conversion and dissociative disorders and personality disorders.

NARCOANALYSIS

The unconscious mind can be reached through the help of narcotic drugs such as short-acting barbiturates like thiopentone sodium and sodium amytal. Usually a 2.5% solution of thiopentone sodium is slowly administered intravenously to produce a state of cerebral disinhibition. The patient is then allowed to talk freely and uninhibited. Suggestions are given if needed.

Narcoanalysis is employed in the following conditions:

- Dissociate and conversion disorders
- Anxiety disorder and
- Differential diagnosis of catatonic schizophrenia from depressive and organic stupors.

ABREACTION

Abreaction is the secret of religious healing. Abreaction refers to the process of letting out of pent up emotions very freely. It may be done through verbal suggestions or by use of drugs like short-acting barbiturates or stimulant drugs. It is used to bring into conscious mind the unconscious (forgotten) traumatic events and thereby to remove symptoms and disability.

SUPPORTIVE PSYCHOTHERAPY

In this form of therapy the patient gets support from the therapist, who may be perceived as an authority figure. The patient is given acceptance and he is listened to. The unexpressed emotions are ventilated. It helps to release the inner tensions and strengthens the defense mechanism. The patient is helped to tackle his problem of guilt, shame, anxiety and frustration. The goal is achieved through the process of guidance, persuasion and environmental support. Finally, he may get self-confidence and better outlook of the environment and of himself.

Group psychotherapy: In this form of therapy a group of patients are getting the benefit of psychotherapy simultaneously. A group is formed of 6-10 selected patients and the therapists. The group forms a social environment for each patient and that forms the therapeutic agent. Uninhibited free talk is encouraged between members. Each one shares the experiences and problems of others. The group may focus on activities of problem solving and provision of support. Each session may last for 90-120 minutes. The group may meet once or twice a week. Group therapy is indicated in neurotic disorders, psychotic disorders, substance abuse, sexual deviations and personality disorders.

BEHAVIOR THERAPY

Behavior therapy works on the principle of ‘learning theory’. The neurosis is regarded as a maladaptive behavior learned by the patient and the symptoms as conditioned maladaptive pattern of behavior. The patient can be made to unlearn it. Systematic desensitization, implosion (flooding), aversion, exposure and response prevention, and thought stopping are some of the common techniques used in behavior therapy.

Cognitive Therapy (Cognitive Behavior Therapy-CBT)

This therapy is developed by **Aron Beck** based upon experimental psychology with respect to depression, but later applied to other disorders as well. It is a short-term psychotherapy where the patient and the therapist actively participate (collaborate). It is focused on current problems and finding their solutions. CBT is employed in the management of depressive disorder, anxiety disorders, phobic disorders, panic disorder, obsessive compulsive disorder (OCD) and others. The concept is that behavior and emotions are determined by the patient’s cognition. Patient’s emotions may be the result of *cognitive errors*. Beck found that symptoms of depression were due to disordered ways of thinking (*cognitive distortions*) and not primarily due to downing of the mood. If the errors in thinking are corrected the rest of the symptoms ought to change and the depression should disappear. In the initial stage of cognitive therapy the cognitive distortions are elicited by repeated interviews and daily monitoring of the thought process. These are analyzed. The patient is made to understand the errors. Correction of the irrational ideas and distortions are then brought out by verbal and behavioral technique.

Systematic Desensitization: It is employed in the treatment of phobic disorders. The subject is gradually deconditioned to the phobic stimulus which is thus made innocuous. Initially, the phobic stimulus or object is identified. A graded list (hierarchy) of the anxiety

provoking situations is charted out with minimum anxiety at one end and maximum at the other end. The patient is trained to relax. He is then exposed to the phobic stimulus at the minimum end of the hierarchy. Any anxiety that may develop is got over by relaxation. This process is worked upwards serially till the maximum anxiety-arousing situation is got over. This treatment is good for simple phobia.

Implosion (flooding): In this technique the patient is suddenly exposed to the phobic stimulus. The patient is made to tackle the resulting anxiety manifestations by relaxation and, if necessary, with the help of drugs. He is not allowed to escape from the situation. By a series of such exposures the patient is deconditioned to the phobic stimulus. This kind of treatment is effective in phobic neurosis. If desensitization is done in real situation it is called *flooding* and if it is done in imagination it is called *implosion*.

Aversion therapy: This is used in the treatment of alcoholism, drug dependence, sexual deviations, tics,

mannerisms, and certain dissociative symptoms. The principle is to associate a noxious stimulus with the maladaptive habit and this helps to eliminate the abnormality by negative reinforcement, e.g. In the case of alcohol dependence a strong painful electric shock can be applied on the arm as soon as the patient starts to gulp alcohol in a therapeutic setting. This aversive stimulus may help him to get rid of the habit. The pain produces aversive conditioning.

Exposure and response prevention: It is a good treatment technique for obsessions with ritualistic practice, i.e. when obsessions are accompanied by compulsive rituals. The patient is trained to withdraw from carrying out the act in spite of strong urge to do so. The anxiety may mount up, but lyses gradually within an hour. Slowly the patient gets confidence. His behaviour is modified in this way.

Thought stopping: It is a process of distraction of attention from the obsessive thought when it intrudes into the mind by specific techniques, e.g. snapping an elastic band tied around the wrist at the moment.

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Psychiatric Disorders Special to Childhood

N. Krishnan Kutty

Chapter Summary

- Childhood Autism (Infantile Autism) 1440
- Attention Deficit Hyperactivity Disorder 1441
- Conduct Disorders 1441
- Enuresis 1441

Children also suffer frequently from psychiatric disorders affecting adults. But a few disorders such as childhood autism, attention deficit hyperactivity disorders, conduct disorders and enuresis are peculiar to them. These disorders are briefly outlined.

reality. Childhood autism was originally described by **Leo Kanner** in 1943 as *Early infantile autism*. Autistic aloneness, language abnormality and restricted and compulsive behavior are the symptom triad of this disorder. Boys are more affected than girls. The disorder is unmasked by the third year of life. The child is abnormally quiet. He lacks the usual emotional warmth and likes to be left alone. Eye-to-eye contact is avoided. He does not communicate through conversation. Pronouns are reversed. 'You' is used to mean 'I'. Echolalia is common. Words and behavior are stereotypic. The child is fond of sameness in everything. Bizarre behavior such as rocking, whirling the head and flapping of hand may be present. Impulsive violence is common. The arithmetic skill is relatively high. Intelligence quotient (IQ) may be around 70 in most cases. Birth trauma is probably the common cause in many cases.

The term autism denotes a state of absorption into ones own world of phantasy with loss of contact with the

Two gene defects are recently reported. One is in an unknown gene in chromosome 11. Another is in a protein called neurexin-1 which is closely associated with brain glutamate which enhances the communication between neighbouring neurons.

There is no specific treatment. Anti-psychotics are given to control violence and hyperactivity. Behavior therapy may be helpful. Parents are to be counselled regarding management of the child at home.

A small percentage may improve spontaneously and may be able to attend normal school. A few may require training in special schools. The majority require special residential care.

Attention Deficit Hyperactivity Disorder (ADHD)

Syn: Attention Deficit Hyperkinetic Syndrome (ADHS)

This disorder is more common in boys. Persistent inattention and hyperactivity are the cardinal features. These affect their scholastic performance. Impulsive and reckless activity are common. Brain damage due to birth trauma, allergy to food containing tartrazine, toxicity to lead and overactivity of peripheral adrenergic system are some of the recognized causes.

Treatment

Stimulant drugs such as dextroamphetamine 2.5-5 mg twice a day, clonidine, tricyclic antidepressants and monoamine oxidase inhibitors are beneficial. Many children become normal as they reach adolescence. Atomoxetine HCl is a recently introduced drug for the condition.

Conduct Disorders

This is the most common disorder of childhood. Persistent dissocial, aggressive or defiant behavior are the presenting features. It is manifested as quarrelsomeness, dis-

obedience, lying, cruelty to people and animals, destructiveness, stealing, lying, absenting from school, fire setting, temper tantrums, running away from home and the like. The disorder may be the outcome of unsatisfactory family environment, poor academic performance and such other psychosocial adversities.

Treatment

Some may improve spontaneously. Drugs are of little value. Psychosocial therapy is important. The child is given insight oriented psychotherapy to bring up problem solving skills. Adverse domestic factors are identified and removed. The child's behavior is rectified through rewards, praise and approval (contingency management).

Enuresis (Bed wetting)

Almost all children get bladder control by the age of five years. Enuresis is the voiding of urine during sleep persisting after the age of five years. In primary enuresis the child has never attained bladder control after birth. In secondary enuresis the child attained bladder control, which is subsequently lost. Delay in brain maturation, emotional factors such as school problems, birth of a younger child, loss of parental affection and other stressful factors may be the underlying cause. Local causes include low volume capacity of the urinary bladder, urinary tract infection, congenital abnormalities of the lower urinary tract and others.

Treatment

Behavior therapy techniques using mattress alarm (bell or buzzer and pad) bladder training exercises and reassurance are the therapeutic modalities. Drugs such as imipramine 25-50 mg at night are useful. Intranasal administration of synthetic antidiuretic hormone (ADH) is effective in many cases.

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