PATHOPHYSIOLOGY

As per PCI Regulations

B. Pharm. Sem. II

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Syllabus

UNIT I 10 Hours

- Basic principles of Cell injury and Adaptation: Introduction, Definitions, Homeostasis, Components and Types of Feedback systems, Causes of cellular injury, Pathogenesis (Cell membrane damage, Mitochondrial damage, Ribosome damage, Nuclear damage), Morphology of cell injury – Adaptive changes (Atrophy, Hypertrophy, Hyperplasia, Metaplasia, Dysplasia), Cell swelling, Intra cellular accumulation, Calcification, Enzyme leakage and Cell death, Acidosis & Alkalosis, Electrolyte imbalance
- Basic mechanism involved in the process of inflammation and repair: Introduction, Clinical signs of inflammation, Different types of Inflammation, Mechanism of Inflammation – Alteration in vascular permeability and blood flow, migration of WBC's, Mediators of inflammation, Basic principles of wound healing in the skin, Pathophysiology of Atherosclerosis

Unit II 10 Hours

- Cardiovascular System: Hypertension, Congestive heart failure, Ischemic heart disease (angina, myocardial infarction, atherosclerosis and arteriosclerosis)
- Respiratory System: Asthma, Chronic obstructive airways diseases.
- Renal System: Acute and chronic renal failure.

Unit III 10 Hours

- Haematological Diseases: Iron deficiency, Megaloblastic anemia (Vit B_{12} and folic acid), Sickle cell anemia, Thalasemia, Hereditary acquired anemia, Hemophilia
- Endocrine System: Diabetes, Thyroid diseases, Disorders of sex hormones
- Nervous system: Epilepsy, Parkinson's disease, Stroke, Psychiatric disorders: Depression, Schizophrenia and Alzheimer's disease.
- Gastrointestinal System: Peptic ulcer

Unit IV 8 Hours

- Inflammatory Bowel Diseases, Jaundice, Hepatitis (A, B, C, D, E, G), Alcoholic liver disease.
- Disease of Bones and Joints: Rheumatoid arthritis, Osteoporosis and Gout
- Principles of Cancer: Classification, etiology and pathogenesis of cancer

Unit V 7 Hours

- Infectious Diseases: Meningitis, Typhoid, Leprosy, Tuberculosis, Urinary tract infections
- Sexually Transmitted Diseases: AIDS, Syphilis, Gonorrhea

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Chapter...1

INTRODUCTION TO PATHOPHYSIOLOGY

1.1 INTRODUCTION

Pathophysiology is a modern integrative biomedical science founded on basic and clinical research concerned with the mechanisms responsible for the initiation, development, and treatment of pathological processes in humans and animals. There are two separate medical fields involved in pathophysiology. The first is physiology, the study of the body and its functions. The second is pathology, the study of disease and its impact on the body. When combined, pathophysiology means to know the way in which a disease progresses and to predict the next stage of a disease, which provides appropriate care to the patient.

Pathophysiology is 'the study of the changes of normal mechanical, physical and biochemical functions, either caused by a disease or resulting from an abnormal syndrome'. When something disrupts normal physiological processes, it enters the realm of pathophysiology. It looks at the specific malfunctioning that comes from or alternately causes disease. The study of pathology and the study of pathophysiology often involves substantial overlap in diseases and processes, but pathology emphasizes direct observations, while pathophysiology emphasizes quantifiable measurements. An example from the field of infectious disease would be the study of a toxin released by a bacterium, and what that toxin does to the body to cause harm, one possible result being sepsis. Another example is the study of the chemical changes that take place in body tissue due to inflammation. Following are important aspects among pathophysiology and related subjects.

Biology: Biology is a natural science. It is the study of life and living organisms, including their structure, function, growth, evolution, distribution and taxonomy. Pathological processes begin frequently at the cell level.

Anatomy and histology: Macro and micro structural properties of the human body are essential for understanding their pathology.

Biochemistry: Biochemistry is the branch of science that explores the chemical processes within and related to living organisms. It is a laboratory based science that brings together biology and chemistry. By using chemical knowledge and techniques, biochemists can understand and solve biological problems. Biochemical processes are changed under pathological condition.

Biophysics: Biophysical properties of cells, tissues and organs determine their structural and functional characteristics.

Physiology: It is the branch of biology dealing with the functions and activities of living organisms and their parts, including all physical and chemical processes. It is helpful to recognize pathologic functions.

Pathological anatomy: The ultrastructural and macro structural changes under pathological conditions help to understand functional changes and vice versa.

Microbiology and immunology: It helps to understand the mechanisms involved in development of disease caused mainly by pathogenic micro-organisms and disorders of immune system.

Etiology: Etiology is a branch of medical science dealing with the causes and origin of diseases.

Pathogenesis: Pathogenesis means the gradual development of a disease and the chain of events leading to disease in response to etiologic factor.

Clinical manifestations: These are the observable symptoms by which a disease may be diagnosed by a physician. Clinical presentations are the whole package of the disease process including epidemiology, history, physical examination and laboratory tests etc.

Need of pathophysiology study: It helps the health care professionals to find answers to important questions related to disease processes:

(a) What are the cause/causes of the disease, and why the disease is developing?

(b) What are the mechanisms responsible for disease onset, progression and recovery?

(c) What are the mechanisms responsible for development of symptoms and signs of disease?

It is important to understand the causes and mechanisms of the disease to find the way how to treat them safe and effectively.

In the clinical setting, pathologists, histotechnologists and cytotechnologist study tissues and cells to establish the cause of a disease. Physicians use that information to form a treatment plan.

Pathophysiology is a required area of study for nearly all healthcare professional school programs (medical, dental, physician assistant, occupational therapy, physical therapy, nurse practitioner, pharmacy, nursing, and paramedic programs) in the world.

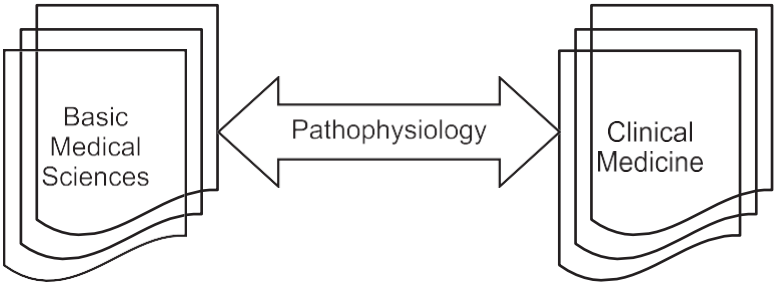

Fig. 1.1: Position of pathophysiology

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UNIT I

Chapter...2

BASIC PRINCIPLES OF CELL INJURY AND ADAPTATION

2.1 INTRODUCTION TO HOMEOSTASIS

The concept of internal harmony was proposed by Claude Bernard in the 19th century, Walter Cannon coined the term homeostasis to describe the state of internal (Physiologic and psychological) balance or organization of function.

Homeostasis may be defined as "The maintenance of the internal conditions of body at equilibrium, despite changes in the external environment". For example, the core temperature of human body remains at about 37°C despite fluctuations in the surrounding temperature. Similarly, the blood glucose level remains normal despite carbohydrate rich diet. Stable internal conditions are important for the efficient functioning of enzymes.

2.2 ADAPTATION

Adaptation refers to process by which a system seeks to restore or maintain homeostasis. Adaptive mechanism may also be referred to as compensatory mechanisms, homeostatic mechanisms, control and regulatory mechanism. Although adaptation may be physiological, psychological, behavioural, in system's terminology adaptive mechanisms are examples of feedback to the system and may be represented by either negative or positive feedback loops.

a. Negative Feedback Loops:

Nearly, all physiologic adaptive responses are negative feedback loops. These processes act to restore homeostasis by inducing changes in the opposite direction of a force perturbing the system. For example, if injury with haemorrhage causes a decrease in blood pressure, sensors in blood vessels activate neural responses that causes increase in cardiac pumping and constriction of blood vessels. These changes cause an increase in blood pressure a change that negates the original disruption, completing the feedback loop and restoring the steady state. Other examples of Homeostasis are temperature control is vital to the maintenance of homeostasis within the body. Heat is sensed by thermo-regulators in both, the skin and the hypothalamus. The internal temperature is sensed by the hypothalamus, and external temperature is sensed by the skin. When the external temperature outside is too cold, messages are sent from the many thermo-receptors located within the skin, to the cerebellum leading to the hypothalamus.

The role of the cerebellum is to make the individual aware of feeling cold, which may cause voluntary behavioural changes such as putting on more layers of clothing or a coat.

Once the message is received by the hypothalamus, a series of reactions follow. The first of which is by the hypothalamus, which secretes thyroid releasing hormone (TRH). This hormone's target is the anterior lobe of the pituitary gland. When the TRH reaches its target, it releases Thyroid Stimulating Hormone (TSH) which enters the blood stream and stimulates thyroid gland to produce thyroxin. The role of thyroxin is to increase cellular metabolism in order to generate heat. This hormone also inhibits vasoconstriction, the process in which blood is diverted from the skin in order to conserve heat by keeping it deep within the body. Sweating is also reduced to keep the surface of the skin dry, thus preventing heat loss. In addition to all of these processes, the erector pilli muscles contract, causing the skin hairs to stand erect. This traps air between the hairs and the skin and creates a layer of insulation, therefore keeping the body warmer. In addition, the phenomenon of shivering is displayed and the bodies' metabolic rate is increased.

When the body temperature increases, messages are sent in the same way as if the body is cold to the hypothalamus. This causes an increase in the amount of sweating, this is releasing heat via water, and the water on the skin evaporates, cooling the body down. Vasodilatation is also apparent. In this instance, blood is diverted to the skin in order to loose heat. The erector pilli muscles relax, allowing the skin hairs to be lowered, and the bodies' metabolic rate is reduced. The reactions are different for each of the environmental states as the messages sent for each are different.

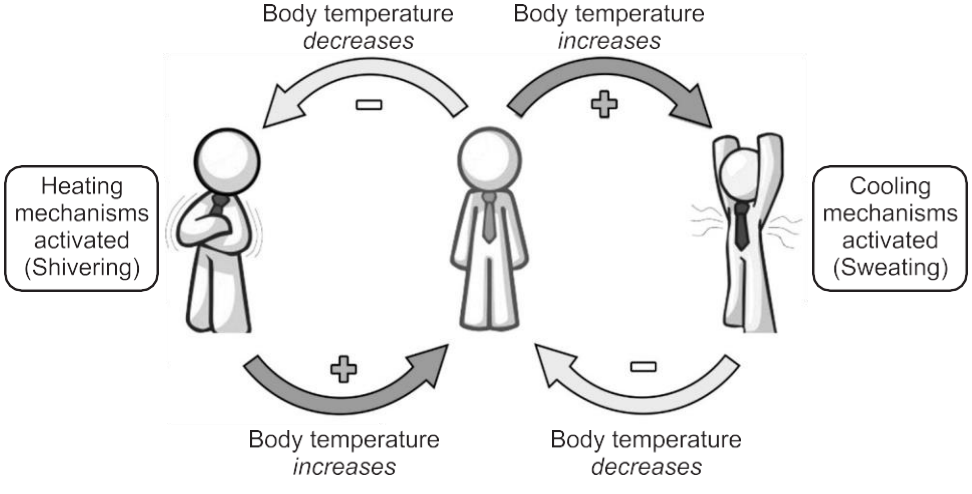

Fig. 2.1 : Homeostasis of temperature by negative feedback loop

Water balance is another very important aspect of homeostasis, which needs to be controlled within narrow limits. The control of water balance is conducted using the following series of events. The osmoreceptors located within the hypothalamus detect the condition of fluid balance within the body. If the fluid balance is too low, then the hypothalamus will act to bring the level back, by keeping more water

within the body. If the concentration of water within the body is too high, then the hypothalamus will react to excrete more water from the body. In the event of the hypothalamus sensing a change in fluid balance, messages are sent to the cerebellum, from where a feeling of thirst is produced. This is only when there is not enough water within the body. In addition, the hypothalamus sends a message also to the posterior pituitary gland to induce the secretion of ADH. The action of the ADH in this instance is to increase the permeability of the collecting duct of the kidney and increase the amount of water which is reabsorbed into the body.

Blood glucose is another contributing factor to homeostasis. The blood glucose concentration in the blood is vital to the functioning of cells within the body and is controlled by a number of internal structures and external influence (food and drink). If too much glucose is present within the blood, then specific receptors located within the pancreas detect this. These receptors then send messages to the cerebellum, feelings of satiety (feeling full) are induced, and therefore the individual's intake of food is decreased. Messages are also sent to the islets of Langerhans for the production of insulin to commence. Once insulin is produced, it is secreted into the capillary circulation and eventually into the systemic blood stream. The insulin has many effects, mainly consisting of increasing the intake of glucose by all the cells of the body. This action uses up surplus glucose and brings back a stable equilibrium. The insulin also aids in the conversion of glucose into a substance called glycogen in the liver, thus lowering the level of glucose in the blood and restoring equilibrium.

On the other hand, if there is not enough glucose in the bloodstream, then the very same receptors, which are located in the pancreas, detect the change. Once again, a message is sent to the cerebellum, which brings around feelings of hunger, therefore increases the consumption of food and drink. Messages are also sent to cells in the islets of Langerhans to start the production of glucagon. This glucagon is released by the islets of Langerhans into the capillary circulation. In turn, the systemic blood stream stimulates the liver to convert stored glycogen into glucose. In addition, the liver is stimulated also to start the conversion of amino acids into glucose, therefore the levels of glucose in the bloodstream rise and equilibrium is achieved.

Homeostasis is also heavily involved with the control of the respiratory rate. In the norm, individuals are not conscious of their respiration. This is because the act of respiration is involuntary. Respiration is under involuntary control through an area of the brain termed as the medulla. Within the medulla is an area known as the breathing centre. The breathing centre is composed into sections, allowing each to tackle an alternate aspect to respiration. Both the dorsal and the lateral areas assist with inspiration and provide stimulation for respiration. In addition, the ventral area increases both the depth and rate of respiration. The centre is linked with the intercostal nerves and the phrenic nerves, leading to the diaphragm. These routes provide a method of communication between the thorax, the respiratory system, and the medulla.

The medulla is chief in maintaining a constant rate of respiration and

depth. However, both external and internal stimuli can alter the rate of respiration, making it higher or lower than the norm. The main influence to this is the level of carbon dioxide in the blood stream. If the concentration of carbon dioxide in the blood stream increases, then chemo-receptors located within both aortic and carotid bodies become aroused. Medulla receives sensory impulses from chemoreceptors, and integrated impulses are send to the intercostal muscles and the diaphragm through phrenic and intercostal nerves. This causes them to contract and relax more quickly and therefore increase the breathing rate, in order to introduce more oxygen to the blood stream and bring back equilibrium of both oxygen and carbon dioxide levels in the blood stream. This process is an example of negative feedback.

As for the control of the breathing rate, the medulla also controls the heart rate. The set process for the regulation of the heart rate is rather complex and is as follows. As an individual exercises, special receptors located within the muscles send impulses to the medulla. Once these messages are received, the medulla secretes epinephrine and norepinephrine. The combination of these two chemicals proceed through pathways within the nervous system until they reach the Sino-atrial node, located within the myocardium. It acts like a pacemaker, controlling its electrical activity. These chemicals arouse the Sino-atrial node, making it produce more electrical energy, thus making the heart rate increase.

On the other hand, when exercise is ceased, the muscles send additional impulses to the medulla which responds by secreting the hormone acetylcholine. This hormone decreases the heart rate by slowing down the electrical impulses from the Sino-atrial node and therefore, decreases the heart rate. In addition, the medulla can also recognize other factors which cause an increase in heart rate. These include emotional stress. In this instance, the medulla also takes information from the thalamus, which informs the medulla of the stressor. This is with the addition of information received from the nervous system. The combination of the two would enable the best response possible to be triggered. Homeostatic processes are controlled by negative feedback and hence these systems occur more commonly within the body.

b. Positive Feedback Loops:

The response to disruptive forces is in the same direction as the force; thus tending to increase the instability of the system. Positive feedback loops are almost always maladaptive or harmful and are often termed vicious cycles, downward spirals, or decompensation states.

These states can lead to death if not interrupted by treatment. In advanced shock, for example, the increased rate and pumping force of the heart eventually increase the demand of the heart muscle for oxygenated blood. The gap between oxygen supply and demand widens, and cardiac failure results. Positive feedback systems generally control infrequent conditions such as ovulation, childbirth and blood clotting.

Two positive feedback mechanisms control release of oxytocin:

- Uterine contractions during childbirth: When contractions start, oxytocin is released which stimulates more contractions and more oxytocin is released,

hence contractions increase in intensity and frequency. Production and release of oxytocin stops after the baby is delivered.

- Secretion of breast milk: The stimulation of a baby sucking its mother's breast leads to secretion of oxytocin into the mother's blood, which leads to milk being available to the baby via the breast. The mother's production and release of oxytocin ceases when the baby stops feeding.

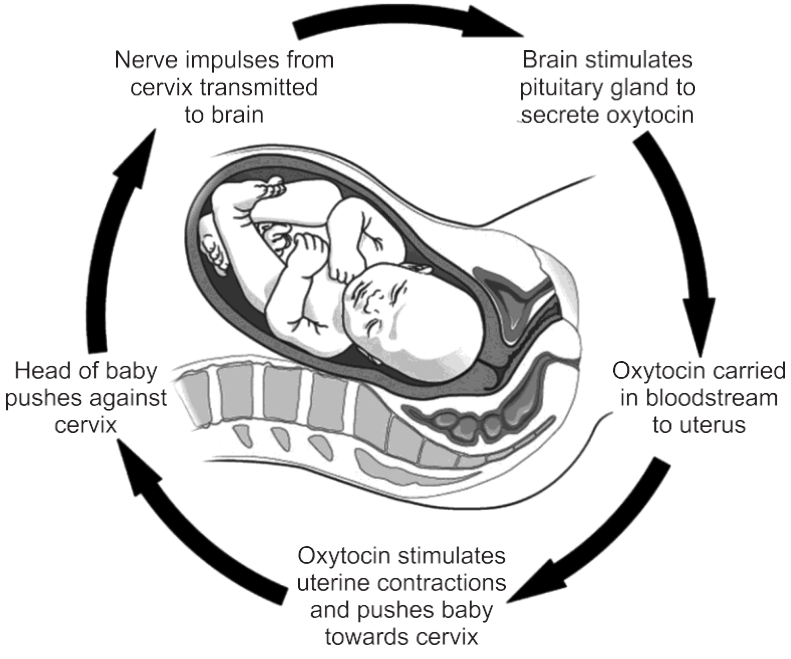

Fig. 2.2 : Uterine contractions during childbirth by positive feedback mechanism

Table 2.1 : Example for Negative and Positive feedback mechanism

Negative Feedback mechanism	Positive Feedback mechanism
Thermoregulation: If body temperature changes, mechanisms are induced to restore normal levels.	Childbirth: Stretching of uterine walls cause contractions that further stretch the walls (this continues until birth occurs).
Blood sugar regulation: Insulin lowers blood glucose when levels are high; glucagon raises blood glucose when levels are low.	Lactation: The child feeding stimulates milk production which causes further feeding (continues until baby stops feeding).
Osmoregulation: ADH is secreted to retain water when dehydrated and its release is inhibited when the body is hydrated.	Ovulation: The dominant follicle releases oestrogen which stimulates LH and FSH release to promote further follicular growth.
Sex Hormones: The synthesis and release of sex hormones is regulated by negative feedback mechanism.	Blood clotting: Platelets release clotting factors which cause more platelets to aggregate at the site of injury.

2.3 CELL INJURY

Cell injury is the common denominator in almost all diseases. It is defined as 'an alteration in cell structure or biochemical functioning, resulting from some stress that exceeds the ability of the cell to compensate through normal physiologic adaptive mechanisms'. Cell injury results when cells are stressed so severely that they are no longer able to adapt or when cells are exposed to inherently damaging agents or suffer from intrinsic abnormalities. Different injurious stimuli affect many metabolic pathways and cellular organelles. Injury may progress through a reversible stage and culminate in cell death.

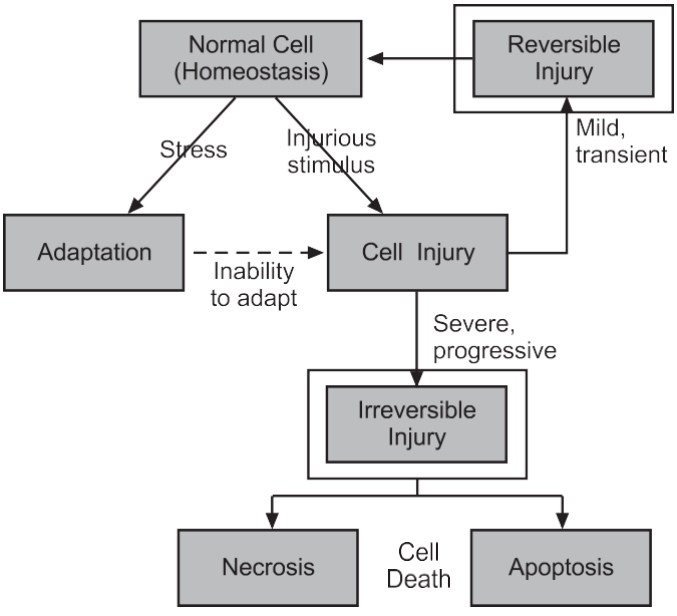

Fig. 2.3 : Cell injury

a. Reversible cell injury: In early stages or mild forms of injury the functional and morphologic changes are reversible if the damaging stimulus is removed. At this stage, although there may be significant structural and functional abnormalities, the injury has typically not progress to severe membrane damage and nuclear dissolution.

b. Irreversible cell injury (Cell death): Because of cell death with continuing damage, the injury becomes irreversible, at which time the cell cannot recover and it dies. There are two types of cell death, necrosis and apoptosis which differ in their morphology, mechanisms, and roles in disease and physiology. When damage to membranes is severe, enzymes leak out of lysosomes, enter the cytoplasm, and digest the cell, resulting in necrosis. Cellular contents also leak out through the damaged plasma membrane and elicit a host reaction (inflammation). Necrosis is the major pathway of cell death in many commonly encountered injuries, such as those resulting

from ischemia, exposure to toxins, various infections and trauma. When a cell is deprived of growth factors or the cell's DNA or proteins are damaged beyond repair, the cell kills itself by another type of death, called apoptosis, which is characterized by nuclear dissolution without complete loss of membrane integrity. Apoptosis is an active, energy dependent, tightly regulated type of cell death that is seen in some specific situations. Whereas necrosis is always a pathologic process, apoptosis serves many normal functions and is not necessarily associated with pathologic cell injury.

i. Necrosis: Necrosis is one of the basic patterns of irreversible cell injury and death. Necrosis has long been considered the "unregulated" pattern of cell injury and death, representing a messy end to a damaged cell that consequently causes a potent inflammatory response.

ii. Apoptosis: This is a pathway of cell death that is induced by a tightly regulated suicide program in which cells destined to die by activating enzymes capable of degrading the cell's own nuclear DNA, nuclear and cytoplasmic proteins. Fragments of the apoptotic cells then break off; giving the appearance that is responsible for the name (apoptosis, "falling off"). The plasma membrane of the apoptotic cell remains intact, but the membrane is altered in such a way that the cell and its fragments become avid targets for phagocytes. The dead cell is rapidly cleared before its contents have leaked out, and therefore cell death by this pathway does not elicit an inflammatory reaction in the host. Thus, apoptosis differs from necrosis, which is characterized by loss of membrane integrity, enzymatic digestion of cells, leakage of cellular contents, and frequently a host reaction. However, apoptosis and necrosis sometimes coexist, and apoptosis induced by some pathologic stimuli may progress to necrosis.

Table 2.2 : Difference between Necrosis and Apoptosis

	Necrosis	Apoptosis
Stimuli	Hypoxia, Toxins	Physiologic and Pathologic.
Histology	Cellular swelling, coagulation, necrosis, disruption of organelles.	Single cells, Chromatin condensation, apoptic bodies.
DNA breakdown	Random diffuse.	Internucleosomal.
Mechanism	ATP depletion, membrane injury, free radical damage.	Gene activation, endonuclease.
Tissue reaction	Inflammation.	No inflammation, phagocytosis of apoptotic bodies.

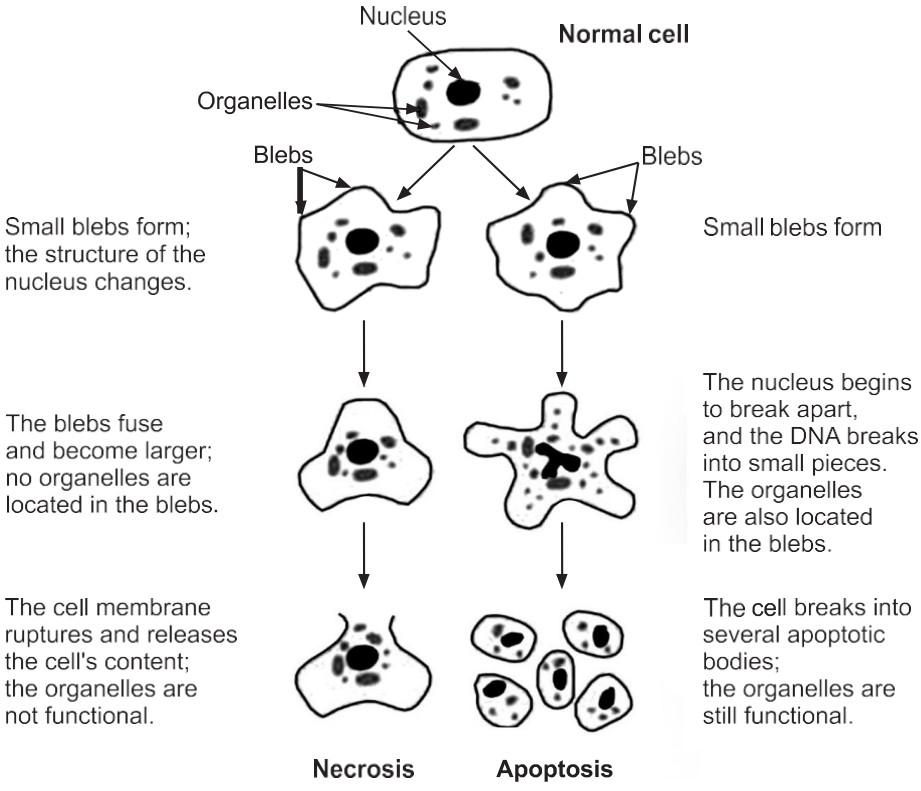

Fig. 2.4 : Mechanisms of necrosis and apoptosis

Etiology of Cell Injury

Cell injury is a sequence of events that occur if the limits of adaptive capability are exceeded or no adaptive response is possible. This can be due to physical, chemical, infectious, biological, immunological factors and nutritional cellular abnormalities.

A) Acquired cause:

Acquired causes of cell injury are further categorized as:

(a) Oxygen deprivation (Hypoxia)
(b) Physical agents
(c) Chemical agents and drugs
(d) Microbial agents
(e) Immunologic agents
(f) Nutritional derangement
(g) Psychological factors
(h) Idiopathic agents

(a) xygen deprivation: Hypoxia is a deficiency of oxygen, which causes cell injury by reducing aerobic oxidative respiration. Hypoxia is an extremely important and common cause of cell injury and cell death. Causes of hypoxia include reduced blood flow (ischemia), inadequate oxygenation of the blood due to cardiorespiratory failure, and decreased oxygen-carrying capacityof the blood, as in anemia or carbon monoxide poisoning (producing a stable carbon monoxyhemoglobin that blocks oxygen carriage) or after severe blood loss. Depending on the severity of the hypoxic state, cells may adapt, undergo injury, or die. For example, if an artery is narrowed, the tissue supplied by that vessel may initially shrink in size

(atrophy), whereas more severe or sudden hypoxia induces injury and cell death.

(b) Physical agents for cell injury: Mechanical trauma (e.g., Road accident), Thermal trauma (e.g., Heat and cold), Electricity, Radiation (e.g., U.V. radiation), Rapid changes in atmosphere pressure.

(c) Chemicals and Drugs: The list of chemicals that may produce cell injury defines compilation. Simple chemicals such as glucose or salt in hypertonic concentrations may cause cell injury directly or by deranging electrolyte balance in cells. Even oxygen at high concentrations is toxic. Trace amounts of poisons, such as arsenic, cyanide or mercuric salts, may damage sufficient number of cells within minutes or hours to cause death. Other potentially injurious substances are our daily companions: environmental and air pollutants, insecticides, and herbicides; industrial and occupational hazards, such as carbon monoxide and asbestos; recreational drugs such as alcohol; and the ever-increasing variety of therapeutic drugs.

(d) Microbial agents: Injuries by microbes include infection caused by bacteria, rickettsiae, viruses, fungi, protozoa and other parasites.

(e) Immunological Agents: The immune system serves an essential function in defence against infectious pathogens, but immune reactions may also cause cell injury. Injurious reactions to endogenous self-antigens are responsible for several autoimmune diseases. Immune reactions to many external agents, such as viruses and environmental substances, are also important causes of cell and tissue injury. Example: Hypersensitivity reactions, anaphylactic reactions, autoimmune diseases.

(f) Nutritional derangement: A deficiency or an excess of nutrients may results in nutritional imbalances. Nutritional deficiency diseases may be due to overall deficiency of nutrients (starvation), protein calorie (Marasmus, Kwashiorkor), and minerals (Anaemia) or of trace elements. Nutritional excess is a problem of society which results from obesity, in atherosclerosis, heart diseases and hypertension.

(g) Psychological factors: There are number of specific biochemical or morphological changes in common acquired mental diseases due to mental stress, strain, anxiety, overwork and frustration. Problems of drug addiction, alcoholism and smoking results in various diseases such as liver damage, chronic bronchitis, lung cancer, peptic ulcer, hypertension, ischemic heart diseases etc.

(h) Idiopathic factor: The causative factor of cell injury is unknown.

B) Genetic cause:

In western countries, genetic defects constitute about 50% total mortality in infancy and childhood, while in developing and under developing countries 95% of infant mortality occurs. Genetic cases are such as, Developmental defect (Errors in morphogenesis), cytogenic defects (chromosomal abnormalities), Single-gene defects (Mendelian syndrome), Storage diseases (Inborn Errors of metabolism), Disorders with multifactorial inheritation.

Pathogenesis of Cell Injury

Cell damage can be reversible or irreversible. Depending on the extent of injury, the cellular response may be adaptive and homeostasis is maintained. Cell death occurs when the severity of the injury (Stress) exceeds the cell's ability to repair itself. Cell death is relative to both the length of exposure to a harmful stimulus and the severity of the damage caused. Cell death may occur by severe cell swelling or cell rupture, denaturation and coagulation of cytoplasmic proteins and breakdown of cell organelles (necrosis) or internally controlled cell death, chromatin condensation and fragmentation (apoptosis). Now, we have discussed the causes of cell injury and necrosis and their morphologic and functional correlates, we next consider in more detail the molecular basis of cell injury, and then illustrate the important principles with a few selected examples of common types of injuries. The biochemical mechanisms linking any given injury with the resulting cellular and tissue manifestations are complex, interconnected, and tightly interwoven with many intracellular metabolic pathways. It is therefore often difficult to pinpoint specific molecular alterations caused by a particular insult.

The cellular response to injurious stimuli depends on the type of injury, its duration, and its severity. Thus, low doses of toxins or a brief duration of ischemia may lead to reversible cell injury, whereas larger toxin doses or longer ischemic intervals may result in irreversible injury and cell death. The consequences of an injurious stimulus depend on the type, status, adaptability, and genetic makeup of the injured cell. The same injury has vastly different outcomes depending on the cell type; thus, striated skeletal muscle in the leg accommodates complete ischemia for 2 to 3 hours without irreversible injury, whereas cardiac muscle dies after only 20 to 30 minutes. The nutritional (or hormonal) status can also be important; clearly, a glycogen-replete hepatocyte will tolerate ischemia much better than one that has just burned its last glucose molecule. Genetically determined diversity in metabolic pathways can also be important. For instance, when exposed to the same dose of a toxin, individuals who inherit variants in genes encoding cytochrome P-450 may catabolize the toxin at different rates, leading to different outcomes. Much effort is now directed toward understanding the role of genetic polymorphisms in responses to drugs and toxins and in disease susceptibility.

Cell injury results from functional and biochemical abnormalities in one or more of several essential cellular components. The most important targets of injurious stimuli are:

- Mitochondria, the sites of ATP generation;
- Cell membranes, on which the ionic and osmotic homeostasis of the cell and its organelles depends;
- Protein synthesis;
- The cytoskeleton; and
- The genetic apparatus of the cell.

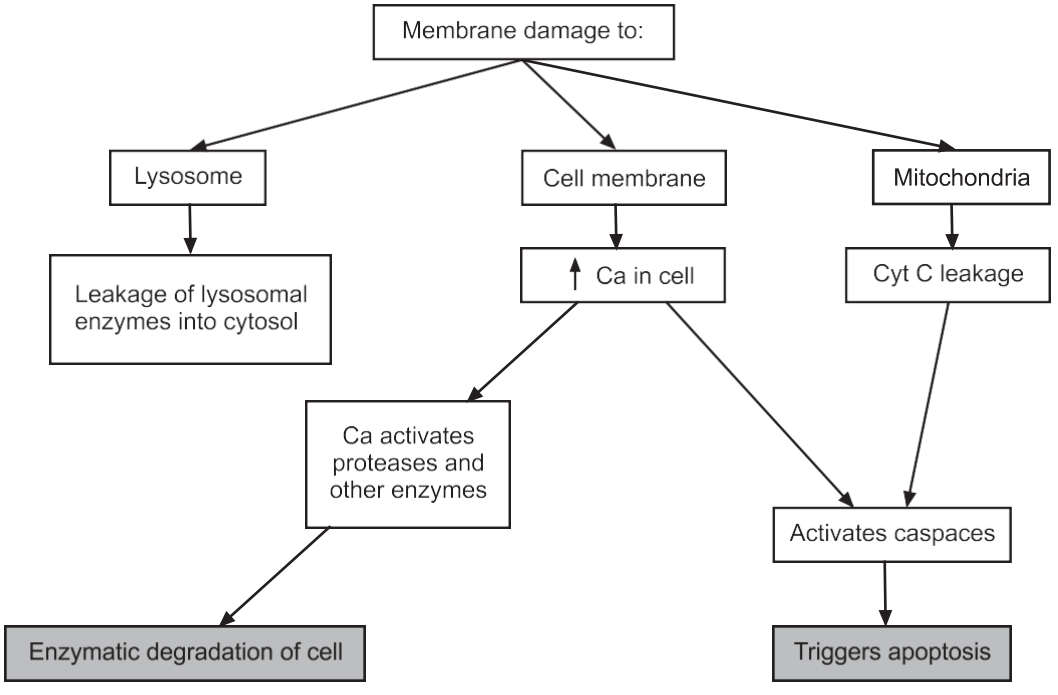

Fig. 2.5 : Pathogenesis of cell injury

A) Mechanism of Reversible Cell Injury: As the name implies, this occurs if extreme stress persists and the cell is unable to adapt to overcome the stress. Reversible cell injury results in cellular and morphological changes that can still be reversed if the stress is eventually removed. There are three mechanisms by which reversible cell injury may occur.

- Depleted resources of ATP in the cell owing to decreased levels of Oxidative Phosphorylation.
- Hydropic cellular swelling, a phenomenon caused by changes in ion concentrations and water influx.
- Organelles within the cell show minute alterations.

a) ATP depletion: ATP depletion and decreased ATP synthesis are frequently associated with both hypoxic and chemical (toxic) injury. High-energy phosphate in the form of ATP is required for many synthetic and degradative processes within the cell. These include membrane transport, protein synthesis, lipogenesis, and the deacylation-reacylation reactions necessary for phospholipid turnover. Depletion of ATP to 5% to 10% of normal levels has widespread effects on many critical cellular systems. The activity of the plasma membrane energy-dependent sodium pump is reduced. Failure of this active transport system, due to diminished ATP concentration and enhanced ATPase activity, causes sodium to accumulate intracellularly and potassium to diffuse out of the cell. The net gain of solute is accompanied by isosmotic gain of water, causing cell swelling, and dilation of the endoplasmic reticulum and cellular energy metabolism is altered. If the supply of oxygen to cells is reduced, as in ischemia, oxidative phosphorylation ceases and cells rely on glycolysis for energy production.

This switch to anaerobic metabolism is controlled by energy pathway metabolites acting on glycolytic enzymes.

The decrease in cellular ATP and associated increase in adenosine monophosphate stimulate phosphofructo-kinase and phosphorylase activities. These result in an increased rate of anaerobic glycolysis designed to maintain the cell's energy sources by generating ATP through metabolism of glucose derived from glycogen. As a consequence, glycogen stores are rapidly depleted.

Glycolysis results in the accumulation of lactic acid and inorganic phosphates from the hydrolysis of phosphate esters. This reduces the intracellular pH, resulting in decreased activity of many cellular enzymes.

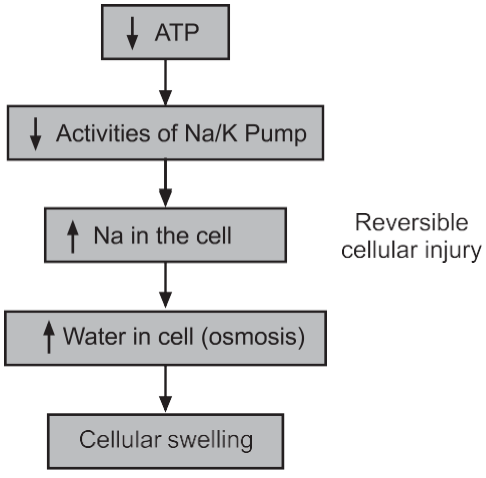

Fig. 2.6 : Mechanism of cellular swelling due to depletion of ATP synthesis

b) Damage to Mitochondria: Mitochondria are the cell's suppliers of life-sustaining energy in the form of ATP, but they are also critical players in cell injury and death. Mitochondria can be damaged by increase of cytosolic Ca^{2+}, reactive oxygen species, and oxygen deprivation, and so they are sensitive to virtually all types of injurious stimuli, including hypoxia and toxins.

There are two major consequences of mitochondrial damage:

- Mitochondrial damage often results in the formation of a high-conductance channel in the mitochondrial membrane, called the mitochondrial permeability transition pores. The opening of this channel leads to the loss of mitochondrial membrane potential and pH changes, resulting in failure of oxidative phosphorylation and progressive depletion of ATP, culminating in necrosis of the cell.
- The mitochondria also contain several proteins that are capable of activating apoptotic pathways, including cytochrome C (the major protein involved in electron transport). Increased permeability of the mitochondrial membrane may result in leakage of these proteins into the cytosol and death by apoptosis. Thus, cytochrome C plays a key dual role in cell survival and

death. In its normal location inside mitochondria, it is essential for energy generation and the life of the cell, but when mitochondria are damaged so severely that cytochrome C leaks out, it signals cells to die.

c) Influx of Calcium: Failure of the Ca^{2+} pump leads to influx of Ca^{2+}, with damaging effects on numerous cellular components. With prolonged or worsening depletion of ATP, structural disruption of the protein synthetic apparatus occurs, manifested as detachment of ribosomes from the rough endoplasmic reticulum and dissociation of polysomes into monosomes, with a consequent reduction in protein synthesis. Ultimately, there is irreversible damage to mitochondrial and lysosomal membranes, and the cell undergoes necrosis.

In cells deprived of oxygen or glucose, proteins may become misfolded, and misfolded proteins trigger a cellular reaction called the unfolded protein response that may lead to cell injury and even death. A protein misfolding is also seen in cells exposed to stress, such as heat, and when proteins are damaged by enzymes and free radicals.

1. Defects in membrane permeability: Early loss of selective membrane permeability leading ultimately to overt membrane damage is a consistent feature of most forms of cell injury. The plasma membrane can be damaged by ischemia, various microbial toxins, lytic complement components, and a variety of physical and chemical agents. Several biochemical mechanisms may contribute to membrane damage.
2. Decreased phospholipid synthesis: The production of phospholipids in cells may be reduced whenever there is a fall in ATP levels, leading to decreased energy dependent enzymatic activities. The reduced phospholipid synthesis may affect all cellular membranes including the mitochondria themselves, thus exacerbating the loss of ATP.
3. Increased phospholipid break-down: Severe cell injury is associated with increased degradation of membrane phospholipids, probably due to activation of endogenous phospholipases by increased levels of cytosolic Ca^{2+}.
4. ROS: Oxygen-free radicals cause injury to cell membranes by lipid peroxidation, discussed earlier.
5. Cytoskeletal abnormalities: Cytoskeletal filaments serve as anchors connecting the plasma membrane to the cell interior. Activation of proteases by increased cytosolic Ca^{2+} may cause damage to elements of the cytoskeleton.
6. Lipid breakdown products: These include unesterified free fatty acids, acyl carnitine, and lysophospholipids, catabolic products that are known to accumulate in injured cells as a result of phospholipid degradation. They have a detergent effect on membranes. They also either insert into the lipid bilayer of the membrane or exchange with membrane phospholipids, potentially causing changes in permeability and electrophysiologic alterations. The most important sites of membrane damage during cell injury are the mitochondrial

membrane, the plasma membrane and membranes of lysosomes.

7. Mitochondrial membrane damage: As discussed above, damage to mitochondrial membranes results in decreased production of ATP, culminating in necrosis, and release of proteins that trigger apoptotic death.
8. Plasma membrane damage: Plasma membrane damage leads to loss of osmotic balance and influx of fluids and ions, as well as loss of cellular contents. The cells may also leak metabolites that are vital for the reconstitution of ATP, thus further depleting energy stores.
9. Injury to lysosomal membranes: Injury to lysosomal membranes results in leakage of their enzymes into the cytoplasm and activation of the acid hydrolases in the acidic intracellular pH of the injured (e.g., ischemic) cell. Lysosomes contain RNAases, DNAases, Proteases, Glucosidases, and other enzymes. Activation of these enzymes leads to enzymatic digestion of cell components, and the cells die by necrosis.
10. Damage to DNA and proteins: Cells have mechanisms that repair damage to DNA, but if this damage is too severe to be corrected (e.g., after radiation injury or oxidative stress), the cell initiates its suicide program and dies by apoptosis. A similar reaction is triggered by improperly folded proteins, which may be the result of inherited mutations or external triggers such as free radicals. Since these mechanisms of cell injury typically cause apoptosis.
11. Reduced protein synthesis: As a result of continued hypoxia, membranes of endoplasmic reticulum and Golgi apparatus swell up. Ribosomes are detached from granular endoplasmic reticulum and polysomes are degraded to monosomes, thus dispersing ribosomes in the cytoplasm and inactivating their function. Similarly reduced protein synthesis occurs in Golgi apparatus. Up to this point, withdrawal of acute stress that resulted in reversible cell injury can restore the cell to normal state.

B) Mechanism of Irreversible Cell Injury: The long term decrease in oxygenated blood supply results in irreversible damage of the cellular structure and functions. The sequence of the reversible cell injury continues and reach into irreversible cell damage (cell death). In irreversible cell injury, the inability of the cell to reverse mitochondrial and plasma membrane dysfunction on reperfusion or reoxygenation. Beside this there is further reduction in ATP continued depletion to proteins, reduced intracellular pH and leakage of lysosomal enzymes into the cytoplasm. These biochemical changes alter the normal functions of cell which are described as follows:

1. Mitochondrial damage: As a result of continued decrease in oxygenated blood supply, irreversible cell damage occurs and on reperfusion with injured cell, excess intracellular calcium collects in the mitochondria disabling its function. Morphologically, mitochondrial changes are vacuoles in the mitochondria and deposition of amorphous calcium salts in the mitochondrial matrix.

2. Membrane damage: Damage to plasma membrane loses its normal function is the most important event in irreversible cell injury. Due to damage of the plasma membrane, cytosolic influx of calcium in the cell increases. Calcium activates endogenous phospholipase. Activated phospholipase degrade membrane phospholipids progressively which are the main constituents of lipid bilayer membrane. Besides these, activation of lytic enzymes ATPase which causes further depletion of ATP leads to decrease in the synthesis of new phospholipid for replacement.
3. Cytoskeletal damage: Activated intra-cellular protease or by physical effect of cell swelling, damages of cytoskeleton may lead to irreversible cell membrane injury.
4. Nuclear damage: The nucleoproteins are damaged by the activated lysosomal enzymes such as proteases and endo-nucleases. Irreversible damage to the nucleus can be in three forms.
   - Pyknosis: Condensation and clumping of nucleus which becomes dark basophilic.
   - Karyorrhexis: Nuclear fragmentation in to small bits dispersed in the cytoplasm.
   - Karolysis: Dissolution of the nucleus.
5. Lysosomal damage, cell death and phagocytosis: The lysosomal membranes are damaged and result in escape of lysosomal hydrolytic enzymes. These enzymes are activated due to lack of oxygen in the cell and acidic pH. These hydrolytic enzymes include, Hydrolase, protease, glycosidase phosphatase, lipase, amylase, RNAase and DNAase which on activation bring about enzymatic digestion of cellular components and hence cell death. The dead cell is eventually replaced by masses of phospholipids called myelin figures which are either phagocytosed by macrophages or there may be formation of calcium soaps. Liberated enzymes just mentioned leak across the abnormally permeable cell membrane into the serum, the estimation of which may be used as clinical parameters of cell death. In myocardial infarction, estimation of SGPT, LDH, CKMB and cardiac troponins useful guides for death of heart muscle.

Mechanism of Hypoxia Induced Cell Injury

Hypoxia is caused by inadequate oxygenation to the cell because of the lack of blood supply to a tissue due to thrombosis. Haemorrhage can cause hypoxia by interrupting the blood supply or blood is not getting oxygenated properly, as it occurs in cardiorespiratory failure, and the oxygen carrying capacity of blood is diminished in carbon monoxide poisoning hypoxia will occur.

The first point of attack of hypoxia is on the cell's aerobic respiration, in other words, oxidative phosphorylation. Lack of ATP generation leads to an inability of the cell to maintain its ion-transport systems and the cell begins to swell. If the hypoxia continues, extensive damage to the cell membrane and cell death will ensue.

Free Radical Induced Injury

Most agents acting this way cause cell damage by affecting directly cell membranes and trigger a lethal sequence of events. Free radicals are chemical species

that have a single unpaired electron in outer orbit, it initiate autocatalytic reaction which mainly occur in reperfusion of the ischemic cell. Activated oxygen radicals are now known to be the common mechanism to cell in injury in many conditions, i.e. aging, chemical and radiation injury, bacterial infections, inflammation, tumor necrosis etc. Free radicals like superoxide radicals, hydroxyl ions and peroxide ions are very destructive to cells which cause lipid peroxidation, oxidation of protein, DNA damage, and cytoskeleton damage etc. They are initiated within cells by enzymatic reactions and non-enzymatic systems. The system have a series of protective mechanisms to protect the cells from these free radicals like antioxidant enzymes such as catalase, glutathione peroxidase and superoxide dismutase. Vitamin E and selenium also help for protection from free radical induced cellular damage.

The deficiency of all these protective mechanism may lead to free radical reactive cellular damage, especially in muscle.

Different causes for initiation of free radical:

- Ionizing Radiation: Exposure of Ionizing Radiation causes the generation of a variety of free radical species. This occurs following radiation-induced splitting of molecules which often generates free radical products.

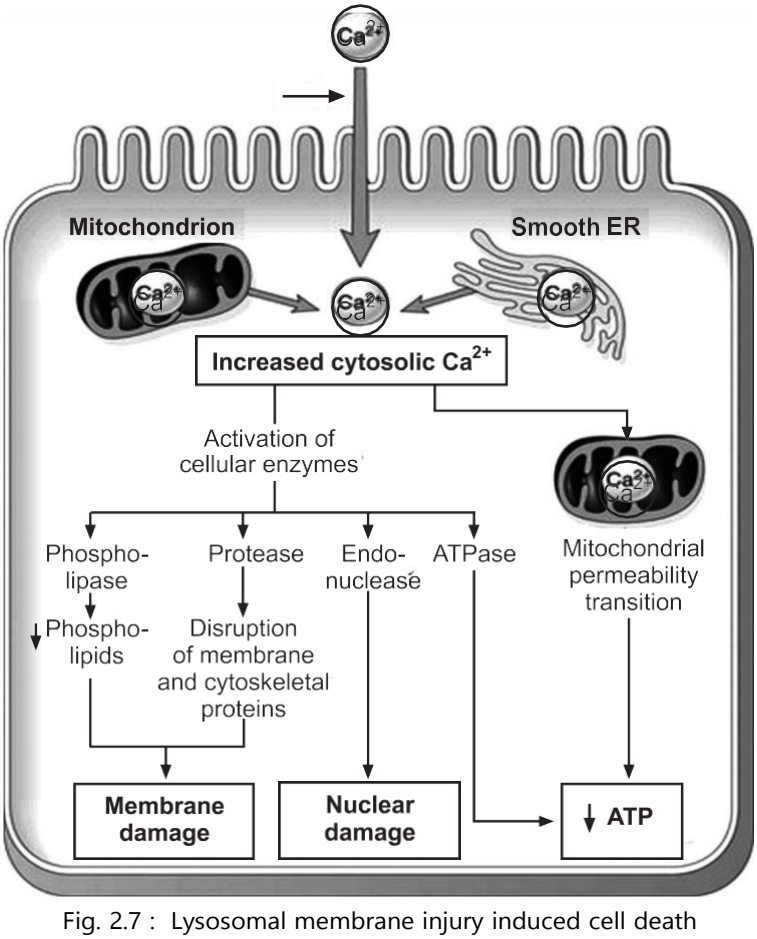

Fig. 2.7 : Lysosomal membrane injury induced cell death

- Enzymatic metabolism of chemicals or drugs. For e.g, carbon tetrachloride can generate $[CCl_3]$* which cause autooxidation of the polyenic fatty acid present within membrane phospholipids.
- Cellular Respiration: Regulated transfer of free radicals is the basis of the Electron Transport Chain that powers Cellular Respiration. Although the free radicals generated during electron transport are tightly controlled, a small amount can escape and cause damage. Escape of free radicals is substantially enhanced when mitochondria are injured which occurs frequently following metabolic cell injury.
- Chemical Cell Injury: Metabolism of several exogenous chemicals can result in the generation of free radicals. Some metals which accept or donate electron (e^-). For e.g. Cu and Fe (Fenton reaction). Nitric oxide (NO) can act as a free radical and converted into highly reactive peroxynitrate anion ($ONOO^-$) as well as NO_2* and NO_3^-. Normally, NO can be produced by endothelial, neurons, macrophages etc.

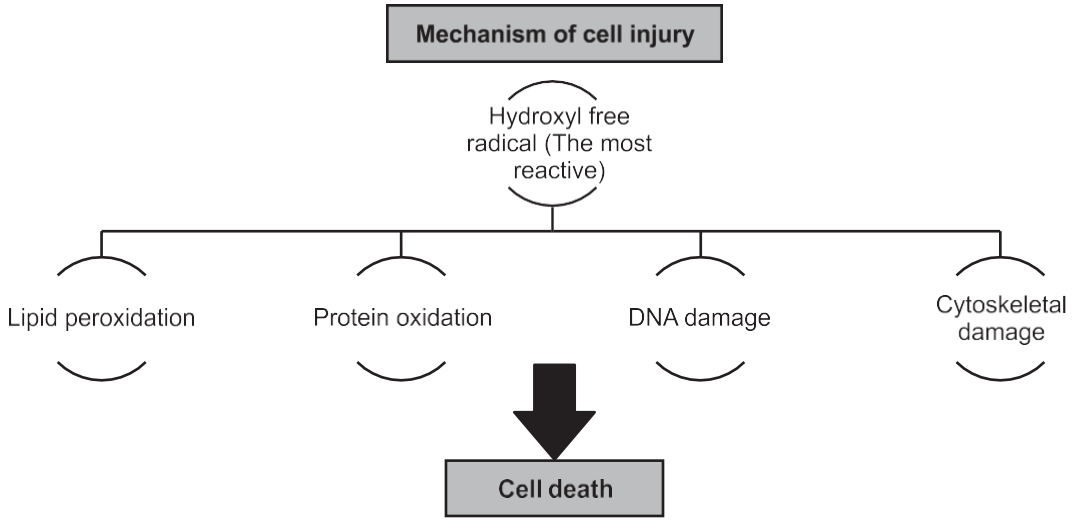

Fig. 2.8 : Pathogenesis of free radical induced cellular damage and cell death

The redox reactions occur during normal metabolism. For e.g, in respiration, molecular oxygen is reduced to water by accepting 4 electrons. During this process, small amount of toxic intermediates are formed. Free radical reaction can be studied as follows:

1. Lipid Peroxidation: Polyunsaturated fatty acid of membrane is attacked repeatedly by free radicals to form highly destructive polyunsaturated fatty acid (PUFA) radicals like lipid hydroperoxy radicals and lipid hypoperoxides. This is termed as lipid peroxidation. These lipids are widely spreaded to other part of membrane that is lipid peroxidation takes place at adjoining part of membrane causing damage to entire cell membrane.

2. Oxidation of protein: Free radical causes cleavage by oxidation of protein

macromolecules of cell causing cross linkage in the amino acid sequences of protein and fragmentation of polypeptides.

3. Effect on DNA damage: Free radical breaks DNA fragments to single strand, so there will be formation of DNA which is defective. Replication of this DNA is not possible and thereby cell death may occur.

4. Cytoskeleton Damage: Free radicals interfere with mitochondrial aerobic phosphorylation and decreases synthesis of ATP leading to cytoskeleton damage. There are certain anti-oxidants present endogenously to fight against these oxidative free radicals like Vitamin-E, sulphahydral containing substances like cystine, SOD, catalase, GTH & serum proteins.

2.4 MORPHOLOGY OF CELL INJURY– ADAPTIVE CHANGES

Cell adaptation within limits: Most cells have the ability to adapt to changes in their environment by altering their morphology, pattern of growth and metabolic activity. These adaptive responses may be part of the normal physiology of a cell or tissue, or they may represent an attempt to limit the harmful effects of a pathological stress. Several basic patterns of macroscopic change have been described and are detailed below. It should be pointed out that physiologic signals such as hormonal stimuli can also cause tissues to change with similar patterns. Consequently, the adaptive mechanisms described below can be considered basic patterns of macroscopic change which can be induced by both pathological injury and in certain cases physiologic stimuli. Common examples include: atrophy, hypertrophy, hyperplasia, metaplasia and dysplasia.

a. Hypertrophy: Hypertrophy refers to an increase in the physical size of cells. When hypertrophy occurs simultaneously in a population of adjacent cells this can lead to increased tissue or organ size. In certain clinical settings, the word "Hypertrophy" is loosely used in reference to any increase in tissue or organ size even if the increase is due to cellular Hyperplasia. Such conflation of hypertrophy and hyperplasia is difficult to avoid since in most cases hyperplasia and hypertrophy occur concurrently. The few cases in which an increased organ size occurs purely due to cellular hypertrophy (and includes no component of hyperplasia) is in expansion of skeletal muscle and the myocardium whose cells cannot divide. In general, hypertrophy is due to increased functional demand on a tissue or due to specific hormonal stimulation.

b. Hyperplasia: Hyperplasia refers to an increase in the number of cells within a tissue due to mitosis. It is important to note that hyperplastic cells still maintain strict regulatory control of their cell cycle. Consequently, when the stimuli which induce hyperplasia are removed, cells will terminate their divisions. In contrast, cell division in the absence of stimuli is considered as neoplasia. Hyperplasia can be induced by specific hormonal stimuli, increased functional demand on the tissue or by injury to the tissue. Due to tissue injury, surviving cells often enter mitosis to replace those lost due to cell death. Use the search function for specific examples.

c. Atrophy: Atrophy refers to a decrease in the physical size of cells. When atrophy occurs simultaneously in a

population of adjacent cells this can lead to decreased tissue or organ size. In certain clinical settings, the word "Atrophy" is loosely used in reference to any decrease in tissue or organ size even if the decrease is due to reduction in cell number. Such usage is difficult to avoid since in most cases reduction in cell size and number frequently occur together. Atrophy can occur due to reduced functional demand or reduced nervous or hormonal stimulation of the tissue. Long-term declines in blood supply can also lead to atrophic regression of perfused tissues.

d. Metaplasia: Metaplasia refers to a reversible histological replacement of one differentiated cell type with another. Although by definition metaplasia is a reversible adaptation, it frequently precedes and may represent the initial steps of malignant transformation. Metaplasia is frequently induced by chronic cellular injury and represents an adaptation in which a tissue replaces a sensitive cell type with one better able to resist the injury.

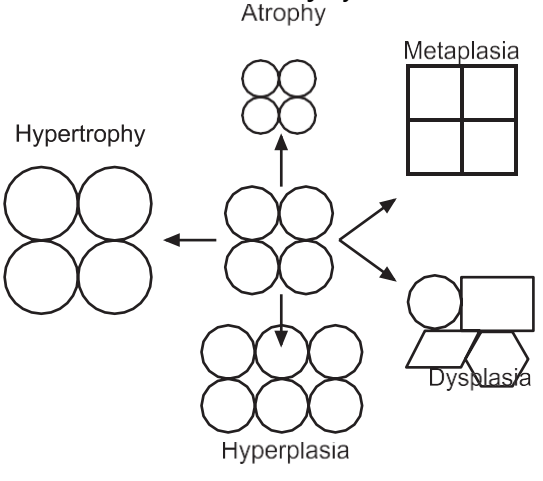

Fig. 2.9 : Morphological changes after cell injury

e. Dysplasia: The cells look abnormal under a microscope but are not cancer cells. Hyperplasia and dysplasia may or may not become cancer. Dysplasia refers to an abnormal and potentially reversible process where there is disordered growth and maturation of cells and the tissues and organs. The number of adult and mature cells decreases while the number of immature cells increases. The microscopic changes which occur in reversible cell injury are cellular swelling (organelle changes) and fatty changes.

2.5 CELLULAR SWELLING

The plasma membrane forms a barrier against excessive amounts of Na^+ within the extracellular fluid from entering the cell. However, the plasma membrane is slightly "leaky" to Na^+, allowing minimal amounts of Na^+ to gradually move into the cell. To compensate this, there is a perpetually active Na^+/K^+ATPase pump, which move Na^+ out of the cell constantly, in exchange for K^+ into the cell. The normal functioning of these pumps is hampered due to depletion of ATP which leads to accumulation of Na^+ intracellularly creating osmotic pressure which causes cellular swelling.

Fatty Change (Steatosis): This steatosis is caused in hypoxic, toxic and metabolic injuries and is related to a dysfunction in the cell's regulation of synthesis and elimination of triglycerides. Excess lipids accumulate within the cells, usually parenchymal cells that form numerous vacuoles that displace the cytoplasm. If these vesicles are large enough to displace and distort the nucleus, it is referred to as macrovesicular steatosis.

2.6 INTRACELLULAR ACCUMULATIONS

Under some circumstances, cells may accumulate abnormal amounts of various

substances, which may be harmless or associated with varying degrees of injury. The substance may be located in the cytoplasm, within organelles (typically lysosomes), or in the nucleus, and it may be synthesized by the affected cells or may be produced elsewhere. There are three main pathways of abnormal intracellular accumulations:

1. A normal substance is produced at a normal or an increased rate, but the metabolic rate is inadequate to remove it. An example of this type of process is fatty change in the liver.
2. A normal or an abnormal endogenous substance accumulates because of genetic or acquired defects in its folding, packaging, transport, or secretion. Mutations that cause defective folding and transport may lead to accumulation of proteins (e.g., α1-antitrypsin deficiency).
3. An inherited defect in an enzyme may result in failure to degrade a metabolite. The resulting disorders are called storage diseases.

An abnormal exogenous substance is deposited and accumulates, because the cell has neither the enzymatic machinery to degrade the substance nor the ability to transport it to other sites. Accumulations of carbon or silica particles are examples of this type of alteration.

Fatty change refers to any abnormal accumulation of triglycerides within parenchymal cells. It is most often seen in the liver, since this is the major organ involved in fat metabolism, but it may also occur in heart, skeletal muscle, kidney and other organs. Steatosis (fatty changes) may be caused by toxins, protein malnutrition, diabetes mellitus, obesity and anoxia. Alcohol abuse and diabetes associated with obesity are the most common causes of fatty change in the liver (fatty liver) in industrialized nations. Free fatty acids from adipose tissue or ingested food are normally transported into hepatocytes, where they are esterified to triglycerides, converted into cholesterol or phospholipids, or oxidized to ketone bodies. Some fatty acids are synthesized from acetate within the hepatocytes as well.

Excess accumulation of triglycerides may result from defects at any step from fatty acid entry to lipoprotein exit, thus accounting for the occurrence of fatty liver after diverse hepatic insults. Hepatotoxins (e.g., alcohol) alter mitochondrial and smooth endoplasmic reticulum function and thus inhibit fatty acid oxidation; CCl_4 and protein malnutrition decrease the synthesis of apoproteins; anoxia inhibits fatty acid oxidation; and starvation increases fatty acid mobilization from peripheral stores. The significance of fatty acid change depends on the cause and severity of the accumulation. When mild, it may have no effect on cellular function. More severe fatty acid change may transiently impair cellular function, but unless some vital intracellular process is irreversibly impaired, fatty acid change is reversible. In the severe form, fatty acid change may precede cell death, and may be an early lesion in a serious liver disease called non-alcoholic steatohepatitis.

2.7 CALCIFICATION

It occurs when calcium builds up in body tissue, blood vessels or organs. This buildup can harden and disrupt body's normal processes. Calcium is transported through the bloodstream and found in every cell. As

a result, calcification can occur in almost any part of the body. About 99 % of body's calcium is in teeth and bones. The other 1 % is in the blood, muscles, fluid outside the cells, and other body tissues.

Types of Calcification: Calcifications can form in many places throughout body, including:

- Small and large arteries
- Heart valves
- Brain, where it is known as cranial calcification
- Joints and tendons, such as knee joints and rotator cuff tendons
- Soft tissues like breasts, muscles, and fat
- Kidney, bladder and gallbladder

Some calcium buildup is harmless. These deposits are believed to be the body's response to inflammation, injury, or certain biological processes. However, some calcifications can disrupt organ function and affect blood vessels.

Causes of Calcification: Many factors have been found to play a role in calcification. These include: infections, calcium metabolism disorders that cause hyperkalaemia, genetic or autoimmune disorders affecting skeletal system and connective tissues, persistent inflammation.

2.7.1 Alkalosis

Alkalosis is excessive blood alkalinity caused by an overabundance of bicarbonate in the blood or a loss of acid from the blood (metabolic alkalosis), or by a low level of carbon dioxide in the blood that results from rapid or deep breathing (respiratory alkalosis).

Metabolic Alkalosis:

Metabolic alkalosis is a primary increase in serum bicarbonate (HCO_3^-) concentration. This occurs as a consequence of a loss of H^+ from the body or a gain in HCO_3. Metabolic alkalosis is a pH imbalance in which the body has accumulated too much of an alkaline substance, such as bicarbonate, and does not have enough acid to effectively neutralize the effects of alkali.

Respiratory Alkalosis:

Respiratory alkalosis is a condition where the amount of carbon dioxide found in the blood drops to below normal range. This condition produces a shift in the body's pH balance and causes the body's system to become more alkaline). This condition results in rapid, deep breathing called hyperventilation.

2.7.2 Acidosis

Acidosis is caused by an overproduction of acid in the blood or an excessive loss of bicarbonate from the blood (metabolic acidosis) or by a build-up of carbon dioxide in the blood that results from poor lung function or depressed breathing (respiratory acidosis).

Metabolic Acidosis:

Metabolic acidosis is a pH imbalance in which the body has accumulated too much acid and does not have enough bicarbonate to effectively neutralize the effects of the acid or when the kidneys are not removing enough acid from the body. If unchecked, metabolic acidosis leads to acidemia, i.e., blood pH is low (less than 7.35) due to increased production of hydrogen ions by the body or the inability of the body to form bicarbonate (HCO^-) in the kidney.

Respiratory Acidosis:

Respiratory acidosis is a condition which occurs when the lungs are unable to remove all the carbon dioxide processed in body. The acid-base balance of body is hampered by this, causing the blood to become acidic.

2.8 ELECTROLYTES

There are many chemicals in blood stream that regulate important functions of bodies. These chemicals are called electrolytes. When dissolved in water, electrolytes separate into positively and negatively charged ions. Human body's nerve reactions and muscle functions are dependent upon the proper exchange of these electrolyte ions outside and inside cells. Examples of electrolytes are calcium, magnesium, potassium and sodium. Electrolyte imbalance can cause a variety of symptoms.

Normal Adult values:

Calcium : 4.5-5.5 mEq/L
Chloride : 97-107 mEq/L
Potassiuim : 3.5-5.3 mEq/L
Magnesium : 1.5-2.5 mEq/L
Sodium : 136-145 mEq/L

Note: Normal values may vary from laboratory to laboratory

Electrolyte Imbalance: The level of electrolyte in the body is abnormal called as electrolyte imbalance. An excess or deficiency of certain electrolytes may lead to abnormality in various functions of the body. The most serious electrolyte disturbance involves abnormalities in the levels of Sodium, Potassium or Calcium. Other electrolyte imbalance is less common. There are many causes of electrolyte imbalance, including rapid water loss through diarrhoea, vomiting, perspiration, injury, blood loss, fluid loss from burns, eating disorders, alcoholism, cancer, diabetes and certain medication.

There are many causes for an electrolyte imbalance. Causes for an electrolyte imbalance may include: Loss of body fluids from prolonged vomiting, diarrhoea, sweating or high fever. Inadequate diet and lack of vitamins from food.

Malabsorption: The body may be unable to absorb these electrolytes due to a variety of stomach disorders, medications, or may be how food is taken in Hormonal or endocrine disorders and Kidney disease. A complication of chemotherapy is tumorlysis syndrome. This occurs when body breaks down tumor cells rapidly after chemotherapy, causing a low blood calcium level, high blood potassium levels, and other electrolyte abnormalities. Certain medications may cause an electrolyte imbalance such as: Chemotherapy drugs (Cisplatin) Diuretics (furosemide [Lasix] or Bumetanide) Antibiotics (Amphotericin B) Corticosteroids (Hydrocortisone).

Symptoms of Electrolyte Imbalance:

An electrolyte imbalance may create a number of symptoms. The symptoms of electrolyte imbalance are based on which of the electrolyte levels are affected.

- Blood test results indicate an altered potassium, magnesium, sodium, or calcium levels, may experience muscle spasm, weakness, twitching, or convulsions.
- Blood test results showing low sodium levels may lead to: irregular heartbeat, confusion, blood pressure changes, nervous system or bone disorder.
- Blood test results showing high levels of calcium may lead to: weakness or twitching of the muscles, numbness, fatigue, and irregular heartbeat and blood pressure changes.

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Chapter...3

BASIC MECHANISM INVOLVED IN THE PROCESS OF INFLAMMATION, REPAIR AND ATHEROSCLEROSIS

INTRODUCTION

Inflammation is a critical homeostatic process that is activated by cellular injury regardless of the mechanism of that injury. Inflammation is essentially local in nature, although cellular mediators released during inflammation may initiate systemic responses as well. Systemic inflammatory response syndrome is the most extreme form of inflammatory response and may be life threatening in critically ill patients. This syndrome nearly always occurs in the setting of systemic infection and is termed as sepsis.

Inflammation is defined as "the local response of living mammalian tissues to injury due to any agent". It is a body defense reaction in order to eliminate or limit the spread of injurious agent, followed by removal of the necrosed cells and tissues. Inflammatory processes are defensive or adaptive by design; however they may contribute to distressing clinical manifestations of disease. At the same time they are helping to eradicate it. Inflammation is the body's attempt of self-protection; the aim being to remove harmful stimuli, including damaged cells, irritants, or pathogens and begin the healing process.

Inflammation does not mean infection, even when an infection causes inflammation. Infection is caused by a bacterium, virus or fungus, while inflammation is the body's response to it. Any injury, including an invasion by micro-organisms, causes inflammation in the affected area. Inflammation, a complex reaction, results from many different conditions. The damaged tissue releases substances that cause inflammation and that direct the immune system to do the following:

- Attack and kill any invaders.
- Dispose off dead and damaged tissue.
- Begin the process of repair.

Etiology of Inflammation

The agents causing inflammation may be as follows:

1. Physical agents: Heat, cold, radiation and mechanical trauma.
2. Chemical agents: Organic and inorganic poisons.
3. Infective agents: Bacteria, virus and their toxins.
4. Immunological agents: Cell mediated and antigen antibody reaction.

3.2 CARDINAL SIGNS OF INFLAMMATION

The Roman writer Celsus in 1st Century A.D. named the famous four cardinal signs of inflammation:

Table 3.1 : Signs of inflammation

Rubor	Redness
Tumor	Swelling
Calor	Heat
Dolar	Pain
Function laesa	Loss of unction

- Rubor: Latin term for "redness". This is because the capillaries are filled up with more blood than usual.
- Tumor: a Latin term for "swelling". Caused by an accumulation of fluid.
- Calor: Latin term for "heat". As with the reason for the redness, more blood in the affected area makes it feel hot to the touch.
- Dolor: Latin term for "pain". The inflamed area is likely to be painful, especially when touched. Chemicals that stimulate nerve endings are released, making the area much more sensitive.
- To these, fifth sign function laesa (loss of function) was later added by Virchow.

3.3 TYPES OF INFLAMMATION

Depending upon the defense capacity of the host and duration of response, inflammation can be classified as acute or chronic.

1. Acute inflammation: Acute inflammation is of short duration and represents the early body reaction and is usually followed by healing.

Examples of diseases, conditions and situations which can result in acute inflammation include:

- Acute bronchitis
- Sore throat from a cold or flu
- A scratch/cut on the skin
- Acute appendicitis
- Acute dermatitis
- Acute tonsillitis
- Acute infective meningitis
- Acute sinusitis

Table 3.2 : Comparison between acute and chronic inflammation

	Acute Inflammation	Chronic Inflammation
Causative agents	Harmful bacteria or injury to tissue.	Non-degradable pathogens that cause persistent inflammation infection with some types of viruses, persistent foreign bodies, overactive immune system reactions.
Major cells involved	Mainly neutrophils, basophils (in the inflammatory response), and eosinophil (response to parasites and worms), and mononuclear cells (macrophages, monocytes).	Macrophages, lymphocytes, plasma cells (these three are mononuclear cells), and fibroblasts.

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Primary mediators	Eicosanoids, vasoactive amines.	Reactive oxygen species, hydrolytic enzymes, IFN-γ and other cytokines, growth factors.
Duration outcomes	Short-lived, only for a few days. The inflammation either gets better (resolution), develops into an abscess, or becomes a chronic inflammation.	From several months to years the destruction of tissue, thickening and scarring of connective tissue (fibrosis), death of cells or tissue (necrosis).
Systemic effects	Fever, leukocytosis, lymphangitis (inflammation of lymph node), shock.	Fever, anemia, leukocytosis, increases ESR, Amyoidosis.

2. Chronic inflammation: Chronic inflammation is of a longer duration and occurs either after the causative agents of acute inflammation persists for a long time or the stimulus that induces chronic inflammation from the beginning.

The characteristic features of chronic inflammation are presence of chronic inflammatory cells such as lymphocytes, plasma cells and macrophages.

Macrophage (phagocytic cells) derived from monocyte, walls of blood vessels and in loose connective tissue. They interact with lymphocytes to facilitate antibody production.

Examples of diseases and conditions with chronic inflammation include:

- Asthma
- Chronic peptic ulcer
- Tuberculosis
- Rheumatoid arthritis
- Chronic periodontitis
- Ulcerative colitis and Crohn's disease
- Chronic sinusitis
- Chronic active hepatitis.

3.4 BASIC MECHANISM INVOLVED IN THE PROCESS OF INFLAMMATION

Acute Inflammation:

The changes in acute inflammation can be conveniently described under the following two headings.

I) Vascular Events
   a. Haemodynamic changes.
   b. Altered vascular permeability.

II) Cellular Events
   a. Exudation of leukocytes.
   b. Phagocytosis.

I) Vascular Events:

Alteration in the microvasculature (arterioles, capillaries and venules) is the earliest response to tissue injury. These alterations include hemodynamic changes and changes in vascular permeability.

a. Haemodynamic changes: The earliest features of inflammatory response result from change in the vascular flow and caliber of small blood vessels in the injured tissue.

The sequence of these changes is as under.

1. Irrespective of the injury, immediate vascular response is the transient vasoconstriction of arterioles. With mild form of injury, the blood flow may be re-established in 3-5 seconds. While with more severe injury, the vasoconstriction may last for about 5 min.

2. Next follows persistent progressive vasodilatation which involves mainly the arterioles and lesser extents to venules and capillaries. This change is obvious within half an hour of injury. Vasodilatation results in increased blood volume in microvascular bed of the area, which is responsible for redness and warmth at the site of acute inflammation.

3. Progressive vasodilatation in turn may elevate the local hydrostatic pressure resulting in transudation of fluid into the extracellular space. This is responsible for swelling at the local site of acute inflammation.

4. Slowing or stasis is attributed to increased permeability of microvasculature that results in increased concentration of red cells and thus raised blood viscosity.

5. Slowing or stasis is followed by leukocytes margination or peripheral orientation of leukocytes (mainly neutrophils) along the vascular endothelium. The leucocytes stick to the vascular endothelium briefly, and then move and migrate through the gaps between the endothelial cells into the extravascular space known as emigration.

The features of haemodynamic changes in inflammation are best demonstrated by the Lewis experiment. Lewis induced the changes in the skin of inner aspect of forearm by firm stroking with a blunt point. The reaction so elicited is known as triple response or red line response consisting of the following:

(i) Red line appears within a few seconds following stroking and is due to local vasodilation of capillaries and venules.

(ii) Flares are the bright reddish appearance or flush surrounding the red line and results from vasodilation of the adjacent arterioles.

(iii) Wheal is the swelling or oedema of the surrounding skin occurring due to transudation of fluid into the extravascular space.

b. Altered vascular permeability: In acute inflammation, normally non-permeable endothelial layer of microvasculature becomes leaky. This is explained by one or more of the following mechanisms.

1. Contraction of endothelial cells: This is the most common mechanism of increased leakiness that affects venules exclusively, while capillaries and arterioles remain unaffected.

The endothelial cells develop temporary gaps between them due to their contraction resulting in vascular leakiness. It is mediated by the release of histamine, bradykinin, and other chemical mediators. The response begins immediately after injury, is usually reversible and is for short duration (15-30 minutes).

2. Retraction of endothelial cells: In this mechanism, there is structural re-organization of the cytoskeleton of endothelia cells that causes reversible

retraction at the intercellular junctions. This change affects the venules and is mediated by cytokines such as Interleukin-1 (IL-1) and tumor necrosis factor α (TNF-α). The onset of response takes 4-6 hours after injury and lasts for 2-4 hours or more.

3. Direct injury to endothelial cells: Direct injury to the endothelium causes cell necrosis and appearance of physical gaps at the sites of detached endothelial cells. Process of thrombosis is initiated at the site of damaged endothelial cells. The change affects all levels of microvasculature. The increased permeability may either appear immediately after injury and lasts for several hours or days (immediate sustained leakage) or may occur after a delay of 2-12 hours and last for hours to days (delayed prolonged leakage).

4. Endothelial injury mediated by leukocytes: Adherence of leukocytes to the endothelium at the site of inflammation may results in activation of leukocytes. The activated leukocytes release proteolytic enzymes and toxic oxygen species which may cause endothelial injury and increased vascular leakiness. This form of increased vascular leakiness affects only venules is a late response.

5. Other Mechanism: In addition, the newly formed capillaries during the process of repair are excessively leaky.

II) Cellular Events:

a. Exudation of leukocytes: The escape of leukocytes from the lumen of microvasculature to the interstitial tissue is the most important feature of inflammatory response. In acute inflammation, polymorpholonuclear neutrophils comprise the first line of body defense, followed later by monocytes and macrophages. The changes leading to migration of leukocytes are as follows:

1. Changes in the formed elements of blood: In the early stage of inflammation the rate of flow of blood increases due to vasodilation. But subsequently there is slowing or stasis of blood stream. With stasis, changes in the normal axial flow of blood in the microcirculation takes place. The normal axial flow consists of central stream of cell comprised by leukocytes and RBC and peripheral cell free layer of plasma close to vessel wall. Due to slowing and stasis, the central stream of cells widens and peripheral plasma zone becomes narrower because of loss of plasma by exudation. This phenomenon is known as 'margination'. As a result of redistribution, the neutrophils of the central column come close to the vessel wall, this is known as 'pavementing'.

2. Rolling and Adhesion: Peripherally marginated and pavemented neutrophils slowly roll over the endothelial cell lining of the vessel wall (Rolling phase). Neutrophils first roll among the surface of the endothelium in a process mediated by selectins, adhesion molecules that are expressed by endothelial cells and that bind reversibly to sites on the leukocyte membrane. Later, neutrophils become firmly adherent to the endothelium by binding of leukocyte adhesion molecules (Selectins, Integrins, Intercellular adhesion molecules-1, vascular cell adhesion molecule-1, platelet endothelial cell adhesion molecule-1 etc.) This is followed by the transient bond between leukocytes and endothelial cells becoming firmer. (Adhesion phase). The following adhesion molecules bring about rolling and adhesion phases.

3. Transmigration: After sticking of neutrophils to endothelium, the former move along the endothelial cell is found where the neutrophils throw out cytoplasmic pseudopods. Subsequently the neutrophils are lodged between the endothelial cells and cross the basement membrane by damaging it locally with secreted collagenase and escape out into the extravascular space. This is known as 'transmigration'. The damaged basement membrane is repaired almost immediately, simultaneous to emigration of leukocytes, escape of RBC's through the gaps between the endothelial cells. It is passive phenomenon, RBCs being forced out either by raised hydrostatic pressure or may escape through the endothelial defects left after emigration of leukocytes.

4. Chemotaxis: The movement of leukocytes from the vessel lumen into a damaged area is called chemotaxis and is mediated by substance known as chemotactic factors that diffuse from the area of tissue damage. All granulocytes and monocytes respond to chemotactic factors and move along a concentration gradient. Chemo attractants can be exogenous or endogenous. Most exogenous chemotactic factors are bacterial or other microbial products. There are many endogenous chemotactic factors like fibrin, fibrinopeptides, bacterial components, IL-8, IL-5, histamine, monocyte chemotactic factors (MCP-1 & MCP-5).

Chemotactic factors bind to receptors on the surface of leukocytes and activate secondary messenger systems. These messenger systems work by stimulating increased intracytoplasmic calcium. The calcium then interacts with the cytoskeleton resulting in active movement of the cell.

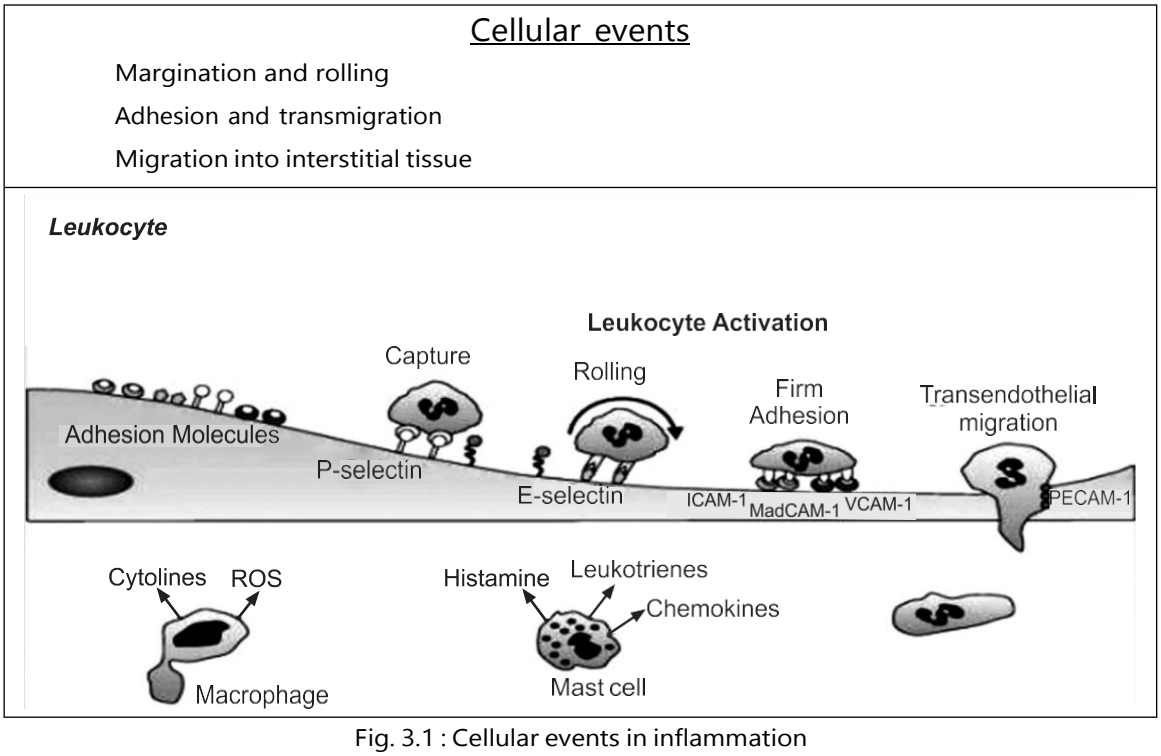

Fig. 3.1 : Cellular events in inflammation

b. Phagocytosis: It is defined as "the process of engulfment of solid particulate material by the cells".

There are two main types of phagocytic cells:

- Polymorphonuclear neutrophils (PMN's) which appear early in acute inflammatory response also called as microphage.
- Circulating Monocytes and fixed tissue mononuclear phagocytes are called as macrophages.

Neutrophils and macrophages on reaching the tissue space produce several proteolytic enzymes lysozyme, protease, collagenase, elastase, lipase, proteinase, gelatinase and acid hydrolases. These enzymes degrade collagen and extracellular matrix that will kill bacteria.

3.4.1 Inflammatory Mediators

Biochemical mediators released during inflammation, intensify and propagate the inflammatory response. These mediators are soluble, diffusible molecules that can act locally and systemically. Mediators derived from plasma include complement and complement-derived peptides and kinins. Released via the classic or alternative pathways of the complement cascade, complement-derived peptides (C3a, C3b, and C5a) increase vascular permeability, cause smooth muscle contraction, activate leukocytes, and induce mast-cell degranulation. C5a is a potent chemotactic factor for neutrophils and mononuclear phagocytes. The kinins are also important inflammatory mediators. The most important kinin is bradykinin, which increases vascular permeability and vasodilation and, importantly, activates phospholipase A_2 (PLA_2) to liberate arachidonic acid (AA). Bradykinin is also a major mediator involved in the pain response.

Other mediators are derived from injured tissue cells or leukocytes recruited to the site of inflammation. Mast cells, platelets, and basophils produce the vasoactive amines serotonin and histamine. Histamine causes arteriolar dilation, increased capillary permeability, contraction of nonvascular smooth muscle, and eosinophil chemotaxis and can stimulate nociceptors (a sensory receptor for painful stimuli) responsible for the pain response. Its release is stimulated by the complement components C3a and C5a and by lysosomal proteins released from neutrophils. Histamine activity is mediated through the activation of one of four specific histamine receptors, designated H_1, H_2, H_3 or H_4, in target cells. Most histamine-induced vascular effects are mediated by H_1 receptors. H_2 receptors mediate some vascular effects but are more important for their role in histamine-induced gastric secretion. Less is understood about the role of H_3 receptors, which may be localized to the CNS. Serotonin (5-hydroxytryptamine) is a vasoactive mediator similar to histamine found in mast cells and platelets in the GI tract and CNS. Serotonin also increases vascular permeability, dilates capillaries, and causes contraction of nonvascular smooth muscle. In some species, including rodents and domestic ruminants, serotonin may be the predominant vasoactive amine.

Cytokines, including interleukins 1–10, tumor necrosis factor α (TNF-α), and

interferon γ (INF-γ) are produced predominantly by macrophages and lymphocytes but can be synthesized by other cell types as well. Their role in inflammation is complex. These polypeptides modulate the activity and function of other cells to co-ordinate and control the inflammatory response. Two of the more important cytokines, interleukin-1 (IL-1) and TNF-α, mobilize and activate leukocytes, enhance proliferation of B and T cells and natural killer cell cytotoxicity, and are involved in the biologic response to endotoxins. IL-1, IL-6, and TNF-α mediate the acute phase response and pyrexia that may accompany infection and can induce systemic clinical signs, including sleep and anorexia. In the acute phase response, interleukins stimulate the liver to synthesize acute-phase proteins, including complement components, coagulation factors, protease inhibitors, and metal-binding proteins. By increasing intracellular Ca^{2+} concentrationsin leukocytes, cytokines are also important in the induction of PLA_2. Colony-stimulating factors (GM-CSF, G-CSF, and M-CSF) are cytokines that promote expansion of neutrophil, eosinophil, and macrophage colonies in bone marrow. In chronic inflammation, cytokines IL-1, IL-6, and TNF-α contribute to the activation of fibroblasts and osteoblasts and to the release of enzymes such as collagenase and stromelysin that can cause cartilage and bone resorption. Experimental evidence also suggests that cytokines stimulate synovial cells and chondrocytes to release pain-inducing mediators.

Lipid-derived autacoids play important roles in the inflammatory response and are a major focus of research into new anti-inflammatory drugs. These compounds include the eicosanoids such as prostaglandins, prostacyclin, leukotrienes, and thromboxane A and the modified phospholipids such as platelet activating factor (PAF). Eicosanoids are synthesized from 20-carbon polyunsaturated fatty acids by many cells, including activated leukocytes, mast cells and platelets, and are therefore widely distributed. Hormones and other inflammatory mediators (TNF-α, bradykinin) stimulate eicosanoid production either by direct activation of PLA_2, or indirectly by increasing intracellularCa^{2+} concentrations, which in turn activate the enzyme. Cell membrane damage can also cause an increase in intracellular Ca^{2+}. Activated PLA_2 directly hydrolyses AA, which is rapidly metabolized via one of two enzyme pathways — the cyclooxygenase (COX) pathway leading to the formation of prostaglandin and thromboxanes, or the 5-lipoxygenase (5-LOX) pathway thatproduces the leukotrienes.

Cyclooxygenase catalyzes the oxygenation of AA to form the cyclic endoperoxide PGG_2, which is converted to the closely related PGH_2. Both PGG_2 and PGH_2 are inherently unstable and rapidly converted to various prostaglandins, thromboxane A_2 (TXA_2), and prostacyclin (PGI_1). In the vascular beds of most animals, PGE_1, PGE_2 and PGI_1 are potent arteriolar dilators and enhance the effects of other mediators by increasing small-vein permeability. Other prostaglandins, including $PGF_{2\alpha}$ and thromboxane, cause smooth muscle contraction and

vasoconstriction. Prostaglandins sensitize nociceptors to pain-provoking mediators such as bradykinin and histamine and, in high concentrations, can directly stimulate sensory nerve endings. TXA_2 is a potent platelet-aggregating agent involved in thrombus formation. Found predominately in platelets, leukocytes, and the lungs, 5-LOX catalyzes the formation of unstable hydroxyperoxides from AA. These hydroxyperoxides are subsequently converted to peptide leukotrienes. Leukotriene B_4 (LTB_4) and 5-hydroxy-eicosatetranoate (5-HETE) are strong chemoattractants stimulating polymorpho-nuclear leukocyte movement. LTB_4 also stimulates the production of cytokines in neutrophils, monocytes, and eosinophils and enhances the expression of C3b receptors. Other leukotrienes facilitate the release of histamine and other autacoids from mast cells and stimulate bronchiolar constriction and mucous secretion. In some species, leukotrienes C_4 and D_4 are more potent than histamine in contracting bronchial smooth muscle.

Platelet activating factor (PAF) is also derived from cell membrane phospholipids by the action of PLA_2. PAF, synthesized by mast cells, platelets, neutrophils and eosinophils, induces platelet aggregation and stimulates platelets to release vasoactive amines and synthesize thromboxanes. PAF also increases vascular permeability and causes neutrophils to aggregate and degranulate.

The role of the free radical gas nitric oxide (NO) in inflammation is well established. NO is an important cell-signaling messenger in a wide range of physiologic and pathophysiologic processes. Small amount of NO play a role in maintaining resting vascular tone, vasodilation, and antiaggregation of platelets. In response to certain cytokines (TNF-α, IL-1) and other inflammatory mediators, the production of relatively large quantities of NO is stimulated. In larger quantities, NO is a potent vasodilator, facilitates macrophage-induced cytotoxicity, and may contribute to joint destruction in some types of arthritis.

Table 3.3 : Inflammatory mediators

Mediator	Source	Actions
Cell Derived:		
Histamine	Mast cells, basophils, platelets.	Vasodilation, increased vascular permeability
Serotonin	Platelets	Vasoconstriction
Prostaglandins	Mast cells , leukocytes	Vasodilation, pain fever
Leukotrienes	Mast cells , leukocytes	Increased vascular permeability, leukocyte adhesion, and chemotaxis.

Contd...

Platelet activating factors	Leukocytes , mast cells.	Vasodilation, increased vascular permeability, leukocyte adhesion, chemotaxis, degranulation ,oxidative burst.
Reactive oxygen species	Leukocytes, mast cells.	Killing of microbes, tissue damage.
Nitric oxide	Endothelium macrophages.	Vascular smooth muscle relaxation, killing microbes.
Cytokines	Macrophage, endothelial cell, mast cells.	Expression of adhesion molecules, systemic fever metabolic abnormalities, Hypotension (shock).
Chemokines	Leukocytes activated macrophages.	Chemotaxis, leukocyte activation.
Plasma Protein Derived:		
Complement	Plasma	
Kinins	Plasma (Production Liver)	Increased vascular permeability, smooth muscle contraction, vasodilation, pain.
Proteases activated during coagulation	Plasma (Production Liver)	Endothelial activation, leukocyte recruitment.

3.5 HEALING

Injury to tissue may result in cell death and tissue destruction. Healing on the other hand is the body response to injury in an attempt to restore normal structure and function.

The process of healing involves two distinct processes:

Regeneration: When healing takes place by proliferation of parenchymal cells and usually result in complete restoration of the original tissues.

Repair: When the healing takes place by proliferation of connective tissue elements resulting in fibrosis and scarring.

These two processes take place simultaneously.

1. Regeneration:

Some parenchymal cells are short lived while others have long life span. In order to maintain proper structure of tissue, these cells are under the constant regulatory control of their cell cycle. These include growth factors such as epidermal growth factor, fibroblast growth factor; platelet derived growth factor and endothelial growth factor.

Regeneration of any type of parenchymal cells involves the following two processes.

- Proliferation of original cells form the margin of injury with migration so as to cover the gap.
- Proliferation of migrated cells with subsequent differentiation and maturation so as to reconstitute the original tissue.

Depending upon their capacity to divide, cells of the body can be divided into three groups.

I. Labile cells: These cells continue to multiply throughout life under normal physiologic conditions. These include surface epithelial cells of epidermis, alimentary tract, respiratory tract, urinary tract, vagina, cervix, uterine endometrium, haemotopoietic cells of bone marrow and cells of lymph nodes and spleen.

II. Stable cells: These cells decrease or lose their ability to proliferate after adolescence but retain the capacity to multiply in response to stimuli throughout adult life. These include parenchymal cells of organs like liver, pancreas, kidneys, adrenal and thyroid. Mesenchymal cells like smooth muscle cells, fibroblasts vascular endothelium bone and cartilage cells.

III. Permanent cells: These cells lose their ability to proliferate around the time of birth. These include neuron, skeletal muscle and cardiac cells.

2. Repair:

Repair is the replacement of injured tissue by fibrous tissue. These responses take place by participation of mesenchymal cells (consisting of connective tissue, stem cells fibrocytes and histocytes).

The process of repair involves:

I. Granulation tissue formation

II. Contraction of wounds.

I. Granulation Tissue Formation:

The term granulation tissue derives its name from slightly granular and pink appearance of the tissue. Each granule corresponds histologically to proliferation of new small blood vessels which are slightly lifted on the surface by the covering of fibroblasts and young collagen.

The following three phases are observed in the formation of granulation tissue.

a. Phase of inflammation: Following trauma, blood clots at the site of injury. There is acute inflammatory response with exudation of plasma, neutrophils and some monocytes within 24 hours.

b. Phase of clearance: Combination of proteolytic enzyme liberated from neutrophils autolytic enzymes from dead tissue cells and phagocytic activity of macrophages clear off the necrotic tissue, debris and red blood cells.

c. Phase of growths of granulation tissue: This phase consists of two main processes.

(i) Angiogenesis

Formation of new blood vessels at the site of injury takes place by proliferation of endothelial cells from the margins of several blood vessels. Initially the proliferated endothelial cells are solid buds but within a few hours develop into the lumen and start carrying blood. The newly formed blood vessels are leakier, accounting for the edematous appearance of new granulation tissue. Soon these blood vessels differentiate into muscular arterioles, thin walled venules and true capillaries.

(ii) Fibrogenesis

The newly formed blood vessels are present in an amorphous ground of surface

matrix. The new fibroblasts originate from fibrocytes as well as mitotic division of fibroblasts. Some of these fibroblasts have combination of morphologic and functional characteristics of smooth muscle cells.

Collagen fibril begin to appear by about 6th day. As maturation proceeds, more and more of collagen is formed while the number of active fibroblasts and new blood vessels decreases. This results in formation of inactive looking scar.

II. Contraction of Wounds:

The wound starts contracting after 2-3 days and the process is completed by the 14th day. During this period the wound is reduced by approximately 80% of its original size. Contracted wound results in rapid healing since lesser surface area of the injured tissue has to be replaced.

In order to explain the mechanism of wound contraction a number of factors have been proposed.

1. Dehydration as a result of removal of fluid by drying of wound was first suggested but without being substantiated.
2. Contraction of collagen was thought to responsible for contraction but wound contraction proceeds at a stage when the collagen content of granulation tissue is very small.
3. Discovery of myofibroblasts appearing in active granulation tissue has resolved the controversy. These cells have features intermediate between those of fibroblasts and smooth muscle cells. Their migration into the wound area and their active contraction decreases the size of defect.

Wound Healing

Healing of skin wounds provides a classical example of combination of regeneration and repair described above. Wound healing can be accomplished in one of the following two ways:

(i) Healing by first intention

(ii) Healing by second intention

(i) Healing by first intention: One of the simplest examples of wound repair is the healing of a clean, uninfected surgical incision approximated by surgical sutures. This is referred to as healing by first intention. The incision causes only focal disruption of epithelial basement membrane continuity and death or a relatively few epithelial and connective tissue cells.

As a result, epithelial regeneration predominates over fibrosis. The narrow incisional space rapidly fills with fibrin clotted blood; dehydration at the surface produces a scar to cover and protect the healing repair site.

On day first, neutrophils are seen at the incision margin, migrating toward the fibrin clot. Basal cells at the cut edge of the epidermis begin to exhibit increased mitotic activity. Within 24 to 48 hours, epithelial cells from both edges have begun to migrate and proliferate along the dermis, depositing basement membrane component as they progress. The cells meet in the midline beneath the surface scab, yielding the thin but continuous epithelial layer.

On days two to three neutrophils have been largely replaced by macrophages, and granulation tissue progressively invades the incision space. Collagen fibers are now evident at the incision margins, but these

are vertically oriented and do not bridge the incision. Epithelial cell proliferation continues, yielding a thickened epidermal covering layer.

On days 4 to 5 neovascularization reaches its peak as granulation tissue fills the incisional space. Collagen fibrils become more abundant and begin to bridge the incision. The epidermis recovers its normal thickness as differentiation of surface cells yields a mature epidermal architecture with surface keratinization.

On second week there is continued collagen accumulation and fibroblast proliferation. The leukocyte infiltrate, edema and increased vascularity are substantially diminished. The long process of blanching begins, accomplished by increasing collagen deposition within the incisional scar and the regression of vascular channels.

On first month, the scar comprises a cellular connective tissue largely devoid of inflammatory cells and covered by an essentially normal epidermis. However, the dermal appendages destroyed in the line of the incision and permanently lost.

(ii) Healing by second intention: When cell or tissue loss is more extensive, as in infraction, inflammatory ulceration, abscess formation, or even just large wounds, the reparative process is more complex. In these situations, regeneration of parenchymal cells alone cannot restore the original architecture. As a result, there is extensive ingrowth of granulation tissue from the wound margin, followed in time by accumulation of extracellular matrix and scarring. This form of healing is referred to as secondary union or healing by second intention.

Phases of Wound Healing

The response of tissue to injury goes through several phases which are:

(a) Inflammatory phase

(b) Proliferative phase

(c) Maturation phase

(a) Inflammatory Phase:

Also called the lag or executive phase, the inflammatory phase is characterized by vascular and cellular responses that occur immediately after tissue injury takes place. The length of this phase lasts for about 1-4 days. The following events occur during this phase:

1. Blood clot formation: Right after tissue injury takes place, vasoconstriction of vessels occurs and in an attempt to stop or control bleeding, a fibrinoplatelet clot forms. Lasting for about 5 to 10 minutes, this reaction is followed by vasodilation of the venules. Vasoconstriction is stopped as norepinephrine is destroyed by the intracellular enzymes. The result is an increased permeability of the capillary due to the destruction of norepinephrine and the release of histamine.
2. Wound becomes edematous: Damage of the microcirculation results to the infiltration of blood elements such as antibodies, plasma proteins, electrolytes, complement and water for approximately 2 to 3 days after the tissue injury. This mechanism causes the occurrence of edema, warmth, redness and pain on the affected area.

3. Phagocytes engulf debris of damaged tissue and blood clot: The first leukocytes that move into the damaged tissue are the neutrophils. The component of WBC that transforms to macrophages to engulf the debris, monocytes, transports the phagocytized debris from the injured area. Antigen-antibodies also appear and the basal cells present at the edges of the wound undergo mitosis and the resulting daughter cells migrate. Through this activity, the secretion of proteolytic enzymes and its breakdown at the base of the clot is made possible. Thus, the break in the continuity of the cells is progressively bridged and by about 24 to 48 hours the sides of the wound would eventually meet.

Hyperplastic bone marrow activity enhances cell migration progressing to the next phase of wound healing.

(b) Proliferative Phase:

The proliferative phase, also called the fibroblastic or connective tissue phase, is the time where fibroblasts are multiplying and a lattice framework is formed for migrating cells. Proliferative phase occurs during the 5th to the 20th day after tissue injury took place. The following events are noted during this phase of wound healing:

1. Granulation tissue forms: By this time, epithelial cells form beds at the edges of the wound. These beds are the ones that develop into capillaries. These capillaries serve as the nutritional source for the new granulation tissue.
2. Collagen production: The primary component of replaced connective tissue is collagen. It is the fibroblasts that initiate the synthesis of collagen and mucopolysaccharides. Chains of amino acids convert into fibers of increasing length and diameter in about 2 to 4 weeks. The formed fibers become a well-structured pattern of packed bundles. Collagen synthesis causes depletion in the number of capillaries.

(c) Increased wound tensile strength:

Synthesis of collagen and lysis of capillaries results in the increased tensile strength of the wound. About 3% to 5% of the original skin strength is the amount of skin present 2 weeks after the injury. About in a month, only 35% to 59% of wound strength has been reached. Never more than 70% to 80% of the strength is regained after wound has occurred. Vitamin C aid in the metabolic process necessary for wound healing.

3.6 ATHEROSCLEROSIS

Atherosclerosis (or arteriosclerotic vascular disease) is a condition where the arteries become narrowed and hardened due to an excessive buildup of plaque around the artery wall. Plaque is made up of fat, cholesterol, calcium, and other substances found in the blood. Over time, plaque hardens and narrows arteries. The disease disrupts the flow of blood around the body, posing serious cardiovascular complications. Atherosclerosis can lead to serious problems, including heart attack, stroke, or even death.

Healthy arteries are flexible and elastic, but over time, the walls in arteries can harden, a condition commonly called

hardening of the arteries. The word atherosclerosis is of Greek origin and literally means focal accumulation of lipid and thickening of arterial intima (sclerosis [hardening]).

Atherosclerosis can affect any artery in the body, including arteries in the heart, brain, arms, legs, pelvis and kidneys. As a result, different diseases may develop based on which arteries are affected.

Arteriosclerosis is the stiffening or hardening of the artery walls. Atherosclerosis is the narrowing of the artery because of plaque build-up.

All patients with atherosclerosis have arteriosclerosis, but those with arteriosclerosis might not necessarily have atherosclerosis. However, the two terms are frequently used with the same meaning.

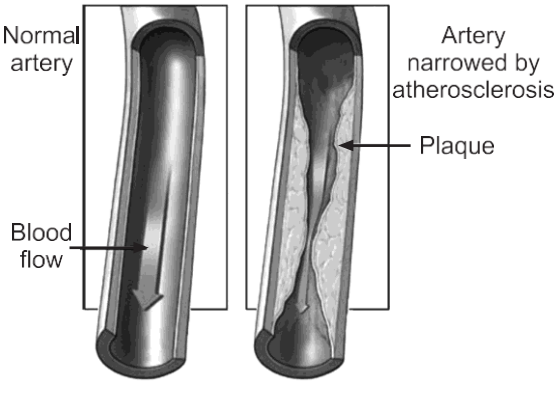

Fig. 3.2 : Differences between normal and atherosclerosised artery

Causes

Atherosclerosis can begin in the late teens, but it usually takes decades to cause symptoms. Some people experience rapidly progressing atherosclerosis during their thirties, other during their fifties or sixties.

Certain factors that can damage the inner area of the artery (endothelium) and can trigger atherosclerosis include:

- High blood pressure
- High levels of cholesterol
- Smoking
- High levels of sugar in the blood

Areas of the artery that are damaged are likely to have plaque buildup which can eventually break open. When the plaque breaks open, blood cell fragments called thrombocytes (or platelets) accumulate at the affected area. These fragments can then stick together, forming blood clots.

High triglycerides: Most fat in food and in the body takes the form of triglycerides. Blood triglyceride levels above 400 mg/dL have been linked to coronary artery disease in some people. Triglycerides, however, are not nearly as harmful as LDL cholesterol.

Diabetes: Patients with poorly controlled diabetes, who frequently have excess blood glucose levels, are much more likely to develop atherosclerosis.

Genetics: People with a parent or sibling who has/had atherosclerosis and cardiovascular disease have a much higher risk of developing atherosclerosis than others.

Obesity: Excess weight increases the strain on the heart and increases the risk of developing atherosclerosis even if no other risk factors are present.

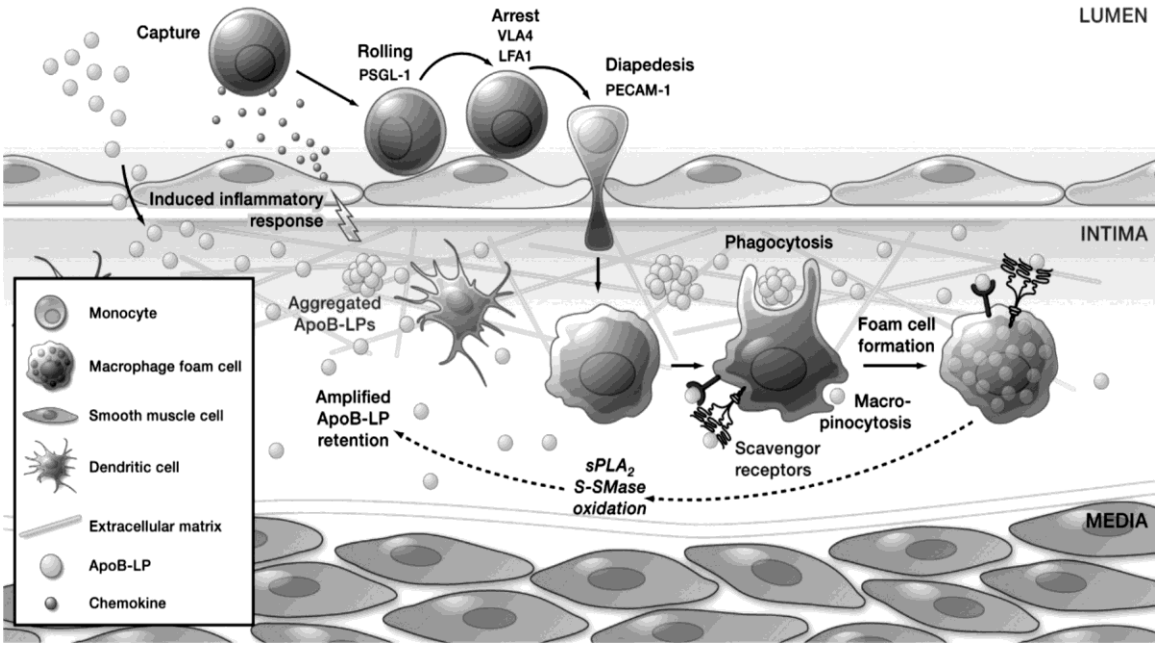

Fig. 3.3 : Mechanism of atherosclerosis

Pathophysiology

Very low density lipoprotein (VLDL) is produced by the liver and is changed into LDL by means of lipoprotein lipase. This process removes triglycerides from VLDL by hydrolysis, releasing fatty acids and leaving greater numbers of cholesterol, thus increasing the density of the molecule.

The LDL crosses the endothelium and moves into the extracellular matrix where it is oxidized (by the aforementioned steps above), and forms oxidized LDL (OxLDL).

OxLDL is a cause of inflammation and signals monocytes (white blood cells) to enter the arterial wall to fix the inflammation. As monocytes enter the arterial wall, they transform into macrophages.

Since the LDL is now oxidized due to aldehydes and lipid hydroperoxides, the modified apolipoprotein B in LDL attaches to macrophage scavenger receptor cells. At this stage, OxLDL has a very high number of cholesterol and cholesterol esters, since it lost antioxidants, triglycerides, and fatty acids in previous steps. Macrophages are supposed to remove cholesterol by use of high density lipoprotein (HDL) particles, but if there is too much excess cholesterol, it causes the macrophages to enlarge and fill with lipids.

Eventually the macrophages build up and convert into lipid-laden foam cells (a collection of fatty materials and cholesterol) which die and become part of the plaque that causes atherosclerosis.

As this process continues, more and more LDL becomes trapped within the tunica intima (the innermost layer of the arterial wall) creating a pool of cholesterol called a fatty streak.

The smooth muscle cells move from the tunica media (the thickest layer of the

artery) to the tunica intima and become proliferated by way of released cytokines (proteins that help with immunity) within the macrophages. The major atherosclerosis causing plaque has a fibrous cap, which sticks out into the artery, causing vasoconstriction, and blocking blood flow (the plaque always forms in the lumen, which is between the intima and the musculature of the wall.

Symptoms

Atherosclerosis does not usually produce symptoms until blood circulation becomes restricted or blocked, leading to cardiovascular disease (CVD).

The type of cardiovascular disease and its associated symptoms depends on, where the blockage occurs. The first signs of atherosclerosis can begin to develop during adolescence, with streaks of white blood cells appearing on the artery wall. The symptoms of the disease depend on, which arteries are affected.

Carotid Arteries: These arteries provide blood to the brain. When the blood supply is limited, patients can suffer stroke and may experience:

- Weakness
- Difficulty in breathing
- Headache
- Facial numbness
- Paralysis

Coronary Arteries: These arteries provide blood to the heart, when the blood supply to the heart is limited, it can cause angina and heart attack. Symptoms include:

- Vomiting
- Extreme anxiety
- Chest pain
- Coughing
- Feeling faint

Heart attack: If one of the plaques in coronary arteries ruptures, it could create a blood clot. If the blood clot blocks the supply of blood to heart, it will cause to have a heart attack. Symptoms of a heart attack include:

- Chest pain – usually located in the centre of chest and giving the sensation of pressure, tightness or squeezing.
- Pain in other parts of the body that can feel as though it is travelling from chest to arms. (usually the left arm, although both arms can be affected), jaw, neck, back and abdomen.
- An overwhelming sense of anxiety.
- (Similar to apanic attack), Shortness of breath, feeling sick, lightheadedness, coughing, vomiting, wheezing.

Aneurysm: If atherosclerosis weakens the walls of blood vessels, it can lead to the formation of an aneurysm (a bulge in a blood vessel).

If the aneurysm grows too large, there is a danger. It will rupture, which can cause potentially fatal internal bleeding and organ damage.

An aneurysm can develop anywhere in the body, but the two most common types of aneurysm are:

- A brain aneurysm (also known as a cerebral aneurysm), which develops inside the brain.
- An aortic aneurysm, which develops inside the aorta (a large blood vessel that runs down the abdomen and transports blood away from heart).

If an aortic aneurysm ruptures, the person will experience a sudden and severe pain in the middle or side abdomen. In men, the pain can spread down into the scrotum (the sac containing the testicles).

Symptoms of a ruptured brain aneurysm usually begin with a sudden and severe headache, which has been described as like being hit on the head.

Renal arteries: These supply blood to the kidneys; if the blood supply becomes limited, there is a serious risk of developing chronic renal failure, and the patient may experience:

- Loss of appetite.
- Swelling of the hands and feet.
- Difficulty in concentrating.

Peripheral arterial disease: The arteries to the limbs, usually the legs, are blocked. The most common symptom is leg pain, either in one or both legs, usually in the calves, thighs or hips. The pain may be described as one of heaviness, cramp, or dullness in the leg muscles. Other symptoms may include:

- Hair loss on legs or feet
- Male impotence (erectile dysfunction)
- Numbness in the legs
- The colour of the skin on the legs change
- The toenails get thicker
- Weakness in the legs

Table 3.3 : Location of the atherosclerosis and their symptoms

Location of the atherosclerosis	Symptoms
In the coronary (heart) arteries	Chest pain, heart attack, or sudden death
In the coarotid (brain) arteries	weakness, loss of speech, or blindness
In the fermoral (leg) arteries	Diseases of the blood vessels in the outer parts of the body (peripheral vascular disease) causer-scramping and fatigue in the caluves when walking.
In the renal (kidney) arteries, in the arteries leading to genitals	High blood pressure that is difficult to treat, pain during sex. Sometimes, atherosclerosis can cause eractile dysfunction in men. In women, high blood pressure can reduce blood flow to the vagina, making sex less pleasurable

Diagnosis

Physicians may be able to make a diagnosis of atherosclerosis during a physical exam by means of a stethoscope and gentle probing of the arteries with the hand (palpation) to find signs of narrowed, enlarged or hardened arteries, including: A weak or absent pulse below the narrowed area of artery. Decreased blood pressure in an affected limb. Whooshing sounds (bruits) over arteries, heard using a stethoscope. Signs of a pulsating bulge (aneurysm) in abdomen or behind knee. Evidence of poor wound healing in the area where blood flow is restricted.

Depending on the results of the physical exam, more diagnostic tests, including:

Blood tests: Blood tests can detect increased levels of cholesterol and blood sugar that may increase the risk of atherosclerosis.

Doppler ultrasound: It is a special ultrasound device (Doppler ultrasound) used to measure blood pressure at various points along arm or leg. These measurements can help doctor to measure the degree of any blockages, as well as the speed of blood flow in arteries.

Ankle-brachial index: This test can reveal the atherosclerosis in the arteries in legs and feet. Doctor may compare the blood pressure in ankle with the blood pressure in arm. This is known as the ankle-brachial index. An abnormal difference may indicate peripheral vascular disease, which is usually caused by atherosclerosis.

More definite tests are:

Electrocardiography (ECG): An electrocardiogram measures the electrical activity of heart. This test can measure how well heart is functioning and can often detect the presence of heart disease.

Stress test: A stress test, also called an exercise stress test, is used to gather information about how well heart works during physical activity. Because exercise makes heart pump harder and faster than it does during most daily activities, an exercise stress test can reveal problems within heart that might not be noticeable otherwise. An exercise stress test usually involves walking on a treadmill or riding a stationary bike while heart rhythm, blood pressure and breathing are monitored.

Cardiac catheterization and angiogram: This test can show if coronary arteries are narrowed or blocked. A liquid dye is injected into the arteries of heart through a long, thin tube (catheter) that is fed through an artery, usually in leg, to the arteries in heart. As the dye fills arteries, the arteries become visible on X-ray, revealing areas of blockage.

Ultrasound: An ultrasound scanner uses sound waves to build up a picture of the inside of body. This can be used to measure blood pressure at different points in body. Any variation in pressure could point to the site of a blockage in arteries. Ultrasound tests can also be used to study the larger arteries.

Computerised tomography scan: A computerised tomography (CT) scan takes a series of X-ray images and uses a computer to assemble them into a more detailed three-dimensional image. It can often detect narrowing or hardening in the larger arteries.

Treatment

Lifestyle changes: The changes will focus on weight management, physical activity and a healthy diet. Doctor may recommend eating foods high in soluble fiber and limiting intake of saturated fats, sodium and alcohol.

Medication: The medications may be prescribed:

- To prevent the deposition of plaque or blood clots using antiplatelet agents or Thrombolytic agents.
- To lower cholesterol such as statins.
- To lower blood pressure such as Angiotensin-converting enzyme (ACE) inhibitors, Diuretics (Water pills).

Surgery: Severe cases of atherosclerosis may be treated by surgical procedures, such as angioplasty or coronary artery bypass grafting (CABG).

Angioplasty involves expanding the artery and opening the blockage, so that the blood can flow through properly again. CABG is another form of surgery that can improve blood flow to the heart by using arteries from other parts of the body to bypass a narrowed coronary artery.

Angioplasty and stent placement: Angioplasty is a procedure in which a tiny device is inserted into narrowed blood vessels that supply blood to the heart. This device widens the arteries and increases blood flow.

Balloon angioplasty, also known as percutaneous transluminal coronary angioplasty (PTCA), uses a small, thin tube (called a catheter) with a tiny balloon at its tip. The tube is inserted into the bloodstream through a large vessel in the arm or leg. By watching the progress of the tube on an X-ray, the cardiologist guides the tube into the heart, where it is inserted into a narrowed coronary artery. The tiny balloon is then inflated to widen the narrowed area.

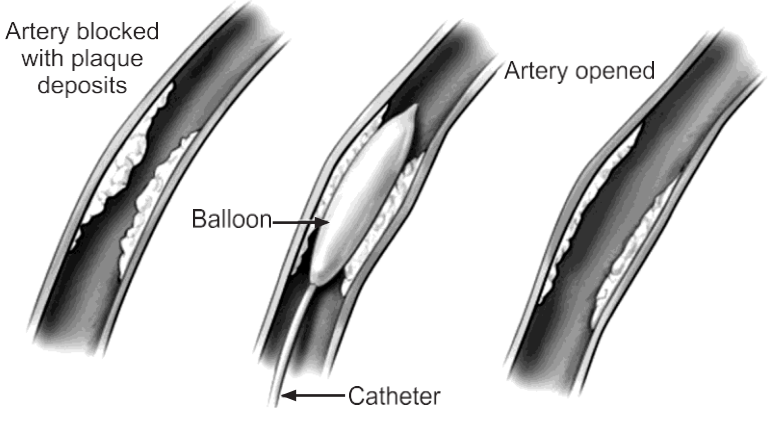

Fig. 3.4 : Balloon angioplasty

During most of these procedures, cardiologists also insert a metal wire frame that serves as a scaffolding to help keep the artery open. This device is called a stent. A blocked artery is less likely to close up if a stent is in place.

There are two types of stents:

- Bare metal stents
- Drug coated stents

Endarterectomy: In some cases, fatty deposits must be surgically removed from the walls of a narrowed artery. When the procedure is done on arteries in the neck (the carotid arteries), it is called a carotid endarterectomy.

Bypass surgery: In this, a graft bypass may be created using a vessel from another part of body or a tube made of synthetic fabric. This allows blood to flow around the blocked or narrowed artery.

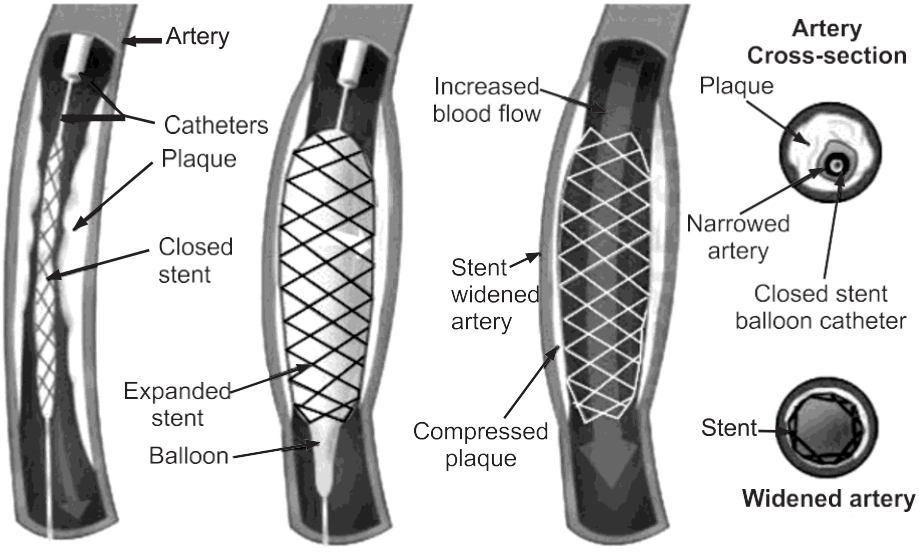

Fig. 3.5 : Stent with ballon angioplast

Table 3.4 : Drugs used in the treatment of atherosclerosis

Statins to lower bad cholesterol (LDL)	Lovastatin, Simvastatin, Pravastatin, Fluvastatin, Atorvastatin, Rosuvastatin
Fibrates to reduce Triglycerides	Gemfibrozil, Fenofibrate
Reducing triglycerides and LDL. It also increases HDL.	Nictoinic acid.
Other drugs for atherosclerosis	Cholestyramine, Colestipol, Colesevelam

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UNIT II

Chapter...4

CARDIOVASCULAR SYSTEM

4.1 INTRODUCTION TO CARDIOVASCULAR SYSTEM

The heart is muscular organ about the size of a closed fist located in the chest between the lungs behind the sternum and above the diaphragm. It is surrounded by the pericardium. On its superior end, the base of the heart is attached to the aorta, pulmonary arteries and veins, and the vena cava. The inferior tip of the heart, known as the apex, rests just superior to the diaphragm. The base of the heart is located along the body's midline with the apex pointing toward the left side. Because the heart points to the left, about 2/3 of the heart's mass is found on the left side of the body and the other 1/3 is on the right.

Heart is the pump which is responsible for maintaining adequate circulation of oxygenated blood around the vascular network of the body. It takes in deoxygenated blood through the veins and delivers it to the lungs for oxygenation before pumping it into the various arteries.

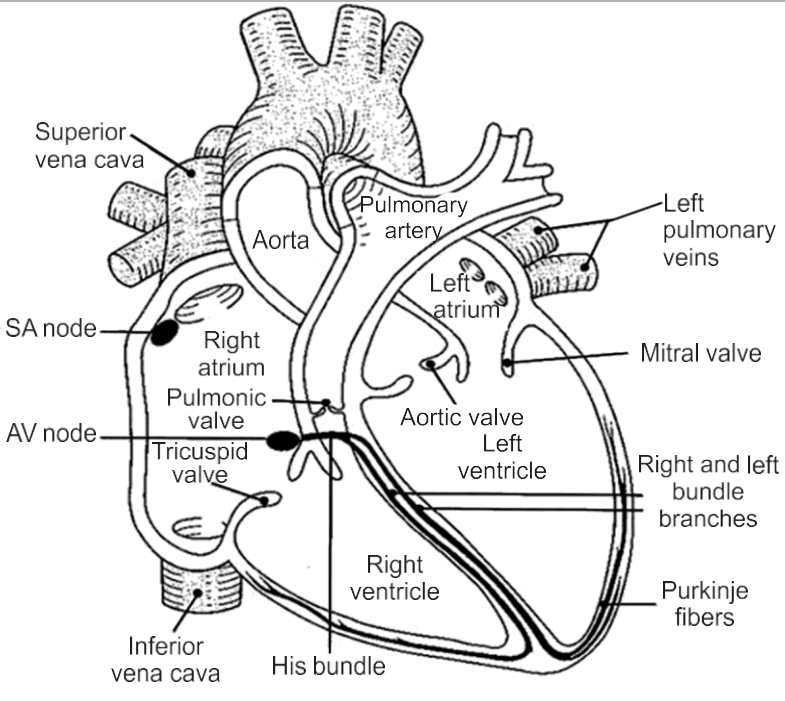

Fig. 4.1 : Internal structure of heart

Anatomy of the Heart

Pericardium: The heart is placed within a fluid filled cavity called as pericardial cavity. The walls and lining of the pericardial cavity are made up of a special membrane known as the pericardium. Pericardium is a type of serous membrane that produces serous fluid to lubricate the heart and prevent friction between the ever beating heart and its surrounding organs. Besides lubrication, the pericardium serves to hold the heart in position and maintain a hollow space for the heart to expand when it is full. The pericardium has two layers, a visceral layer that covers the outside of the heart and a parietal layer that forms a sac around the outside of the pericardial cavity.

The heart wall is made of three layers: epicardium, myocardium and endocardium.

Epicardium: The epicardium is the outermost layer of the heart wall. It is also referred to as visceral pericardium, which is inner layer of pericardium. The epicardium is a thin layer of serous membrane that helps to lubricate and protect the outside of the heart.

Myocardium: Myocardium is the thick middle layer of heart wall and consists of numerous layers of cardiac muscle fibers that wrap around the heart. Contraction of myocardium pumps blood out of the heart into the aorta and pulmonary trunk arteries.

Endocardium: Endocardium is the simple squamous endothelium layer that lines inside the heart. The endocardium is very smooth and is responsible for keeping blood from sticking to the inside of the heart and forming potentially deadly blood clots.

The thickness of the heart wall varies in different parts of the heart. The atria of the heart have a very thin myocardium because they do not need to pump blood very far, but only to the nearby ventricles. The ventricles, on other hand, have a very thick myocardium to pump blood to the lungs or throughout the entire body. The right side of the heart has less myocardium in its walls than the left side because the left side has to pump blood through the entire body while the right side only has to pump to the lungs.

Heart Chambers: The heart contains four chambers: the right atrium, left atrium, right ventricle and left ventricle. The atria are smaller than the ventricles and have thinner, less muscular walls than the ventricles. The atria act as receiving chambers for blood, so they are connected to the veins that carry blood to the heart.

The ventricles are the larger, stronger pumping chambers that send blood out of the heart. The ventricles are connected to the arteries that carry blood away from the heart.

Heart Valves: The heart functions by pumping blood both to the lungs and to the systems of the body. To prevent blood from flowing backwards or "regurgitating" back into the heart, a system of one way valves are present in the heart. The heart valves can be divided into two types: atrioventricular and semilunar valves.

Atrioventricular Valves (AV): The AV valves are located in the middle of the heart between the atria and ventricles and only allow blood to flow from the atria into the ventricles. The AV valve on the right side of the heart is called the tricuspid valve because it is made of three cusps (flaps) that separate to allow blood to pass through and

flow backward. The AV valve on the left side of the heart is called the mitral valve or the bicuspid valve because it has two cusps. The AV valves are attached on the ventricular side to tough strings called chordae tendineae. The chordae tendineae pull on the AV valves to keep them from folding backwards and allowing blood to flow backward.

Semilunar Valves: The semilunar valves, so named for the crescent moon shape of their cusps, are located between the ventricles and the arteries that carry blood away from the heart. The semilunar valve on the right side of the heart is the pulmonary valve, so named because it prevents the backflow of blood from the pulmonary trunk into the right ventricle. The semilunar valve on the left side of the heart is the aortic valve, named for the fact that it prevents the aorta from flowing blood back into the left ventricle. The semilunar valves are smaller than the AV valves and do not have chordae tendineae to hold them in place. Instead, the cusps of the semilunar valves are cup shaped to catch the backward flowing blood and use the blood pressure to snap shut.

Table 4.1 : Heart valves and chambers with their function

Anatomy	Function
Left and right atria	Chambers that receive blood returning from body through veins.
Left and right ventricles	Chambers where blood is pumped to body through arteries.
Mitral valve	The mitral valve controls the flow of oxygen-rich blood from the left atrium to the left ventricle.
Tricuspid valve	The tricuspid valve controls the flow of oxygen-poor blood from the right atrium to the right ventricle.
Aortic valve	The aortic valve controls flow of oxygen-rich blood from the left ventricle to the body.
Pulmonary valve	The pulmonary valve controls flow of oxygen-poor blood from the right ventricle to the lungs.

Conduction System of the Heart

The heart is able to set its own rhythm and also to conduct the signals necessary to maintain and co-ordinate this rhythm throughout its structures. About 1% of the cardiac muscle cells in the heart are responsible for forming the conduction system that sets the pace for the rest of the cardiac muscle cells.

The conduction system starts with the pacemaker of the heart and a small bundle of cells known as the sinoatrial (SA) node. The SA node is located in the wall of the right atrium, inferior to the superior vena cava. The SA node is responsible for setting the pace of the heart as a whole and directly signals the atria to contract. The signal from the SA node is picked up by another mass of conductive tissue known as the atrioventricular (AV) node.

The AV node is located in the right atrium in the inferior portion of the interatrial septum. The AV node picks up the signal sent by the SA node and transmits it to the bundle of His. The AV bundle is a strand of conductive tissue that runs through the interatrial septum and into the interventricular septum. The AV bundle splits into left and right branches in the interventricular septum and continues running through the septum until they reach the apex of the heart. From the left and right bundle branches are many. Purkinje fibers that carry the signal to the walls of the ventricles, stimulate the cardiac muscle cells to contract in a co-ordinated manner to efficiently pump blood out of the heart.

Physiology of the Heart

At any given time, the chambers of the heart may found in one of two states:

Systole: During systole, cardiac muscle tissue is contracting to push blood out of the chamber.

Diastole: During diastole, the cardiac muscle cells relax to allow the chamber to fill with blood.

Blood pressure increases in the major arteries during ventricular systole and decreases during ventricular diastole. This leads to the two values associated with blood pressure, (i) systolic blood pressure is the higher value and (ii) diastolic blood pressure is the lower value. For example, a blood pressure of 120/80 describes the systolic pressure (120) and the diastolic pressure (80).

The Cardiac Cycle

The cardiac cycle includes all of the events that take place during one heartbeat. There are three phases to the cardiac cycle: atrial systole, ventricular systole and relaxation.

Atrial systole: During the atrial systole phase of the cardiac cycle, the atria contract and push blood into the ventricles. To facilitate this filling, the AV valves stay open and the semilunar valves stay closed to keep arterial blood from re-entering the heart. The atria are much smaller than the ventricles, so they only fill about 25% of the ventricles during this phase. The ventricles remain in diastole during this phase.

Ventricular systole: During ventricular systole, the ventricles contract to push blood into the aorta and pulmonary trunk. The pressure of the ventricles forces the semilunar valves to open and the AV valves to close. This arrangement of valves allows for blood flow from the ventricles into the arteries. The cardiac muscles of the atria repolarize and enter the state of diastole during this phase.

Relaxation phase: During the relaxation phase, all four chambers of the heart are in diastole as blood pours into the heart from the veins. The ventricles fill to about 75% capacity during this phase and will be completely filled only after the atria enter systole. The cardiac muscle cells of the ventricles repolarize during this phase to prepare for the next round of depolarization and contraction. During this phase, the AV valves open to allow blood to flow freely into the ventricles while the semilunar valves close to prevent the regurgitation of blood from the great arteries into the ventricles.

Blood Flow Through the Heart

Deoxygenated blood returning from the body first enters the heart from the superior and inferior vena cava. The blood enters the right atrium and is pumped through the

tricuspid valve into the right ventricle. From the right ventricle, the blood is pumped through the pulmonary semilunar valve into the pulmonary arteries.

The pulmonary artery carries blood to the lungs where it releases carbon dioxide and absorbs oxygen. The blood in the lungs returns to the heart through the pulmonary veins. From the pulmonary veins, blood enters the heart again in the left atrium. The left atrium contracts to pump blood through the bicuspid (mitral) valve into the left ventricle. The left ventricle pumps blood through the aortic semilunar valve into the aorta. From the aorta, blood enters into systemic circulation throughout the body tissues until it returns to the heart via the vena cava and the cycle repeats.

The Electrocardiogram

The electrocardiogram (also known as an EKG or ECG) is a non-invasive device that measures and monitors the electrical activity of the heart through the skin. The ECG produces a distinctive waveform in response to the electrical changes taking place within the heart.

The first part of the wave, called the P wave, is a small increase in voltage of about 0.1 mV that corresponds to the depolarization of the atria during atrial systole. The next part of the EKG wave is the QRS complex which features a small drop in voltage (Q) a large voltage peak (R) and another small drop in voltage (S). The QRS complex corresponds to the depolarization of the ventricles during ventricular systole. The atria also repolarize during the QRS complex, but have almost no effect on the EKG because they are so much smaller than the ventricles.

The final part of the EKG wave is the T wave, a small peak that follows the QRS complex. The T wave represents the ventricular repolarization during the relaxation phase of the cardiac cycle. Variations in the waveform and distance between the waves of the EKG can be used clinically to diagnose the effects of heart attacks, congenital heart problems, and electrolyte imbalances.

Heart Sounds

The sounds of a normal heartbeat are known as “lubb” and “dupp” and are caused by blood pushing on the valves of the heart. The “lubb” sound comes first in the heartbeat and is the longer of the two heart sounds. The “lubb” sound is produced by the closing of the AV valves at the beginning of ventricular systole. During a normal heartbeat, these sounds repeat in a regular pattern of lubb-dupp-pause. Any additional sounds such as liquid rushing or gurgling indicate a structure problem in the heart. The most likely causes of these extraneous sounds are defects in the atrial or ventricular septum or leakage in the valves.

Cardiac Output

Cardiac output (CO) is the volume of blood being pumped by the heart in one minute. The equation used to find cardiac output is:

$$CO = \text{Stroke Volume} \times \text{Heart Rate}$$

Stroke volume is the amount of blood pumped into the aorta during each ventricular systole, usually measured in millilitres. Heart rate is the number of heart beats per minute. The average heart can push around 5 to 5.5 litres per minute at rest.

In closed circulatory system, blood is circulated through closed vessels such as arteries, veins and capillaries.

Arteries: The blood vessels which carry blood from the heart to various body organs are called arteries. All arteries carry oxygenated blood, except pulmonary artery, which carries deoxygenated blood.

Veins: The vessels which carry blood from various body organs to the heart are known as veins. All veins carry deoxygenated blood except pulmonary vein, which carries oxygenated blood.

Capillaries: Capillaries are the most common, smallest and thinnest of the blood vessels in the body. They can be found running throughout almost every tissue of the body and border the edges of the body's vascular tissues. Capillaries connect to arterioles on one end and venules on the other. Capillaries carry blood very close to the cells of the tissues of the body in order to exchange gases, nutrients, and waste products. The walls of capillaries consist of only a thin layer of endothelium, acts as a filter to keep blood cells inside of the vessels while allowing liquids, dissolved gases, and other chemicals to diffuse along their concentration gradients into or out of tissues.

Functions of Cardiovascular System

The cardiovascular system has three major functions: transportation, protection and regulation of the body's homeostasis.

Transportation: The cardiovascular system transports blood to almost all of the body's tissues. The blood delivers essential nutrients and oxygen and removes wastes and carbon dioxide to be processed or removed from the body. Hormones are transported throughout the body via the blood's liquid plasma.

Regulation: The cardiovascular system is instrumental in the body's ability to maintain homeostatic control of several internal conditions. Blood vessels help maintain a stable body temperature by controlling the blood flow to the surface of the skin. Blood vessels near the skin's surface open during times of overheating to allow hot blood to dump its heat into the body's surroundings. In the case of hypothermia, these blood vessels constrict to keep blood flowing only to vital organs in the body's core. Blood also helps to balance the body's pH due to the presence of bicarbonate ions, which act as a buffer solution. Finally, the albumins in blood plasma help to balance the osmotic concentration of the body's cells by maintaining an isotonic environment.

The Circulatory Pump: The heart is a four-chambered "double pump", where each side (left and right) operates as a separate pump. The left and right sides of the heart are separated by a muscular wall of tissue known as the septum of the heart. The right side of the heart receives deoxygenated blood from the systemic veins and pumps it to the lungs for oxygenation. The left side of the heart receives oxygenated blood from the lungs and pumps it through the systemic arteries to the tissues of the body. Each heartbeat results in the simultaneous pumping of both sides of the heart, making the heart a very efficient pump.

Regulation of Blood Pressure: Several functions of the cardiovascular system can control blood pressure. Certain hormones along with autonomic nerve signals from the brain affect the rate and strength of heart contractions. Greater contractile force and heart rate lead to an increase in blood

pressure. Blood vessels can also affect blood pressure. Vasoconstriction decreases the diameter of an artery by contracting the smooth muscle in the arterial wall. The sympathetic (fight or flight) division of the autonomic nervous system causes vasoconstriction, which leads to increase in blood pressure and decrease in blood flow in the constricted region. Vasodilatation is the expansion of an artery as the smooth muscle in the arterial wall relaxes after the fight-or-flight response wears off or under the effect of certain hormones or chemicals in the blood. The volume of blood in the body also affects blood pressure. A higher volume of blood in the body raises blood pressure by increasing the amount of blood pumped by each heartbeat. Thicker, more viscous blood from clotting disorders can also raise blood pressure.

4.2 HYPERTENSION

Hypertension is a chronic medical condition that arises when the blood pressure is abnormally high (greater than 140 mm of Hg systolic and 90 mm of Hg diastolic). Hypertension occurs when the body's smaller blood vessels (the arterioles) narrow, causing the blood to exert excessive pressure against the vessel walls and forcing the heart to work harder to maintain the pressure. Although the heart and blood vessels can tolerate increased blood pressure for months and even years, eventually the heart may enlarge (a condition called hypertrophy) and be weakened to the point of failure.

Hypertension risk factors include obesity, drinking too much alcohol, smoking and family history.

Blood pressure is actually a measure of two pressures, the systolic and the diastolic. The systolic pressure is the force that blood exerts on the artery walls as the heart contracts to pump the blood to the peripheral organs and tissues. The diastolic pressure is residual pressure exerted on the arteries as the heart relaxes between beats. A diagnosis of hypertension is made when blood pressure reaches or exceeds 140/90 mmHg (read as "140 over 90 millimetres of mercury").

Types of Hypertension

There are two major types of hypertension and four less frequently found types.

1. Primary (Essential) Hypertension: About 95% of people with high blood pressure have essential hypertension or primary hypertension. This condition has no identifiable medical cause. Elevated blood pressure usually begins to appear between age 30 and 50, but can begin at older ages.

Usually people with essential hypertension have no symptoms, but may experience frequent headaches, tiredness, dizziness, or nose bleeds. Although the cause is unknown, but contributing factors for essential hypertension may be, obesity, smoking, alcohol, diet and inherited.

2. Secondary Hypertension: About 5%-10% of people with high blood pressure have secondary hypertension. This condition has definite cause; the most common cause of secondary hypertension is an abnormality in the arteries supplying blood to the kidneys. Other causes include airway obstruction during sleep, diseases and tumors of the adrenal glands, hormone

abnormalities, thyroid disease, and too much salt or alcohol in the diet. Drugs can cause secondary hypertension, including OTC medications such as ibuprofen and pseudoephedrine.

Table 4.2 : Classification of severity of hypertension

Stage	Systolic (mm Hg)	Diastolic (mm Hg)
None	<130	<85
None or very mild	130-139	85-89
Mild	140-159	90-99
Moderate	160-179	100-109
Severe	180-209	110-119
Very severe	210 or greater	120 or greater

3. Isolated Systolic Hypertension: In this case, the systolic blood pressure (the top number) is consistently above 160 mm Hg, and the diastolic below 90 mmHg. This may occur in older people, and results from the age-related stiffening of the arteries. The loss of elasticity in arteries, like the aorta, is mostly due to arteriosclerosis. The Western lifestyle and diet is believed to be the root cause.

4. Malignant hypertension: Malignant hypertension is the most threatening form of high blood pressure. It is marked by an unusually sudden rise in blood pressure to dangerous levels. Diastolic pressure often reaches 130 mm Hg or higher. However, malignant hypertension may also occur at lower, less alarming levels, if the rise is particularly sudden. Unlike other kinds of high blood pressure, malignant hypertension is usually accompanied by dramatic symptoms such as severe headache, shortness of breath, chest pain, nausea and vomiting, blurred vision, or even blindness, seizures and loss of consciousness.

Malignant hypertension is an emergency condition. Patient with malignant hypertension must be hospitalized immediately. It places people at immediate risk for heart attack, stroke, heart failure, permanent kidney damage, bleeding into the brain (hemorrhagic stroke) and brain swelling.

Malignant hypertension develops in less than 1 % of people who already have high blood pressure. Rarely, the appearance of malignant hypertension is the first sign that a person has high blood pressure. The cause of this condition is usually unknown, but occasionally it can be a reaction of body to a drug abuse, like cocaine, or a reaction to stopping a blood-pressure medicine.

5. Resistant Hypertension: If blood pressure cannot be reduced to below 140/90 mmHg, despite a triple-drug regimen of antihypertensive medications called as resistant hypertension.

Resistant hypertension may occur in 20 to 30 % of high blood pressure cases. It may have a genetic component and is more common in people who are older, obese, and female or have an underlying illness, such as diabetes or kidney disease.

6. Hypertension during Pregnancy: High blood pressure occurs in 6 % to 8 % of pregnancies, and in most of these cases, it is diagnosed during a first pregnancy. Pregnancy can cause high blood pressure due to hormonal changes or from a serious complication of pregnancy known as preeclampsia, a condition that causes tightening of arteries throughout the mother's body and placenta, as well as unpredictable blood clotting.

Epidemiology

As per the World Health Statistics 2012, of the estimated 57 million global deaths in 2008, 36 million (63%) were due to non-communicable diseases (NCDs). The largest proportion of NCD deaths is caused by cardiovascular diseases (48%). In terms of attributable deaths, raised blood pressure is one of the leading behavioural and physiological risk factor to which 13% of global deaths are attributed. Hypertension is reported to be the fourth contributor to premature death in developed countries and the seventh in developing countries. Recent reports indicate that nearly 1 billion adults (more than a quarter of the world's population) had hypertension in 2000, and this is predicted to increase to 1.56 billion by 2025. Earlier reports also suggest that the prevalence of hypertension is rapidly increasing in developing countries and is one of the leading causes of death and disability.

Children: Most childhood hypertension, particularly in preadolescents, is secondary to an underlying disorder. Apart from obesity, kidney disease is the most common (60–70%) cause of hypertension in children. Adolescents usually have primary (essential) hypertension, which accounts for 85–95% of cases.

Etiology

The exact causes of high blood pressure are not known, but several factors and conditions may play a role in its development, including:

- Smoking
- Being overweight or obese
- Lack of physical activity
- Too much salt in the diet
- Too much alcohol consumption
- Stress
- People with family members who have high blood pressure
- Chronic renal failure
- Adrenal and thyroid disorders

Many people with kidney disorders have secondary hypertension. The kidneys regulate the balance of salt and water in the body if the kidneys cannot rid the body of excess salt and water, blood pressure goes up.

Kidney infections, a narrowing of the arteries that carry blood to the kidneys, called renal artery stenosis and other kidney disorders can disturb the salt and water balance.

Cushing's syndrome and tumors of the pituitary and adrenal glands often increase levels of the adrenal gland hormones like cortisol, adrenaline and aldosterone, which can cause hypertension.

Certain medications, such as birth control pills, cold remedies, decongestants, over-the-counter pain relievers and some prescription drugs, illegal drugs, such as cocaine and amphetamines or chronic alcohol use, obstructive sleep apnea and pregnancy may lead to hypertension.

Pathophysiology

Hypertension causes three major circulatory abnormalities: increased arteriolar resistance, increased large artery stiffness, and early or premature reflection of arterial pulse waves.

Increased resistance and vessel stiffness in younger hypertensive patients result from structural changes, including thinning and fracturing of elastin, increased collagen deposition, and increased wall thickness. These changes manifest primarily as a greater rise in systolic pressure greater than diastolic pressure.

In elderly, an increased arterial stiffness is the greater factor and may contribute to isolated systolic hypertension, in which systolic pressure is elevated but diastolic pressure is normal or low. Patients with isolated systolic hypertension are at substantially increased risk for stroke, coronary heart disease, and congestive heart failure. Pulse wave reflection referes to the backward rebound of some of the cardiac output as it encounters the resistance of the arteries. When arteries are normally complaint, this reflected flow occurs during diastole and assists with filling of the coronary arteries. In hypertension, however, reflection occurs prematurely, during systole, contributing to vascular overload in the aortic arch and in the coronary carotid and renal arteries.

Secondary hypertension accounts for approximately 5-10% of all cases of hypertension, with the remaining being primary hypertension.

Secondary hypertension has an identifiable cause whereas primary hypertension has no known cause (i.e. idiopathic).

There are many known conditions that can cause secondary hypertension. Regardless of the cause, arterial pressure becomes elevated either due to an increase in cardiac output, an increase in systemic vascular resistance, or both. When cardiac output is elevated, it is generally due to either increased neurohumoral activation of the heart or increased blood. Increased systemic vascular resistance is most commonly caused, at least initially, by increased sympathetic activation or by the effects of circulating vasoconstrictors (e.g., angiotensin II). Anatomic considerations, such as narrowing of the aorta (e.g., coarctation) or chronic changes in vascular structure (e.g., vascular hypertropy) can also cause or contribute to increased systemic vascular resistance. Renal artery disease can cause because of narrowing of the vessel lumen (stenosis). The reduced lumen diameter decreases the pressure at the afferent arteriole in the kidney and reduces renal perfusion. This stimulates renin release by the kidney, which increases circulating angiotensin II and aldosterone. These hormones increase blood volume by enhancing renal reabsorption of sodium and water. Increased angiotensin II also causes systemic vasoconstriction and enhances sympathetic activity. Chronic elevation of angiotensin II promotes cardiac and vascular hypertrophy. The net effect of these renal mechanisms is an increase in blood volume that augments cardiac output.

Therefore, hypertension caused by renal artery stenosis results from both an increase in systemic vascular resistance and an increase in cardiac output.

Chronic renal failure: A number of pathologic processes (e.g., diabetic nephropathy, glomerulonephritis) can damage nephrons in the kidney. When this occurs, the kidney cannot excrete normal amount of sodium which leads to sodium and water retention, increased blood volume, and increased cardiac output by the Frank-Starling mechanism.

Renal disease may also result in increased release of renin leading to a renin-dependent form of hypertension. The elevation in arterial pressure secondary to renal disease can be viewed as an attempt by the kidney to increase renal perfusion and restore glomerular filtration.

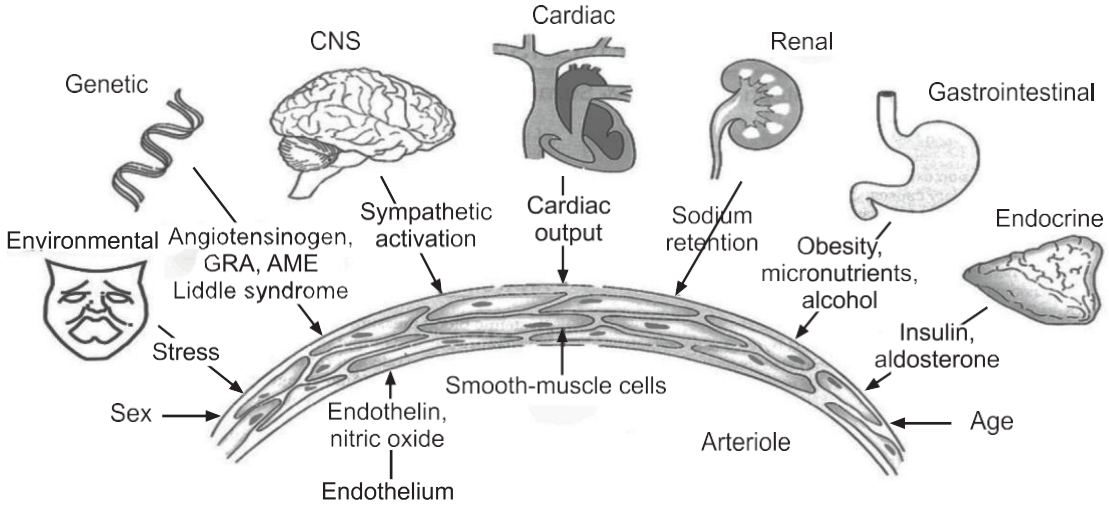

Fig. 4.2: Pathogenesis of hypertension

Primary hyperaldosteronism: Increased secretion of aldosterone generally results from adrenal adenoma or adrenal hyperplasia. Increased circulating aldosterone causes renal retention of sodium and water, so blood volume and arterial pressure increases. Plasma renin levels are generally decreased as the body attempts to suppress the renin-angiotensin system; there is also hypokalemia associated with the high levels of aldosterone.

Stress: Emotional stress leads to activation of the sympathetic nervous system, which causes increased release of norepinephrine from sympathetic nerves in the heart and blood vessels, leading to increased cardiac output and increased systemic vascular resistance. Furthermore, the adrenal medulla secretes more catecholamines (epinephrine and norepinephrine). Activation of the sympathetic nervous system increases circulating angiotensin II, aldosterone, and vasopressin, which can increase systemic vascular resistance. Prolonged elevation of angiotensin II and catecholamines can lead to cardiac and vascular hypertrophy, both of which can contribute to a sustained increase in blood pressure.

Sleep Apnea: Sleep apnea is a disorder in which people repeatedly stop breathing for short periods of time (10-30 seconds) during their sleep. This condition is often associated with obesity, although it can have other causes such as airway obstruction or disorders of the central nervous system. These individuals have a higher incidence of hypertension. The mechanism of hypertension may be related to sympathetic activation and hormonal changes associated with repeated periods of apnea-induced hypoxia and hypercapnea, and from stress associated with the loss of sleep.

Pheochromocytoma: Catecholamine secreting tumors in the adrenal medulla can lead to very high levels of circulating catecholamines (both epinephrine and norepinephrine). This leads to α-adrenoceptor mediated systemic

vasoconstriction and β-adrenoceptor mediated cardiac stimulation, both of which contribute to significant elevations in arterial pressure. Despite the elevation in arterial pressure, tachycardia occurs because of the direct effects of the catecholamines on the heart and vasculature. Excessive β-adrenoceptor stimulation in the heart often leads to arrhythmias. The pheochromocytoma is diagnosed by measuring plasma or urine catecholamine levels and their metabolites (vanillylmandelic acid and metanephrine).

Preeclampsia: This is a condition that sometimes develops during the third trimester of pregnancy that causes hypertension, sometimes with fluid retension and priteinuria due to increased blood volume and tachycardia. The former increases cardiac output by the Frank-Starling mechanism.

Arch of the aorta: Obstruction of the aorta at this point reduces distal arterial pressures and elevates arterial pressures in the head and arms. The reduced systemic arterial pressure activates the renin-angiotensin-aldosterone system, which leads to an increase in blood volume. This further increases arterial pressures in the upper body and may largely offset the reduction in lower body arterial pressures. This condition is readily diagnosed by comparing arterial pressures measured in the arms and legs. Normally, these pressures are very similar, but with coarctation, arterial pressures in the arms can be much greater than arterial pressures measured in the legs. Because this is a chronic condition, the baroreceptors are desensitized and upper body arterial pressures remain elevated because of the increased cardiac output to these parts of the body.

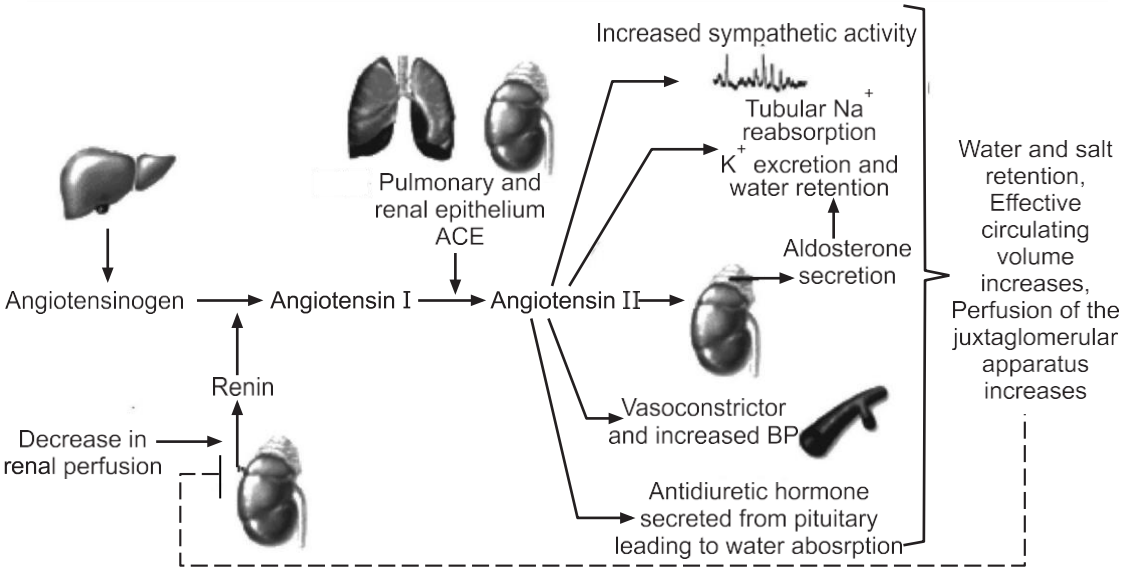

Fig. 4.3 : Role of renin in pathogenesis of hypertension

Aortic coarctation: Coarctation (narrowing) of the aorta is a congenital defect that most commonly is found just distal to the left subclavian artery in the arch of aorta.

Symptoms

High blood pressure usually causes no symptoms and high blood pressure often is labelled "the silent killer". People who have high blood pressure typically do not know it until their blood pressure is measured.

Sometimes people with markedly elevated blood pressure may develop:

- Headache
- Dizziness
- Blurred vision
- Nausea and vomiting, and
- Chest pain and shortness of breath.

People often do not seek medical care until they have symptoms arising from the organ damage caused by chronic (ongoing, long-term) high blood pressure. The following types of organ damage are commonly seen in chronic high blood pressure:

- Heart attack.
- Heart failure.
- Stroke or transient ischemic attack (TIA).
- Kidney failure.
- Eye damage with progressive vision loss.
- Peripheral arterial disease causing leg pain with walking (claudication).
- Outpouchings of the aorta, called Aneurysms.

About 1% of people with high blood pressure do not seek medical care until the high blood pressure is very severe, a condition known as malignant hypertension.

- In malignant hypertension, the diastolic blood pressure (the lower number) often exceeds 140 mm Hg.
- Malignant hypertension may be associated with headache, lightheadedness, nausea, vomiting, and stroke like symptoms.
- Malignant hypertension requires emergency intervention and lowering of blood pressure to prevent brain hemorrhage or stroke.

It is of extreme importance to realize that high blood pressure can be unrecognized for years, causing no symptoms but causing progressive damage to the heart, other organs, and blood vessels.

Diagnosis

High blood pressure is diagnosed based on the results of a blood pressure test. The test yields two numbers: systolic and diastolic. Blood pressure values are often written as systolic pressure/diastolic pressure; for example, 120/80. The unit of measurement for blood pressure is millimetres of mercury (mmHg).

Blood Pressure Categories in Adults:

The National Heart, Lung and Blood Institute divide blood pressure levels into several categories. Below are the values that define each of these categories in adults.

Normal: Systolic pressure, less than 120 mmHg and Diastolic pressure, less than 80 mmHg.

Prehypertension: Systolic pressure, 120-139 mmHg or Diastolic pressure, 80-89 mmHg.

Stage 1 high blood pressure: Systolic pressure, 140-159 mmHg or Diastolic pressure, 90-99 mmHg.

Stage 2 high blood pressure: Systolic pressure, 160 mmHg and above or Diastolic pressure, 100 mmHg and above. When systolic and diastolic pressures fall into different categories, the higher one is used. For example, a blood pressure reading of

165/85 is considered stage 2 high blood pressure.

Isolated systolic hypertension: It refers to high blood pressure in which only the systolic number is high. It occurs in about two-thirds of people over ages 60 who have high blood pressure. This condition should be taken as seriously as high blood pressure in which both values are elevated, because it can cause just as much harm if left untreated.

Diagnosis in Children and Teens: Blood pressure is measured the same way in children and teens as it is in adults. However, the younger and smaller the child, the lower the values normally are. To diagnose high blood pressure, the blood pressure values for a particular child or teen are compared to average blood pressure readings for young people of the same age, gender and height.

Following points are also taken into consideration in diagnosis:

1. Medical and family history
2. Physical examination
3. Ophthalmoscopy
4. Chest-X-ray
5. Electrocardiograph
6. Blood and urine tests

Treatment

There is no cure for primary hypertension but blood pressure can almost always be lowered with the correct treatment. The goal of treatment is to lower blood pressure to levels that will prevent heart disease and other complications of hypertension.

In secondary hypertension, the disease that is responsible for the hypertension is treated in addition to the hypertension itself. Successful treatment of the underlying disorder may cure the secondary hypertension.

Antihypertensive medicines fall into several classes of drugs (see table 4.3)

Prevention

Having high blood pressure can be prevented by eating healthily, maintaining a healthy weight, taking regular exercise, drinking alcohol in moderation and not smoking, reducing salt intake, managing stress.

Table 4.3 : Antihypertensive drugs

Classification	Mechanism of action	Examples
Central acting agents	These prevent the brain from signaling nervous system to increase heart rate and narrow blood vessels.	Clonidine and methyldopa
Calcium Channel Blockers	These vasodilates the blood vessels and slow heart rate by blocking calcium channel	Amlodipine, Felodipine, Nicardipine, Nifedipine, Diltiazem verapamil
Drugs acts on RAA system	Vasodilatation of blood vessels. Decreases release of renin. Antagonise the angiotensin II receptor.	Captopril, Enalapril Aliskiren Losartan, Telmisartan

Contd...

Anti-adrenergic drugs	Vasodilatation of blood vessels Reduce conduction of nerve impulses to blood vessels.	Atenolol, Metoprolol Doxazosin, Phentolamine Carvedilol, Labetalol
Aldosterone Receptor Antagonists	Block aldosterone that can lead to salt and fluid retention, which can contribute to high blood pressure.	Eplerenone, Spironolactone
Diuretics	Eliminate sodium and water, reducing blood volume.	Ethacrynic acid, Furosemide hydrochlorothiazide and chlorothiazide.

CONGESTIVE HEART FAILURE

Congestive Cardiac failure is a condition associated with heart disorders leading to impairment of the heart to supply sufficient blood to meet the body requirements. Cardiac Failure may be associated with the failure of the right or left ventricle or both. Cardiac failure causes the blood to move through the heart and body at a slower rate, leading to increased pressure in the heart. As a result, the heart is unable to pump enough oxygen and nutrients to meet the body's requirements. The heart chambers thus respond by stretching in order to hold more blood to pump through the body or by becoming more stiff and thickened. Such mechanism helps to keep the blood moving for a short while, but the heart muscle walls tend to weaken with time and then are unable to pump with enough strength.

The direct result of the reduced contractility of the cardiac muscles especially those of the ventricles, cause a decrease in the cardiac output and increase in the blood volume of the heart. This causes the kidneys to often respond by causing the body to retain fluid (water) and sodium, as the systemic blood pressure and the renal blood flow both are reduced. This results into building up of fluid in the arms, legs, ankles, feet, lungs or other organs causing oedema which makes the body congested, hence the name Congestive cardiac failure.

The term congestive heart failure is used for the chronic form of heart failure in which the patient has evidence of congestion of peripheral circulation and of lungs; CHF is the end result of various forms of serious heart diseases.

Etiology

There are many causes of congestive heart failure including:

1. Coronary artery disease leading to heart attacks and heart muscle weakness.
2. Primary heart muscle weakness from viral infections or toxins such as prolonged alcohol exposure.
3. Heart valve disease causing heart muscle weakness due to too much leaking of blood or heart muscle stiffness from a blocked valve, and
4. Hypertension

Rarer causes of heart failure include:

- Viral myocarditis (an infection of the heart muscle).
- Infiltrations of the muscle such as amyloidosis.

- HIV cardiomyopathy (caused by Human Immunodeficiency Virus).
- Connective tissue diseases such as Systemic lupus erythematosus.
- Abuse of drugs such as alcohol.
- Pharmaceutical drugs such as chemotherapeutic agents.
- Arrhythmias.

Major causes include Ischemic heart, Hypertension, Cardiomyopathy.

Pathogenesis

Heart failure may be caused by one of the following factors either singly or in combination.

1. Intrinsic Pump Failure: The most common and most important cause of heart failure is weakening of the ventricular muscle due to disease so that the heart fails to act as an efficient pump. The various diseases which may culminate in pump failure by these mechanisms are as under:

(i) Ischaemic heart disease,
(ii) Myocarditis,
(iii) Cardiomyopathies,
(iv) Metabolic disorders like beriberi,
(v) Disorders of the rhythm e.g. atrial fibrillation and flutter.

2. Increased workload on the heart: Increased mechanical load on the heart results in increased myocardial demand resulting in myocardial failure. Increased load on the heart may be in the form of pressure load or volume load.

(a) Increased pressure load may occur in the following states:

(i) Systemic and pulmonary arterial hypertension.
(ii) Valvular disease e.g. mitral stenosis, aortic stenosis, pulmonary stenosis.
(iii) Chronic lung diseases.

(b) Increased volume load occurs when a ventricle is required to eject more than normal volume of the blood resulting in cardiac failure. This is seen in the following conditions:

(i) Valvular insufficiency
(ii) Severe anaemia
(iii) Thyrotoxicosis
(iv) Arteriovenous shunts
(v) Hypoxia due to lung diseases.

3. Impaired filling of cardiac chambers: Decreased cardiac output and cardiac failure may result from extra cardiac causes or defect in filling of the heart in pericarditis.

Types of Heart Failure

Congestive heart failure (CHF) is generally classified as systolic or diastolic heart failure and becomes progressively more common with increasing age. In addition, patients with risk factors for heart disease are more likely to develop congestive heart failure.

1. Systolic heart failure: This condition occurs when the pumping action of the heart is reduced or weakened. A common clinical measurement is ejection fraction (EF). The ejection fraction is a calculation of how much blood is ejected out of the left ventricle (stroke volume) divided by the maximum volume remaining in the left ventricle at the end of diastole, or when the heart is relaxed after filling with blood. A normal ejection fraction is greater than 55%. Systolic heart failure is diagnosed when the ejection fraction has significantly decreased below the threshold of 55%.

2. Diastolic heart failure: This condition occurs when the heart can contract normally but is stiff, or less compliant, when it is relaxing and filling with blood. The heart is

unable to fill with blood properly, which produces backup into the lungs and heart failure symptoms. Diastolic heart failure is more common in patients older than 75 years of age, especially in patients with high blood pressure, and it is also more common in women. In diastolic heart failure, the ejection fraction is normal or increased.

3. Acute heart failure: It is sudden and rapid development of failure following massive myocardial infarction, valve rupture, myocarditis etc. The sudden reduction in cardiac output, hypotension without edema is prominent features.

4. Chronic heart failure: It develops slowly with gradual reduction in cardiac output. It is commonly seen in slowly progressive valvular heart disease, systemic arterial hypertension, chronic obstructive pulmonary diseases etc. Blood pressure is well maintained but is associated with peripheral edema.

Table 4.4 : Sign and symptoms of CHF

Symptoms may notice first	Symptoms that indicate condition has worsened	Symptoms that indicate a severe heart condition
Fatigue	Irregular heartbeat	Chest pain that radiates through the upper body
Swelling in ankles, feet and legs	A cough that develops from congested lungs	Rapid breathing
Weight gain	Wheezing	Skin that appears blue, which is due to lack of oxygen in lungs
Increased need to urinate, especially at night	Shortness of breath, which may indicate pulmonary edema	Fainting

Clinical Manifestations

The most common manifestation of left ventricular failure is dyspnoea, or a sense of breathlessness. This is caused predominantly by decreased lung compliance resulting from pulmonary edema and congestion, and by increased activity of autonomic stretch receptors within the lung. Dyspnoea is most noticeable during periods of physical activity. It is also prominent when the person is lying down (Orthopnoea), because of the increased amount of venous blood returned to the thorax from the lower extremities and because the diaphragm is elevated in this position.

Paroxysmal nocturnal dyspnea is an especially dramatic form of dyspnea that awakens the patients with sudden severe shortness of breath, accompanied by coughing, a chocking sensation, and wheezing. Other manifestations of left ventricular failure include muscle fatigue, an enlarged heart, tachycardia, a third heat sound and fine edematous pulmonary alveoli. With progressive ventricular dilation, the papillary muscles are displaced laterally, causing mitral regurgitation and a high pitched systolic murmur. Chronic dilation of the left atrium may also occur and it is often associated with the development of atrial fibrillation manifested by an irregular heartbeat.

As CHF progresses, patients may become frankly cyanotic and acidotic owing to decreased tissue perfusion. Ventricular arrhythmias caused by myocardial irritability and over activity of the sympathetic nervous system are common and are an important cause of sudden death in this setting.

Fluid Retention and Swelling:

- Puffy swelling (edema) in the legs, the feet, and the ankles may occur, particularly at the end of the day or after prolonged sitting. Often, the swelling is more noticeable in the ankles or on the lower leg in the front where the bone, the tibia, is close to the skin.
- Pitting edema can occur when pressing down on the skin in the puffy areas. The indentation where the finger pressed may be visible for a few minutes. Pitting edema is not synonymous with heart failure; it can have other causes, including liver and kidney failure. Nonpitting edema is generally not caused by heart failure.
- Swelling may be so severe as to reach upto the hips, scrotum, abdominal wall, and eventually, the abdominal cavity (ascites).
- Daily weight checks are necessary in persons with heart failure because the amount of fluid retention is usually reflected by the amount of weight gain and increasing shortness of breath. Persons with heart failure should know their dry weight, which is what they weigh when they feel good with no pitting edema.

Treatment

Treatment of Congestive Cardiac Failure is focused on improving the symptoms and preventing the progression of the disease. The major and often neglected form of treatment is lifestyle improvement, which includes:

1. Regulation of the salt and fluid intake: As the entire body suffers from congestion due to fluid accumulation and also that sodium leads to increased fluid accumulation in the body tissues, it is often recommended to restrict the sodium and fluid intake during the cardiac failure.
2. Exercise: It is recommended to do any activity which one can sustain for more than just a few minutes while your heart, lungs and muscles work overtime. Such an exercise is known as aerobic exercise. Regular exercise, according to the patient's tolerance level, appears to provide significant benefits and should be used only when the patient is compensated and stable.

Pharmacological Treatment

Pharmacological treatment involves the use of following category of medications:

(a) Inotropic Drugs:
   i. Caridac glycosides: The digitalis glycosides are used due to its positive inotropic effect and negative chronotropic effect e.g. Digoxin, digitoxin etc.
   ii. Sympathomimetic amines: e.g. Dopamine dobutamine.
   iii. Phosphodiesterase enzyme inhibiters: Amrinone and milrinone

b) ACE inhibitors: These agents act by inhibiting the Angiotensin converting enzyme which is responsible for conversion of Angiotensin I (inactive) to Angiotensin II (active). ACE Inhibitors improve symptoms, decrease mortality and reduce ventricular hypertrophy. E.g: Candesartan.

c) Diuretics: These removes excess extracellular fluid in patients with systolic or diastolic heart failure.
- Loop diuretics: Furesemide
- Potassium sparing diuretics: Amiloride
- Thiazide diuretics: Chlorthiazide, Hydrochlorthiazide

d) Surgical treatment: Heart transplantation may be recommededed for a person who does not respond to medication.

4.4 ISCHAEMIC HEART DISEASE

Ischaemic heart disease (IHD) is defined as 'acute or chronic form of a cardiac disability arising from imbalance between the myocardial supply and demand of oxygenated blood'. The alternate term coronary artery disease (CAD) is used synonymously with IHD. Depending on the rate and severity of coronary artery narrowing and the myocardial response, one of four syndromes may develop.

- Angina pectoris (Chest pain),
- Acute myocardial infarction,
- Chronic ischemic heart disease with congestive heart failure,
- Sudden cardiac death.

Etiology

The most common cause of ischemic heart disease is a reduction in coronary arterial blood supply due to atherosclerosis of the coronary arteries. Factors that contribute to the development of ischaemic heart disease are similar to those responsible for atherosclerosis in general, and include: Hypertension, diabetes mellitus, smoking, high cholesterol, high levels of low density lipoprotein, and genetic factors and non-atherosclerotic causes are vasospasm, coronary artery stenosis, inflammation of coronary arteries, thrombotic disease, trauma, aneurysms and compression.

Pathogenesis

Symptomatic ischemic heart disease is typically associated with a critical stenosis, defined as a 75% or greater reduction in the lumen of one or more coronary arteries by atherosclerotic plaque. With this level of fixed obstruction, the augmented coronary blood follow that may occur as a result of compensatory coronary vasodilation is insufficient to meet even moderate increase in myocardial oxygen demand. In addition to chronic, fixed atherosclerotic plaques, various superimposed lesions also play an important role in the development of myocardial ischemia. These include —

1. Acute changes in the morphology of chronic atherosclerotic plagues include fissuring, haemorrhage into the plaque, and plaque rupture with embolization of atheromataous debris into distal coronary vessels. In addition to causing enlargement of the plaque, local disruption of plaque increases the risk of platelet aggregation and thrombosis at the site.
2. Local plated aggregation in the coronary arteries has been documented in patients with unstable angina pectoris and in patients who undergo sudden cardiac death. Both mechanical occlusion of small blood vessels by small platelet aggregates and coronary vasospasm induced by mediators released from the platelet aggregates may contribute to myocardial ischemia.

3. Coronary artery thrombosis is almost always associated with a severe atherosclerotic plaque. Local disruption of atheromataous plaques plays an important role in the development of thrombi by exposing thrombogenic, lipid rich plaque debris to the blood. Thrombi are identified most often in patients who have suffered a myocardial infarct involving the full thickness of the myocardium although they may also occur in patients with other clinical manifestations of cardiac ischemia, such as unstable angina pectoris.
4. Coronary artery spasm usually occurs in patients with at least some pre-existing atherosclerosis. It has been associated with one particular type of angina pectoris, termed Prinzmental's (variant) angina. At the site of plaque disruption, it may be induced by the release of vasospastic mediators such as thromboxane A_2 by platelet aggregates. Endothelial dysfunction may also precipitate vasospasm by reduced elaboration of endothelial cell derived relaxing factors. Increased sympathetic activity and smoking have also been implicated.

The process other than atherosclerosis or its complications may compromise blood flow through the coronary arteries such as vasospasm, coronary artery stenosis, inflammation of coronary arteries, thrombotic disease, trauma, aneurysms and compression etc. In addition to factors that compromise coronary blood flow, increased myocardial demand may also contribute the development of myocardial ischemia. This may occur with left ventricular myocardial hypertrophy, as well as other conditions that place an increased demand on the heart such as hypertension and diseases of the heart valves.

Clinical Manifestations

Depending on the rate and severity of coronary artery narrowing and the myocardial response, one of four syndromes may develop.

1. Angina pectoris (Chest pain),
2. Acute myocardial infarction,
3. Chronic ischemic heart disease with congestive heart failure,
4. Sudden cardiac death.

Prevention

Fatty diet, smoking, sedentary lifestyle and stress should be avoided, as they are the main causes of Ischemic heart diseases. Avoiding food rich in saturated fats is important to reduce lipid levels in the blood and to prevent arteriosclerosis. Adequate regular exercise is also essential. Cholesterol and hypertension should be kept under good control with proper treatment.

Treatment

Organic Nitrates: These stimulates the intracellular cyclic-GMP, which results in vascular smooth muscle relaxation of both arterial and venous vasculature. e.g. Isosorbide dinitrate.

β-Blockers: β-Blockers act by reducing cardiac work and O_2 consumption. e.g. Propranolol, Atenolol.

Calcium Channel Blockers: Calcium antagonist inhibits the passage of calcium ions through voltage-dependent L-type calcium channels in cell membranes in the heart and vascular smooth muscle as well as some other excitable tissues. e.g. Amlodipine Nifedipine.

Statins: IHD is also due to the increased cholesterol levels. Statins are used to reduce the cholesterol levels in hyper-cholesterolemia. Statins are the HMG-CoA reductase inhibitors. e.g. Atorvastatin, Rusvastatin.

Aspirin: Aspirin improves the rate of survival in patients with acute myocardial infarction and reduces the risk of myocardial infarction in patients with unstable angina, and after recovery from myocardial infarction.

4.4.1 Angina Pectoris

Angina pectoris is a clinical syndrome of Ischemic heart disease (IHD) resulting from transient myocardial ischaemia if the heart muscle does not get as much blood as it needs. This usually happens because one or more of the heart's arteries is narrowed or blocked. It is characterised by paroxysmal pain in the substernal or precordial region of the chest which is aggravated by an increase in the demand of the heart and relived by a decrease in the work of hear. Often, the pain radiates to the left arm, neck jaw or right arm.

There are thee overlapping clinical patterns of angina pectoris with some differences in their pathogenesis:

Stable or Typical Angina:

It can also be referred to as exertional angina. It is associated with sever narrowing of the coronary artery due to build-up of plaque (plaque is excess cholesterol and other debris that has built up inside a coronary artery). With exertion, like walking up a hill or climbing stairs, the heart works harder and needs more oxygen. If it can not get enough oxygen, a person develops symptoms of Angina, the condition improves with rest. During the attacks, there is depression of ST segment in the ECG due to poor perfusion of the subendocardial region of the left ventricle. But there is no elevation of enzymes in the blood as there is no irreversible myocardial injury.

Unstable Angina: Unstable angina occurs when the narrowing of the coronary artery due to build-up of plaque becomes so severe that not enough blood gets through to keep the heart functioning normally, even at rest. In most patients, it is induced by acute plaque change with superimposed partial thrombosis, distal embolization of the thrombus, and/or vasospasm. The morphologic changes in the heart are essentially those of coronary atherosclerosis and its associated lesions. In unstable angina, lack of oxygen to the heart leads to necrosis of heart tissue. Thus, increasing the chances of myocardial infarction, requires emergency treatment. Distinction between unstable angina and acute myocardial infarction is made by ST segment changes on ECG. In acute MI, ST segment elevates while in unstable angina may have non ST segment elevation.

Variant Angina (Vasospastic angina, Prinzmental's angina.):

Rare type of angina caused basically due to spasm of coronary arteries. Variant angina may occur during resting or active state, presence or absence of clogged arteries from atherosclerosis. Spasms lead to decreased blood flow to the heart and hence increase the risk of heart attack. ECG shows ST segment elevation due to transmural ischaemia. These patients respond well to vasodilators like nitroglycerin.

Symptoms

The most prominent symptom of angina is pain or pressure in the chest. It may feel like squeezing or fullness in the middle of the chest and it can radiate outward to the neck, jaw, shoulder, back or arms.

With stable angina, episodes of pain are a regular occurrence and become predictable as triggers are identified. It normally lasts less than five minutes and goes away with rest and/or medication.

With unstable angina, the pain is different from that experienced with stable angina and is not predictable. It is sharper, unexpected (no trigger has been identified), and does not go away with rest or medication.

Variant angina causes sharp bursts of pain, often in the middle of the night. They can last upto 30 minutes but may respond to medication.

Other symptoms can include numbness or tingling, anxiety, fainting, dizziness, sweating, shortness of breath, pale skin, irregular heartbeat, nausea or fatigue.

Treatment

Treatment options include:

- Rest
- Medications (Nitroglycerine, β-blockers, calcium channel blockers),
- Percutaneous transluminal coronary angioplasty (PTCA), or
- Coronary artery bypass graft surgery (CABG).

Myocardial Infarction (Heart Attack)

Myocardial Infarction is a condition resulting from decreased blood and oxygen supply to the heart, causing cell death. The major cause is sudden blockage of coronary arteries.

Coronary arteries are blood vessels that supply the heart muscle with blood and oxygen. Blockage of a coronary artery deprives the heart muscle of blood and oxygen, causing injury to the heart muscle causing chest pain and chest pressure sensation. If blood flow is not restored to the heart muscle within 20 to 40 minutes, irreversible death of the heart muscle will begin to occur. Muscle continues to die for six to eight hours at which time the heart attack usually is "complete." The dead heart muscle is eventually replaced by scar tissue.

Etiology

Myocardial infarction (MI) is the irreversible death (necrosis) of heart muscle which usually results from an imbalance in oxygen supply and demand, which is most often caused by plaque rupture with thrombus formation in an epicardial coronary artery, resulting in an acute reduction of blood supply to a portion of the myocardium. Acute MI is the single most common cause of death in industrialized nations. Among fatal cases, nearly half of the patients die before reaching the hospital.

Major risk factors include previous cardiovascular disease (such as angina, a previous heart attack or stroke), older age (especially men over 40 and women over 50), tobacco smoking, high blood levels of certain lipids (triglycerides, low-density lipoprotein or "bad cholesterol") and low levels of high density lipoprotein (HDL, "good cholesterol"), diabetes, high blood pressure, obesity, chronic renal failure, heart failure, excessive alcohol consumption, the abuse of certain drugs (such as cocaine and methamphetamine), and chronic high stress level.

Pathogenesis

1. Myocardial Ischaemia: Myocardial ischaemia is brought about by one or more of the following mechanisms:
   (i) Diminised coronary blood flow e.g. in coronary artery disease shock.
   (ii) Increased myocardial demand e.g. In exercise, emotions.
   (iii) Hypertrophy of the heart without simultaneous increase of coronary blood flow e.g. in hypertension, valvular heart disease.
2. Role of platelets: Rupture of an atherosclerotic plaque exposes the subendothelial collagen to platelets which undergo aggregation, activation and release reaction. These events contribute to the build-up of the platelet mass that may give rise to emboli or initiate thrombosis.
3. Acute plaque rupture: In general, slowly developing coronary ischaemia from stenosis coronary atherosclerosis of high grade may not cause acute MI but continue to produce episodes of angina pectoris. But acute complications in coronary atherosclerotic plaques in the form of superimposed coronary thrombosis due to plaque rupture and plaque haemorrhage is frequently encountered in cases of acute MI:
   (i) Superimposed coronary thrombosis due to disruption of plaque is seen in about half the cases of acute MI. Infusion of intracoronary fibrinolysins in the first half an hour of development of acute MI in such cases restores blood flow. Development of acute MI in such cases restores blood flow in the blocked vessel in majority of cases.
   (ii) Intramural haemorrhage is found in about one third cases of acute MI.
4. Non-atherosclerotic causes: About 10% cases of acute MI are caused by non-atherosclerotic factors such as coronary vasospasm, arteritis, coronary l stenosis embolism, thrombotic diseases, trauma and outside compression as already described.

The location of an MI is determined by the site of the occlusion and by the anatomy of the coronary circulation. Occlusion of the left anterior descending coronary artery typically causes an infarct in the anterior and apical areas of the left ventricle and adjacent interventricular septum. Occlusion of the right coronary artery is responsible for most infarcts involving the posterior and basal portions of the left ventricle. The underlying anatomy of the coronary circulation also has a significant influence on the location of the infarct. For example, occlusion of the right coronary artery would have different consequences in an individual whose posterior ventricle was supplied by branches of the right coronary than in a person whose posterior wall was supplied by branches of the circumflex coronary artery.

Signs and Symptoms

Patients with typical MI may have the following symptoms in the days or even weeks preceding the event: Fatigue, Chest discomfort, Malaise.

Typical chest pain in acute MI has the following characteristics:

- Intense and unremitting for 30-60 minutes.
- Substernal, and often radiates upto the neck, shoulder, and jaw, and down the left arm.

- Usually described as a substernal pressure sensation that also may be characterized as squeezing, aching, burning, or even sharp.
- In some patients, the symptom is epigastric, with a feeling of indigestion or of fullness and gas.

Other symptoms of myocardial infarction include the following:

- Anxiety, commonly described as a sense of impending doom.
- Pain or discomfort in areas of the body, including the arms, left shoulder, back, neck, jaw, or stomach.
- Light-headedness, with or without syncope.
- Cough.
- Nausea, with or without vomiting.
- Profuse sweating.
- Shortness of breath.
- Wheezing.
- Rapid or irregular heart rate.
- Fullness, indigestion, or choking feeling.

Treatment

The primary goal of the treatment is to first open the blocked artery and restore blood flow to the heart muscle. This process is called reperfusion. As the reperfusion takes place, the patient is slowly relieved from the pain. The early reperfusion i.e. within 4-6 hours of the heart attack can not only prevent further damage to the heart but also preserves the pumping action of the heart. The damage to the pumping action of the heart develops heart failure, decreased ability to exercise, and abnormal heart rhythms.

Emergency agents: Emergency agents are used in the process of reperfusion of the heart muscle. These agents basically help in relieving the severe heart pain, cause Vasodilatation to open the blocked artery, restore the oxygen supply and prevent the further damage of the heart muscle. These agents are morphine, oxygen, nitroglycerine, aspirin.

Anti-platelet agents: Anti-platelet medications prevent formation of blood clots in the arteries. In NSAID, aspirin inhibits cyclooxygenase-1 enzyme and thus prevents blood clotting by blocking the production of thromboxane A-2 by platelets, the chemical that causes platelets to clump. In addition to thromboxane A-2, platelets also produce adenosine diphosphate (ADP), which when acts on its receptor causes clumping of the platelets. The thienopyridines, clopidogrel, block the ADP receptor thus preventing the platelets from clumping.

Anti-coagulants: Anti-coagulant medications prevent growth of blood clots in the arteries. Anti-coagulants such as intravenous or subcutaneous heparin, subcutaneous low molecular weight heparin, and oral warfarin, prevent the formation of blood clots either by inhibiting the production of clotting factors or by interfering with the action of the clotting factors. e.g. Enoxaparin.

Clot-dissolving medications: Fibrinolytic or thrombolytic agents are known as clot dissolving agents used to open blocked arteries and dissolve the existing clots. Intravenous administration of clot-dissolving drugs such as tissue plasminogen activator (TPA) or TNK can open upto 80% of acutely blocked coronary arteries. Drugs such as streptokinase can be used for breaking up or dissolving the clots,

by converting the intrinsic plasminogen present in the fibrin clot to its active agent form plasmin.

β-adrenergic receptor blockers: β-blockers act by decreasing the workload of the heart. Decrease in the workload decreases the demand for oxygen by the heart and limits the amount of damage to the heart muscle. Long-term administration of β-blockers following a heart attack has been shown to improve survival and reduce the risk of future heart attacks. Esmolol, Propranolol, Atenolol, Timolol.

Arteriosclerosis

Arteriosclerosis can occur when arteries grow thick and stiff and restrict blood flow to organs and tissues in the body. This gradual process, also known as hardening of the arteries, weakens arteries and can develop in various organs, most commonly the heart.

Arteries circulate blood throughout the body, but when plaque, fat, cholesterol and other cellular waste deposite on artery walls, arteriosclerosis can develop.

Arteriosclerosis can develop into atherosclerosis. This condition can cause heart disease, strokes, circulation problems in the arms and legs, aneurysms that can cause life-threatening internal bleeding and chronic renal failure.

Causes

A number of factors can contribute to arteriosclerosis:

- High cholesterol
- High blood pressure
- Insulin resistance or diabetes
- Obesity
- Smoking or use of other tobacco products

Risk factors that contribute to arteriosclerosis include:

Family history: People with a family history of heart disease or arteriosclerosis are at higher risk for the condition.

Symptoms

- Chest pain or angina.
- Pain in leg, arm, and anywhere else that has a blocked artery.
- Shortness of breath.
- Fatigue.
- Confusion, which occurs if the blockage affects circulation to brain.
- Muscle weakness in legs from lack of circulation.

Pathophysiology

The lesions of arteriosclerosis begin as the intima (innermost layer of blood vessel wall) of the arterial wall start to fill up with the deposition of cellular wastes. As these start to mature, they can take different forms of arteriosclerosis. All are linked through common features such as the stiffening of arterial vessels, thickening of arterial walls and degenerative nature of the disease.

- Arteriolosclerosis, unlike atherosclerosis, is a sclerosis that only affects small arteries and arterioles, which carry important nutrients and blood to the cells.
- Atherosclerosis is the narrowing of arteries because of deposition of plaque, usually made up of cholesterol, fatty substances, cellular waste products, calcium and fibrin, inside the arteries. This affects large and medium-sized arteries; however, its positioning varies person to person.
- Monckeberg's arteriosclerosis or medial calcific sclerosis is seen mostly in the old

age patients, commonly in arteries of the extremities.

- Hyperplastic: Hyperplastic arteriosclerosis refers to the type of arteriosclerosis that affects large and medium-sized arteries.
- Hyaline type: Hyaline arteriosclerosis, also referred to as arterial hyalinosis and arteriolar hyalinosis, refers to lesions that are caused by the deposition of homogenous hyaline in the small arteries and arterioles.

Arteriosclerosis subtypes: Pathologically, there are two subtypes of arteriosclerosis:

- Hyperplastic type
- Hyaline type

A subclassification of arteriolosclerosis is the fibromuscular intimal thickening. There is typically hyalinosis or deposition of hyaline protein in these lesions as well. This includes the categories like:-

- Transplant related arteriopathy or arterial damage.
- Restenosis lesions that are seen after balloon angioplasty or stenting of the heart's coronary blood vessels.
- Non-specific intimal thickening as occurs in temporal arteries (arteries around the forehead and temples) with aging.

Transplant arteriopathy is intimal enlargement without atherosclerotic changes seen in the walls. Transplant arteriopathy affects large and small muscular arteries and veins as well. It commonly causes inflammation in the 1 or more of the 3 layers in the blood vessel walls.

Usually, the intima is affected more than the media or adventitia, but all three layers may be affected. After inflammation there is fibrosis and finally calcification and thrombosis may occur.

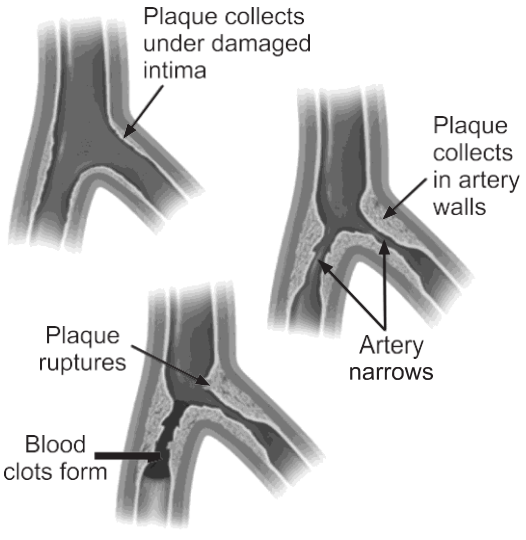

Fig. 4.4 : Arteriosclerosis

Diagnosis

Blood test: Blood tests check the levels of certain fats, cholesterol, sugar and protein in the blood that could indicate heart conditions.

CT scan: X-rays and computers are used to create images of the aorta, heart and blood vessels. This provides a more detailed picture than an ultrasound.

Electrocardiogram (EKG): This test measures the electrical activity of the heart and can help to determine if parts of the heart are enlarged, overworked or damaged.

Stress testing: Used along with an EKG, the test can show changes to the heart's rate, rhythm or electrical activity as well as blood pressure.

Ultrasound: An ultrasound device can measure blood pressure on various points of arm or leg, which will help to determine any blockages and how quickly blood flows through arteries.

Treatment

Treatment for arteriosclerosis includes a healthy diet, exercise and medication to control or possibly reverse condition.

Medications to treat arteriosclerosis are based on the location of enlarged blood vessels and other underlying conditions may include.

- Cholesterol medications can protect heart arteries.
- Aspirin can prevent platelets from forming blood clots.
- β-blocker medications can reduce blood pressure and heart rate and diminish chest pains, the risk of heart attack and irregular heart rhythm.
- Angiotensin-converting enzyme (ACE) inhibitors can lower blood pressure and lower the possibility of heart attack.
- Calcium channel blockers and diuretics (water pills) can reduce blood pressure.
- A clot-busting drug may dissolve blood clots.

Complications

If arteriosclerosis is not diagnosed and treated, it could develop into atherosclerosis and cause serious health problems, including:

- Coronary artery disease: Narrowed arteries near the heart may lead to chest pain, heart attack or heart failure.
- Peripheral artery disease: Narrowed arties in the arms or legs may cause circulation problems that make it difficult to feel heat and cold, and cause gangrene that can lead to limb amputation.
- Carotid artery disease: Narrowed arteries near the brain may cause transient ischemic attack (TIA) or stroke.
- Aneurysms: A bulge in the wall of an artery, if it bursts, can cause a slow leak or life-threatening internal bleeding.
- Chronic renal failure: Narrow arteries near the kidneys can prevent effective kidney function.

Chapter...5

RESPIRATORY SYSTEM

5.1 INTRODUCTION TO RESPIRATORY SYSTEM

The cells of the human body require a constant stream of oxygen to stay alive. The respiratory system provides oxygen to the body's cells while removing carbon dioxide, a waste product that can be lethal if allowed to accumulate. There are 3 major parts of the respiratory system: the airway, the lungs, and the muscles of respiration. The airway, which includes the nose, mouth, pharynx, larynx, trachea, bronchi, and bronchioles, carries air between the lungs and the body's exterior. The lungs act as the functional units of the respiratory system by passing oxygen into the body and carbon dioxide out of the body. Finally, the muscles of respiration, including the diaphragm and intercostal muscles, work together to act as a pump, pushing air into and out of the lungs during breathing.

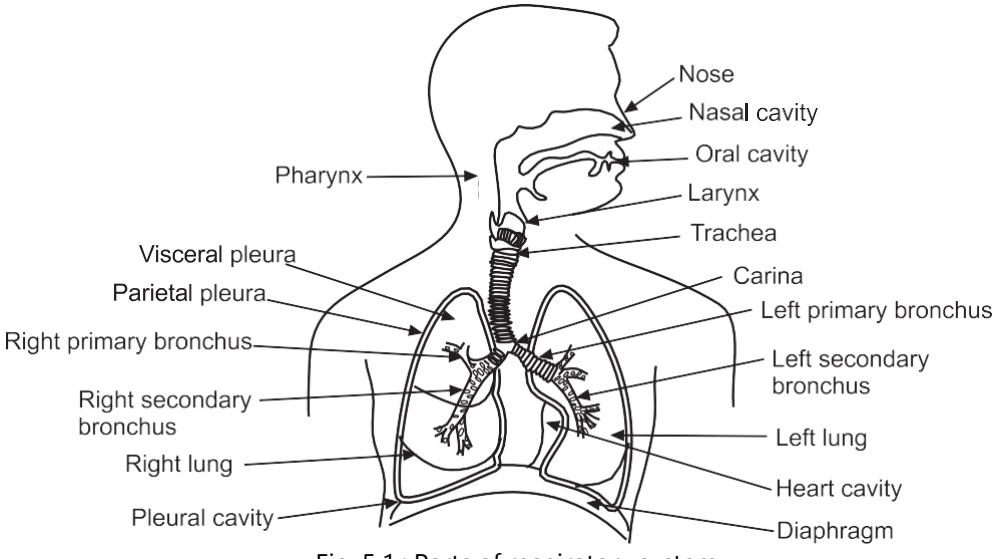

Fig. 5.1 : Parts of respiratory system

Nose and Nasal Cavity: The nose and nasal cavity form the main external opening for the respiratory system and are the first section of the body's airway, the respiratory tract through which air moves. The nose is a structure of the face, made of cartilage, bone, muscle and skin that supports and protects the anterior portion of the nasal cavity. The nasal cavity is a hollow space within the nose and skull that is lined with hairs and mucus membrane. The function of the nasal cavity is to warm, moisturize, and filter air entering the body before it reaches the lungs. Hairs and mucus lining the nasal

cavity help to trap dust, mold, pollen and other environmental contaminants before they can reach the inner portions of the body.

Mouth: The mouth is the secondary external opening for the respiratory tract. Mostly, normal breathing takes place through the nasal cavity, but the oral cavity can be used as supplement or replace the nasal cavity's functions when needed. Because the pathway of air entering the body from the mouth is shorter than the pathway for air entering from the nose, the mouth does not warm and moisturize the air entering the lungs.

The mouth also lacks the hairs and sticky mucus that filter air passing through the nasal cavity. The one advantage of breathing through the mouth is that its shorter distance and larger diameter allows more air to quickly enter the body.

Pharynx: The pharynx, also known as the throat, is a muscular funnel that extends from the posterior end of the nasal cavity to the superior end of the esophagus and larynx. The pharynx is divided into 3 regions: the nasopharynx, oropharynx, and laryngopharynx. The nasopharynx is the superior region of the pharynx found in the posterior of the nasal cavity. Inhaled air from the nasal cavity passes into the nasopharynx and descends through the oropharynx, located in the posterior of the oral cavity. Air inhaled through the oral cavity enters the pharynx at the oropharynx. The inhaled air then descends into the laryngopharynx, where it is diverted into the opening of the larynx by the epiglottis. The epiglottis is a flap of elastic cartilage that acts as a switch between the trachea and the esophagus. Because the pharynx is also used to swallow food, the epiglottis ensures that air passes into the trachea by covering the opening to the esophagus. During the process of swallowing, the epiglottis moves to cover the trachea to ensure that food enters the esophagus and to prevent choking.

Larynx: The larynx, also known as the voice box, is a short section of the airway that connects the laryngopharynx and the trachea. The larynx is located in the anterior portion of the neck, just inferior to the hyoid bone and superior to the trachea. Several cartilage structures make up the larynx and give it its structure. The epiglottis is one of the cartilage pieces of the larynx and serves as the cover of the larynx during swallowing. Inferior to the epiglottis is the thyroid cartilage, which is often referred to as the Adam's apple as it is most commonly enlarged and visible in adult males. The thyroid holds open the anterior end of the larynx and protects the vocal folds. Inferior to the thyroid cartilage is the ring shaped cricoid cartilage which holds the larynx open and supports its posterior end.

Trachea: The trachea connects the larynx to the bronchi and allows air to pass through the neck and into the thorax. The rings of cartilage making up the trachea allow it to remain open to air at all times. The open end of the cartilage rings faces posteriorly toward the esophagus, allowing the esophagus to expand into the space occupied by the trachea to accommodate masses of food moving through the esophagus.

The main function of the trachea is to provide a clear airway for air to enter and exit the lungs. In addition, the epithelium lining the trachea produces mucus that traps dust and other contaminants and prevents it

from reaching the lungs. Cilia on the surface of the epithelial cells move the mucus superiorly toward the pharynx where it can be swallowed and digested in the gastrointestinal tract.

Bronchi and Bronchioles: At the inferior end of the trachea, the airway splits into left and right branches known as the primary bronchi. The left and right bronchi run into each lung before branching off into smaller secondary bronchi. The secondary bronchi carry air into the lobes of the lungs two in the left lung and three in the right lung. The secondary bronchi in turn split into many smaller tertiary bronchi within each lobe. The tertiary bronchi split into many smaller bronchioles that spread throughout the lungs. Each bronchiole further splits into many smaller branches less than a millimeter in diameter called terminal bronchioles. Finally, the millions of tiny terminal bronchioles conduct air to the alveoli of the lungs.

The main function of the bronchi and bronchioles is to carry air from the trachea into the lungs. Smooth muscle tissue in their walls helps to regulate airflow into the lungs. When greater volumes of air are required by the body, such as during exercise, the smooth muscle relaxes to dilate the bronchi and bronchioles. The dilated airway provides less resistance to airflow and allows more air to pass into and out of the lungs. The smooth muscle fibers are able to contract during rest to prevent hyperventilation. The bronchi and bronchioles also use the mucus and cilia of their epithelial lining to trap and move dust and other contaminants away from the lungs.

Lungs: The lungs are a pair of large, spongy organs found in the thorax, lateral to the heart and superior to the diaphragm. Each lung is surrounded by a pleural membrane that provides the lung with space to expand as well as a negative pressure space relative to the body's exterior. The negative pressure allows the lungs to passively fill with air as they relax. The left and right lungs are slightly different in size and shape due to the heart pointing to the left side of the body. The left lung is therefore slightly smaller than the right lung.

The interior of the lungs is made up of spongy tissues containing many capillaries and around 30 million tiny sacs known as alveoli. The alveoli are cup-shaped structures found at the end of the terminal bronchioles and surrounded by capillaries. The alveoli are lined with thin simple squamous epithelium that allows air entering the alveoli to exchange its gases with the blood passing through the capillaries.

Muscles of Respiration

Surrounding the lungs are sets of muscles that are able to cause air to be inhaled or exhaled from the lungs. The principal muscle of respiration in the human body is the diaphragm, a thin sheet of skeletal muscle that forms the floor of the thorax. When the diaphragm contracts, it moves inferiorly a few inches into the abdominal cavity, expanding the space within the thoracic cavity and pulling air into the lungs. Relaxation of the diaphragm allows air to flow back out the lungs during exhalation.

Between the ribs are many small intercostal muscles that assist the diaphragm with expanding and compressing the lungs. These muscles are divided into two groups: the internal intercostal muscles and the external intercostal muscles.

The internal intercostal muscles are the deeper set of muscles and depress the ribs to compress the thoracic cavity and force air to be exhaled from the lungs. The external intercostals are found superficial to the internal intercostals and function to elevate the ribs, expanding the volume of the thoracic cavity and causing air to be inhaled into the lungs.

Physiology of the Respiratory System

Pulmonary Ventilation:

Pulmonary ventilation is the process of moving air into and out of the lungs to facilitate gas exchange. The respiratory system uses both a negative pressure system and the contraction of muscles to achieve pulmonary ventilation. The negative pressure system of the respiratory system involves the establishment of a negative pressure gradient between the alveoli and the external atmosphere. The pleural membrane seals the lungs and maintains the lungs at a pressure slightly below that of the atmosphere when the lungs are at rest. This results in air following the pressure gradient and passively filling the lungs at rest. As the lungs fill with air, the pressure within the lungs rises until it matches the atmospheric pressure. At this point, more air can be inhaled by the contraction of the diaphragm and the external intercostal muscles, increasing the volume of the thorax and reducing the pressure of the lungs below that of the atmosphere again.

To exhale air, the diaphragm and external intercostal muscles relax while the internal intercostal muscles contract to reduce the volume of the thorax and increase the pressure within the thoracic cavity. The pressure gradient is now reversed, resulting in the exhalation of air until the pressures inside the lungs and outside of the body are equal. At this point, the elastic nature of the lungs causes them to recoil back to their resting volume, restoring the negative pressure gradient present during inhalation.

External Respiration:

External respiration is the exchange of gases between the air filling the alveoli and the blood in the capillaries surrounding the walls of the alveoli. Air entering the lungs from the atmosphere has a higher partial pressure of oxygen and a lower partial pressure of carbon dioxide than does the blood in the capillaries. The difference in partial pressures causes the gases to diffuse passively along their pressure gradients from high to low pressure through the simple squamous epithelium lining of the alveoli. The net result of external respiration is the movement of oxygen from the air into the blood and the movement of carbon dioxide from the blood into the air. The oxygen can then be transported to the body's tissues while carbon dioxide is released into the atmosphere during exhalation.

Internal Respiration:

Internal respiration is the exchange of gases between the blood in capillaries and the tissues of the body. Capillary blood has a higher partial pressure of oxygen and a lower partial pressure of carbon dioxide than the tissues through which it passes. The difference in partial pressures leads to the diffusion of gases along their pressure gradients from high to low pressure through the endothelium lining of the capillaries. The net result of internal respiration is the diffusion of oxygen into the tissues and the diffusion of carbon dioxide into the blood.

5.2 ASTHMA

Asthma is a chronic inflammatory disorder of the airways associated with variable (usually reversible) airflow obstruction and enhanced bronchial hyper responsiveness to a variety of stimuli.

Causes

Asthma is characterized by excessive sensitivity of the lungs to various stimuli. There is increasing evidence to suggest genetics play an important role in the etiology of the disease.

Apparently, environmental factors interact with inherited factors to increase the risk of asthma. Environmental triggers range from viral infections and allergies, to irritating gases and particles in the air. Each person reacts differently to the factors that may trigger asthma.

Physiological factors that may trigger or increase asthma symptoms include:

- Viral upper respiratory infections.
- Heavy exercise.
- Untreated conditions such as rhinitis, sinusitis, and gastroesophageal reflux (GERD).
- Drugs: NSAIDS such as aspirin.
- Ibuprofen, acetaminophen, naproxen sodium and Ketoprophen; statin drugs (cholesterol reducing medications) and other anti-inflammatory drugs.
- Stress and strong emotions.
- Menstrual cycle/hormone changes.

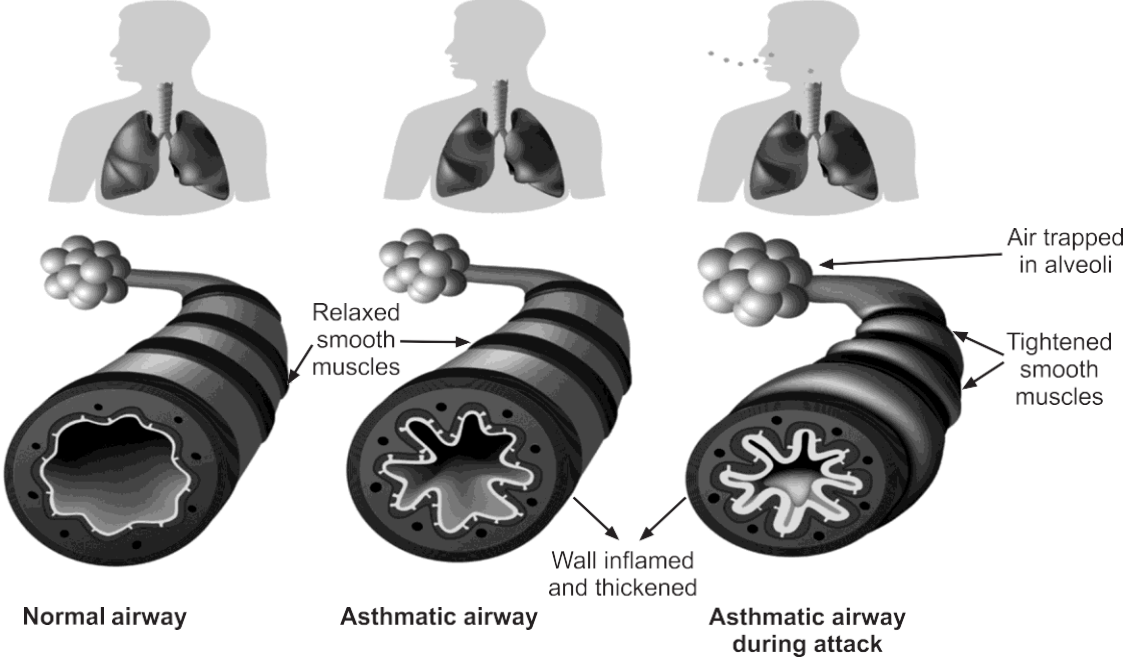

Fig. 5.2 : Normal and inflamed airway wall in asthma

Common indoor environmental irritants and allergens that can trigger asthma symptoms or an asthma attack, include:

- Pet fur or feathers, pet urine, saliva and dander.
- House-dust mites.
- Cockroach waste and decomposed body of dead animals.
- Mold and mildew spores. (leaking plumbing, leaking roof etc.)
- Tobacco smoke and wood smoke.
- Perfumes, hairsprays, scented lotions, and cologne.
- Air fresheners, incense sticks and scented candles.
- Cleaning solutions, pesticides and paint fumes.

Common outdoor environmental irritants and allergens that can trigger asthma symptoms or an asthma attack, include:

- Pollen from trees, grasses and weeds.
- Mold and mildew spores. (wet rotting leaves on the ground)
- Changes in humidity (high humidity).
- Exposure to cold air or hot humid air.
- Industrial emissions, vehicle or truck exhaust, and other air pollutants such as coal dust.
- Ozone: [O_3] is a highly reactive form of oxygen that results from sunlight mixing with hydrocarbons (also called volatile organic compounds) and nitrogen oxides released in fuel combustion)

Food Allergy: Food allergies involve the body's immune system reacting to proteins found in food. The body treats these proteins the same way as it would be a disease. Different people react to different types of food although some types have a greater chance of becoming a trigger. Between 2% to 10% of people are affected by food allergies, with a greater percentage occurring in children. Reactions can occur within a few minutes or over a period of several hours. Undiagnosed and untreated, severe attacks can be fatal.

Based upon causes, the asthma is divided into two types:

a. Intrinsic asthma: Usually develop beyond age 40 and have many causes other than exposure to allergens.

b. Extrinsic asthma: Most commonly develop in childhood and caused by exposure to definite allergens.

Classification of Asthma

Current classification of asthma is based on clinical severity. This allows asthma sufferers and clinicians to better manage treatment choices and clinical outcomes.

1. Mild Intermittent Asthma: It occurs in people with daytime symptoms that occur no more frequently than twice a week and night-time symptoms that occur no more than twice a month. These people are usually asymptomatic with normal Peak Expiratory Flow Rate between exacerbations. Exacerbations vary in intensity but are usually brief, lasting only hours to days. They do not take daily medications for long term control, only short for quick relief.

2. Mild Persistent Asthma: It is characterized by daytime symptoms that occur more than twice a week but less than once a day with night-time symptoms more frequent than twice a month. These people are asymptomatic but have abnormal pulmonary function tests. Exacerbations begin to limit their activity. They usually take one medication on a daily basis for long term control. Using medications for quick relief on a daily basis indicates a need for additional long term therapy.

3. Moderate Persistent Asthma: It occurs in people who have daytime symptoms every day and night-time symptoms more than once a week. Exacerbations limit their activity and occur at least twice a week, and may last for several days. These individuals take one or two long term control medications. Also using medications for quick relief on a daily basis indicates a need for additional long term therapy.

4. Severe Persistent Asthma: It is characterized by continual daytime symptoms and frequent night-time symptoms. They experience limited physical activity and exacerbations are frequent. These people often take two medications daily for long term control. Also using medications for quick relief on a daily basis indicates a need for additional long term therapy.

Pathophysiology

The various common allergens are pollens, dust, mites, some food material and certain drugs which precipitate the asthmatic attack. The allergens upon exposure stimulate production of IgE which further bind to mast cells. Upon re-exposure to same allergen, the said allergens readily bind to IgE and result in degranulation of mast cell to release certain inflammatory mediators such as histamine, leukotriens, prostaglandins etc.

In a response to above changes, WBC's migrate into the area to engulf the allergens. The phagocyic reaction causes release of basic proteins which are lytic agents for tissue and further promote inflammation.

With exposure to a trigger, a cascade of cellular responses cause:

1. Increased production of thick tenacious mucus with impaired mucocilary function.
2. Mucosal swelling due to increased vascular permeability and vascular congestion.
3. Bronchial smooth muscle contraction
4. These changes cause bronchial hyper responsiveness and obstruction. Airway obstruction increases resistance to air flow and decreases flow rates, including expiratory flow. Impaired expiration causes hyperinflation distal to the obstruction and increases the work of breathing. These changes are not uniform throughout the lungs but regional. Continued air trapping causes increased intrapleural and alveolar gas pressures resulting in decreased perfusion of the alveoli, the result is hypoxia.
5. Late Asthma Response occurs in cases of significant allergen exposure. The symptoms can recur 4 to 12 hours after the initial attack due to persistent cellular activation. It can be more severe than the initial attack.
6. Untreated inflammation can cause long term airway damage that is irreversible (airway remodelling).

Symptoms

Asthma affects the airways, causing them to tighten, become inflamed or to fill with mucus. Asthma symptoms can range from mild to severe. Most people will only experience occasional symptoms, although a few people will have problems most of the time and include:

- Coughing, especially at night, during exercise or when laughing.
- Shortness of breath.
- Chest tightness.
- Wheezing (a whistling or squeaky sound in chest when breathe, especially while exhaling).

- Any asthma symptom is serious and can become deadly if left untreated.
- Symptoms may be triggered by exposure to an allergen (such as ragweed, pollen and pet hair or dust mites), irritants in the air (such as smoke, chemical fumes or strong odours) or extreme weather conditions.

Diagnosis

Exacerbations of asthma symptoms equates to an individual's control of their asthma. To prevent long term complications of airway remodeling, early detection with an accurate diagnosis is needed to exclude other diseases and causes for difficulty breathing. For example, Chronic obstructive pulmonary disease, Congestive heart failure, Pulmonary embolisms or mechanical obstruction (from tumors).

Asthma diagnosis is based on several factors, including a detailed medical history, a physical exam, symptoms and overall health and test results.

Medical History and Physical Examination:

The first step in diagnosing asthma is to look for signs of asthma or allergies. These signs include wheezing (high pitched whistling sounds when breathe out) and a runny nose or swollen nasal passages, and allergic skin conditions (such as eczema).

Lung Function Tests:

Lung function tests are asthma tests that assess lung function. The two most common lung function tests used to diagnose asthma are spirometry and methacholine challenge tests.

Asthma and COPD (Chronic Obstructive Pulmonary Disease) cause problems by narrowing the bronchial tubes (or airways), resulting in shortness of breath. Narrowed airways are difficult to breathe through. The greater the narrowing, the more difficult breathing becomes.

Spirometry:

It is a simple breathing test which is of great value for measuring exactly how much bronchial tubes have narrowed. Spirometer measures the amount (volume) and speed (flow) of air that can be inhaled and exhaled, giving an indication of how well lungs are performing. It is often used to determine the amount of airway obstruction. This enables to make decisions about lung condition and to plan the best treatment for asthma.

Methacholine Challenge Test:

This lung function test for asthma is more commonly used in adults than in children. It might be performed if symptoms and screening spirometry do not clearly or convincingly establish a diagnosis of asthma. Methacholine is an agent that, when inhaled, causes the airways to spasm (contract involuntarily) and narrow if asthma is present. A methacholine challenge test is a type of bronchoprovocation test, which measures lung function after exposure to factors that commonly trigger wheezing and other asthma symptoms.

Purpose of the Methacholine Challenge Test is:

- To identify bronchial hyper responsiveness in people who have normal results on standard pulmonary function tests.
- To diagnose mild asthma in some atypical cases, such as persistent cough
- To diagnose occupational (workplace) asthma caused by certain dusts or chemicals.

- To help determine the risk of developing asthma, evaluate asthma severity and assess response to asthma treatment.
- To evaluate the effectiveness of asthma medications and determine the risk for developing asthma in the future.

Exhaled Nitric Oxide Test:

It is a quick and easy way to measure inflammation (swelling) in the bronchial tubes of the lungs. During inflammation, higher than normal levels of nitric oxide (NO) are released from epithelial cells of the bronchial wall. The concentration of NO in exhaled breath, or fractional exhaled nitric oxide (FeNO), can help to identify airway inflammation, and thereby support a diagnosis of asthma when other objective evidence is lacking.

Allergy Tests:

Allergy skin tests are vital in finding out whether asthma is due to inhalant allergens. Drops of a number of allergen extracts are placed on the skin (usually the forearm) and the skin is pricked lightly through the drops. A positive reaction will cause some itching and a bump at the site within 10 minutes.

A blood test for allergic antibodies to various allergens is an alternative but in some cases can be less likely to detect an allergy than skin tests.

Prevention and Treatment

Prevention of exposure to known triggers is warranted. Hyposensitization may be beneficial if the asthma has an allergic mechanism, in such cases:

- Identify and avoid asthma triggers.
- Identify and treat attacks early and monitor breathing.
- Other measures include dust free house.
- Intake of selective type of food.
- Avoid exposure to extreme cold condition.
- Get vaccinated for influenza and pneumonia.

Pharmacological Treatment:

Drug therapy depends on frequency and severity of attacks. The bronchodilators are often considered rescue inhalers, while the other medications are considered more prophylactic or therapeutic medications.

1. Bronchodilators (Sympathomimetics): The mechanism of action for sympathomimetic bronchodilators is to bind the receptors in airway smooth muscle thus causing bronchodilation and increased ciliary beat frequency. e.g. Albuterol, Salbutamol and Terbutaline.

2. Anticholinergic agents: The effect of anticholinergic bronchodilators are bronchodilation through inhibition of bronchoconstriction secondary to blockade of the effects of acetylcholine. The mechanism of action for anticholinergic bronchodilators is non-selective antagonism of muscarinic receptors leads to down regulation of cGMP which results in bronchodilation. Additional acetylcholine is released in response, thus overcoming the effect in smooth muscle. e.g. Ipratropium, Aclidinium.

3. Corticosteroids: The effect of inhaled corticosteroids is reduced airway inflammation. Overall airway bronchial hyper-responsiveness decreases. Improved asthma control and increased sensitivity of β-receptors in smooth muscle. The mechanism of action for inhaled corticosteroids is to suppress granuloma formation, reduce arachidonic acid metabolism, up-regulate β-adrenergic receptors on leukocytes, and decrease

synthesis of prostaglandins and leukotrienes.

e.g. Beclomethasone, Flunisolide, Triamcinolone.

4. Biologic Response Modifiers (Monoclonal Antibodies): The effect of Biologic Response Modifiers is decreased frequency of allergen induced asthma exacerbations. The mechanism of action for Biologic Response Modifiers is, when the monoclonal antibody binds to IgE, interfers with mast cell binding. This prevents mast cell degranulation and release of inflammatory mediators. Cytokine release seen in the late phase of an allergic reaction is also prevented through blocking the receptors on dendritic cells, epithelial cells, eosinophils, monocytes and platelets. E.g. Omalizumab.

5. Leukotriene Receptor Antagonists: The effect of leukotriene receptor antagonists is prevention of allergen induced bronchoconstriction. The mechanism of action for leukotriene receptor antagonists is antagonism of cysteinyl-leukotriene receptors, thus preventing histamine release. e.g. Montelukast and Zafirlukast.

6. Mast Cell Stabilizers: The effect of mast cell stabilizers is prevention of bronchocon-striction and inflammation. The mechanism of action of mast cell stabilizers is to antagonize mast cell degranulation to prevent the release of histamine and other mediators of allergic reaction. Agents do not interfere with IgE. The anti-inflammatory mechanism is unknown. e.g. Cromolyn and Nedocromil

7. Methylxanthene Derivatives: The mechanism of action for methylxanthene derivatives is bronchodilation. The mechanisms of action include prostaglandin antagonism, stimulation of endogenous catecholamines, inhibition of calcium influx into smooth muscle (preventing muscle contraction), antagonism of adenosine receptors, and inhibition of release of mediators from leukocytes and mast cells. E.g. Theophylline.

5.3 CHRONIC OBSTRUCTIVE AIRWAYS DISEASES

Chronic Obstructive Airways Diseases (COPD) is a lung disease that includes —

1. Respiratory failure
2. Bronchitis
3. Emphysema

5.3.1 Respiratory Failure

Respiratory failure is inadequate gas exchange by the respiratory system, with the result that levels of arterial oxygen, carbon dioxide or both cannot be maintained within their normal ranges. A drop in blood oxygenation is known as hypoxemia; a rise in arterial carbon dioxide levels is called hypercapnia. The normal reference values are: oxygen PaO_2 more than 80 mmHg (11 kPa), and carbon dioxide $PaCO_2$ lesser than 45 mmHg (6.0 kPa). It is classified into type I or type II which relates to the absence or presence of hypercapnia respectively.

Hypoxemic respiratory failure (type I): It is characterized by an arterial oxygen tension (Pa O_2) lower than 60 mm Hg with a normal or low arterial carbon dioxide tension (Pa CO_2). This is the most common form of respiratory failure, and it can be associated with virtually all acute diseases of the lung, which generally involve fluid filling or collapse of alveolar units. Some examples

of type I respiratory failure is cardiogenic or non-cardiogenic pulmonary edema, pneumonia and pulmonary hemorrhage.

Hypercapnic respiratory failure (type II): It is characterized by a $PaCO_2$ higher than 50 mm Hg. Hypoxemia is common in patients with hypercapnic respiratory failure who are breathing room air. The pH depends on the level of bicarbonate, which, in turn, is dependent on the duration of hypercapnia. Common etiologies include drug overdose, neuromuscular disease, chest wall abnormalities, and severe airway disorders (e.g, asthma and chronic obstructive pulmonary disease).

Respiratory failure may be further classified as either acute or chronic.

Acute respiratory failure is characterized by life threatening derangements in arterial blood gases and acid-base status. The manifestations of chronic respiratory failure are less dramatic and may not be as readily apparent.

Acute hypercapnic respiratory failure develops over minutes to hours; therefore, pH is less than 7.3 (blood). Chronic respiratory failure develops over several days or longer, allowing time for renal compensation and an increase in bicarbonate concentration. Therefore, the pH usually is only slightly decreased.

Causes

Common causes of type I (hypoxemic) respiratory failure include the following:

- COPD
- Pneumonia
- Pulmonary edema
- Pulmonary fibrosis
- Asthma
- Pneumothorax
- Pulmonary embolism
- Pulmonary arterial hypertension
- Pneumoconiosis
- Granulomatous lung diseases
- Cyanotic congenital heart disease
- Bronchiectasis
- Acute respiratory distress syndrome (ARDS)
- Fat embolism syndrome
- Kyphoscoliosis
- Obesity

Common causes of type II (hypercapnic) respiratory failure include the following:

- COPD
- Severe asthma
- Drug overdose, poisonings
- Myasthenia gravis
- Polyneuropathy
- Poliomyelitis
- Primary muscle disorders
- Porphyria
- Cervical cordotomy
- Head and cervical cord injury
- Primary alveolar hypoventilation
- Obesity-hypoventilation syndrome
- Pulmonary edema
- ARDS (adult respiratory distress syndrome)
- Myxedema
- Tetanus

Symptoms

A majority of patients with respiratory failure are short of breath. Both low oxygen and high carbon dioxide can impair mental functions. Patient may become confused and disoriented and find it impossible to carry out their normal activities and work.

- Marked CO_2 excess can cause headaches and, in time, a semiconscious state, restlessness, anxiety, confusion, seizures, or even coma.
- Low blood oxygen causes bluish coloration in skin, fingertips and lips.
- Tachycardia and cardiac arrhythmias may result from hypoxaemia and acidosis.

- Polycythaemia is a complication of long-standing hypoxaemia.
- Corpulmonale (failure of the right side of the heart): Pulmonary hypertension is frequently present and may induce right ventricular failure, leading to hepatomegaly and peripheral oedema.
- Physical examination may show a patient who is breathing rapidly, is restless and has a rapid pulse.
- Lung disease may cause abnormal sounds; wheezing in asthma, "crackles" in obstructive lung disease.

A patient with ventilatory failure is prone to gasp (catch one's breathe with an open mouth, owing to pain or astonishment) for breath, and may use the neck muscles to help expand the chest.

Complications

- Pulmonary fibrosis.
- Collapsed lung (pneumothorax).
- Blood clots.
- Infections.
- Abnormal lung function.
- Memory, cognitive and emotional problems.

Diagnosis

The symptoms and signs of respiratory failure are not specific. Rather, they depend on what is causing the failure and on the patient's condition before it developed.

Physical Examination

It includes history of duration of fever, cough and sputum. Other signs include open mouth respiration, sweating, clicking of tongue etc. Headache, confusion and impaired consciousness may result from high levels of carbon dioxide. Cyanosis may result from low level of oxygen.

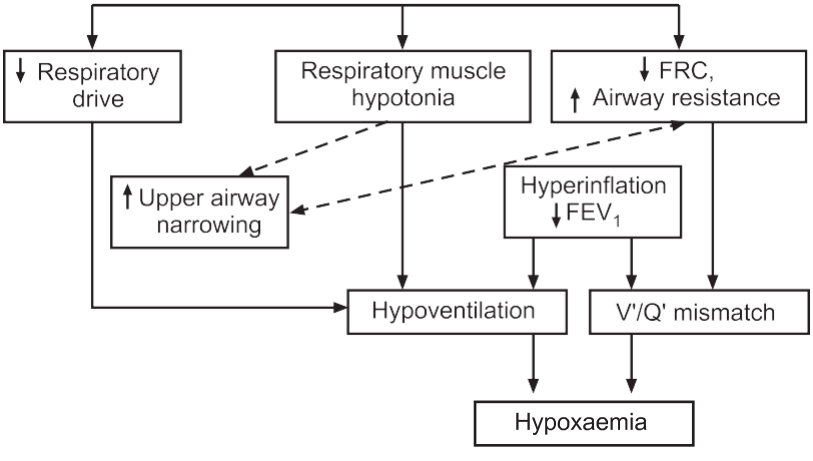

Fig. 5.3 : Pathophysiology of respiratory failure

Lab Tests:

Arterial blood gas analysis: A test using blood from an artery in wrist can measure oxygen level. A low level of oxygen or a high level of carbon dioxide in the blood (or both) is a possible sign of respiratory failure. Other types of blood tests can check for signs of infection or anemia.

Complete blood count (CBC): Anaemia can contribute to tissue hypoxia; polycythaemia may indicate chronic hypoxaemic respiratory failure.

Renal function tests and Liver function tests: It may provide clues to the etiology or identify complications associated with respiratory failure. Abnormalities in electrolytes such as potassium, magnesium, and phosphate may aggravate respiratory failure and other organ dysfunction.

Serum creatine kinase and troponin I: To help exclude recent myocardial infarction. Elevated creatine kinase may also indicate myositis.

Thyroid function tests: Hypothyroidism may cause chronic hypercapnic respiratory failure.

Spirometry: It is useful in the evaluation of chronic respiratory failure.

Heart tests: The signs and symptoms of respiratory failure are similar to those of certain heart problems.

Echocardiography: If a cardiac cause of acute respiratory failure is suspected.

Pulmonary function tests: These tests are useful in the evaluation of chronic respiratory failure.

ECG: To evaluate a cardiovascular cause; it may also detect dysrhythmias resulting from severe hypoxaemia or acidosis.

Right heart catheterization: It should be considered if there is uncertainty about cardiac function, adequacy of volume replacement, and systemic oxygen delivery.

Imaging Tests:

Chest X-ray: A chest X-ray can reveal, which parts of lungs have fluid in them and whether heart is enlarged.

Computerized tomography (CT): CT scans can provide detailed information about the structures within the heart and lungs.

Treatment

The goals of treatment for respiratory failure are to increase oxygenation and improve ventilation. Treatment depends on the severity of the respiratory failure and the cause. Acute respiratory failure treatment will address the underlying cause and include ventilation and oxygenation as needed. Exacerbation of chronic respiratory failure by infection may require hospitalization, and treatment may include oxygenation and ventilator support. Bronchodilators may improve airway patency.

Multiple options are available for the treatment of respiratory failure. Examples include:

- Antibiotics to prevent and treat respiratory infections.
- Bi-level positive airway pressure (BiPAP).
- Bronchodilators, like anticholinergics, such as tiotropium or β-agonists, such as Albuterol.
- Continuous positive airway pressure (CPAP).
- Inhaled steroid medications to decrease inflammation.
- Lung transplant, in rare cases.
- Mechanical ventilation, if oxygen therapy is not sufficient to increase blood oxygen levels.
- Oxygen therapy to increase blood oxygen levels.
- Tracheostomy, a hole made in the front of the neck to help breathing.
- A patient whose breathing remains very poor will require a ventilator to aid breathing.
- Suctioning the lungs through a small plastic tube passed through the nose, in order to remove secretions from the airways that the patient cannot cough up.

5.3.2 Bronchitis

Bronchitis is an inflammation of the lining of the bronchial tubes, the airways that connect the trachea (windpipe) to the lungs. Bronchitis is more specifically when the lining of the bronchial tubes becomes inflamed or infected. People with bronchitis breathe less air and oxygen into their lungs; they also have heavy mucus or phlegm forming in their airways.

Bronchitis can be acute or chronic. An acute medical condition occurs quickly and can cause severe symptoms, but it lasts only a short time (no longer than a few weeks). Acute bronchitis is most often caused by viruses that can infect the respiratory tract and attack the bronchial tubes. Infection by certain bacteria can also cause acute bronchitis. Most people have acute bronchitis at some point in their lives.

Chronic bronchitis can be mild to severe and is longer lasting from several months to years. With chronic bronchitis, the bronchial tubes continue to be inflamed (red and swollen), irritated, and produce excessive mucus over time. The most common cause of chronic bronchitis is smoking.

[I] Acute Bronchitis

Acute bronchitis is swelling and inflammation of the main air passages to the lungs. This swelling narrows the airways, making it harder to breath and causing other symptoms, such as a cough.

Causes

Acute bronchitis almost always follows a cold or flu-like infection. The infection is caused by viruses (influenza, parainfluenza, respiratory syncitial virus, rhinovirus and adenovirus). At first, it affects nose, sinuses, and throat. Then it spreads to the airways leading to lungs. Sometimes, bacteria (Mycoplasma, Streptococcus, Bordetella, Moraxella, Haemophilus and Chlamydia pneumoniae) also infect the airways. This is called a secondary infection. In addition, other agents such as tobacco smoke, chemicals and environmental air pollution may irritate the bronchi and cause acute bronchitis.

Symptoms

The symptoms of acute bronchitis may include:

- Chest discomfort.
- Cough that produces mucus; it may be clear or yellow green.
- Fatigue.
- Fever, usually low grade.
- Shortness of breath that gets worse with activity.
- Wheezing, in people with asthma.
- Even after acute bronchitis has cleared, a dry and nagging cough may remains for 1 to 4 weeks.

Diagnosis

In acute bronchitis, coughing usually lasts between 10 to 20 days. There are no specific tests for acute bronchitis. Certain tests may be required if there is recurrent or persistent cough that may suggest asthma or chronic bronchitis. Coughing for period of greater than four weeks may be due to whooping cough (pertussis).

Sputum tests: Sputum can be tested to see whooping cough (pertussis) or other illnesses that could be helped by antibiotics. Sputum can also be tested for signs of allergies.

- Chest X-ray
- Spirometry
- Pulse oximetry

Treatment

Acute bronchitis usually resolves its own within a couple of weeks, with complete healing of the airways and return to full function. Hence, the aim of treatment is to control symptoms.

Treatment of acute bronchitis involves:

- Getting adequate rest and fluid intake.
- Use of analgesic and antipyretic medications to relieve muscle aches, pains, headaches, and to reduce fever.
- Use of cough suppressants for a dry cough, but not for a productive cough.
- Use of expectorants for productive cough, to help clear the airways of mucus.
- Stopping smoking and avoidance of other airborne irritants.

Bronchitis usually results from a viral infection, so antibiotics are not effective.

Antibiotics: Sometimes bacteria may also infect the airways along with the virus.

Cough medicine: It is best not to suppress a cough that brings up mucus, because coughing helps to remove irritants from lungs and air passages.

Other medications: Use bronchodilator like ipratropium bromide, theophylline to open obstructed airways in people who have associated wheezing with their coughing or underlying asthma or COPD.

[II] Chronic Bronchitis

Chronic bronchitis is a long-term, often irreversible respiratory illness. It is a chronic inflammatory condition in the lungs that causes the respiratory passages to be swollen and irritation increases the mucus production and damages the lungs.

Causes

Bronchitis is considered "chronic" if symptoms continue for three months or longer. Bronchitis caused by allergies can also be classified as chronic bronchitis.

There are many causes of chronic bronchitis, but the main cause is cigarette smoke.

Many other inhaled irritants (for example, smog, industrial pollutants, toxic gases in the environment or workplace and solvents) can also result in chronic bronchitis.

Viral and bacterial infections that result in acute bronchitis may lead to chronic bronchitis if people have repeated attack with infectious agents. Also, underlying disease processes (for example, asthma, cystic fibrosis, immunodeficiency, congestive heart failure, familial genetic predisposition to bronchitis, and congenital or acquired dilation of the bronchioles) may cause chronic bronchitis to develop, but these are infrequent causes compared to cigarette smoking.

Risk Factors for Chronic Bronchitis

The major risk factor for individuals to develop chronic bronchitis are; Tobacco smoking and second - hand tobacco smoke exposure, repeated exposure to pollutants (especially airborne materials such as ammonia, sulphur dioxide, chlorine, bromine, hydrogen sulphide), dust, repeated attack of acute bronchitis or pneumonia, and gastric reflux (by inhalation of gastric contents).

Pathophysiology

The disease is caused by an interaction between noxious inhaled agents and host factors, such as genetic predisposition or

respiratory infections which cause injury or irritation to the respiratory epithelium of the walls and lumen of the bronchi and bronchioles. Chronic inflammation, edema, temporary bronchospasm, and increased production of mucus by goblet cells are the result. As a consequence, airflow into and out of the lungs is reduced, sometimes to a dramatic degree.

Most cases of chronic bronchitis are caused by smoking cigarettes or other tobacco products, although other examples of noxious agents include fumes from cleaning products and solvents, dust from occupational exposure, and air pollution. Ammonia, sulphur dioxide, chlorine, bromine, and hydrogen sulphide are especially harmful pollutants which are linked to respiratory diseases.

Chronic bronchitis must be distinguished from common allergies which also cause mucus hypersecretion and coughing fits. When chronic bronchitis progresses to include the pathologic changes of emphysema, it is often referred to as COPD.

Symptoms

- Bluish skin due to lack of oxygen (cyanosis).
- Breathing difficulty including wheezing and shortness of breath.
- Cough and sputum production are the most common symptoms; they usually last for at least 3 months and occur daily. The intensity of coughing and the amount and frequency of sputum production vary from patient to patient. Sputum may be clear, yellowish, greenish, or occasionally, blood-tinged.
- Fatigue.
- Fever may indicate a secondary viral or bacterial lung infection.
- Muscles around the ribs sink in as the child tries to breathe in (called intercostal retractions).
- Infant's nostrils get wide when breathing
- Rapid breathing (tachypnea).

In addition, symptoms of sore throat, muscle aches, nasal congestion, and headaches can accompany the major symptoms. Severe coughing may cause chest pain.

Diagnosis

Medical history: It include past and current smoking habits and live with someone who smokes, any history of on the job exposure to airborne irritants and any family history of respiratory diseases, such as cystic fibrosis or emphysema.

Physical exam: Physical exam include wheezes (high-pitched sounds that occur when air is pushed out through constricted airways), and rales (small rattling sounds that result when air moves through airways filled with fluid). The vibration from the chest percussion helps to determine the size and condition of the lungs.

- Complete blood cell count (CBC).
- Arterial blood gases (ABG) test.
- Chest X-ray.
- Spirometry.
- ECG.

Treatment

The goal of therapy for chronic bronchitis is to relieve symptoms, prevent complications and slow the progression of the disease. Quitting smoking is the most important and most successful treatment for chronic bronchitis, since continuing to use tobacco will only further damage the lungs.

Medications used for treatment bronchitis are:

Bronchodilator: Salmeterol, Albuterol, Metaproterenol and Formoterol

Anticholinergic: Ipratropium bromide and Tiotropium

Steroids: Presnisone, Dexamethasone

PDE4 inhibitors: Roflumilast

Antibiotics: Macrolides, Azithromycin sulfonamides, Tetracyclines, Trimetho-prim and Fluoroquinolones

Vaccines: Patients with chronic bronchitis should receive a flu shot annually and pneumonia shot every five to seven years to prevent infections.

Oxygen Therapy: As a patient's disease progresses, they may find it increasingly difficult to breathe on their own and may require supplemental oxygen.

Surgery: Lung volume reduction surgery, during which small wedges of damaged lung tissue are removed, may be recommended for some patients with chronic bronchitis.

Pulmonary Rehabilitation: An important part of chronic bronchitis treatment is pulmonary rehabilitation, which includes education, nutrition counselling, learning special breathing techniques, help with quitting smoking and starting an exercise regimen. Because people with chronic bronchitis are often physically uncomfortable, they may avoid any kind of physical activity. However, regular physical activity can actually improve a patient's health and well-being.

Cough suppressants: Cough suppressants such as dextromethorphan may be helpful in reducing cough symptoms.

Prevention

The majority of instances of chronic bronchitis can be prevented by quit smoking and avoiding second-hand smoke.

Flu and pneumococcal vaccines can help to prevent repeated infections that may lead to the disease.

Certain industries (for example, chemical, textile, thermal etc.) and farm workers are often associated with air-borne chemicals and dust; avoiding air-borne chemicals and dust with appropriate masks may prevent or reduce the individual's chance of developing chronic bronchitis.

Good control of asthma may prevent chronic bronchitis from developing. The genetic predisposition to chronic bronchitis is not currently preventable.

5.3.3 Emphysema

Emphysema is a long-term, progressive disease of the lungs that primarily causes shortness of breath due to over-inflation of the alveoli (air sacs in the lung). In people with emphysema the lung tissues involved in exchange of gases (oxygen and carbon dioxide) is impaired or destroyed. It is included in a group of diseases called chronic obstructive pulmonary disease or COPD. Emphysema is called an obstructive lung disease because the destruction of lung tissue around smaller airways (bronchioles), makes these airways unable to hold their shape properly when exhale. This makes them inefficient at transferring oxygen into the blood, and in taking carbon dioxide out of the blood.

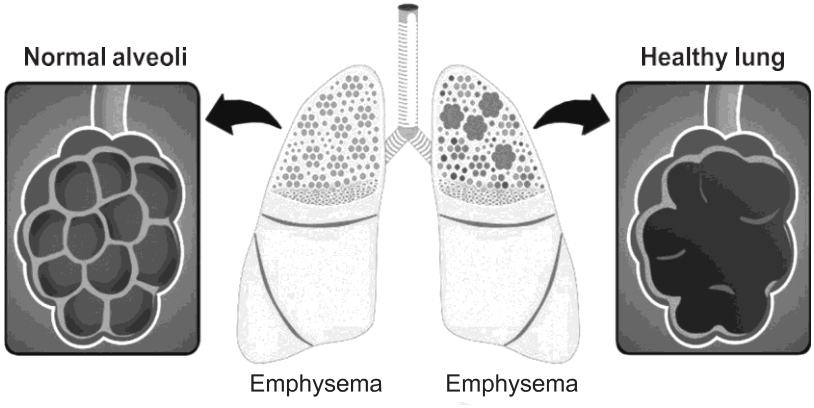

Fig. 5.4: Emphysema

Causes

The main cause of emphysema is long-term exposure to airborne irritants, including:

- Tobacco smoke
- Marijuana smoke
- Air pollution
- Chemical fumes and dust

Cigarette smoking is by far the most dangerous behaviour that causes people to develop emphysema, and it is also the most preventable cause. Other risk factors include a deficiency of an enzyme called α-1-antitrypsin, air pollution, airway reactivity, heredity, male sex and age.

The importance of cigarette smoking as a risk factor for developing emphysema cannot be overemphasized. Cigarette smoke contributes to this disease process in two ways. It destroys lung tissue, which results in the obstruction of air flow, and it causes inflammation and irritation of airways that can add to air flow obstruction.

- Destruction of lung tissue occurs in several ways. First, cigarette smoke directly affects the cells in the airway responsible for clearing mucus and other secretions. Occasional smoking temporarily disrupts the sweeping action of tiny hairs called cilia that line the airways. Continued smoking leads to longer dysfunction of the cilia. Long-term exposure to cigarette smoke causes the cilia to disappear from the cells lining the air passages. Without the constant sweeping motion of the cilia, mucous secretions cannot be cleared from the lower respiratory tract. Furthermore, smoke causes mucous secretion to be increased, at the same time that the ability to clear the secretions is decreased. The resulting mucous deposition can provide bacteria and other organisms with a rich source of food and lead to infection.
- The immune cells in the lung, whose job is to prevent and fight infection, are also affected by cigarette smoke. They cannot fight bacteria as effectively, or clear the lungs of the many particles (such as tar) that cigarette smoke contains. In these ways, cigarette smoke sets the stage for frequent lung infections. Although these infections may not even be serious enough to require medical care, the inflammation caused by the immune system constantly attacking bacteria or tar leads to the release of destructive enzymes from the immune cells.

- Over time, enzymes released during this persistent inflammation lead to the loss of proteins responsible for keeping the lungs elastic. In addition, the tissue separating the air cells (alveoli) from one another also is destroyed. Over years of chronic exposure to cigarette smoke, the decreased elasticity and destruction of alveoli leads to the slow destruction of lung function.
- Air pollution acts in a similar manner to cigarette smoke. The pollutants cause inflammation in the airways, leading to lung tissue destruction.
- Close relatives of people with emphysema are more likely to develop the disease themselves. This is probably because the tissue sensitivity or response to smoke and other irritants may be inherited. The role of genetics in the development of emphysema, however, remains unclear.
- Abnormal airway reactivity, such as bronchial asthma, has been shown to be a risk factor for the development of emphysema.
- Men are more likely to develop emphysema than women. The exact reason for this is unknown, but differences between male and female hormones are suspected.
- Older age is a risk factor for emphysema. Lung function normally declines with age. Therefore, it is the reason that the older the person, the more likely they will have enough lung tissue destruction to produce emphysema.

Rarely, emphysema is caused by an inherited deficiency of a protein that protects the elastic structures in the lungs. It is called α-1-antitrypsin deficiency emphysema.

α-1-antitrypsin deficiency

α-1-antitrypsin (also known as α-1-antiprotease) AAT is a glycoprotein member of the serine protease inhibitor family that is synthesized in the liver and is secreted into the blood stream. It is a substance that fights a destructive enzyme in the lungs called trypsin (or protease). Trypsin is a digestive enzyme, most often found in the digestive tract, where it is used to help the body digest food. It is also released by immune cells in their attempt to destroy bacteria and other material. People with α-1-antitrypsin deficiency cannot fight the destructive effects of trypsin once it is released in the lung. The destruction of tissue by trypsin produces similar effects to those seen with cigarette smoking. The lung tissue is slowly destroyed, thus decreasing the ability of the lungs to perform appropriately. Foreign objects (e.g. bacteria) are trying to be destroyed but this enzyme destroys normal tissue since the second enzyme (antiprotease) responsible for controlling the first enzyme (protease) is not available or is poorly functioning. This is referred to as the "Dutch" hypothesis of emphysema formation.

The American Thoracic Society/ European Respiratory Society Guidelines recommend screening for AAT deficiency if emphysema is suspected in any patient younger than 45 years and with any of the following:

- Absence of recognized emphysema, risk factors such as smoking or occupational inhalational exposure.
- Unexplained liver disease.
- Family history of AAT deficiency, COPD, bronchiectasis, or panniculitis.
- Positive c-ANCA (anti-neutrophilic cytoplasmic antibody) vasculitis.
- Unclear/idiopathic bronchiectasis.
- Asthma with persistent, fixed-airways obstruction despite therapy.

Risk Factors

Factors that increase risk of developing emphysema include:

- Smoking: Emphysema is most likely to develop in cigarette smokers, but cigar and pipe smokers also are susceptible. The risk for all types of smokers increases with the number of years and amount of tobacco smoked.
- Age: The lung damage that occurs in emphysema develops gradually; most people with tobacco-related emphysema begin to experience symptoms of the disease between the ages of 40 and 60.
- Exposure to second-hand smoke: Second-hand smoke, also known as passive or environmental tobacco smoke, is smoke that you inadvertently inhale from someone else's cigarette, pipe or cigar. Being around second-hand smoke increases your risk of emphysema.
- Occupational exposure to fumes or dust: Breathe fumes from certain chemicals or dust from grain, cotton, wood or mining products, are more likely to develop emphysema. This risk is even greater in cigarette smokers.
- Exposure to indoor and outdoor pollution: Breathing indoor pollutants, such as fumes from heating fuel, as well as outdoor pollutants, car exhaust, for instance increases risk of emphysema.

Symptoms

Two of the key symptoms of emphysema are shortness of breath and a chronic cough appears in the early stages.

A person with shortness of breath, or dyspnea, feels being unable to catch a breath may start only during physical exertion, but as the disease progresses, it can start to happen during rest, too.

Emphysema and COPD develop over a number of years.

In the later stages, the person may have:

- Frequent lung infections,
- Excess production of mucus,
- Wheezing,
- Reduced appetite and weight loss,
- Fatigue,
- Blue-tinged lips or fingernail beds, or cyanosis, due to a lack of oxygen,
- Anxiety and depression,
- Sleep problems,
- Morning headaches due to a lack of oxygen, when breathing at night is difficult.

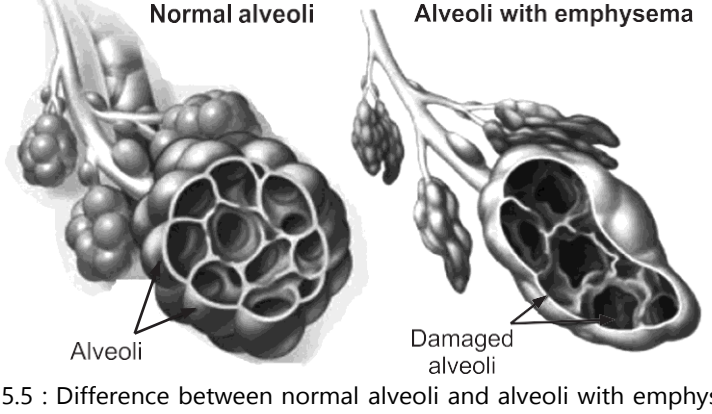

Fig. 5.5 : Difference between normal alveoli and alveoli with emphysema

Complications

People who have emphysema are also more likely to develop:

- Collapsed lung (pneumothorax): A collapsed lung can be life-threatening in people who have severe emphysema, because the function of their lungs is already so compromised. This is uncommon but serious when it occurs.
- Heart problems: Emphysema can increase the pressure in the arteries that connect the heart and lungs. This can cause a condition called corpulmonale, in which a section of the heart expands and weakens.
- Large holes in the lungs: Some people with emphysema develop empty spaces in the lungs called bullae. They can be as large as half the lung. In addition to reducing the amount of space available for the lung to expand, giant bullae can increase your risk of pneumothorax.

Tests and Diagnosis

Diagnosis will carry out a physical examination and ask the patient about their symptoms and medical history. Some diagnostic tests may also be used, to confirm that the patient has emphysema rather than asthma and heart failure. If the patient has never smoked; a test may be carried out to see if the person has an α_1-antitrypsin deficiency.

- A chest X-ray helps to identify changes in lung that may indicate emphysema. The X-ray also may show the presence of an infection or a mass in the lung (such as a tumor) that could explain symptoms. Shortness of breath has many causes. The chest X-ray is considered to be the quickest and easiest test to begin to separate the different possible causes and formulate a diagnosis.
- Lung function tests can give the specific information about how the lungs work mechanically. In these tests, the patient have to breathe into a tube that is connected to a computer or some other monitoring device, which can record the necessary information. The tests measure how much air in lungs can hold, how quickly lungs can expel air during expiration, and how much reserve capacity of lungs have for increased demand, such as during exercise.
- Blood test is used to detect family history of α_1-antitrypsin deficiency to evaluate genetic disease.
- Blood tests may also be used to check white blood cell count, which can sometimes indicate an acute infection. This information can be used with the chest X-ray to evaluate for pneumonia, bronchitis, or other respiratory infections that can make emphysema worse.
- Another blood test that may be helpful, especially in the hospital setting, is called the arterial blood gas. This test helps determine how much oxygen and carbon dioxide are in blood.

Treatment

Treatment for emphysema can take many forms in a step-wise approach, depending on the severity of condition.

Medications used for treatment of emphysema are:

Bronchodilator: Salmeterol, Albuterol, Metaproterenol, and Formoterol

Anticholinergic: Ipratropium bromide and Tiotropium

Steroids: Prednisone, Dexamethasone

PDE4 inhibitors: Roflumilast

Stop smoking: This recommendation for peoplewith emphysema, quitting smoking may halt the progression of the disease and improve the function of the lungs to some extent. Lung function deteriorates with age. In those susceptible to developing COPD, smoking can result in a five-fold deterioration of lung function. Smoking cessation may return lung function from this rapid deterioration to its normal rate after smoking is stopped.

Antibiotics: These medications are often prescribed for people with emphysema who have increased shortness of breath. Even when the chest X-ray does not show pneumonia or evidence of infection, people treated with antibiotics tend to have shorter episodes of shortness of breath. It is suspected that infection may play a role in an acute bout of emphysema, even before the infection worsens into a pneumonia or acute bronchitis.

Oxygen Therapy: As a patients' disease progresses, they may find it increasingly difficult to breathe on their own and may require supplemental oxygen.

Surgery: People with severe emphysema sometimes undergo surgery to reduce lung volume or carry out lung transplantation. Lung volume reduction surgery removes small wedges of the damaged, emphysematous, lung tissue. This is thought to enhance lung recoil and to improve the function of the diaphragm. In severe cases, this can improve lung function, exercise tolerance and quality of life.

Lung transplantation improves quality of life, but not life-expectancy, for people with severe emphysema. Lifelong drug therapy is necessary to prevent the immune system from rejecting the new tissue. One or both lungs may be transplanted.

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Chapter...6

RENAL SYSTEM

6.1 INTRODUCTION TO URINARY SYSTEM

The urinary system consists of the kidneys, ureters, urinary bladder and urethra. The kidneys filter the blood to remove wastes and produce urine. The ureters, urinary bladder and urethra together form the urinary tract, which acts as a plumbing system to drain urine from the kidneys, store it, and then release it during urination. Besides filtering and eliminating wastes from the body, the urinary system also maintains the homeostasis of water, ions, pH, blood pressure, calcium and red blood cells. The kidneys have extensive blood supply via the renal arteries which leave the kidneys via the renal vein.

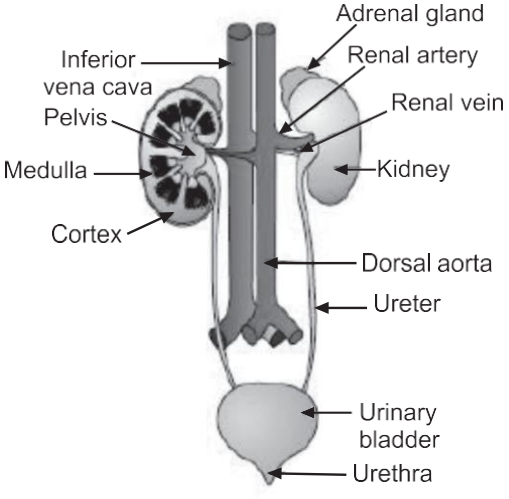

Fig. 6.1 : Parts of urinary system

Kidneys: The kidneys are a pair of bean-shaped organs found along the posterior wall of the abdominal cavity. The left kidney is located slightly higher than the right kidney because the right side of the liver is much larger than the left side. The kidneys, unlike the other organs of the abdominal cavity, are located posterior to the peritoneum and touch the muscles of the back. The kidneys are surrounded by a layer of adipose that holds them in place and protects them from physical damage. The kidneys filter metabolic wastes, excess ions, and chemicals from the blood to form urine.

Ureters: The ureters are a pair of tubes that carry urine from the kidneys to the urinary bladder. The ureters are about 10 to 12 inches long and run on the left and right sides of the body parallel to the vertebral column. Gravity and peristalsis of smooth muscle tissue in the walls of the ureters move urine toward the urinary bladder. The ends of the ureters extend slightly into the urinary bladder and are sealed at the point of entry to the bladder by the ureterovesical valves. These valves prevent urine from flowing back towards the kidneys.

Urinary Bladder: The urinary bladder is a sac-like hollow organ used for the storage of urine. The urinary bladder is located along the body's midline at the inferior end of the pelvis. Urine entering the urinary bladder from the ureters slowly fills the hollow space of the bladder and stretches its elastic walls. The walls of the bladder allow it

to stretch to hold anywhere from 600 to 800 millilitres of urine.

Urethra: The urethra is the tube through which urine passes from the bladder to the exterior of the body. The female urethra is around 2 inches long and ends inferior to the clitoris and superior to the vaginal opening. In males, the urethra is around 8 to 10 inches long and ends at the tip of the penis. The urethra is also an organ of the male reproductive system as it carries sperm out of the body through the penis. The flow of urine through the urethra is controlled by the internal and external urethral sphincter muscles. The internal urethral sphincter is made of smooth muscle and opens involuntarily when the bladder reaches a certain set level of distention. The opening of the internal sphincter results in the sensation to have needed to urinate.

The external urethral sphincter is made of skeletal muscle and may be opened to allow urine to pass through the urethra or may be held closed to delay urination.

There are several functions of the Urinary System:

1. Removal of waste product from the body (mainly urea and uric acid).
2. Regulation of electrolyte balance (e.g. sodium, potassium and calcium).
3. Regulation of acid-base homeostasis
4. Controlling blood volume and maintaining blood pressure.
5. Production of Hormones. (e.g. Erythropoietin, Calcitriol, Renin).

6.2 ACUTE RENAL FAILURE

Acute renal failure or Acute kidney failure (AKF) occurs when kidneys suddenly become unable to filter waste products from blood. When kidneys lose their filtering ability, it results in accumulation of nitrogenous wastes and fluid and electrolyte imbalance. Acute renal failure is also called acute kidney injury (AKI). It develops rapidly over a few hours or a few days.

Epidemiology

Acute kidney injury is common among hospitalized patients particularly in critically ill people who need intensive care. It affects some 3-7% of patients admitted to the hospital and approximately 25-30% of patients in the intensive care unit.

Causes

Acute renal failure can occur when:

(i) Impaired Blood Flow to the Kidneys:

Diseases and conditions that may slow blood flow to the kidneys and lead to kidney failure include:

- Blood or fluid loss.
- Blood pressure medications.
- Heart attack.
- Heart disease.
- Infection.
- Liver failure.
- Use of Aspirin, Ibuprofen and Naproxen.
- Severe allergic reaction (anaphylaxis).
- Severe burns.
- Severe dehydration.

(ii) Damage to the Kidneys:

Certain diseases, conditions and agents may damage the kidneys and lead to acute renal failure includes:

- Blood clots in the veins and arteries in and around the kidneys.

- Cholesterol deposits that block blood flow in the kidneys.
- Glomerulonephritis, inflammation of the tiny filters in the kidneys (glomeruli).
- Hemolytic uremic syndrome, a condition that results from premature destruction of red blood cells.
- Lupus, an immune system disorder causing glomerulonephritis.
- Medications, such as certain chemotherapy drugs, antibiotics, dyes used during imaging tests and zoledronic acid, used to treat osteoporosis and high blood calcium levels (hypercalcemia).
- Multiple myeloma, a cancer of the plasma cells.
- Scleroderma, a group of rare diseases affecting the skin and connective tissues.
- Thrombotic thrombocytopenic purpura (TTP), a rare blood disorder.
- Toxins, such as alcohol, heavy metals and cocaine.
- Vasculitis, an inflammation of blood vessels.

(iii) Urine Blockage in the Kidneys:

Diseases and conditions that block the passage of urine out of the body (urinary obstructions) and can lead to acute renal failure include:

- Bladder cancer,
- Blood clots in the urinary tract,
- Cervical cancer,
- Colon cancer,
- Enlarged prostate,
- Kidney stones,
- Nerve damage involving the nerves that control the bladder,
- Prostate cancer.

Etiologic Mechanisms inAcute Renal Failure

Table 6.1 : Etiologic mechanisms in ARF

Prerenal Failure
Mechanism: Reduced renal blood flow
Severe dehydration shock (all forms)
Cardiac failure
Renal artery stenosis
Renal artery embolism or thrombosis
Sickle cell crisis
Intrarenal Failure
Mechanism: Renal parenchymal disease Ischemic necrosis Nephrotoxicity
Autoimmune or isoimmune disorders
Hypertensive nephropathy
Diabetic nephropathy
Renal trauma
Acute glomerulonephritis
Vasculitis
Acute interstitial nephritis, Rhabdomyolysis
Postrenal Failure
Mechanism: Prevention of Filtration Due to
High tubular pressure (obstructed outflow)
Urolithiasis
Renal-urinary neoplasms
Congenital obstructive uropathies
Detrusor areflexia
Surgical trauma to ureters
Obstructive lymphadenopathy

Risk Factors

Acute renal failure almost always occurs in connection with another medical

condition or events. Conditions that can increase risk of acute renal failure include:

- Being hospitalized, especially for a serious condition that requires intensive care,
- Advanced age,
- Blockages in the blood vessels in arms or legs (peripheral artery disease),
- Diabetes,
- High blood pressure,
- Heart failure,
- Kidney diseases,
- Liver diseases.

Pathophysiology

The driving force for glomerular filtration is the pressure gradient from the glomerulus to the Bowman space. Glomerular pressure depends primarily on renal blood flow (RBF) and is controlled by the combined resistances of renal afferent and efferent arterioles. Regardless of the cause of AKI, reductions in RBF represent a common pathologic pathway for decreasing glomerular filtration rate (GFR). The etiology of AKI consists of 3 main mechanisms: prerenal, intrinsic and obstructive.

In prerenal failure, GFR is depressed by compromised renal perfusion. Tubular and glomerular function remain normal.

Intrinsic renal failure includes diseases of the kidney itself, predominantly affecting the glomerulus or tubule, which are associated with the release of renal afferent vasoconstrictors. Ischemic renal injury is the most common cause of intrinsic renal failure. Patients with chronic renal failure may also present with superimposed AKI from prerenal failure and obstruction, as well as intrinsic renal disease.

Obstruction of the urinary tract initially causes an increase in tubular pressure, which decreases the filtration driving force. This pressure gradient soon equalizes, and maintenance of a depressed GFR then depends on renal efferent vasoconstriction.

Symptoms

Signs and symptoms of acute renal failure may include:

- Decreased urine output, although occasionally urine output remains normal,
- Fluid retention, causing swelling in legs, ankles or feet,
- Drowsiness,
- Shortness of breath,
- Fatigue,
- Confusion,
- Nausea,
- Seizures or coma in severe cases,
- Chest pain or pressure.

Sometimes Acute renal failure causes no signs or symptoms and is detected through lab tests done for another reason.

Complications

Potential complications of acute renal failure include:

Fluid build-up: Acute renal failure may lead to a build-up of fluid in chest, which can cause shortness of breath.

Chest pain: If the lining that covers heart becomes inflamed, it may lead to chest pain.

Muscle weakness: When body's fluids and electrolytes are out of balance, muscle weakness can result. Elevated levels of potassium in blood are particularly dangerous.

Permanent kidney damage: Occasionally, Acute renal failure causes permanent loss of kidney function, or end-stage renal disease.

Death: Acute renal failure can lead to loss of kidney function and, ultimately death. The risk of death is highest in people who had kidney problems before acute kidney failure.

Tests And Diagnosis

Urine output measurements: The amount of urine excrete in a day may help to determine the cause of kidney failure.

Urine tests: Analyzing a sample of urine, may reveal abnormalities that suggest kidney failure.

Blood tests: Blood sample may reveal rapidly rising levels of urea and creatinine.

Imaging tests: Imaging tests such as ultrasound and computerized tomography may be used to help any abnormalities in kidneys.

Biopsy: In certain situations, a kidney biopsy may recommend to remove a small sample of kidney tissue for lab testing.

Treatments and Drugs

Treatment for Acute renal failure involves identifying the illness or injury that originally damaged kidneys.

Balance the amount of fluids in blood: If Acute renal failure is caused by a lack of fluids in blood, may recommend intravenous fluids. In other cases, acute renal failure may cause to have too much fluid, leading to swelling in arms and legs. In these cases, diuretics may use.

Medications to control blood potassium: If potassium is not properly filtering from blood, may require calcium, glucose or sodium polystyrene sulfonate to prevent the accumulation of high levels of potassium in blood. Too much potassium in the blood can cause dangerous arrhythmias and muscle weakness.

Medications to restore blood calcium levels: In hypocalcemia, calcium infusion is recommonded.

Treatment for end-stage kidney disease: If kidneys cannot keep up with waste and fluid clearance on their own and develop complete kidney failure lead to end-stage kidney disease. At that point, dialysis or a kidney transplant is needed.

Dialysis: Dialysis artificially removes waste products and extra fluid from blood when kidneys can no longer perform normally. In hemodialysis, a machine filters waste and excess fluids from the blood.

In peritoneal dialysis, a thin tube (catheter) inserted into abdomen fills abdominal cavity with a dialysis solution that absorbs waste and excess fluids. After a period of time, the dialysis solution drains from body, carrying the waste with it.

Kidney transplant: A kidney transplant involves surgically placing a healthy kidney from a donor into body. Transplanted patient may need to take medications for the rest of life to keep body from rejecting the new organ.

Prevention

Acute renal failure is often difficult to predict or prevent. But may reduce risk by taking care of kidneys.

Yearly physical examination include blood tests and urinalysis to monitor kidney and urinary tract health.

Drink enough fluids to keep the kidneys functioning properly.

Avoid taking substances or medications that can poison or damage kidney tissues.

Patients having other diseases or conditions that increase risk of acute kidney failure, such as diabetes or high blood

pressure, must follow recommendations for managing these conditions.

Persons at risk for chronic renal failure may need more frequent testing for kidney function and other problems that occur with declining kidney function.

6.3 CHRONIC RENAL FAILURE

Chronic Kidney disease (CKD), also called chronic renal failure, is the irreversible loss of renal function due to replacement of functional nephrons with fibrous scar tissue. Kidneys filter wastes and excess fluids from blood, which are then excreted in urine. When chronic renal failure reaches an advanced stage, dangerous levels of fluid, electrolytes and wastes can build up in body. In early stage of chronic renal failure, become clinically apparent as renal insufficiency, evidenced by azotemia and possibly polyurea and nocturia resulting from impaired tubular transport and concentration of urine. Chronic renal failure may not become apparent untill kidney function is significantly impaired. Chronic renal failure can progress to end-stage kidney failure, which is fatal without artificial filtering (dialysis) or a kidney transplant. Chronic renal failure represents progressive and irreversible destruction of kidney structures, leading to the accumulation of metabolic products, drugs and poisons, and disorders of water, electrolyte, acid-base balance, and renal endocrine functions.

Causes

Chronic renal failure occurs when a disease or condition impairs kidney function, causing kidney damage to worsen over several months or years.

Diseases and conditions that commonly cause chronic renal failure include:

- Type 1 or type 2 diabetes,
- High blood pressure.

One of the complications resulting from diabetes or high blood pressure is the damage to the small blood vessels in the body. The blood vessels in the kidneys also become damaged, resulting in CKD.

The most common cause of end-stage renal failure worldwide is IgA nephropathy (Inflammation in the kidney).

Other common causes of chronic renal failure include:

- Recurring pyelonephritis (kidney infection).
- Polycystic kidney disease (multiple cysts in the kidneys), Prolonged obstruction of the urinary tract, from conditions such as enlarged prostate, kidney stones and some cancers.
- Autoimmune disorders such as systemic lupus erythematosus.
- Hardening of the arteries, which can damage blood vessels in the kidney.
- Urinary tract blockages and reflux, due to frequent infections, stones, or an anatomical abnormality that happened at birth.
- Excessive use of medications that are excreated through the kidneys.
- Vesicoureteral reflux, a condition that causes urine to back up into kidneys.

Pathophysiology

A normal kidney contains approximately 1 million nephrons, each of which contributes to the total glomerular filtration rate (GFR). In the face of renal injury (regardless of the etiology), the kidney has an innate ability to maintain GFR, despite progressive destruction of nephrons, as the remaining healthy nephrons manifest hyperfiltration and compensatory

hypertrophy. This nephron adaptability allows for continued normal clearance of plasma solutes. Plasma levels of substances such as urea and creatinine start to show measurable increase only after total GFR has decreased to 50%.

The plasma creatinine value will approximately double with a 50% reduction in GFR. For example, a rise in plasma creatinine from a baseline value of mg/dL to 1.2 mg/dL in a patient, although still within the adult reference range, actually represents a loss of 50% of functioning nephron mass.

The increased glomerular capillary pressure may damage the capillaries, leading initially to secondary focal and segmental glomerulosclerosis (FSGS) and eventually to global glomerulosclerosis.

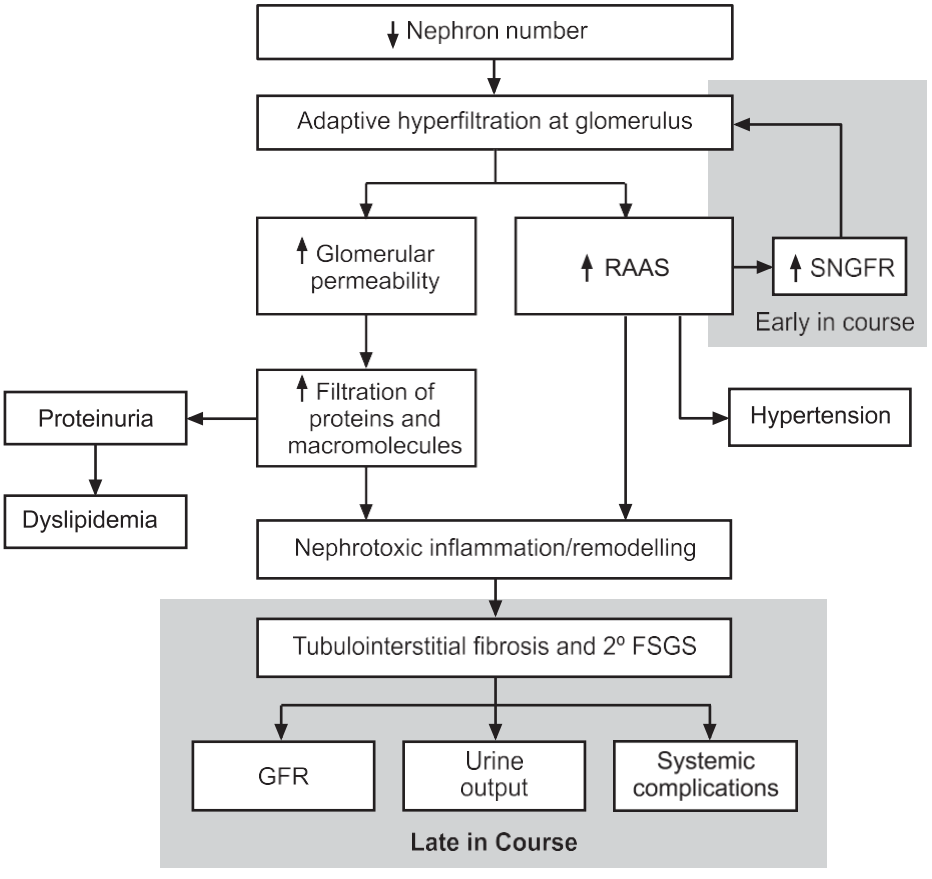

Fig. 6.2 : Pathogenesis of kidney failure

Symptoms

Signs and symptoms of chronic renal failure develop over time if kidney damage progresses slowly. Signs and symptoms of chronic renal failure may include:

- Nausea,
- Vomiting,
- Loss of appetite,
- Fatigue and weakness,
- Sleep problems,
- Changes in urine output,
- Decreased mental sharpness,

- Muscle twitches and cramps,
- Hiccups,
- Swelling of feet and ankles,
- Persistent itching,
- Chest pain, if fluid builds up around the lining of the heart,
- Shortness of breath, if fluid builds up in the lungs,
- High blood pressure (hypertension).

Signs and symptoms of kidney disease are often nonspecific; they can also be caused by other illnesses. Because kidneys are highly adaptable and able to compensate for lost function, signs and symptoms may not appear until irreversible damage has occurred.

Table 6.2: Mechanisms of nephropathy in renal failure

Mechanism	Description
Glomerulosderosis	Progressive, destructive hardening of glomerular capillaries initiated by adaptive changes in the nephrons, which are initially unaffected by a primary disease process. Epithelial and endothelial injury results in proteinuria. Hardening is due to mesangial cell proliferation, increased production of extracellular matrix, and intraglomerular coagulation.
Tubulointerstitial injury	Defects in tubular transport function associated with interstitial edema, leukocyte infiltration, and focal tubular necrosis.
Vascular injury	Diffuse or focal ischemia of the renal parenchyma associated with thickening, fibrosis, or focal lesions of renal blood vessels. Reduced blood flow may result in tubular atrophy and interstitial fibrosis as well as functional disruption (e.g., reduced glomerular filtration rate, proteinuria, and alteration of the medullary gradient with loss of concentrating ability).

Tests and Diagnosis

Blood tests: Kidney function tests look for the level of waste products, such as creatinine and urea in blood. Higher levels of creatinine indicate a lower glomerular filtration rate and as a result a decreased capability of the kidneys to excrete waste products.

Urine tests: Testing of a urine sample shows that the kidney is allowing the loss of protein or red blood cells into the urine. It may reveal abnormalities that point to chronic kidney failure and help to identify the cause of chronic renal failure.

Treatments

There are two treatments for kidney failure:

1. Dialysis.
2. Kidney transplantation

1. Dialysis:

Two different types of dialysis can be done.

- Hemodialysis (HD).
- Peritoneal Dialysis (PD).

(i) Hemodialysis Purpose: Hemodialysis cleans and filters blood using a machine to temporarily rid of the body from harmful wastes, extra salt and extra

water. Hemodialysis helps to control blood pressure and helps body to keep the proper balance of important chemicals such as potassium, sodium, calcium and bicarbonate.

Dialysis can replace part of the function of kidneys. Diet, medications and fluid limits are often needed as well. Diet, fluids, and the number of medications need will depend on treatment.

Hemodialysis Working: Hemodialysis uses a special filter called a dialyzer that functions as an artificial kidney to clean blood. The dialyzer is a canister connected to the hemodialysis machine.

During treatment, blood travels through tubes into the dialyzer, which filters out wastes, extra salt and extra water. Then the cleaned blood flows through another set of tubes back into body. The hemodialysis machine monitors blood flow and removes wastes from the dialyzer.

(ii) Peritoneal Dialysis: Peritoneal dialysis is another procedure that removes wastes, chemicals, and extra water from body. This type of dialysis uses the lining of abdomen, or belly, to filter blood. This lining is called the peritoneal membrane and acts as the artificial kidney.

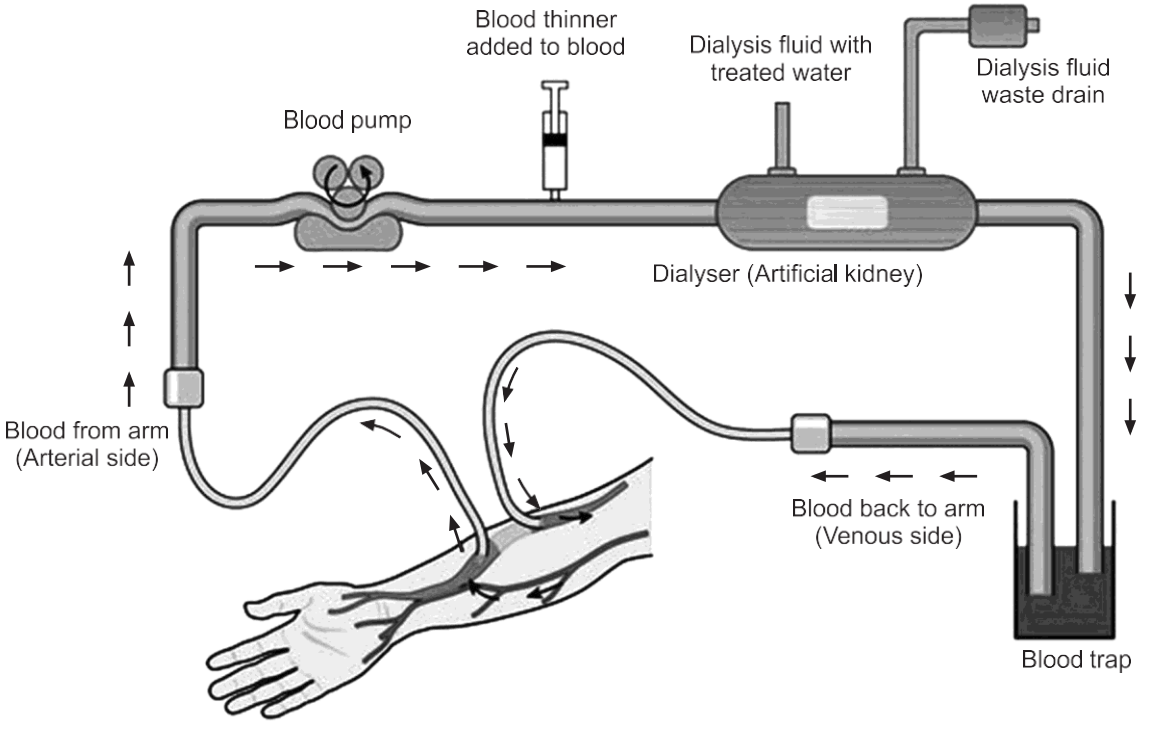

Fig. 6.3: Hemodialysis

Peritoneal Dialysis Working: A mixture of minerals and sugar dissolved in water, called dialysis solution, travels through a catheter into belly. The sugar (dextrose) draws wastes, chemicals and extra water from the tiny blood vessels in peritoneal membrane into the dialysis solution. After several hours, the used solution is drained

from abdomen through the tube, taking the wastes from blood with it. Then abdomen is refilled with fresh dialysis solution, and the cycle is repeatesd. The process of draining and refilling is called an exchange.

Dialysis is not a cure: Hemodialysis and peritoneal dialysis are treatments that help to replace the work kidneys did. These treatments help to feel better and live longer, but they do not cure kidney failure. Although patients with kidney failure may live longer than ever, over the years kidney disease can cause problems such as heart disease, bone disease, arthritis, nerve damage, infertility and malnutrition.

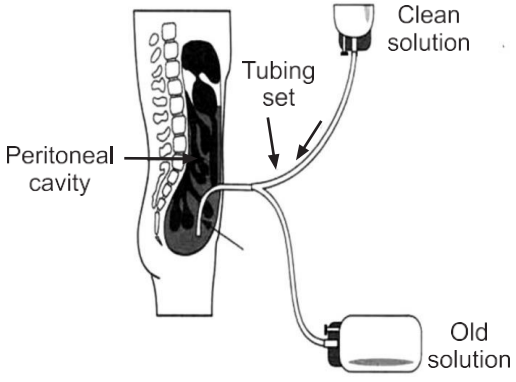

Fig. 6.4: Peritoneal dialysis

2. Kidney Transplant:

A kidney transplant involves surgically placing a healthy kidney from a donor into body. Transplanted patient may need to take medications for the rest of life to keep body from rejecting the new organ.

Treatments and Drugs: Chronic renal failure has no cure. In general, treatment consists of measures to help control signs and symptoms, reduce complications, and slow progression of the disease. If kidneys become severely damaged, may need treatment for end-stage kidney disease.

Treating Complications: Kidney disease complications can be controlled to make more comfortable. Treatments may include:

High blood pressure medications:

People with kidney disease may experience worsening high blood pressure. Recommend medications to lower blood pressure, commonly angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers and to preserve kidney function. High blood pressure medications can initially decrease kidney function and change electrolyte levels, may need frequent blood tests to monitor condition.

Medications to lower cholesterol levels:

Medications (statins) used to lower the cholesterol. People with chronic renal failure often experience high levels of bad cholesterol, which can increase the risk of heart disease.

Medications to treat anemia:

In certain situations, may recommend supplements of the hormone erythropoietin, sometimes with added iron. Erythropoietin supplements aid in production of more red blood cells, which may relieve fatigue and weakness associated with anemia.

Medications to relieve swelling:

People with Chronic renal failure may retain fluids. This can lead to swelling in the legs, as well as high blood pressure. Diuretics can help maintain the balance of fluids in body.

Medications to protect bones:

Calcium and vitamin D supplements may be useful to prevent weak bones and lower risk of fracture.

Table 6.3 : Levels of treatment in CRF

Treatment Mode	Description
Conservative Treatment: Protein restriction Tight glycemic control (in diabetics)	 Protein intake restricted to 0.6-0.8 g/day. Frequent glucose testing with appropriate dose insulin, divided-oral hypoglycemic therapy, or dietary measures.
Angiotensin-converting enzyme inhibitors (e.g., captopril)	Drug therapy to interrupt the renin angiotensin aldosterone system, improving renal blood flow and protecting against hypertensive nephropathy.
Diuretics Erythropoietin	Drug therapy to augment sodium and water excretion. Use of recombinant erythropoietin to treat anemia due to defective production of this hormone in renal disease.
Low phosphate diet, calcium supplementation, vitamin D	Prevention and treatment of renal osteodystrophy.
Renal Replacement Therapy: Hemodialysis	 Use of an extracorporeal circuit to create a blood flow rate of 200-400 mL/min through an artificial Kidney (dialyzer). Patient's blood flows countercurrent to dialysate fluid, with exchange of water and solutes to effect normal fluid and electrolyte balance.
Peritoneal dialysis	Use of the peritoneal membrane for exchange of water and solute between patient's blood (in abdominal wall and visceral capillaries) and dialysate instilled into peritoneal cavity.

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UNIT III

Chapter...7

HAEMATOLOGICAL DISEASES

7.1 INTRODUCTION

Anemia is a medical condition in which the red blood cell count or hemoglobin (Hb) is less than normal. The oxygen carrying capacity of the blood is therefore, decreased. Red blood cells carry hemoglobin, an iron-rich protein that attaches to oxygen in the lungs and carries it to tissues throughout the body. Anemia is sign, not diagnosis. There are many kind of anemia, each with its own cause. It is characterized by insufficient erythrocytes or hemoglobin. Loss of blood is the most common cause of anemia. Anemia can be temporary or long term, and it can range from mild to severe. These condition leads to fatigue and intolerance to cold, which related to lack of oxygen needed for energy and heat production, and paleness which is due to low hemoglobin content.

Types of Anemia

- Iron deficiency anemia
- Pernicious anemia
- Sickle cell anemia
- Megaloblastic anemia
- Anemia of chronic disease
- Hemolytic anemia
- Idiopathic aplastic anemia
- Thalassemia

Epidemiology

A moderate degree of iron-deficiency anemia affected approximately 610 million people worldwide or 8.8% of the population. It is slightly more common in female (9.9%) than males (7.8%). Mild iron deficiency anemia affects another 375 million.

Prevalence of anemia among non-pregnant women in India is higher than that in other South Asian countries, a recent study published in reputed medical journal 'The Lancet' has revealed. According to 'The Lancet', anemia affects a quarter of the global population, including 293 million (47%) children younger than 5 and 468 million (30%) non-pregnant women.

Sickle cell disease is common in regions of Africa, India, Saudi Arabia, and the Mediterranean basin. The thalassemias are the most common genetic blood diseases and are found in Southeast Asia and in areas where sickle cell disease is common.

Causes

Anemia, like a fever, is a symptom that requires investigation to determine the underlying etiology. Anemia occurs when blood does not have enough red blood cells. This can happen if:

- Body does not make enough red blood cells.

- Bleeding causes to lose red blood cells more quickly than they can be replaced.
- Inherited blood disorder that result in excessive destruction of red blood cells.

Causes of Common Types of Anemia:

Common types of anemia and their causes include:

Iron deficiency anemia: Iron deficiency anemia is caused by a shortage of the element iron in body. Bone marrow needs iron to make hemoglobin. Without adequate iron, body cannot produce enough hemoglobin for red blood cells.

Hemorrhagic anemia: Hemorrhagic anemia is specific type of anemia that causes because of sufficient decrease in red blood cells due to hemorrhage (bleeding). Common causes are large wounds, stomach ulcers and heavy menstrual bleeding.

Megaloblastic anemia: In addition to iron, body needs folate and vitamin B_{12} to produce sufficient number of healthy red blood cells. A diet lacking in these and other key nutrients can cause decreased red blood cell production. Megaloblastic anemia is marked by the appearance of very large red blood cells. This disorder is caused by incomplete formation of the red blood cell resulting in large numbers of immature and incompletely developed cells.

Pernicious anemia: In this condition insufficient production of RBCs result from inability of body to produce intrinsic factor. As a result, person cannot absorb vitamin B_{12}.

Pernicious anemia is deficiency of vitamin B_{12} due to autoimmune attack on cell of the stomach and antibody against intrinsic factor presented with megaloblastic anemia.

Anemia of chronic disease: Certain chronic diseases such as cancer, HIV/AIDS, rheumatoid arthritis, Crohn's disease and other chronic inflammatory diseases can interfere with the production of red blood cells, resulting in chronic anemia. Kidney failure also can cause anemia.

Aplastic anemia: This is very rare life-threatening anemia caused by a decrease in the bone marrow's ability to produce red blood cells. Destruction or inhibition of red bone marrow results in aplastic anemia. Typically, the marrow is replaced by fatty tissues or tumour cells. Toxins, γ-radiations, certain medications and autoimmune diseases are causes of aplastic anemia.

Anemias associated with bone marrow disease: A variety of diseases, such as leukemia, myelodysplasia or myelofibrosis, can cause anemia by affecting blood production in bone marrow. The effects of these types of cancer and cancer-like disorders vary from a mild alteration in blood production to a complete life threatening shutdown of the blood making process. Other cancers of the blood or bone marrow, such as multiple myeloma, myeloproliferative disorders and lymphoma also can cause anemia.

Haemolytic anemia: This group of anemias develop when red blood cells are destroyed faster than bone marrow can replace them. Certain blood diseases can cause increased red blood cell destruction. If erythrocyte cell membrane ruptures prematurely, their Hb pours out into plasma (hemolysis). The premature destruction of RBCs may result from inherent defects such as Hb defects, abnormal RBC enzymes or defects of RBC cell membrane. Agents that may cause hemolytic anemia are parasites,

toxins and antibodies from incompatible blood. A person can inherit a hemolytic anemia, or can develop it later in life.

Sickle cell anemia: The erythrocyte of person with Sickle Cell Anemia (SCA) manufactures an abnormal kind of hemoglobin. When such RBC gives up its oxygen to interstitial fluid, the abnormal hemoglobin tend to lose its integrity in place of low oxygen tension and forms long stiff, rod like structure that bind erythrocyte into sickle shape. The sickle cell ruptures easily. Prolonged oxygen reduction may eventually cause extensive tissue damage. Furthermore because of shape of sickle cells, they tend to get stuck in blood vessels and can cut off blood supply to an organ altogether. SCA is characterized by several symptoms.

In young children, hand-feet syndrome is present, in which there is swelling and pain in wrist and feet. Older patients experience pain in back and extremities without swelling and abdominal pain.

Other complications include neurological disorders (meningitis, seizure, stroke), impaired pulmonary functions, orthopedic abnormalities, genitourinary tract disorders (involuntary urination, blood in urine, kidney failure) ocular disturbance (hemorrhage, detached retina, blindness) convulsions, coma and infections.

Table 7.1 : Etiology and clinical features of anemias

Anemia	Etiology	RBC Characteristics
Hemorrhagic	Acute blood loss.	Normocytic, normochromic, reticulocytosis.
Iron-deficiency.	Chronic, slow blood loss; insufficient intake relative to demands.	Microcytic, hypochromic.
Hemolytic Sickle cell disease Hereditary spherocytosis Autoimmune Transfusion mismatch Hemoglobinopathies Glucose-6-phosphate dehydrogenase deficiency.	Hereditary defect of RBCs; immune, infectious, mechanical, or traumatic injury of RBCs; hypersplenism.	Variable morphology in hereditary forms (e.g., sickle or spherical shape); normocytic, normochromic in other etiologies.
Aplastic or hypoplastic Drug induced Radiation induced Anemia of chronic disease Alcoholism Pernicious anemia Folate deficiency.	Hereditary or nutritional deficiency of substrate for erythropoiesis; bone marrow depression; chronic disease.	Macrocytic (megalobastic) in substrate deficiency; normocytic, normochromic in bone marrow depression; microcytic, hypochromic in chronic disease.

Thalassemia: Thalassemia is a form of inherited autosomal recessive blood disorders, in which the body makes an abnormal form of haemoglobin.

Risk Factors

Following factors lead to increased risk of anemia:

Intestinal disorders: Having an intestinal disorder that affects the absorption of nutrients in small intestine such as Crohn's disease and celiac disease. Surgical removal or surgery to the parts of small intestine where nutrients are absorbed can lead to nutrient deficiencies and anemia.

Menstruation: In general, women who have not experienced menopause have a greater risk of iron deficiency anemia than do men and postmenopausal women. That is because menstruation causes the loss of red blood cells.

Pregnancy: In pregnancy, there is an increased risk of iron deficiency anemia because iron stores have to serve increased blood volume as well as be a source of hemoglobin for growing baby.

Family history: If family has a history of an inherited anemia, such as sickle cell anemia, the person may be at increased risk of the condition.

Other factors: A history of certain infections, blood diseases and autoimmune disorders, alcoholism, exposure to toxic chemicals, and the use of some medications can affect red blood cell production and lead to anemia.

Pathophysiology of Different Types of Anemia

[I] Pathophysiology of Iron Deficiency Anemia:

Iron is distributed in active metabolic and storage pools. Total body iron is about g in healthy men and 2.5 g in women; the difference relates to women's smaller body size, lower androgen levels, and lack of stored iron because of iron loss due to menses and pregnancy.

Iron deficiency anemia is the most common form of anemia and it develops over time if the body does not have enough iron to manufacture RBCs. Without enough iron, the body uses up all the iron it has stored in the liver, bone marrow and other organs. Once the stored iron is depleted, the body is able to make very few RBCs. If erythropoietin is present without sufficient iron, there is insufficient fuel for RBC production. The red blood cells that the body is able to make are abnormal and do not have a normal hemoglobin carrying capacity, as do normal red blood cells.

Table 7.2 : Dietary sources of iron

Dietary sources of iron
Heme and Non-heme iron
Liver
Meats
Fish
Poultry
Non-heme Iron
Iron fortified infant formulas legumes
Eggs
Dairy foods
Wheat
Blackstrap molasses
Dried apricots
Raisins
Mustard greens
Strawberries
Tomatoes
Brussel sprouts
Broccoli

Iron deficiency-consequences:

- Impaired physcial growth,
- Compromised cognitive development,
- Impaired learning capacity,
- Reduced muscle function,
- Decreased physical activity and lower work productivity,
- Lowered immunity,
- Increased risk of infectious disease.

[II] Pathophysiology of Pernicious Anemia

In pernicious anemia vitamin B_{12} is unavailable due to a lack of intrinsic factor, a substance responsible for intestinal absorption of the vitamin B_{12}. In a healthy person, intrinsic factor is produced by the parietal cells of the stomach. Intrinsic factor forms a complex with dietary vitamin B_{12} in the stomach. This complex remains intact, preventing degradation of the vitamin by intestinal juices, until it reaches the ileum of the small intestine, where the vitamin is released and absorbed into the body. When intrinsic factor is prevented from binding with vitamin B_{12} or when the parietal cells are unable to produce intrinsic factor, the vitamin is not absorbed and pernicious anemia results. This is believed to stem from an autoimmune reaction in which the malfunctioning immune system produces antibodies against intrinsic factor and against the parietal cells.

Without an adequate amount of vitamin B_{12}, the body is unable to synthesize DNA properly. This in turn affects red blood cell production: the cells divide, but their nuclei remain immature, these cells are called as megaloblasts. Some megaloblasts mature to become large red blood cells are called macrocytes; they reach the circulation but function abnormally. A deficiency of white blood cells (leukopenia) and of platelets (thrombocytopenia) is also seen in the blood.

Pernicious anemia occurs most often in persons older than 30 years of age, although a juvenile form of the disease does occur, usually in children younger than 3 years of age.

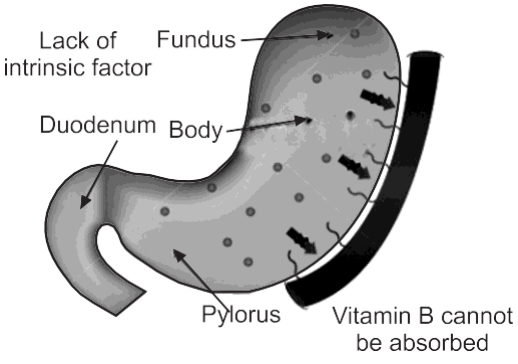

Fig. 7.1 : Pernicious anemia

[III] Pathophysiology of Sickle Cell Anemia

The loss of red blood cell elasticity is central to the pathophysiology of sickle cell anemia. Normal red blood cells are quite elastic, which allows the cells to deform to pass through capillaries. In sickle cell anemia, low-oxygen tensions promotes red blood cell sickling and repeated episodes of sickling damage the cell membrane and decrease the cell's elasticity. These cells fail to return to normal shape when normal oxygen tension is restored. As a consequence, these rigid blood cells are unable to deform as they pass through narrow capillaries, leading to vessel occlusion and ischaemia.

The actual anemia of the illness is caused by hemolysis, the destruction of the red cells inside the spleen, because of their mis-shape. Although the bone marrow attempts to compensate by creating new red cells, it does not match the rate of destruction. Healthy red blood cells typically live for 120 days, but sickle cells only survive 10–20 days.

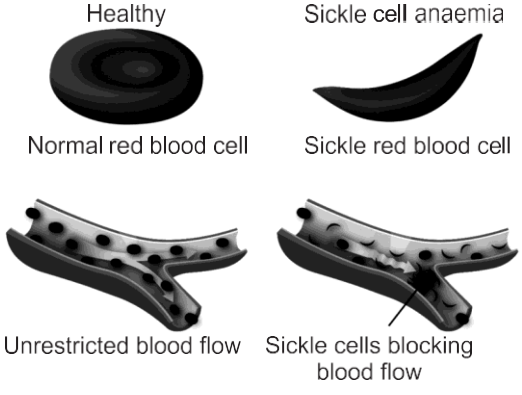

Fig. 7.2 : Normal and Sickle shape RBCs

[IV] Pathophysiology of Thalassemias

Normally, the majority of adult hemoglobin (HbA) is composed of four protein chains, two α and two β globin chains arranged into a heterotetramer. In thalassemia, patients have defects in either the α or β globin chain, causing production of abnormal red blood cells (In sickle-cell disease, the mutation is specific to β globin).

The thalassemias are classified according to which chain of the hemoglobin molecule is affected. In α-thalassemias, production of the α-globin chain is affected, while in β-thalassemia, production of the β-globin chain is affected.

Table 7.3 : Features of normal and sickle RBCs

Normal red blood cell	Sickle red blood cell
Structure: Smooth, flexible disk like structure that allows it to bend and flow through the blood vessels.	Structure : Sticky and stiff crescent shaped cell causing a lack of flow through the blood vessels.
Function: Can flow easily through the body and carry oxygen to all the organs.	Function: Can prohibit blood flow and cause pain to the person and damage to organs.
Hemoglobin: Normal iron rich protein that carries the oxygen throughout the body.	Hemoglobin: It causes the misshape and poor structure in the affected cell.
Recycle about every 120 days	Cells only live about 10-20 days

The β-globin chains are encoded by a single gene on chromosome 11; α-globin chains are encoded by two closely linked genes on chromosome 16. Thus, in a normal person with two copies of each chromosome, two loci encode the β-chain, and four loci encode the α-chain. Deletion of one of the α loci has a high prevalence in people of African or Asian descent, making them more likely to develop α-thalassemia. β-Thalassemias are not only common in Africans, but also in Greeks and Italians.

Symptoms

Anemia symptoms vary depending on the cause of anemia but may include: Fatigue, Weakness, Pale skin, a fast or irregular heartbeat, Shortness of breath, Chest pain, Dizziness, Cognitive problems, Cold hands and feet and Headache.

Initially, anemia can be so mild it goes unnoticed. But symptoms increase as anemia worsens.

Complications

Left untreated, anemia can cause numerous complications, such as:

Heart problems: Anemia can lead to a rapid or irregular heartbeat (arrhythmia). Heart must pump more blood to compensate for the lack of oxygen in the blood in anaemic condition. This can even lead to congestive heart failure.

Death: Some inherited anemias, such as sickle cell anemia, can be serious and lead to life-threatening complications. Losing a lot of blood quickly results in acute, severe anemia and can be fatal.

Tests and Diagnosis

Physical exam: To find out how severe anemia is and to check for possible causes includes:

- Listen to heart for a rapid or irregular heartbeat,
- Listen to lungs for rapid or uneven breathing,
- Feel abdomen to check the size of liver and spleen,
- Pelvic or rectal exam to check for common sources of blood loss.

These findings can be important clues to the underlying etiology of disorder and provide information related to the duration of illness. The skin and mucous membranes are often bypassed, so that pallor, abnormal pigmentation, icterus, spider nevi, petechiae, purpura, angiomas, ulcerations, palmar erythema, coarseness of hair, puffiness of the face, thinning of the lateral aspects of the eyebrows, nail defects, and a usually prominent venous pattern on the abdominal wall are missed in the rush to examine the heart and the lungs.

Complete blood count (CBC): A CBC is used to count the number of blood cells in a sample of blood. For anemia, count of the red blood cells contained in the blood (hematocrit) and the hemoglobin in blood.

Normal adult hematocrit values vary from one to another but are generally between 40 and 52 % for men and 35 and 47 % for women. Normal adult hemoglobin values are generally 14 to 18 grams per deciliter for men and 12 to 16 grams per deciliter for women.

A test to determine the size and shape of red blood cells: Some of red blood cells may also be examined for unusual size, shape and colour. It can help to pinpoint a diagnosis.

For example, in iron deficiency anemia, red blood cells are smaller and paler in colour than normal. In vitamin deficiency anemias, red blood cells are enlarged and fewer in number.

Additional tests:

Iron deficiency anemia can result from chronic bleeding of ulcers, benign polyps in the colon, colon cancer, tumors or kidney problems.

Occasionally, it may be necessary to study a sample of bone marrow to diagnose anemia.

Treatments and Drugs

Anemia treatment depends on the cause.

Ferrous Sulfate Therapy: The appropriate treatment of anemia due to blood loss is correction of the underlying condition and oral administration of ferrous sulfate until the anemia is corrected and for several months afterward to ensure that body stores are replaced with iron. Relatively few indications exist for the use of parenteral iron therapy, and blood transfusions should be reserved for the treatment of shock or hypoxia.

Iron deficiency anemia: This form of anemia is treated with changes in diet and iron supplements. If the underlying cause of iron deficiency is loss of blood, other than from menstruation, the source of the bleeding must be located and stopped. This may involve surgery.

Vitamin deficiency anemia: Folic acid and vitamin C deficiency anemias are treated with dietary supplements and increasing these nutrients in diet. If digestive system has trouble in absorbing vitamin B_{12} from the food the person should take vitamin B_{12} injections.

Anemia of chronic disease: There is no specific treatment for this type of anemia. If symptoms become severe, a blood transfusion or injections of synthetic erythropoietin, a hormone normally produced by kidneys, may help to stimulate red blood cell production and ease fatigue.

Aplastic anemia: Treatment for this anemia may include blood transfusions to boost levels of red blood cells. It may need a bone marrow transplant if bone marrow is diseased and cannot make healthy blood cells.

Hemolytic anemia: Management of hemolytic anemia includes avoiding suspect medications, treating related infections and taking drugs that suppress immune system, which may be attacking red blood cells.

Depending on the severity of anemia, a blood transfusion or plasmapheresis may be necessary. Plasmapheresis is a type of blood-filtering procedure. In certain cases, removal of the spleen can be helpful.

Sickle cell anemia: Treatment for this anemia may include the administration of oxygen, pain-relieving drugs, and oral and intravenous fluids to reduce pain and prevent complications. It may also recommend blood transfusions, folic acid supplements and antibiotics.

A bone marrow transplant may be an effective treatment in some circumstances. A cancer drug called hydroxyurea also used to treat sickle cell anemia.

In anemias of chronic disease, associated with chemotherapy, or associated with renal disease, may require recombinant erythropoietin or epoetin alfa, to stimulate RBC production, since there is also concurrent iron deficiency and inflammation present, parenteral iron is advised to be taken concurrently.

Thalassemia: This anemia may be treated with blood transfusions, folic acid supplements, removal of the spleen (splenectomy) and a bone marrow transplant.

Anemia associated with bone marrow disease: Treatment of these diseases can include simple medication, chemotherapy or bone marrow transplantation.

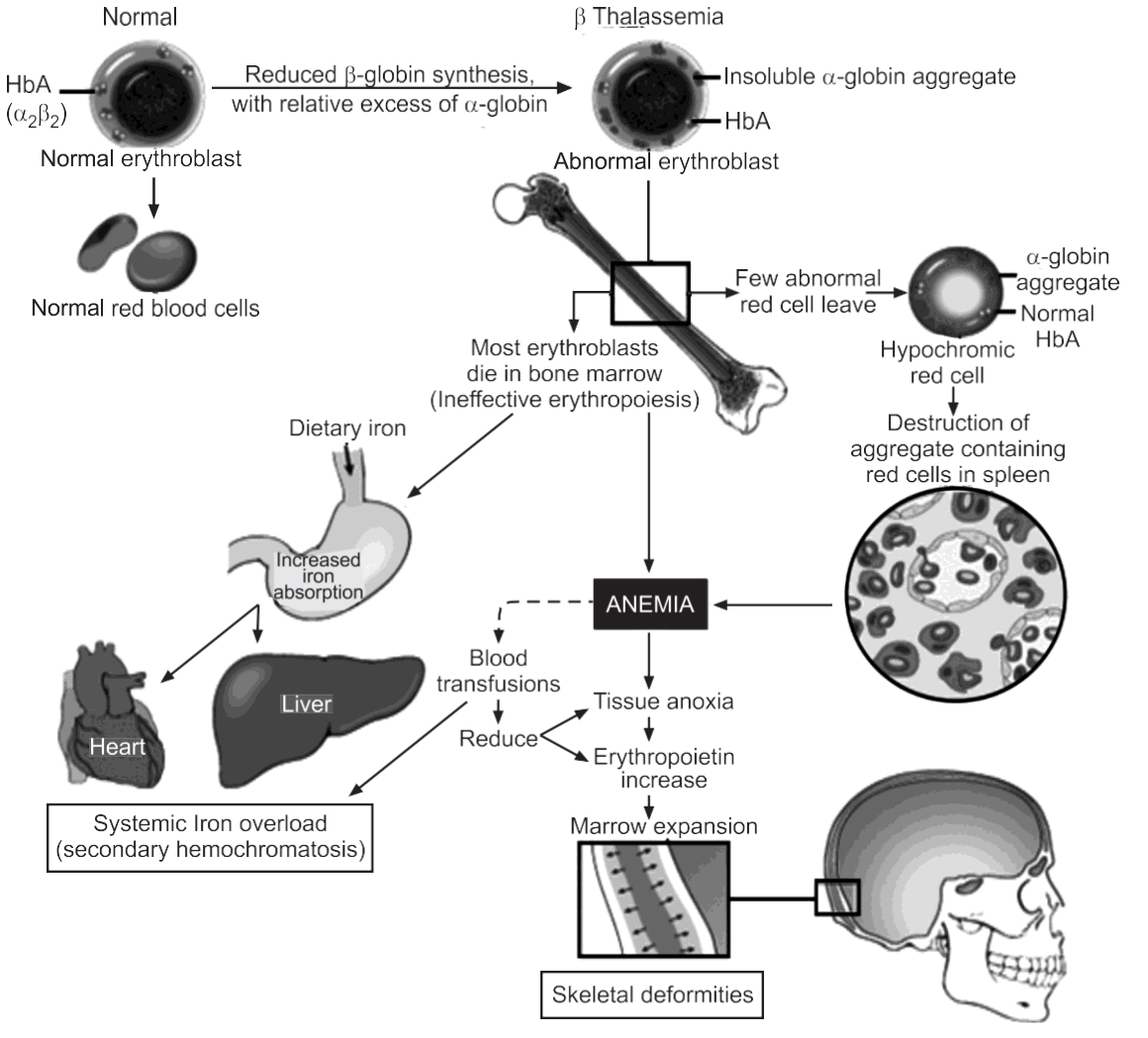

Fig. 7.3 : Pathogenesis of thalassemia

7.1.9 Prevention

Vitamin rich diet: Many types of anemia cannot be prevented. However, iron deficiency anemia and vitamin deficiency anemia can be avoided by choosing a diet that includes a variety of vitamins and nutrients, including:

Iron: Iron-rich foods include beef and other meats, beans, lentils, iron-fortified cereals, dark green leafy vegetables, and dried fruit.

Folate: This nutrient and its synthetic form folic acid can be found in citrus fruits and juices, bananas, dark green leafy vegetables, legumes, and fortified breads, cereals and pasta.

Vitamin B_{12}: This vitamin is found naturally in meat and dairy products. It is also added to some cereals and soya products, such as soya milk.

Vitamin C: Foods containing vitamin C such as citrus fruits, melons and berries help increase iron absorption.

7.2 ACQUIRED HEMOLYTIC ANEMIA

Hemolytic anemia is a condition in which there is destruction of RBC or removal of red blood cells from the circulation before their normal life span of 120 days. Many diseases, conditions, and factors can cause the body to destroy its red blood cells. These causes can be inherited or acquired. "Inherited" means hemolytic anemia occurs due to mutated gene passed from parents to offspring's. "Acquired" means the person is not born with hemolytic anemia, but condition develops later due to failure of his/her own immune system. This happens because the immune system mistakenly recognizes these blood cells as foreign. With acquired hemolytic anemias, red blood cells may be normal. However, some other disease or factor causes the body to destroy red blood cells and remove them from the bloodstream. The destruction of the red blood cells occurs in the bloodstream or, more commonly, in the spleen. Acquired hemolytic anemia can be divided into:

1. Immune Hemolytic Anemia
2. Non- Immune Hemolytic Anemia

Types of Acquired Hemolytic Anemia

1. Immune Hemolytic Anemia: In immune hemolytic anemia, immune system destroys red blood cells.

The three main types of immune hemolytic anemia are:

(i) Autoimmune hemolytic anemia (AIHA),

(ii) Alloimmune hemolytic anemia,

(iii) Drug-induced hemolytic anemia.

(i) Autoimmune hemolytic anemia (AIHA): In this condition, immune system makes antibodies (proteins) that attack red blood cells. AIHA accounts for half of all cases of hemolytic anemia. AIHA may come on very quickly and become serious. Certain diseases or infections can raise risk for AIHA are,

- Autoimmune diseases, such as lupus,
- Chronic lymphocytic leukemia,
- Non-hodgkin's lymphoma and other blood cancers,
- Epstein-Barr virus,
- Cytomegalovirus,
- Mycoplasma pneumonia,
- Hepatitis,
- HIV,
- AIHA also can develop after blood and marrow stem cell transplant.

In some types of AIHA, the antibodies made by the body are called warm antibodies. These are active at warm temperatures and destroy red blood cells. In other types of AIHA, the body makes cold-reactive antibodies. These antibodies are active at cold temperatures. Cold-reactive antibodies can become active when parts of the body, such as the hands or feet, are exposed to temperatures lower than 32 to 50º Fahrenheit (0 to 10º Celsius).Warm antibody AIHA is more common than cold antibody AIHA.

(ii) Alloimmune hemolytic anemia: This type of hemolytic anemia occurs if body makes antibodies against red blood cells that get from a blood transfusion. This occurs due to wrong blood transfusion. This type of hemolytic anemia also can occur during pregnancy if a woman has Rh-negative blood and her baby has Rh-positive blood.

(iii) Drug-induced hemolytic anemia: Certain medication alter normal function of immune system, In these cases, the immune system to mistakenly think the body's own red blood cells are dangerous, foreign substances. Antibodies then develop against the red blood cells. The antibodies attach to red blood cells and cause them to break down too early. Drugs that can cause this type of hemolytic anemia include: Penicillin, Cephalosporin's, Dapsone, Levodopa, Levofloxacin, Methyldopa, Nitrofurantoin, Quinidine, Nonsteroidal anti-inflammatory drugs (NSAIDs), and Phenazopyridine.

2. Non-Immune Hemolytic Anemia:

Non-immune hemolytic anemia associated with high reticulocyte count, slight or marked increase of lactate dehydrogenase (LDH), increase of indirect bilirubin, increase of free Hb in plasma with almost no detection of haptoglobin and negative antihuman immunoglobulin (Coombs) test. Finally in hemolysis is find urobilinogen present in urines.

Non-immune hemolytic anemia occurs due to:

- Microbial infection like malaria, babesiosis, septicemia
- Mechanical trauma
- Antiviral agents (e.g., ribavirin)
- Toxins (e.g., snake venom; plant poisons such as aesculin)
- Paroxysmal nocturnal hemoglobinuria (rare acquired clonal disorder of red blood cell surface proteins)
- Acute viral hepatitis.

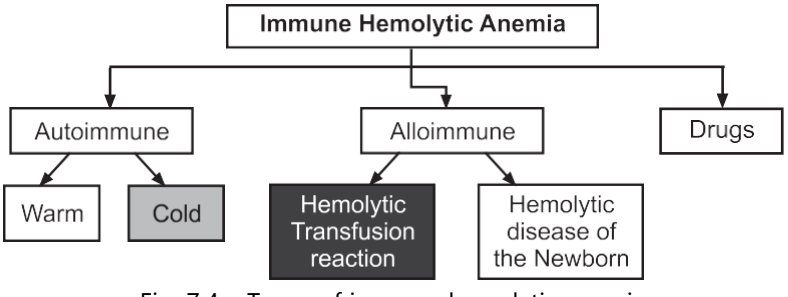

Fig. 7.4 : Types of immune hemolytic anemia

Causes

- Certain chemicals, drugs and toxins.
- Infections.
- Transfusion of blood from a donor with a blood type that does not match.
- Certain cancers.
- When antibodies form against red blood cells for no reason, the condition is called idiopathic autoimmune hemolytic anemia.
- Complication of another disease.
- Past blood transfusions.
- Pregnancy (if the baby's blood type is different from the mother's).

Symptoms

The symptoms acquired in hemolytic anemia are mild. If the problem develops slowly, symptoms that may occur first include:

- Feeling weak or tired more often than usual, or with exercise.
- Headaches.
- Problems concentrating or thinking.

If the anemia gets worse, symptoms may include:

- Lightheadedness when you stand up.
- Pale skin colour (pallor).
- Shortness of breath.
- Sore tongue.

Diagnosis

- Absolute reticulocyte count.
- Direct or indirect Coombs test.
- Hemoglobin in the urine.
- LDH (level of this enzyme rises as a result of tissue damage).
- Red blood cell count (RBC), hemoglobin, and hematocrit.
- Serum bilirubin level.
- Serum free hemoglobin.
- Serum haptoglobin.
- Donath-Landsteiner test.
- Cold agglutinins.
- Free hemoglobin in the serum or urine.
- Hemosiderin in the urine.
- Platelet count.
- Protein electrophoresis – serum.
- Pyruvate kinase.
- Serum haptoglobin level.
- Urine and fecal urobilinogen.

Treatment

The first treatment tried is most often a steroid medicine, such as prednisone. If steroid medicines do not improve the condition, treatment with intravenous immunoglobulin (IVIG) or removal of the spleen (splenectomy) may be considered. If the immune system do not respond to steroids. Drugs such as azathioprine (Imuran), cyclophosphamide (Cytoxan), and rituximab (Rituxan) have been used. Blood transfusions are given with caution, because the blood may not be compatible and it may cause more red blood cell destruction.

Prevention

Screening for antibodies in donated blood and in the recipient may prevent hemolytic anemia related to blood transfusions.

Table 7.4 : Treatment for acquired hemolytic anemia

Type of acquired hemolytic anemia	Treatment	Mechanism
Warm autoimmune hemolytic anemia (WAHA)	Corticosteroid therapy, initiated with the blood transfusion.	Suppress the immune destruction of the transfused red cells.
	High-dose intravenous γ-globulin (IVIgG).	This therapy causes blockage of the reticuloendothelial system and reduces the clearance of the IgG-sensitized red blood cells.
	Splenectomy.	Splenectomy removes the major site of antigen presentation and, in turn, reduces antibody production.
	Vincaalkaloids, azathioprine and cyclophosphamide.	Suppress immune system.

Contd...

	Danazol.	The possible mechanisms include: reduction in red cell bound C_3d; immunomodulation by alteration of T-cell subsets; and reduction of FcR in the reticuloendothelial (RE) system.
Cold autoimmune hemolytic anemia (CAHA)	Plasmapheresis that is transfusion blood in warm temperature.	To reduce the level of IgM cold autoantibody.
	Alkylating agents.	May reduce the production of cold autoantibody.
Alloimmune hemolytic anemia (AHA)	Rh-negative pregnant woman should receive passive immunization with Rh immune globulin at 28-weeks' gestation.	Neutralize antibodies in womb.
Drug-induced hemolytic anemia (DIHA)	Stop drug therapy	
Non-immune hemolytic anemia (NIHA)	Immunosuppressive therapy using corticosteroids, antilymphocyte globulin or cyclosporin A has been used.	

7.3 HEMOPHILIA

Hemophilia is an inherited bleeding disorder in which a person lacks or has low levels of "clotting factors". And as a result, the blood does not clot properly which leads to excessive bleeding. There are 13 types of clotting factors, and these work with platelets to help in formulation of blood clot. According to the World Federation of Hemophilia 9WFH) about one in 10,000 people are born with this disease. People with hemophilia bleed easily, and the blood takes a longer time to clot. People with hemophilia can experience spontaneous or internal bleeding and often have painful, swollen joints due to bleeding into the joints. This rare but serious condition can have life-threatening complications.

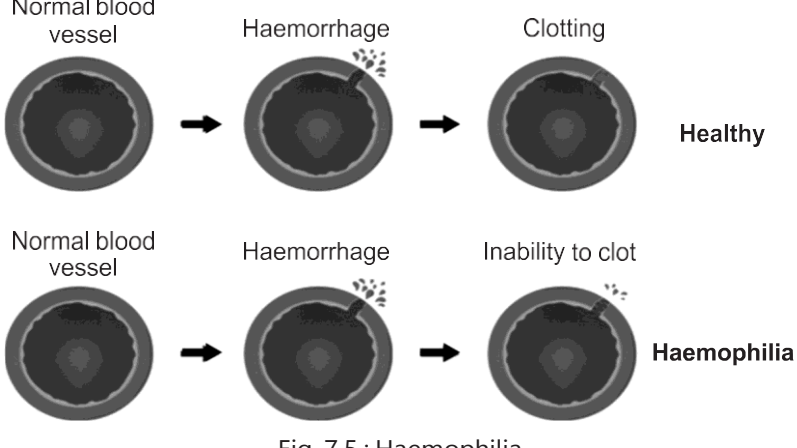

Fig. 7.5 : Haemophilia

Causes

A process in body that is known as "the coagulation cascade" normally pools blood cells together to form a clot to stop bleeding. Blood platelets (platelets and plasma proteins) coagulate, or gather together at the wound site, to form a clot. Then the body's clotting factors work together to create a more permanent plug in the wound. Hemophilia occurs when there is a low level of these clotting factors or the absence of them causes bleeding to continue. Hemophilia is inherited. However, about 30 % of people with hemophilia have no family history of the disorder. In these, people hemophilia is caused by a genetic change (spontaneous mutation).

The three forms of hemophilia are hemophilia A, B and C, and these are classified according to which clotting factor is deficient:

Hemophilia A: Hemophilia A is the most common type of hemophilia, and it is caused by a deficiency in factor VIII. According to the National Heart, Lung and Blood Institute (NHLB), eight out of ten people with hemophilia have hemophilia A.

Hemophilia B: Hemophilia B is also called Christmas disease, which is caused by a deficiency of factor IX.

Hemophilia C: Hemophilia C is a mild form of the disease caused by a deficiency of factor XI. People with this rare type of hemophilia often do not experience spontaneous bleeding. Haemorrhaging typically occurs after trauma or surgery.

Hemophilia is an inherited genetic condition which is not curable, but it can be treated to minimize symptoms and prevent future health complications.

In extremely rare cases, hemophilia can develop after birth called "acquired hemophilia". This is the case in people whose immune system forms antibodies that attack factors VIII or IX.

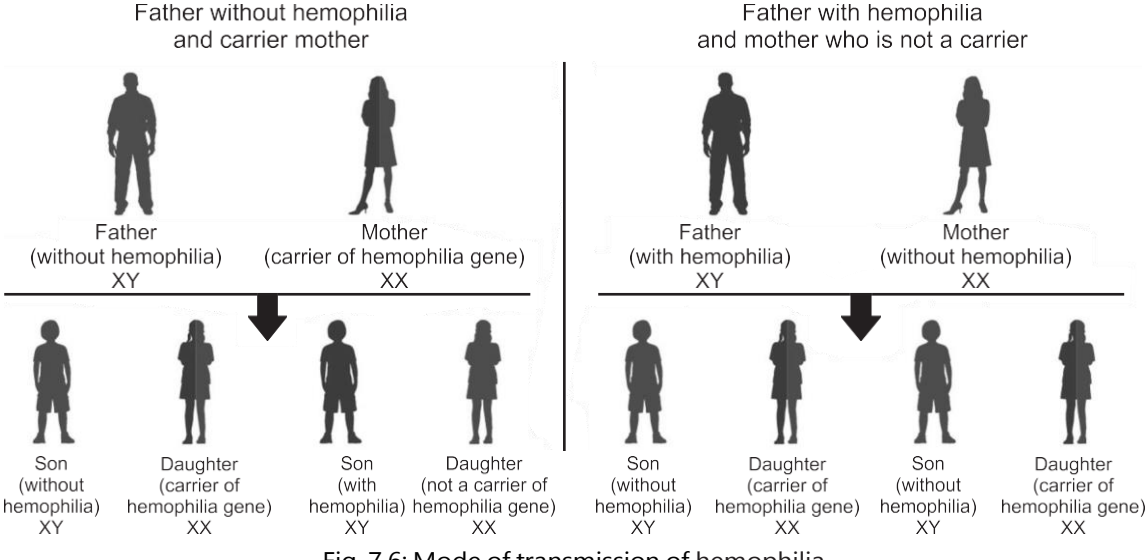

Fig. 7.6: Mode of transmission of hemophilia

Hemophilia inheritance: Everyone has two sex chromosomes, one from each parent. A female inherits an X chromosome from her mother and an X chromosome from her father. A male inherits an X chromosome from his mother and a Y chromosome from his father. Hemophilia inheritance depends on the type of hemophilia:

- Hemophilia A or B: The gene that causes them is located on the X chromosome, so it can not be passed from father to son. Hemophilia A or B almost always occurs in boys and is passed from mother to son through one of the mother's genes. Most women with the defective gene are simply carriers and experience no signs or symptoms of hemophilia. Women can experience bleeding symptoms if their factor VIII or IX is moderately decreased.
- Hemophilia C: This disorder can be passed on to children by either parent. Hemophilia C can occur in girls as well as boys.

Risk Factors

- Hemophilia A and B are more common in males than females because of genetic transmission.
- Hemophilia C is an autosomal inherited form of the disease, meaning that it affects males and females equally. This is because the genetic defect that causes this type of hemophilia is not related to sex chromosomes.

Symptoms of Hemophilia

The extent of symptoms depends on the severity of clotting factor deficiency. People with a mild deficiency may bleed in the case of trauma. People with a severe deficiency may bleed for no reason. This is called "spontaneous bleeding". In children with hemophilia, these symptoms may occur around age 2.

Spontaneous bleeding can cause the following:

- Unexplained and excessive bleeding from cuts or injuries, or after surgery or dental work
- Many large or deep bruises
- Unusual bleeding after vaccinations
- Pain, swelling or tightness in joints
- Blood in urine or stool
- Nosebleeds without a known cause
- In infants, unexplained irritability

Emergency signs and symptoms of hemophilia include:

- Sudden pain, swelling and warmth in large joints, such as knees, elbows, hips and shoulders, and in arm and leg muscles
- Bleeding from an injury, especially in severe form of hemophilia
- Painful, prolonged headache
- Repeated vomiting
- Extreme fatigue
- Neck pain
- Double vision

Complications

Complications of hemophilia may include:

- Deep internal bleeding: Bleeding that occurs in deep muscle can cause limbs to swell. The swelling may press on nerves and lead to numbness or pain.
- Damage to joints: Internal bleeding may also put pressure on joints, causing severe pain. Left untreated, frequent internal bleeding may cause arthritis or destruction of the joint.
- Infection: People with hemophilia are likelier to have blood transfusions, increasing their risk of receiving contaminated blood products. Blood products became safer after the mid-1980s due to screening of donated blood for hepatitis and human

immunodeficiency virus (HIV). The risk of infection through blood products also has decreased substantially since the introduction of genetically engineered clotting products (recombinant factor concentrates).

- Adverse reaction to clotting factor treatment: In some people with hemophilia, the immune system has a negative reaction to the clotting factors used to treat bleeding. When this happens, the immune system develops proteins (known as inhibitors) that inactivate the clotting factors, making treatment less effective.

Diagnosis

Hemophilia is diagnosed through a blood test and measure the amount of clotting factor present. The sample is then graded to determine the severity of the factor deficiency:

- Mild hemophilia is indicated by a clotting factor in the plasma between 5 and 40 %.
- Moderate hemophilia is indicated by a clotting factor in the plasma between 1 and 5 %.
- Severe hemophilia is indicated by a clotting factor in the plasma of less than 1 %.

Treatment

While there is no cure for hemophilia, most people with the disease can lead fairly normal lives.

Treatment for bleeding episodes: Therapies to stop bleeding depend on the type of hemophilia:

- Mild hemophilia A: Slow injection of the hormone desmopressin (DDAVP) into a vein can stimulate a release of more clotting factor to stop bleeding. Occasionally, DDAVP is given as a nasal medication.
- Moderate to severe hemophilia A or hemophilia B: Bleeding may stop only after an infusion of recombinant clotting factor or clotting factor derived from donated human blood. Repeated infusions may be needed if internal bleeding is severe.
- Hemophilia C: Clotting factor XI, the factor missing in this type of hemophilia, plasma infusions are needed to stop bleeding episodes. Patients with Hemophilia C do not generally bleed spontaneously. So there is no need for prophylaxis. If recognized early, all vaccinations should be given subcutaneously because of the risk of inducing a muscle hematoma. These patients should be vaccinated against hepatitis A virus and hepatitis B virus, because they have or may be exposed to plasma products as part of their treatment.
- Clot-preserving medications (antifibrinolytics): These medications help prevent clots from breaking down.
- Fibrin sealants: These medications can be applied directly to wound sites to promote clotting and healing. Fibrin sealants are especially useful in dental therapy.
- Physical therapy: It can reduse signs and symptoms if internal bleeding has damaged joints. If internal bleeding has caused severe damage, may need surgery.
- First aid for minor cuts: Using pressure and a bandage will generally take care of the bleeding. For small areas of bleeding beneath the skin, use an ice pack. Ice pops can be used to slow down minor bleeding in the mouth.

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Chapter...8

ENDOCRINE SYSTEM

8.1 INTRODUCTION TO ENDOCRINE SYSTEM

The endocrine system is a network of glands that produce and release hormones that help to control many important body functions, especially the body's ability to change calories into energy that powers cells and organs.

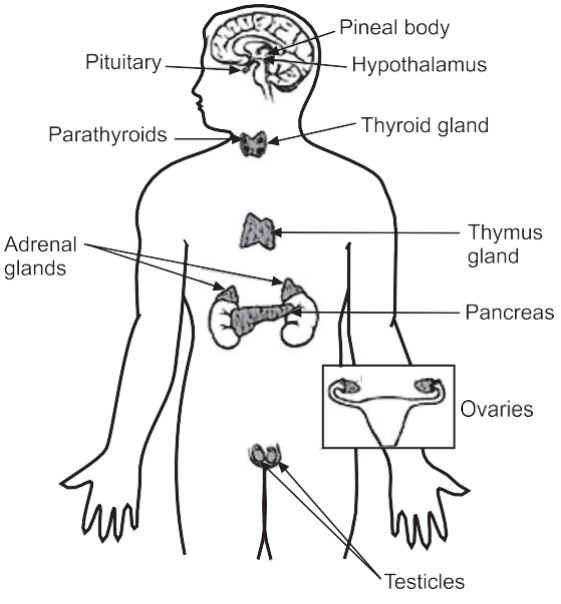


Fig. 8.1 : Location of endocrine glands

Functions

The main function of endocrine glands is to secrete hormones directly into the bloodstream. Hormones are chemical substances that affect the activity of another part of the body (target site). In essence, hormones serve as messengers, controlling and co-ordinating activities throughout the body.

Upon reaching a target site, a hormone binds to a receptor, much like a key fits into a lock. Once the hormone locks into its receptor, it transmits a message that causes the target site to take a specific action. Hormone receptors may be within the nucleus or on the surface of the cell.

Ultimately, hormones control the function of entire organs, affecting such diverse processes as growth and development, reproduction, response to stimuli (stress and injury) and sexual characteristics. Hormones also influence the way the body uses and stores energy and control the volume of fluid and the levels of salts and sugar (glucose) in the blood. Very small amounts of hormones can trigger very large responses in the body.

Although hormones circulate throughout the body, each type of hormone influences only certain organs and tissues. Some hormones affect only one or two organs, whereas others have influence throughout the body. For example, thyroid-stimulating hormone, produced in the pituitary gland, affects only the thyroid gland. In contrast, thyroid hormone, produced in the thyroid gland, affects cells throughout the body and is involved in such important functions as regulating growth of cells, controlling the heart rate, and affecting the speed at which calories are burned.

Insulin, secreted by the islet cells of the pancreas, affects the processing (metabolism) of glucose, protein and fat throughout the body.

Most hormones are proteins. Others are steroids, which are fatty substances derived from cholesterol.

Glands of the Endocrine System

Each gland of the endocrine system releases specific hormones into bloodstream. These hormones travel through blood to other cells and help control or co-ordinate many body processes. Endocrine glands include:

Pituitary gland: A gland found at the base of brain behind the sinuses. It is often called the "master gland" because it influences many other glands, especially the thyroid. The pituitary gland produces several hormones. The front part of pituitary gland commonly called the anterior pituitary produces the following types of hormones:

- Growth hormone: Growth hormone promotes the growth in childhood. For adults, it helps to maintain healthy muscle and bone mass.
- Prolactin: In women, it stimulates milk production. In males, low levels are linked to sexual problems; however, in most of the males, these hormones are inactive.
- Adrenocorticotropic hormone: This hormone promotes the production of cortisol, which helps to reduce stress, and maintains healthy blood pressure.
- Thyroid-stimulating hormone: This hormone helps to regulate the body's thyroid, which is crucial in maintaining a healthy metabolism.
- Luteinizing hormone: In women, this hormone regulates estrogen. In men, it regulates testosterone.
- Follicle-stimulating hormone: Found in both men and women. It stimulates the releasing of eggs in women and in man, it helps ensure the normal function of sperm production.
- The back part of the pituitary gland is called the posterior pituitary. It produces the following two hormones:

  Oxytocin: Oxytocin is involved in a variety of processes, such as contracting the uterus during childbirth and also promotes milk flow in nursing mothers.

  Antidiuretic hormone: Commonly referred to as vasopressin, this hormone helps to regulate water balance in the body.

Hypothalamus

A part of brain that controls hormone production by releasing different chemicals to the pituitary gland. The hypothalamus is in control of pituitary hormones by releasing the following types of hormones:

- Thyrotrophic-releasing hormone
- Growth hormone-releasing hormone
- Corticotrophin-releasing hormone
- Gonadotropin-releasing hormone

Adrenal glands: Two adrenal glands located on the top of the kidneys' release the hormone cortisol and adrenaline. Adrenal glands are involved in:

- Promoting proper cardiovascular function.
- Properly utilizing carbohydrates and fats.
- Helps to distribute stored fat.
- Promotes healthy gastrointestinal functions.

Thyroid: A butterfly-shaped gland in the front of the neck that controls metabolism.

Ovaries: The ovaries are two small organs located on either side of the uterus

in a woman's body that release eggs and produce sex hormones. This gland produces both estrogen and progesterone, which promote the development of breasts. They also help to maintain healthy menstrual periods.

Islet cells in the pancreas: Cells in the pancreas control the release of the hormones insulin and glucagon. The main function of the pancreas is to maintain healthy blood sugar levels.

Parathyroid: This gland is vital to proper bone development because it helps in controlling both calcium and phosphorous levels in the body. The parathyroid gland is actually a group of four small glands located behind the thyroid gland.

Pineal gland: A gland found near the center of the brain that may be linked to sleep patterns.

Testes: The male reproductive glands that produce sperm and sex hormone testosterone. It regulates production of sperm and stimulates the development and maintenance of male secondary sex characteristics, such as beard growth and deepening of the voice. Other functions of testosterone include:

- Maintaining sex drive.
- Maintaining healthy levels of muscle and bone mass.

Thymus: This gland secretes hormones that are commonly referred to as humoral factors and are important during puberty. The role of these hormones is to make sure a person develops a healthy immune system.

Even the slightest hiccup with the function of one or more of these glands can throw off the delicate balance of hormones in body and lead to an endocrine disorder, or endocrine disease.

Causes of Endocrine Disorders

Endocrine disorders are typically grouped into two categories:

- Endocrine disease that results when a gland produces too much or too little of an endocrine hormone, called a hormone imbalance.
- Endocrine disease due to the development of lesions (such as nodules or tumors) in the endocrine system, which may or may not affect hormone levels.

The endocrine's feedback system helps control the balance of hormones in the bloodstream. If body has too much or too little of a certain hormone, the feedback system signals the proper gland or glands to correct the problem. A hormone imbalance may occur if this feedback system has trouble keeping the right level of hormones in the blood stream, or if body does not clear them out of the blood stream properly.

Increased or decreased levels of endocrine hormone may be caused by:

- A problem with the endocrine feedback system.
- Disease condition.
- Failure of a gland to stimulate another gland to release hormones (for example, a problem with the hypothalamus can disrupt hormone production in the pituitary gland).
- A genetic disorder, such as multiple endocrine neoplasia or congenital hypothyroidism.
- Infection.
- Injury to an endocrine gland.
- Tumor of an endocrine gland.

Most endocrine tumors and nodules (lumps) are noncancerous. They usually do not spread to other parts of the body. However, a tumor or nodule on the gland may interfere with the gland's hormone production.

Types of Endocrine Disorders

Numerous problems can occur in the endocrine system. These can be considered as excessive or deficient hormone production. Endocrine organs are also prone to tumours (adenomas) which can over-produce hormones. Some problems of the endocrine system include:

Diabetes mellitus: Too much sugar in the blood caused by problems with insulin production. This includes type 1 diabetes (deficiency of insulin) and type 2 diabetes (initially excessive, then deficiency of insulin).

Diabetes insipidus: The most common abnormality with the dysfunction of posterior pituitary is diabetes insipidus. This disorder is due to defects in antidiuretic hormone receptors or an inability to secrete ADH.

Hyperthyroidism: The thyroid gland produces too much thyroid hormone, leading to weight loss, fast heart rate, sweating, and nervousness. The most common cause for an overactive thyroid is an autoimmune disorder called Grave's disease.

Hypothyroidism: The thyroid gland does not produce enough thyroid hormone, leading to fatigue, constipation, dry skin, and depression. The underactive gland can cause slowed development in children. Some types of hypothyroidism are present at birth.

Menstruation abnormalities: Polycystic ovarian syndrome (PCOS), pituitary adenoma or primary ovarian failure (POF) may cause irregular menstruation or lack of menstruation.

Parathyroid problems: An enlargement of one or more of the parathyroid glands can lead to high calcium levels in the blood (hypercalcemia).

Pituitary adenomas: These are tumours of the pituitary gland that can make too much of a certain hormone or cause deficiencies of hormones. These tumours can be small (microadenomas) or large (macroadenomas).

Adrenal insufficiency: The adrenal gland releases too little of the hormone cortisol and sometimes, aldosterone. Addison's disease is a type of adrenal insufficiency.

Cushing's disease: Overproduction of a pituitary gland hormone leads to an overactive adrenal gland. A similar condition called Cushing's syndrome may occur in people, particularly children, who take high doses of corticosteroid medications.

Gigantism (acromegaly) and other growth hormone problems: If the pituitary gland produces too much growth hormone, a child's bones and body parts may grow abnormally fast. If growth hormone levels are too low, a child can stop growing in height.

Hypopituitarism: The pituitary gland releases little or no hormones. It may be caused by a number of different diseases. Women with this condition may stop getting their periods.

DIABETES MELLITUS

Diabetes mellitus is a metabolic disorder, in which glucose level in the blood is much higher than normal (hyperglycemia) and hence this condition is also commonly referred to as sugar disease. The defect in this condition is that, either the pancreas does not produce enough insulin or it produces sufficient insulin, but the cells of the body are unable to use the insulin properly. Insulin, a hormone released from the pancreas, controls the amount of glucose in the blood. Glucose in the bloodstream stimulates the pancreas to produce insulin. Insulin allows glucose to move from the blood into the cells. Once inside the cells, glucose is converted to energy, which is used immediately, or the glucose is stored as fat or glycogen until it is needed. The levels of glucose in the blood vary normally throughout the day. They rise after a meal and return to normal within about 2 hours after eating. Once the levels of glucose in the blood return to normal, insulin production decreases. The variation in blood glucose levels is usually within a narrow range, about 70 to 110 milligrams per deciliter (mg/dL) of blood in healthy people. If people eat a large amount of carbohydrates, the levels may increase more. People older than 65 years tend to have slightly higher levels, especially after eating. Insulin is like a key which opens the body cell doors to allow glucose to enter. In the absence of enough insulin, glucose cannot enter the cells and remains in the blood stream in high amounts (hyperglycemia). If the body does not produce enough insulin to move the glucose into the cells, or if the cells stop responding normally to insulin, the resulting high levels of glucose in the blood and the inadequate amount of glucose in the cells together produce the symptoms and complications of diabetes.

Multitude of Mechanisms

The body's response to blood sugar requires the co-ordination of an array of mechanisms. Failure of any one component involved in insulin regulation, secretion, uptake or breakdown can lead to the build-up of glucose in the blood.

β-cells damage: Destruction or damage to the β-cells, lead to increased levels of blood glucose.

Classification

There are two major types of diabetes: Primary and Secondary

[I] Primary or Idiopathic Diabetes Mellitus

It is most common with unknown cause of diabetes. It is further divides into

- Type 1 Diabetes (5-10%)
- Type 2 Diabetes (90-95%)
- Gestational Diabetes.

Type I Diabetes mellitus (Insulin-dependent diabetes mellitus (IDDM) or Juvenile diabetes): It results from the body's failure of insulin production by β-cells of the islets of Langerhans in the pancreas, leading to insulin deficiency. This type can be further classified as immune-mediated or idiopathic. Most of type 1 diabetes is of the immune mediated nature, in which a T-cell mediated autoimmune attack leads to the loss of β-cells and thus insulin. Only about 10% of all people with diabetes have type 1 disease. Onset most often occurs in childhood, but most people who have type 1 diabetes develop the disease before age 30, although it can develop later in life.

The exact cause is not known but attributed to an environmental factor; possibly a viral infection or a nutritional factor during childhood or early adulthood

causes the immune system to destroy the insulin producing β-cells of the pancreas. A genetic predisposition may make some people more susceptible to the environmental factor.

Type II Diabetes mellitus (non–insulin-dependent diabetes mellitus, or Adult/maturity onset diabetes mellitus):

This form of diabetes, which accounts for 90% of those with diabetes, encompasses individuals who have insulin resistance, diminished tissue sensitivity to insulin, impaired β-cell function (delayed or inadequate insulin release) and excessive or inappropriate glucagon secretion. Type II diabetes may occur at any age but more common in people older than the age of 40. There are probably many different causes of this form of diabetes. Although the specific etiologies are not known, autoimmune destruction of β-cells does not occur but it is attributed to typical genetic makeup, familial history, obesity and defect in insulin receptor. Type II diabetes also tends to run in families.

Obesity is the chief risk factor for developing type II diabetes, and 80 to 90% of people with this disorder are overweight or obese. Because obesity causes some degree of insulin resistance, obese people need very large amounts of insulin to maintain normal blood glucose levels.

Certain disorders and drugs can affect the way the body uses insulin and can lead to type II diabetes. High levels of corticosteroids (due to Cushing disease or taking corticosteroid drugs) and pregnancy are the most common causes of altered insulin use. Diabetes also may occur in people with excess production of growth hormone (acromegaly) and in people with certain hormone-secreting tumors. Severe or recurring pancreatitis and other disorders that directly damage the pancreas can lead to diabetes.

Gestational diabetes: Diabetes can occur temporarily during pregnancy, and it occurs in 2% to 10% of all pregnancies. Significant hormonal changes during pregnancy can lead to blood sugar elevation in genetically predisposed individuals. Blood sugar elevation during pregnancy is called gestational diabetes.

Gestational diabetes usually resolves once the baby is born. However, 35% to 60% of women with gestational diabetes will eventually develop type II diabetes over the next 10 to 20 years, especially in those who require insulin during pregnancy and those who remain overweight after their delivery.

[II] Secondary Diabetes

It is the type of diabetes mellitus and have definite cause of hyperglycemia.

Secondary diabetes refers to elevated blood sugar levels from another medical condition. Secondary diabetes may develop when the pancreatic tissue responsible for the production of insulin is destroyed by disease, such as chronic pancreatitis (inflammation of the pancreas by toxins like excessive alcohol), trauma, or surgical removal of the pancreas.

Diabetes can also result from other hormonal disturbances, such as excessive growth hormone production (acromegaly) and Cushing's syndrome. In acromegaly, a pituitary gland tumor at the base of the brain causes excessive production of growth hormone, leading to hyperglycemia. In Cushing's syndrome, the adrenal glands produce an excess of cortisol, which promotes blood sugar elevation.

In addition, certain medications may worsen diabetes control, or "unmask" latent diabetes. This is seen most commonly when steroid medications (such as prednisone) are taken and also with medications used in the treatment of HIV infection (AIDS).

Pathophysiology

Insulin is the principal hormone that regulates the uptake of glucose from the blood into most cells of the body, especially liver, muscle and adipose tissue. Therefore, deficiency of insulin or the insensitivity of its receptor plays a central role in all forms of diabetes mellitus.

The body obtains glucose from three main places: the intestinal absorption of food, the breakdown of glycogen; the storage form of glucose found in the liver, and gluconeogenesis, the generation of glucose from non-carbohydrate substrates in the body.

Insulin plays a critical role in balancing glucose levels in the body. Insulin can inhibit the breakdown of glycogen or the process of gluconeogenesis, it can stimulate the transport of glucose into fat and muscle cells, and it can stimulate the storage of glucose in the form of glycogen.

Insulin is released into the blood by β-cells, found in the islets of Langerhans in the pancreas, in response to rising levels of blood glucose, typically after eating. Insulin is used by about two-thirds of the body's cells to absorb glucose from the blood for use as fuel, for conversion to other needed molecules, or for storage. Lower glucose levels result in decreased insulin release from the β-cells and in the breakdown of glycogen to glucose. This process is mainly controlled by the hormone glucagon, which acts in the opposite manner to insulin.

If the amount of insulin available is insufficient, if cells respond poorly to the effects of insulin (insulin sensitivity or insulin resistance) or if the insulin itself is defective, then glucose will not be absorbed properly by the body cells that require it, and it will not be stored appropriately in the liver and muscles. The net effect is persistently high levels of blood glucose, poor protein synthesis, and other metabolic derangements, such as acidosis.

Clinical Manifestations Of Diabetes Mellitus

People with type II diabetes often do not have any symptoms. When symptoms do occur, they are often ignored because they may not seem serious. Symptoms in type I diabetes usually occurs much more suddenly and are often severe.

Common symptoms of diabetes include:

- The early symptoms of untreated diabetes are related to elevated blood sugar levels, and loss of glucose in the urine (glycosuria).
- In response to glycosuria, kidneys excrete additional water to dilute the excessive glucose, called polyuria.
- High amount of glucose in the urine can cause increased urine output and lead to dehydration. Dehydration causes increased thirst (polydipsia) and water consumption.
- The inability of insulin to perform normally has effects on protein, fat and carbohydrate metabolism. Insulin is an anabolic hormone, that is, one that encourages storage of fat and protein.
- Excessive loss of calories in urine results in weakness. The loss of energy in turn, causes excessive hunger called polyphagia.

- A relative or absolute insulin deficiency eventually leads to weight loss despite an increase in appetite.
- Patients with diabetes are prone to developing infections of the bladder, skin, and vaginal areas.
- Fluctuations in blood glucose levels can lead to blurred vision. Extremely elevated glucose levels can lead to lethargy and coma.
- Itching skin, especially in the groin or vaginal area.
- Slow-healing sores or cuts.

Other symptoms of untreated diabetes patients include drowsiness, fatigue, renal failure, various opportunistic infections, nausea and vomiting.

Effects of Diabetes

Poor Control of Diabetes can lead to an Increased Risk of Following Diseases:

Ketoacidosis: The cellular metabolism of untreated type I diabetes is similar to that of a starving person. Because insulin is not present to aid the entry of glucose into body cells, most cells use fatty acids to produce ATP. Stores of triglycerides in adipose tissue are catabolized to yield fatty acids and glycerol. The by-product of fatty acid breakdown is organic acid called ketones and ketone bodies. Accumulation and buildup of ketones causes blood pH to fall, a condition is known as Ketoacidosis, unless treated quickly, ketoacidosis can cause death.

Cardiovascular disease: The breakdown of stored triglycerides also causes weight loss. As lipids are transported by the blood from storage depots to cells, lipid particles are deposited on the walls of blood vessels, leading to atherosclerosis and multitude of cardiovascular problems, including cerebrovascular insufficiency (excess acid is potent poison for brain), ischemic heart disease, peripheral vascular disease and gangrene.

Blindness: A major complication of diabetes is loss of vision either due to cataracts (excessive glucose attaches to lens proteins, causing cloudiness) or due to damage to blood vessels of the retina.

Kidney and bladder failure: Severe kidney problems also may result from damage to renal blood vessels.

Other complication include: Gum disease, foot and leg infections, sexual dysfunction and complications of pregnancy.

Diagnosis

Elevated blood glucose level is often the fundamental basis for the diagnosis of diabetes mellitus. Regular checking of fasting and post meal blood glucose level is a standard method of diagnosis. A random plasma glucose concentration above 250mg/dL is also an indication of diabetes mellitus.

Blood sugar estimation using a glucometer can be done at different times and the three common time points are:

Fasting Plasma Glucose (FPG): Testing blood sugar levels after 8 hours of fasting, usually overnight fasting.

Postprandial Plasma Glucose (PPG): Testing blood sugar levels 2 hours after a meal (usually it is breakfast).

Random or casual sugar: Any time of the day irrespective of meal intake.

The interpretation of results is shown in table 8.1.

Oral Glucose Tolerance Test (OGTT): Test done to confirm the diagnosis in

doubtful cases (i.e. cases were FPG and/or PPG are in the borderline range). In this test, one has to drink 75 g glucose (sugar) in water on empty stomach and blood sugar is to be tested after 2 hours.

The interpretation of the results is shown in table 8.1.

Table 8.1: The tests commonly done and their interpretation

Test	Normal	Borderline (IFG/IGT)	Diabetes
FPG	80-100	100-125	>126
2 hr. PPG	Up to 140	140-199	>200

Table 8.2: OGTT and its interpretation

Test	Normal	Borderline (IFG/IGT)	Diabetes
Result (2 hour value) (mg/dl)	140	>140 but <200	>200
Interpretation	NGT	IGT	DM

NGT = Normal Glucose Tolerance; IFG = Impaired Fasting Glucose (Pre diabetes); IGT = Impaired Glucose Tolerance (Pre diabetes); DM = Diabetes Mellitus; 25 - 40% patients with IGT progress to DM

Urine sugar testing alone is not recommended for diagnosis. Presence of glucose in urine (glycosuria) is also a diagnostic criterion for diabetes but may be false positive or false negative. Since diabetes glycosuria is differentiated from other form of glycosuria.

Test for ketones: Presence of ketone bodies in urine (ketonuria) is used to assess the severity of diabetes mellitus.

Table 8.3: Comparison of BSL in normal and diabetic patients

Blood sugar test	Normal	Diabetes mellitus
Fasting blood glucose	80- 100 mg/dl	> 120 mg/dl
2 hours Post lunch	130-160 mg/dl	> 180 mg/dl

Management and Treatment

The major goal in treating diabetes is to keep blood sugar (glucose) levels as close to normal as possible, without causing abnormally low levels of blood sugar (hypoglycemia).

Lifestyle modifications are the cornerstone of management of diabetes mellitus and include the healthy diet (high protein and low carbohydrate and fat diet), management of stress, avoidance of alcohol and tobacco etc. are found to be effective to control the diabetes along with drugs.

Type I diabetes is treated with insulin, exercise, and a diabetic diet.

Type II diabetes is treated first with weight reduction, a diabetic diet, and exercise.

Patients with type I diabetes mellitus require lifelong insulin therapy. Most require 2 or more injections of insulin daily, with doses adjusted on the basis of self-monitoring of blood glucose levels.

Early initiation of pharmacologic therapy is associated with improved glycemic control and reduced long-term complications in type II diabetes.

Drug classes used for the treatment of type II diabetes include the following:

Metformin: Generally, metformin is the first medication prescribed for type II diabetes. It works by improving the sensitivity of body

tissues to insulin so that, body uses insulin more effectively. Metformin also lowers glucose production in the liver.

Sulfonylureas: These medications help body secrete more insulin. e.g. Glyburide, glipizide, and glimepiride.

Meglitinides: These medications work like sulfonylureas by encouraging the body to secrete more insulin, but they are faster acting, and they do not stay active in the body for as long. e.g. Repaglinide and nateglinide.

Thiazolidinediones: Like metformin, these medications make the body's tissues more sensitive to insulin. e.g. Rosiglitazone and pioglitazone.

Selective Dipeptidyl Peptidase-4 Inhibitors (DPP-4 inhibitors): These medicines help to keep blood sugar in a target range without causing low blood sugar or weight gain, but tend to have a modest effect. e.g. Sitagliptin, saxagliptin, and linagliptin.

GLP (Glucogon like peptide)-1 receptor agonists: These medications slow digestion and help lower blood sugar levels, though not as much as sulfonylureas. e.g. Exenatide and liraglutide.

Sodium-glucose co-transporter 2 (SGLT2) inhibitors (SGLT2 inhibitors): These are a new class of diabetic medications indicated only for the treatment of type II diabetes. In conjunction with exercise and a healthy diet, they can improve glycemic control. They work by preventing the kidneys from reabsorbing sugar in the blood. Instead, the sugar is excreted in the urine and it lowers blood glucose level. e.g. Canagliflozin, and dapagliflozin.

Insulin therapy: Some people who have type II diabetes need insulin therapy as well. In the past, insulin therapy was used as last resort, but today it is often prescribed sooner because of its benefits.

Regular monitoring of the blood and urine glucose level, during treatment is essential part of management. These results indicate the appropriate change required in the treatment.

The overdose of insulin or hypoglycemic agent may result in hypoglycemia. Symptoms of hypoglycemia include: Anxiety, confusion, extreme hunger, fatigue, irritability, sweating or clammy skin and trembling hands which need immediate treatment. If sugar levels continue to fall during an insulin overdose, serious complications such as Seizures, unconsciousness and pale skin can occur. Untreated hypoglycemia may cause permanent brain damage and hypoglycemic coma.

8.3 THYROID DISEASES

Thyroid is a small butterfly-shaped gland inside the neck, located in front of the trachea (windpipe) and below the larynx (voicebox). It produces two thyroid hormones, triiodothyronine (T3) and thyroxine (T4) that travel through the blood to all tissues of the body. Thyroid hormones regulate how the body breaks down food and either uses that energy immediately or stores it for the future. In other words, thyroid hormones regulate body's metabolism as well as the consumption of oxygen and the production of heat. Pituitary glands controls how well the thyroid works by producing thyroid-stimulating hormone (TSH). The bloodstream carries TSH to the thyroid gland to produce more thyroid hormones, as needed.

Hypothyroidism

Too little thyroid hormone from an underactive thyroid gland is called hypothyroidism. In hypothyroidism, the body's metabolism is slowed. Several causes for this condition exist, most of which affect the thyroid gland directly, impairing its ability to make enough hormone. More rarely, there may be a pituitary gland tumor, which blocks the pituitary from producing TSH. Whether the problem is caused by the thyroid or by the pituitary gland, the result is that the thyroid is producing too few hormones, causing many physical and mental processes to become sluggish. The body consumes less oxygen and produces less body heat.

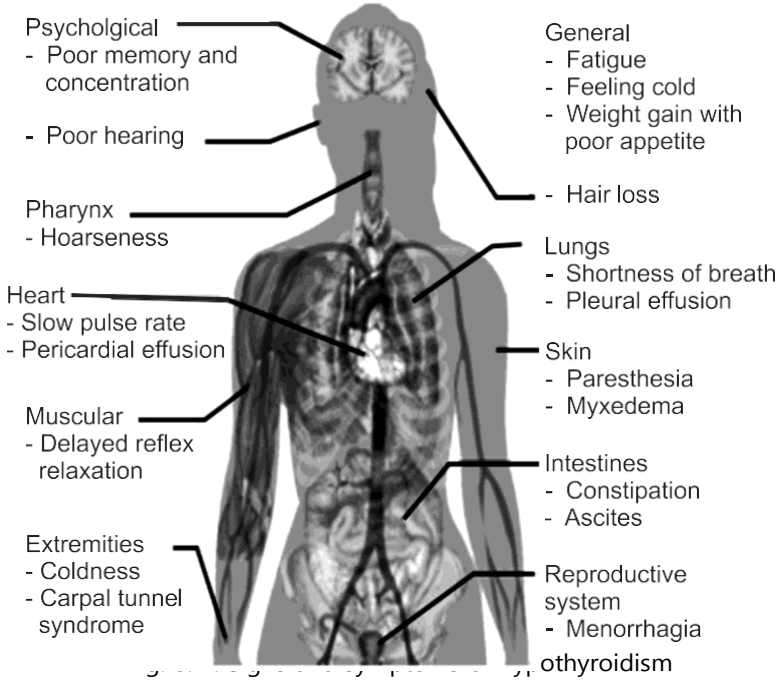
Symptoms of Hypothyroidism:

Symptoms of hypothyroidism can include:

- Fatigue,
- Poor concentration or feeling mentally "foggy",
- Dry skin,
- Constipation,
- Feeling cold,
- Fluid retention,
- Muscle and joint aches,
- Depression,
- Prolonged or excessive menstrual bleeding in women.

Some common causes of hypothyroidism include:

- Hashimoto's thyroiditis (an autoimmune condition that causes inflammation of the thyroid gland).
- Thyroid hormone resistance.
- Other types of thyroiditis (inflammation of the thyroid), such as acute thyroiditis and postpartum thyroiditis.



othyroidism

Hyperthyroidism

Too much thyroid hormone from an overactive thyroid gland is called hyperthyroidism. This hormone imbalance occurs in about 1 % of all women, who get hyperthyroidism more often than men. One of the most common forms of hyperthyroidism is known as Graves' disease. This autoimmune disorder tends to run in families. The thyroid gland is producing too much hormone in hyperthyroidism, the body develops an increased metabolic state, with many body systems developing abnormal function.

In mild cases, there may not be apparent symptoms. Symptoms and signs of hyperthyroidism can include:

- Tremor,
- Nervousness,
- Fast heart rate,
- Fatigue,
- Intolerance for heat,
- Increase in bowel movements,
- Increased sweating,
- Concentration problems,
- Unintentional weight loss,

Some of the most common causes of hyperthyroidism are:

- Graves' disease,
- Toxic multinodular goiter,
- Thyroid nodules that overexpress thyroid hormone (known as "hot" nodules),
- Excessive iodine consumption.

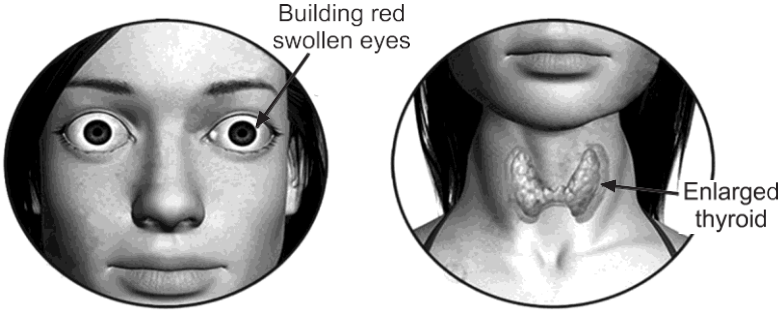


Fig. 8.3 : Symptoms of hyperthyroidism

Thyroiditis

Thyroiditis is inflammation of the thyroid. It occurs when the body's immune system makes antibodies that attack the thyroid. Causes of thyroiditis include:

- Autoimmune diseases like type I diabetes and rheumatoid arthritis,
- Genetics,
- Viral or bacterial infection,
- Certain types of medicines.

Two common types of thyroiditis are Postpartus thyroiditis and Hashimoto's disease.

Postpartus thyroiditis: It is inflammation of the thyroid after giving birth, affects 10% of women. It often goes undiagnosed because symptoms are much like the "baby blues" that may follow delivery. Women with postpartum thyroiditis may feel very tired and moody.

Postpartum thyroiditis typically happens in two phases, though not everyone with the condition goes through both phases:

- The first phase starts 1 to 4 months after giving birth and typically last 1 to 2 months with signs and symptoms of hyperthyroidism, because the damaged

thyroid leaks thyroid hormones out into the bloodstream.

- The second phase starts about 4 to 8 months after delivery and lasts 6 to 12 months with signs and symptoms of hyperthyroidism because the thyroid has lost most of its hormones or because the immune attack is over and the thyroid may recover later.

Hashimoto's disease: Hashimoto's disease is also known as chronic lymphocytic thyroiditis. It can occur at any age, but most common in middle-aged women. The disease occurs when the body's immune system mistakenly attacks and slowly destroys the thyroid gland and its ability to produce hormones.

Some people with mild cases of Hashimoto's disease may have no obvious symptoms. The disease can remain stable for years, and symptoms are often subtle and also not specific, which means they mimic symptoms of many other conditions.

- Fatigue,
- Depression,
- Constipation,
- Mild weight gain,
- Dry skin,
- Dry, thinning hair,
- Pale, puffy face,
- Heavy and irregular menstruation,
- Intolerance to cold,
- Enlarged thyroid, or goiter.

Hashimoto's diagnosis and treatment: Testing the level of TSH is often the first step when screening for any type of thyroid disorder. It include blood test to check for increased levels of TSH as well as low levels of thyroid hormone (T3 or T4) if experiencing some of the above symptoms.

Hashimoto's disease is an autoimmune disorder, so the blood test shows abnormal antibodies that might be attacking the thyroid.

Treatment

There is no known cure for Hashimoto's disease. Hormone-replacing medication is often used to raise thyroid hormone levels or lower TSH levels. It can also help relieve the symptoms of the disease. Surgery might be necessary to remove part or all of the thyroid gland in rare advanced cases of Hashimoto's. The disease is usually detected at an early stage and remains stable for years because it progresses slowly.

8.4 GRAVES' DISEASE

Graves' is an autoimmune disorder that occurs when the body's immune system mistakenly attacks the thyroid gland. This can cause the gland to overproduce the hormone, responsible for regulating metabolism.

The disease is hereditary and may develop at any age in men or women, but it is much more common in women ages 20 to 30. Other risk factors include stress, pregnancy and smoking.

When there is a high level of thyroid hormone in bloodstream, body's systems speed up and cause symptoms that are common to hyperthyroidism. These include:

- Anxiety,
- Irritability,
- Fatigue,
- Hand tremors,
- Increased or irregular heartbeat,
- Excessive sweating,
- Difficulty sleeping,
- Diarrhoea or frequest bowel movements,
- Altered menstrual cycle,
- Goiter,
- Bulging eyes and vision problems.

Graves' Disease: Diagnosis and Treatment:

A simple physical exam can reveal an enlarged thyroid, enlarged bulging eyes, and signs of increased metabolism, including rapid pulse and high blood pressure.

Blood tests to check for high levels of T4 and low levels of TSH, both of which are signs of Graves' disease.

A radioactive iodine uptake test may also be administered to measure how quickly thyroid takes up iodine. A high uptake of iodine is consistent with Graves' disease.

8.4.1 Treatment

There is no treatment to stop the immune system from attacking the thyroid gland and causing it to overproduce hormones. However, the symptoms of Graves' disease can be controlled in several ways, often with a combination of treatments:

- β-blockers to control rapid heart rate, anxiety and sweating.
- Antithyroid medications to prevent thyroid from producing excessive amounts of hormone.
- Radioactive iodine to destroy all or part of thyroid.
- Surgery to remove thyroid gland, a permanent option if one cannot tolerate antithyroid drugs or radioactive iodine.

Successful hyperthyroidism treatment usually results in hypothyroidism and may require hormone-replacement medication from that point forward. Graves' disease can lead to heart problems and brittle bones, if it is left untreated.

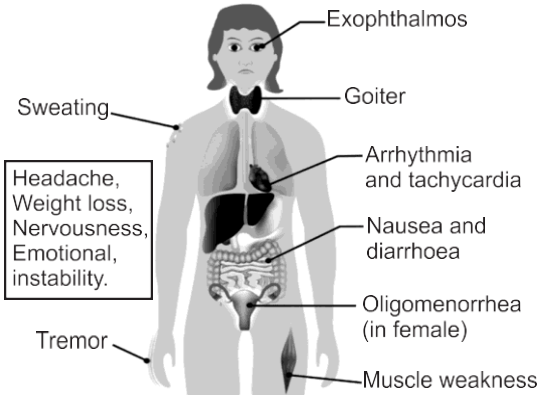


Fig. 8.4 : Symptoms of Grave's disease

Thyroid Nodules

Nodules are lumps or abnormal masses within the thyroid. Nodules can be caused by benign cysts, benign tumors, or, less commonly, by cancers of the thyroid (most nodules are not cancerous). Nodules may be single or multiple and can vary in size. If nodules are excessively large, they may causes symptoms related to compression of nearby structures.

Some thyroid nodules may produce too much thyroid hormone and cause hyperthyroidism, or become too large, interfering with breathing or swallowing or causing neck discomfort.

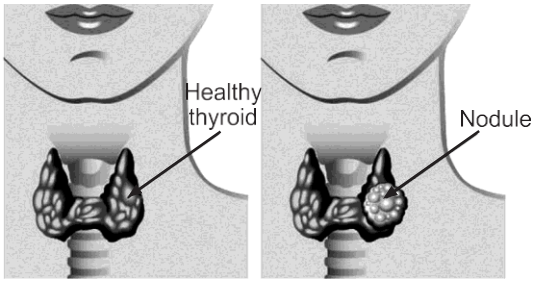


Fig. 8.5 : Thyroid nodule

Thyroid Cancer

Thyroid cancer occurs in the cells of the thyroid gland and it is more common among adult women than men or youth.

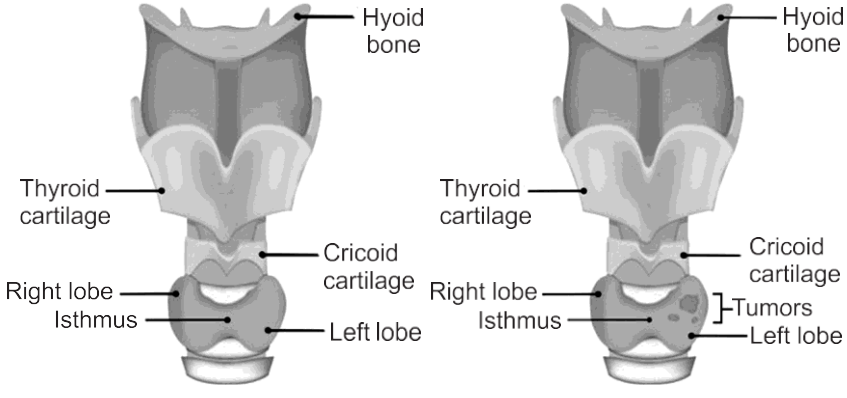
About 2/3rd of cases occur in people under age 55. There are different kinds of thyroid cancer, depending upon the specific cell type within the thyroid that has become cancerous. Most cases of thyroid cancer have a good prognosis and high survival rates, especially when diagnosed in its early stages.

Causes

Thyroid cancer occurs when cells in thyroid undergo genetic changes (mutations). The mutations allow the cells to grow uncontrollably, multiply rapidly and produce lump. The cells also lose the ability to die, as normal cells would. The accumulating abnormal thyroid cells form a tumor. The abnormal cells can invade nearby tissue and can spread throughout the body.

Exact cause of thyroid cancer is not clear but there are a number of things that can increase risk of thyroid cancer includes:

- Other thyroid conditions, such as an inflamed thyroid (thyroiditis) or goitre – but not an overactive thyroid or underactive thyroid.
- A family history of thyroid cancer.
- Radiation exposure in childhood (Radiotherapy).
- Obesity.
- A bowel condition called familial adenomatous polyposis (FAP).
- Acromegaly, a rare condition where the body produces too much growth hormone.



(a) Healthy thyroid (b) Thyroid cancer

Fig. 8.6

Symptoms

Thyroid cancer typically does not cause any signs or symptoms early in the disease. As thyroid cancer grows, it may cause:

- A lump that can be felt through the skin on neck.
- Changes to voice, including increasing hoarseness.
- Difficulty in swallowing.
- Pain in neck and throat.
- Swollen lymph nodes in neck.

Types of Thyroid Cancer

- Papillary thyroid cancer: The most common form of thyroid cancer, papillary thyroid cancer arises from follicular cells, which produce and store thyroid hormones. Papillary thyroid cancer can occur at any age, but most often it affects people in age 30 to 50.

- Follicular thyroid cancer (Hurthle cell thyroid cancer): Follicular thyroid cancer also arises from the follicular cells of the thyroid. It usually affects people older than age 50. Hürthle cell cancer of the thyroid gland is a rare and potentially more aggressive type of follicular thyroid cancer which accounts for only about 3-10% of all differentiated thyroid cancers.
- Medullary thyroid cancer: Medullary thyroid cancer begins in thyroid cells called C cells, which produce the hormone calcitonin. Elevated levels of calcitonin in the blood can indicate medullary thyroid cancer at a very early stage. Certain genetic syndromes increase the risk of medullary thyroid cancer, although this genetic link is uncommon.
- Anaplastic thyroid cancer: Anaplastic thyroid cancer is a rare and rapidly growing cancer that is very difficult to treat. Anaplastic thyroid cancer typically occurs in adults (age 60 and older).
- Thyroid lymphoma: Thyroid lymphoma is a rare form of thyroid cancer that begins in the immune system cells in the thyroid and grows very quickly. Thyroid lymphoma typically occurs in older adults.

Treatments

Treatment for thyroid cancer depends on the type of thyroid cancer and how far it has spread. The main treatments are:

- Surgery: To remove part or all of the thyroid.
- Radioactive iodine treatment: Radioactive iodine (I-131), an isotope of iodine emits radiation. When a small dose of I-131 is swallowed, it is absorbed into the bloodstream in the gastrointestinal (GI) tract and concentrated from the blood by the thyroid gland, where it begins destroying the gland's cells.
- External radiotherapy: A machine is used to direct beams of radiation at the cancer cells to kill them.
- Chemotherapy and targeted therapies: Medications used to kill cancer cells.

8.5 GOITER

A goiter simply describes enlargement of the thyroid gland, regardless of cause. It may be associated with hypothyroidism, hyperthyroidism, or normal thyroid function.

Types of Goiters

Goiters have many causes. As a result, there are different types. These include:

1. Colloid Goiter (Endemic): A colloid goiter develops from the lack of iodine, a mineral essential to the production of thyroid hormones. People who get this type of goiter usually live in areas where iodine is scarce.
2. Non-toxic (Sporadic): The cause of a non-toxic goiter is usually unknown, though it may be caused by medications like lithium. Lithium is used to treat mood disorders such as a bipolar disorder. Non-toxic goiters do not affect the production of thyroid hormone, and thyroid function is healthy. They are also benign.
3. Toxic Nodular or Multinodular Goiter: This type of goiter forms one or more small nodules as it enlarges. The nodules produce their own thyroid hormone, causing hyperthyroidism. It generally forms as an extension of a simple goiter.

Causes

Iodine deficiency is the main cause of goiters. Iodine is essential to help thyroid to produce thyroid hormones. When person do not have enough iodine, the thyroid works extra hard to make thyroid hormone, causing the gland to grow larger.

Symptoms

- Swelling,
- Coughing,
- Throat tightness,
- Trouble breathing,
- Coughing,
- Fast heart rate,
- Heat intolerance,
- Shortness of breath,
- Throat tightness,
- Underactive thyroid,
- Weight gain.

Treatments

1. Supportive care

   Observation: Monitoring for changes or improvement.
2. Medical procedure

   Radioactive iodine therapy: A radioactive medicine taken by mouth to reduce the functioning of the thyroid gland or completely destroy it.
3. Medications
   a. Antithyroid agent: Prevents the thyroid gland from making or releasing thyroid hormone.
   b. Hormone: Affects body processes by regulating the activity of the organs.
4. Surgery
   a. Thyroid removal: Surgical removal of all or part of the thyroid gland.
   b. Partial thyroidectomy: Surgical removal of part of the thyroid.

8.6 DISORDERS OF SEX HORMONES

The sex hormones are a group of hormones responsible for controlling puberty, reproduction, birth and lactation. Sex hormone disorders, also referred to as reproductive hormone disorders, medical conditions that affect the different glands and organs of the body responsible for the production of the sex hormones.

The sex hormones, which include testosterone (male) and estrogen (female) are substances that are essential in almost every body function, but more so in sexual functions and reproduction. Both testosterone and estrogen are present in males and females, but the levels differ according to sex. Males have higher levels of testosterone and females have higher levels of estrogen.

Sex hormone disorders disrupt the normal production of hormones, which results in a reduced sex drive (libido), vaginal dryness, infertility, or excessive body hair, alopecia (hair loss) and may have long-term effects on metabolic, cardiovascular and bone health.

Disorders of Sex Hormones In Females

Polycystic Ovarian Syndrome (PCOS)

This disorder is characterized by oligomenorrhea (irregular menstrual cycles) or amenorrhea (no menstrual cycles) with symptoms of hyperandrogenism (extra male like hormones) such as acne and hirsutism (extra male like hair growth). This is the most common endocrine disorder in young females. Blood tests which may be elevated in this condition are testosterone and DHEAS. The underlying cause of this

disorder is thought to be insulin resistance (poor response of body tissues to insulin). Therefore, blood sugar and insulin levels may also be evaluated. PCOS can result in obesity, infertility, diabetes, heart disease and uterine cancer. Exercise, weight loss and medications can be used to improve insulin sensitivity. Menstrual cycles can also be regulated with birth control pills.

Amenorrhea

Amenorrhea is the absence of a menstrual period in a woman of reproductive age. It may be either primary (woman never developed menstrual periods) or secondary (absence of menstrual periods in a woman who was previously menstruating).

Outside of the reproductive years there is absence of menses during childhood and after menopause. Physiological states of amenorrhea are seen during pregnancy and lactation.

[I] Primary Amenorrhea

It is the absence of secondary sexual characteristics by age 14 with no menarche or normal secondary sexual characteristics but no menarche by 16 years of age occur with or without other signs of puberty.

Etiology

Primary amenorrhea is typically the result of a genetic or anatomic condition in young females that never develop menstrual periods (by age 16) and is not pregnant. Diseases of the pituitary gland and hypothalamus can also cause primary amenorrhea since these areas play a critical role in the regulation of ovarian hormones.

Gonadal dysgenesis, a condition in which the ovaries are prematurely depleted of follicles and oocytes (egg cells), leads to premature failure of the ovaries. It is one of the most common cases of primary amenorrhea in young women.

Another genetic cause is Turner syndrome, in which women are lacking all or part of one of the two X chromosomes normally present in the female. In Turner syndrome, the ovaries are replaced by scar tissue and estrogen production is minimal, resulting in amenorrhea. Estrogen-induced maturation of the external female genitalia and sex characteristics also fails to occur in Turner syndrome.

Other conditions include androgen insensitivity (in which individuals have XY [male] chromosomes but do not develop the external characteristics of males due to a lack of response to testosterone and its effects), congenital adrenal hyperplasia, and polycystic ovary syndrome (PCOS).

Being born with poorly formed genital or pelvic organs can lead to primary amenorrhea. Some of these defects include: blockages or narrowing of the cervix, imperforate hymen, missing uterus or vagina and vaginal septum.

[II] Secondary Amenorrhea

Secondary amenorrhea is ceasing of menstruation cycles. Secondary amenorrhea is the absence of menses for three months in a woman with previously normal menstruation or nine months for women with a history of irregular periods (oligomenorrhea). It is often caused by hormonal disturbances from the hypothalamus and the pituitary gland, from premature menopause or intrauterine scar formation.

Women who are pregnant, breastfeeding, or in menopause are not considered to have secondary amenorrhea.

Etiology

Pregnancy is an obvious cause of amenorrhea and is the most common reason for secondary amenorrhea. Other causes are varied and may include conditions that affect the ovaries, uterus, hypothalamus, or pituitary gland.

Hypothalamic Causes:

- Craniopharyngioma (a brain tumor near the pituitary gland).
- Teratoma (a tumor made up of a mixture of tissues).
- Sarcoidosis (a chronic disease of unknown cause characterized by the formation of nodules in different parts of the body).
- Kallmann syndrome (deficiency of gonadotropins, which promote growth and function of reproductive organs)
- Low body weight or growth delay.

Ovarian Causes:

- Anovulation (lack of the release of an egg).
- Hyperandrogenemia (high blood levels of male hormones).
- Polycystic ovary syndrome (hormonal disorder affecting women of reproductive age).
- Premature ovarian failure.
- Turner syndrome (a genetic disorder characterized by underdeveloped ovaries, absence of menstrual onset, and short stature).
- Pure gonadal dysgenesis (defective development of the ovary).
- Autoimmune oophoritis (cells of the ovaries destroyed by the body's own defense system).
- Radiation or chemotherapy.
- Anatomical abnormalities of the genital tract.
- Intrauterine adhesions (the opposing surfaces of the uterine cavity stick together).
- Imperforate hymen (a hymen in which there is no opening, the membrane completely closes off the vagina).
- Transverse vaginal septum (a dividing wall or membrane in the vagina).
- Aplasia (absence of an organ or tissue) of the vagina, the cervix, or the uterus.

Pathophysiology

Normally, the hypothalamus generates pulses of gonadotropin-releasing hormone (GnRH). GnRH stimulates the pituitary to produce gonadotropins (follicle-stimulating hormone and luteinizing hormone), which are released into the bloodstream. Gonadotropins stimulate the ovaries to produce estrogen (mainly estradiol), androgens (mainly testosterone), and progesterone. These hormones cause the following:

- FSH stimulates tissues around the developing oocytes to convert testosterone to estradiol.
- Estrogen stimulates the endometrium, causing it to proliferate.
- LH, when it surges during the menstrual cycle, promotes maturation of the dominant oocyte, release of the oocyte, and formation of the corpus luteum, which produces progesterone.
- Progesterone changes the endometriumium into a secretory structure and prepares it for egg implantation.

If pregnancy does not occur, estrogen and progesterone production decreases, and the endometrium breaks down and is sloughed during menses. Menstruation occurs 14 days after ovulation in typical cycles.

When part of this system malfunctions, ovulatory dysfunction occurs; the cycle of gonadotropin stimulated estrogen production and cyclic endometrial changes are disrupted, and menstrual flow does not occur, resulting in anovulatory amenorrhea. Most amenorrhea, particularly secondary amenorrhea, is anovulatory.

However, amenorrhea can occur when ovulation is normal, as occurs when genital anatomic abnormalities (e.g. congenital anomalies causing outflow obstruction, intrauterine adhesions, etc.) prevent normal menstrual flow despite normal hormonal stimulation.

Amenorrhea is a symptom of an underlying disorder rather than a condition in and of itself.

A female with primary amenorrhea will have no menstrual flow with or without other signs of puberty.

In a female with secondary amenorrhea, additional symptoms may be present depending on the associated condition.

- Breast size changes.
- Voice changes.
- Galactorrhea, headache, or reduced peripheral vision could be a sign of an intracranial tumor.
- Increased hair growth in a male pattern (hirsutism) may be caused by excess androgen.
- Vaginal dryness, hot flashes, night sweats, or disordered sleep may be a sign of ovarian insufficiency or premature ovarian failure.
- Noticeable weight gain or weight loss may be present.
- Excessive anxiety may be present in women with associated psychiatric abnormalities.

If amenorrhea is caused by a pituitary tumor, there may be other symptoms related to the tumor, such as vision loss and headache.

Diagnosis

(i) Diagnosing Primary Amenorrhea:

Primary amenorrhea can be diagnosed in women by age 14 if no secondary sex characteristics, such as enlarged breasts and body hair, are present.

In the absence of secondary sex characteristics, the most common cause of amenorrhoea is low levels of FSH and LH caused by a delay in puberty. If secondary sex characteristics are present, but menstruation is not, primary amenorrhea can be diagnosed by age 16. A reason for this occurrence may be that a person phenotypically female but genetically male, a situation known as androgen insensitivity syndrome.

Mullerian agenesis (is a congenital malformation characterized by a failure of the Mullerian duct to develop, resulting in a missing uterus and variable degrees of vaginal hypoplasia of its upper portion. It is the most common cause of primary amenorrhea) causes around 15% of primary amenorrhea cases.

If a uterus is present, outflow track obstruction may be responsible for primary amenorrhea.

(ii) Diagnosing Secondary Amenorrhea:

The diagnosis of amenorrhea requires a careful medical history to document the presence of amenorrhea as well as any other coexisting medical conditions that may be the cause of amenorrhea. A physical examination, including a pelvic examination is also performed.

Depending upon the results of the history and physical examination further diagnostic tests may be ordered. Blood tests may be ordered to examine the levels of ovarian, pituitary and thyroid hormones. These tests may include measurements of prolactin, follicle-stimulating hormone (FSH), estrogen, thyrotropin, dehydroepiandro-sterone sulfate (DHEA-S), and testosterone. For some individuals, a pregnancy test is the first test perfomed. Imaging studies, such as ultrasound, X-ray, and CT or MRI scanning may also be recommended in certain individuals to help establish the cause of amenorrhea.

Treatment

Treatment of primary and secondary amenorrhea is determined by the precise cause. Treatment goals can be to relieve symptoms of hormonal imbalance, establish menstruation, prevent complica-tions, and to achieve fertility.

Medical Treatment: Some causes of amenorrhea can be managed by drug therapy.

Dopamine agonists: In most women, treatment with dopamine agonists medications restores normal ovarian endocrine function and ovulation. e.g. Bromocriptine, or Pergolide are effective in treating hyperprolactinemia.

Hormone replacement therapy: An estrogen and a progestin can be used for women in whom estrogen deficiency remains because ovarian function cannot be restored.

Metformin: May used in women with polycystic ovary syndrome to induce ovulation. In premature ovarian failure, hormone therapy may be recommended both to avoid the unpleasant symptoms of estrogen depletion as well as prevent complications of low estrogen level such as osteoporosis.

Amenorrhea Surgery: Amenorrhea caused by pituitary and hypothalamic tumors or structural blockage may require surgery and, in some cases, radiation therapy.

Hirsutism

Hirsutism is the growth of excessive hair in a male pattern which include face, chest, abdomen and back and usually due to the increased production of androgens (male hormones). Disorders in which hirsutism are seen, include: polycystic ovarian syndrome, congenital adrenal hyperplasia, ovarian tumors or adrenal tumors. Blood tests are used to help determine a cause. Occasionally, there is no cause found for the hair growth (idiopathic hirsutism). Medical treatment varies by the underlying cause of the hirsutism. Topical treatments including electrolysis and laser can be used to decrease hair growth.

Androgen Excess

Androgen excess refers to the overproduction of male hormones. This can result from ovarian or adrenal tumors. Other disorders such as polycystic ovarian syndrome, Cushing's syndrome (the overproduction of cortisol), hyperprolactinemia and congenital adrenal hyperplasia can cause extra male hormones to be produced. In women androgen excess can cause hirsutism (excessive hair growth), acne, male pattern baldness, menstrual cycle irregularities and infertility. Diagnosis is generally made through blood tests. CT scans of adrenal glands and ovaries are occasionally needed. Treatments vary by the underlying cause of the androgen excess.

Disorders of Sex Hormones inMales

Hypogonadism

Hypogonadism refers to the decreased production of testosterone. This can result from the pituitary gland not stimulating the testicles to make testosterone or the failure of the testicles to produce adequate testosterone. When testosterone levels are low, men can experience decreased libido (sex drive), erectile dysfunction, decreased energy, decreased muscle mass and thinning of the bones. Testicle size may also decrease and sperm count decrease. Blood testing is done to diagnose hypogonadism and to determine the cause. MRI (magnetic resonance imaging) of the pituitary or testicular biopsy may be needed in some cases. Testosterone when low can be replaced by injection, patches or topical gels.

Gynecomastia

The increase in breast tissue in a man is referred to as gynecomastia. This can occur during puberty and resolve on its own. Gynecomastia can also be due to medications, hypogonadism, thyroid disease, malnutrition, testicular cancers, adrenal cancers, liver disease or kidney disease. The cause of the gynecomastia is usually determined by physical exam, history and blood tests. Additional testing may include testicular ultrasounds or CT scan.

Erectile Dysfunction (ED)

Erectile dysfunction (ED) is the inability to attain or sustain an erection firm enough to have satisfactory sexual intercourse. It is also called as impotence. It is not unusual for this to happen to a man on occasion, but frequent ED can be a sign of a bigger medical problem that needs attention. ED becomes more common in older age but it is not a natural part of aging.

Causes

ED can result from medical, physical or psychological factors. ED may be caused by a combination of factors that could also include medicine, alcohol or drugs. Intermittent ED is common. Many men experience occasional ED. It is generally caused by stress, exhaustion, or similar causes. Occasional ED should not be a cause of concern.

Frequent ED may be a sign of damage to the cardiovascular or nervous systems. It is also be a sign of serious emotional or relationship difficulties.

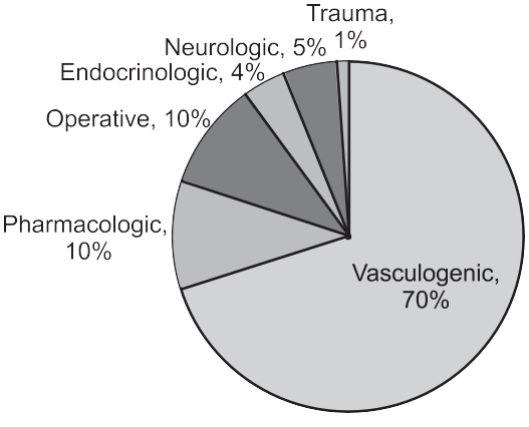


Fig. 8.7 : Causes of erectile dysfunction

Lifestyle Factors Associated With Erectile Dysfunction

There are a number of lifestyle factors that can cause or contribute to ED. In general, any behaviour that can damage cardiovascular or nervous system health can also increase ED risk. Some risk factors include: Smoking, alcohol use, using illegal drugs, such as cannabis, heroin or cocaine, being overweight or obese, failing to control diabetes and lack of exercise.

In addition, any activities that cause physical damage to the nerves or blood vessels around the base of the penis can also increase ED risk. For example, prolonged bicycling is associated with ED. However, this type of ED is usually temporary.

Medical Factors Associated With Erectile Dysfunction

Most common medical causes of ED are diseases or injuries to the cardiovascular system. These can reduce blood flow to the penis.

Some cardiovascular conditions related to ED include:

- High blood pressure,
- Diabetes,
- Atherosclerosis,
- Obesity and metabolic syndrome,
- High cholesterol,

Nervous system problems related to ED include:

- Spinal cord injury,
- Parkinson's disease,
- Multiple sclerosis.

Other medical factors associated with ED include:

- Prostate cancer,
- End-stage kidney disease,
- Radiation therapy to the pelvic region,
- Hormonal disorders including thyroid conditions and testosterone deficiency,
- Surgery on the prostate, bladder, or other organs near the penis,
- Structural/anatomical disorder of the penis, such as Peyronie disease,
- Injury to the penis, testicles, or surrounding area.

Physiological Mechanisms of Normal Penile Erections

During sexual arousal, messages from brain travel down nerves to the penis. Neurotransmitters are then released from the ends of the nerves in the penis. Stimulation of penile shaft by the nervous system leads to the secretion of nitric oxide (NO), causing the creation of cyclic guanosine monophosphate (cGMP) which functions to relax blood vessels (vasodilatation). This allows extra blood to flood into the penis. The rapid inflow of blood causes the penis to swell into an erection. The swollen inner part of the penis also presses on the veins nearer to the skin surface of the penis. These veins normally drain the blood from penis. So, the flow of blood out of the penis is also restricted, which enhances the erection. So erectile tissues in the corpus cavernosa can fill with blood, and subsequently cause a penile erection.

Phosphodiesterase type 5 (PDE5) is always present in the penis and functions to destroy cyclic GMP, causing vasoconstriction of erectile tissues and resulting in the loss of erection. In normal males, the loss of an erection occurs after orgasm and ejaculation of sperm.

Pathophysiology

From the mechanisms of a normal erection, erectile dysfunction may develop due to hormonal deficiency, disorders of the neural system, lack of adequate penile blood supply or psychological problems.

Restriction of blood flow can arise from impaired endothelial function due to the usual causes associated with coronary artery disease, but can also be caused by prolonged exposure to bright light.

Symptoms

Erectile dysfunction symptoms may include persistent:

- Trouble in getting an erection.
- Trouble in keeping enough erection to have intercourse or only be able to have brief erections.
- Reduced sexual desire.

Complications

Complications resulting from erectile dysfunction can include:

- An unsatisfactory sex life,
- Stress or anxiety,
- Embarrassment or low self-esteem,
- Marital or relationship problems,
- The inability to get partner pregnant.

Tests and Diagnosis

Tests for underlying problems may include:

Physical exam: This may include careful examination of penis and testicles to rule out anatomical causes and checking nerves for feeling.

Blood tests: It includes measuring the levels of hormones such as testosterone can rule out hormonal conditions, such as hypogonadism, signs of heart disease, diabetes and other health problems.

Urine tests (urinalysis): Urine tests are used to look for signs of diabetes and other underlying health conditions.

Overnight erection test: Most men have erections during sleep without remembering them. This simple test involves wrapping special tape around penis before go to bed. If the tape is separated in the morning, means the penis was erected at some time during the night. This indicates the cause of erectile dysfunction is most likely psychological and not physical.

Penile biothesiometry: This test uses electromagnetic vibration to evaluate sensitivity and nerve function in the glans and shaft of the penis.

Psychological exam: It includes, screen for depression and other possible psychological causes of erectile dysfunction.

Treatment

Treatment for erectile dysfunction (ED) depends on its cause. If ED is caused by an underlying medical problem, treatment may be the first step towards eliminating ED.

Oral medications: It include: Sildenafil, Tadalafil, Vardenafil.

Other medications (Injectable Drugs) include: Apaverine, Alprostadil, and Phentolamine. These drugs are injected directly into the base of the penis. They have a direct effect on penile blood flow to achieve an erection.

Testosterone replacement: Erectile dysfunction is sometime caused by low levels of the hormone testosterone, and may need testosterone replacement.

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Chapter...9

NERVOUS SYSTEM

9.1 INTRODUCTION TO NERVOUS SYSTEM

The nervous system consists of the brain, spinal cord, sensory organs, and all of the nerves that connect these organs with the rest of the body. Together, these organs are responsible for the control of the body and communication among its parts. The brain and spinal cord form the control center known as the central nervous system (CNS), where information is evaluated and decisions made. The sensory nerves (afferent) and sense organs of the peripheral nervous system (PNS) monitor conditions inside and outside of the body and send this information to the CNS. Motor nerves (efferent) in the PNS carry signals from the control center to the muscles, glands, and organs to regulate their functions. The nervous system uses both electrical and chemical means to send and receive messages.

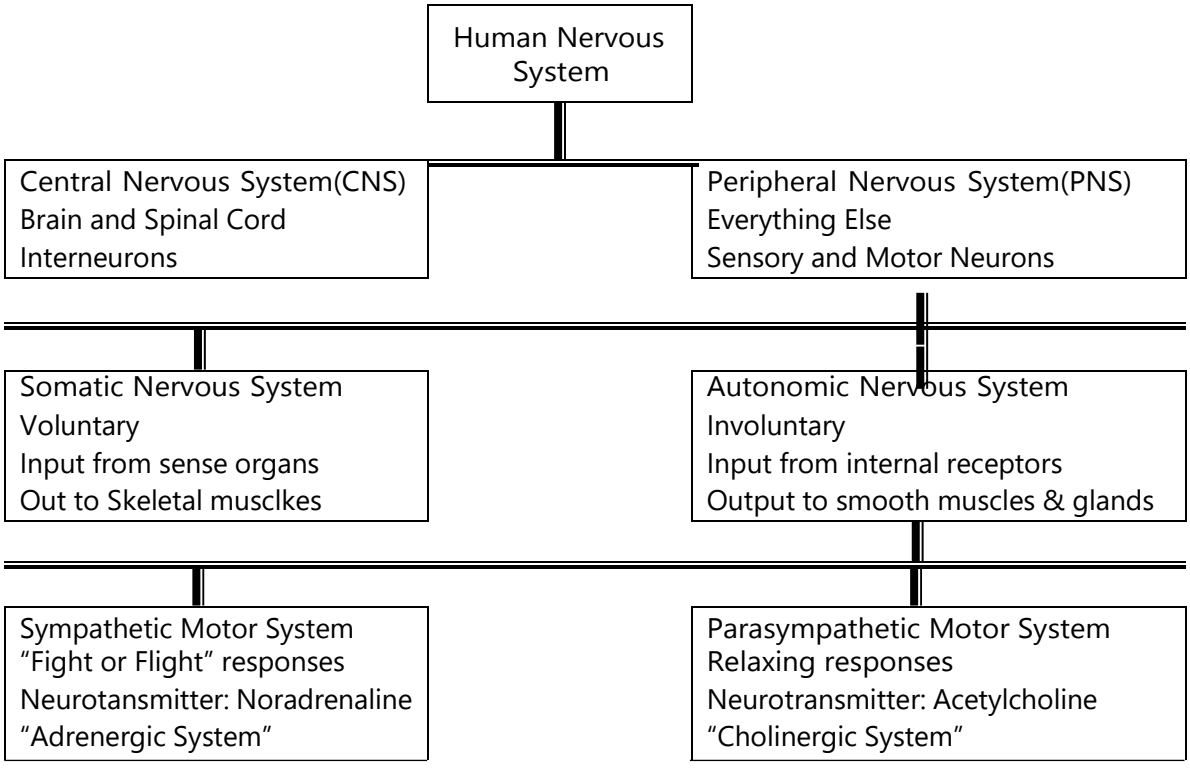


Fig. 9.1 : Classification of nervous system

Neurons: The basic building block of the nervous system is a nerve cell or neuron. Neurons are shaped differently depending on where they are in the body and what role they play. All neurons have finger-like projections called dendrites and a long fibre called an axon.

In many cases, the axon is coated by a specialized membrane called myelin sheath. The axon feathers out and has a number of bumps on it. Each bump sits near to a dendrite from another neuron. The space between the bump and the dendrite is called a synapse. Messages jump the synapse from one neuron to the next, using special chemicals called neurotransmitters. Unlike other cells in the body, neurons are not easily replaced if they die or are damaged by infection or injury.

Central Nervous System: The brain and spinal cord make up the central nervous system. They are wrapped in a thin lining called meninges and bathed with cerebrospinal fluid (CSF).

Brain: The brain is powerhouse of the body, even though it only makes up two percent of the body's weight. This soft, jelly like organ has countless billions of neural cross-connections. Brain organize and supervize the workings of the body, while its higher functions give us consciousness and personality.

Spinal Cord: The spinal cord connects to the brain and runs the length of the body. It is protected by the bones of the spine (vertebrae). Nerves branch off from the spinal cord into the arms, legs and torso.

Peripheral Nervous System (PNS): The portion of the nervous system lying outside the brain and spinal cord. It is made up of two main parts: the autonomic and the somatic nervous systems.

Autonomic Nervous System (ANS): The autonomic nervous system is part of the peripheral nervous system. One of its main roles is to regulate glands and organs without any effort from conscious minds.

The ANS is further divided into the sympathetic nervous system and the parasympathetic nervous system. Both of these systems can stimulate and inhibit effectors. However, the two systems work in opposition, where one system stimulates an organ, the other inhibits. Working in this fashion, each system prepares the body for a different kind of situation, as follows:

The sympathetic nervous system prepares the body for situations requiring alertness or strength, or situations that arouse fear, anger, excitement, or embarrassment ("fight or flight" situations). In these kinds of situations, the sympathetic nervous system stimulates cardiac muscles to increase the heart rate, causes dilation of the bronchioles of the lungs (increasing oxygen intake), and causes dilation of blood vessels that supply the heart and skeletal muscles (increasing blood supply). The adrenal medulla is stimulated to release epinephrine (adrenalin) and norepinephrine (noradrenalin), which in turn increases the metabolic rate of cells and stimulates the liver to release glucose into the blood. Sweat glands are stimulated to produce sweat. In addition, the sympathetic nervous system reduces the activity of various "tranquil" body functions, such as digestion and kidney functioning.

The parasympathetic nervous system is active during periods of digestion and rest. It stimulates the production of digestive enzymes and stimulates the processes of digestion, urination and defecation. It reduces blood pressure, heart rate and respiratory rates. It conserves energy through relaxation and rest.

Somatic Nervous System: The somatic nervous system is also a part of the peripheral nervous system. One of its roles is to relay information from the eyes, ears, skin and muscle to the central nervous system. It also obeys commands from the central nervous system and makes muscles contract or relax, allowing us to move.

Synapse: A synapse is the tiny gap across which a nerve impulse passes from one nerve cell to another nerve cell, a muscle cell or a gland cell.

Synaptic cleft: The gap between two cells at a synapse is called the synaptic cleft. The signal sending cell is called the presynaptic neuron, and the signal-receiving cell is called the postsynaptic neuron.

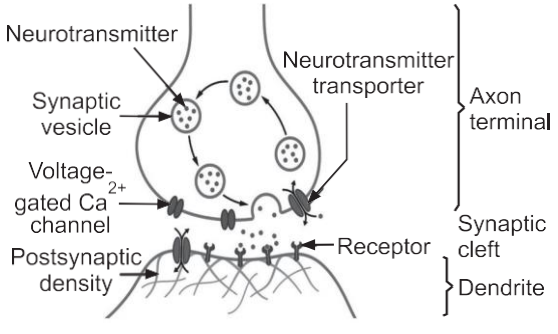


Fig. 9.2 : Synaptic junction

Neurotransmitters: Neurotransmitters are the brain chemicals that communicate information throughout brain and body. They relay signals between nerve cells. The brain uses neurotransmitters to regulate activities such as heart to beat, lungs to breathe, and stomach to digest. They can also affect mood, sleep, concentration, weight, and can cause altered functions when they are out of balance. Neurotransmitter levels can be depleted many ways.

There are two kinds of neurotrans-mitters Inhibitory and Excitatory.

Excitatory neurotransmitters are not necessarily exciting, they stimulate the brain.

Those that calm the brain and help to create balance are called inhibitory neurotransmitters.

Inhibitory neurotransmitters balance mood and are easily depleted when the excitatory neurotransmitters are overactive.

Inhibitory neurotransmitters are serotonin (5-HT), glycine, gama amino butyric acid (GABA) and dopamine.

Excitatory neurotransmitters are glutamate, aspartate, norepinephrine, dopamine and epinephrine.

9.2 EPILEPSY

Seizure is the transient occurrence of signs and/or symptoms due to abnormal, excessive, or synchronous neuronal activity in the brain. Signs or symptoms may include alterations of consciousness, motor, sensory, autonomic, or psychic events. Epilepsy is a condition characterized by the occurrence of two or more seizures that are not acutely provoked by other illnesses or conditions. Medications control rather than curing the seizure disorder. Adherence to the medication regimen is important.

Classification of Epileptic Seizures: Epileptic seizures are classified as either focal or generalized, based on how the abnormal brain activity begins.

[I] Focal or Partial Seizures:

When seizures appear to result from abnormal activity in just one area of brain, they are called focal (partial) seizures. These seizures fall into two categories.

(i) Simple focal seizures: These seizures donot result in loss of consciousness. They may alter emotions or change the way things look, smell, feel, taste or sound. They may also result in involuntary

jerking of a body part, such as an arm or leg, and spontaneous sensory symptoms such as tingling, dizziness and flashing lights.

(ii) Complex partial seizures: Complex partial seizures are characterized by focal seizure activity accompanied by a transient impairment of the patient's ability to maintain normal contact with the environment. The patient is unable to respond appropriately to visual or verbal commands during the seizure and has impaired recollection or awareness of the ictal phase. The seizures frequently begin with an aura (i.e., a simple partial seizure) that is stereotypic for the patient.

(iii) Dyscognitive focal seizures: These seizures alter consciousness or awareness and may cause to lose awareness for a longer period of time. Dyscognitive focal seizures often result in staring and purposeless movements such as hand rubbing, chewing, swallowing or walking in circles.

[II] Generalized Seizures (Convulsive or Non-convulsive):

Seizures that appear to involve all areas of the brain are called generalized seizures. Six types of generalized seizures exist.

(i) Absence seizures (Petit Mal): Petit Mal or Absence seizures are characterized by staring and subtle body movement. These seizures can cause a brief loss of awareness.

(ii) Tonic seizures: Tonic seizures cause stiffening muscles. These seizures usually affect muscles in back, arms and legs and may cause to fall to the ground.

(iii) Clonic seizures: Clonic seizures are associated with rhythmic, jerking muscle movements. These seizures usually affect the neck, face and arms.

(iv) Myoclonic seizures: These usually appear as sudden brief jerks or twitches of arms and legs.

(v) Atonic seizures: Atonic seizures, also known as drop seizures, because a loss of muscle control, which may result in suddenly collapse or fall down.

(vii) Tonic-clonic seizures (Grand Mal): Tonic-clonic seizures are characterized by a loss of consciousness, body stiffening and shaking, and sometimes loss of bladder control or biting tongue.

Status epilepticus is defined as either continuous seizures lasting at least for 5 minutes, or two or more discrete seizures between which there is incomplete recovery of consciousness.

Febrile seizures occur in upto 8% of children between 6 months and 6 years of age. Long term treatment or prophylaxis for simple febrile seizures is not recommended.

Unclassified epileptic seizures:

Not all seizure types can be classified as partial or generalized. This appears to be especially true of seizures that occur in neonates and infants. The distinctive phenotypes of seizures at these early ages likely result, in part, from differences in neuronal function and connectivity in the immature versus mature CNS.

9.2.1 Epidemiology

There are over 2.5 million people diagnosed with epilepsy every year. Epilepsy is one of the most common serious neurological disorders affecting about 65 million people globally. It affects 1% of the population by age 20 and 3% of the population by age 75. It is more common in males than females with the overall difference being small. Most of those with

the disease (80%) are in the developing world.

Epilepsy is usually present in childhood or adolescence but may occur for the first time at any age. About 5% of the population suffers a single seizure at some time. About 0.5-1% of the population have recurrent seizure epilepsy. About 70% patients are well controlled with drugs (prolonged remissions) and 30% epilepsy patients are at least partially resistant to drug treatments.

Intractable Epilepsy: It is a symptom of numerous disorders, but in the majority of sufferers the cause remains unclear despite careful history taking, examination and investigation.

Causes

Epilepsy has no identifiable cause in about half of those, with the condition. In about half the people with epilepsy, the condition may be traced to various factors.

Table 9.1 : Causes of seizures

Neonates (<1 month)	Perinatal hypoxia, ischemia, Intracranial hemorrhage and trauma, Acute CNS infection, Metabolic disturbances (hypoglycemia, hypocalcemia, hypomagnesemia, pyridoxine deficiency), Drug withdrawal, Developmental disorders and Genetic disorders.
Infants and children (>1 month and <12 years)	Febrile seizures, Genetic disorders (metabolic, degenerative, primary epilepsy syndromes), CNS infection, Developmental disorders, Trauma and Idiopathic.
Adolescents (12–18 years)	Trauma, Genetic disorders, Infection, Brain tumor, Illicit drug use and Idiopathic.
Young adults (18–35 years)	Trauma, Alcohol withdrawal, Illicit drug use, Brain tumor and Idiopathic.
Older adults (>35 years)	Cerebrovascular disease, Brain tumor, Alcohol withdrawal, Metabolic disorders (uremia, hepatic failure, electrolyte abnormalities, hypoglycemia), Alzheimer's disease and other degenerative CNS diseases and Idiopathic.

Genetic Influence:

Some types of epilepsy, which are categorized by the type of seizure experience, run in families. In these cases, it is likely that there is a genetic influence.

Researchers have linked some types of epilepsy to specific genes, though it is estimated that upto 500 genes could be tied to the condition. For most people, genes are only part of the cause of epilepsy. Certain genes may make a person more sensitive to environmental conditions that trigger seizures.

Head trauma: Head trauma that occurs due to a car accident or other traumatic injury can cause epilepsy.

Brain conditions: Brain conditions that result in damage to the brain, such as brain tumors or strokes, also can cause epilepsy. Stroke is a leading cause of epilepsy in adults older than age 35.

Infectious diseases: Infectious diseases, such as meningitis, AIDS and viral encephalitis, can cause epilepsy.

Prenatal injury: Before birth, babies are sensitive to brain damage that could be caused by several factors, such as an infection in the mother, poor nutrition or oxygen deficiencies. This brain damage can result in epilepsy or cerebral palsy.

Developmental disorders: Epilepsy can sometimes be associated with developmental disorders, such as autism and neurofibromatosis.

Stroke and other vascular diseases: Stroke and other blood vessel (vascular) diseases can lead to brain damage that may trigger epilepsy.

Dementia: Dementia can increase the risk of epilepsy in older adults.

Pathophysiology

Mechanisms of Seizure Initiation and Propagation:

The hypersynchronous discharges that occur during a seizure may begin in a very discrete region of cortex and then spread to neighbouring regions. Seizure initiation is characterized by two concurrent events: 1) high-frequency bursts of action potentials, and 2) hypersynchronization of a neuronal population. The synchronized bursts from a sufficient number of neurons result in a so-called spike discharge on the EEG. At the level of single neurons, epileptiform activity consists of sustained neuronal depolarization resulting in a burst of action potentials, a plateau-like depolarization associated with completion of the action potential burst, and then a rapid repolarization followed by hyperpolarization. This sequence is called the paroxysmal depolarizing shift. The bursting activity resulting from the relatively prolonged depolarization of the neuronal membrane is due to influx of extracellular Ca^{++}, which leads to the opening of voltage-dependent Na^{+} channels, influx of Na^{+}, and generation of repetitive action potentials. The subsequent hyperpolarizing after potential is mediated by GABA receptors and Cl^{-} influx, or by K^{+} efflux, depending on the cell type.

Seizure propagation, the process by which a partial seizure spreads within the brain, occurs when there is sufficient activation to recruit surrounding neurons. This leads to a loss of surrounding inhibition and spread of seizure activity into contiguous areas via local cortical connections, and to more distant areas via long association pathways such as the corpus callosum.

The propagation of bursting activity is normally prevented by intact hyperpolarization and a region of surrounding inhibition is created by inhibitory neurons. With sufficient activation, there is a recruitment of surrounding neurons via a number of mechanisms. Repetitive discharges lead to: 1) an increase in extracellular K^{+}, which blunts the extent of hyperpolarizing outward K^{+} currents, tending to depolarize neighbouring neurons; 2) accumulation of Ca^{++} in presynaptic terminals, leading to enhanced neurotransmitter release; and 3) depolarization-induced activation of the NMDA subtype of the excitatory amino acid receptor, which causes more Ca^{++} influx and neuronal activation. Of equal interest, but less well understood, is the process by which seizures typically end, usually after seconds or minutes, and what underlies the failure of this spontaneous seizure termination in the life-threatening condition known as status epilepticus.

Symptoms

Because epilepsy is caused by abnormal activity in brain cells, seizures can affect any process that brain co-ordinates. Both partial and generalized seizures at the same time, or one can precede the other. The symptoms can last anywhere from a few seconds to 15 minutes per episode.

Sometimes, symptoms occur before the seizure takes place. These include:

- A sudden feeling of fear or anxiousness,
- A feeling of being sick to your stomach,
- Dizziness,
- A change in vision,
- A jerky movement of the arms and legs that may cause you to drop things,
- An out of body sensation,
- A headache.

Symptoms that indicate a seizure is in progress include:

- Losing consciousness, which is followed by confusion,
- Having uncontrollable muscle spasms,
- Drooling or frothing at the mouth,
- Falling,
- Having a strange taste in mouth,
- Clenching teeth,
- Biting of tongue,
- Having sudden, rapid eye movements,
- Making unusual noises, such as grunting,
- Losing control of bladder or bowel function,
- Having sudden mood changes.

Tests and Diagnosis

Physical examination: Physical examination helps in the diagnosis of specific epileptic syndromes that cause abnormal findings, such as dermatologic abnormalities. In addition, patients who for years have had intractable generalized tonic-clonic seizures are likely to have suffered injuries requiring stitches. Several tests to diagnose epilepsy and determine the cause of seizures includes

Neurological examination: A neurological examination looks at how well brain and the rest of nervous system are functioning and may test behaviour, motor abilities, mental function and other areas to diagnose condition and determine the type of epilepsy.

Blood tests: There are a number of blood tests that may be recommended to check for signs of infections, genetic conditions or other conditions like electrolyte imbalances which may be associated with seizures.

Electroencephalogram (EEG): An electroencephalography test can help to diagnose a seizure. These tests measure brain waves. Viewing brain waves during a seizure can help to diagnose the type of seizure.

Neuroimaging: Imaging scans such as a Computerized tomography (CT) scan, Magnetic resonance imaging (MRI), Functional MRI (fMRI), Positron emission tomography (PET) or Single-photon emission computerized tomography (SPECT) also can help by providing a clear picture of the brain. These scans allow to see abnormalities like blocked blood flow or a tumor.

Neuropsychological tests: These tests are performed to assess thinking, memory and speech skills. The test results help to determine which areas of brain are affected.

Treatments and Drugs

The majority of epileptic seizures are controlled through drug therapy, particularly anticonvulsant drugs. The type of treatment prescribed will depend on several factors including the frequency and severity of the seizures as well as the person's age, overall health, and medical history. An accurate diagnosis of the type of epilepsy is also critical to choosing the best treatment.

The different antiepileptic drugs (AEDs) act by affecting one or more of these processes. Specific mechanisms of action of the AEDs include:

- Modulation of voltage dependent ion channels: Carbamazepine, Phenytoin, Valproic acid.
- Enhancement of activity of the major inhibitory neurotransmitter in the brain, GABA: Phenobarbital, Benzodiazepines, Tiagabine.
- Suppression of excitatory neuro-transmission: Lamotrigine, Felbamate.

Surgery: Surgery includes removal of the area of brain causing the seizures.

Other therapies:

Vagus nerve stimulation: The vagus nerve is stimulated to reduce the frequency and intensity of seizures. This can be suitable for some people with seizures that are difficult to control with medication.

Ketogenic diet: A diet very high in fat, low in protein and almost carbohydrate free. This can be effective in the treatment of difficult to control seizures in some children.

Table 9.2 : Selection of antiepileptic drugs

Primary Generalized Tonic-Clonic	Partial*	Absence	Atypical Absence, Myoclonic, Atonic
First-Line			
Valproic acid Lamotrigine Topiramate	Carbamazepine Phenytoin Lamotrigine Valproic acid	Valproic acid Ethosuximide	Valproic acid Lamotrigine Topiramate
Alternatives			
Zonisamideb Phenytoin Carbamazepine Oxcarbazepine Phenobarbital Primidone Felbamate	Levetiracetam** Topiramate Tiagabine** Zonisamide** Gabapentin** Phenobarbital Primidone	Lamotrigine Clonazepam	Clonazepam Felbamate

* Includes simple partial, complex partial and secondarily generalized seizures.

** As adjunctive therapy

Table 9.3 : Types and symptoms of epileptic seizures

Types of seizures		Symptoms
Generalized seizures (Produced by the entire brain)	1. "Grand Mal" or Generalized tonic-clonic	Unconsciousness, convulsions, muscle rigidity.
	2. Absence	Brief loss of consciousness.
	3. Myoclonic	Sporadic (isolated), jerking movements.
	4. Clonic	Repetitive, jerking movements.
	5. Tonic	Muscle stiffness, rigidity.
	6. Atonic	Loss of muscle tone.
Focal (partial) seizures (Produced by a small area of the brain)	1. Simple (awareness is retained)	
	a. Simple motor	Jerking, muscle rigidity, spasms, head-turning.
	b. Simple sensory	Unusual sensations affecting either the vision, hearing, smell taste, or touch.
	c. Simple psychological	Memory or emotional disturbances.
	2. Complex (Impairment of awareness)	Automatisms such as lip smacking, chewing, fidgeting, walking and other repetitive, involuntary but co-ordinated movements.
	3. Partial seizure with secondary generalization	Symptoms that are initially associated with a preservation of consciousness that then evolves into a loss of consciousness and convulsions..
Unclassified seizures	1. Neonatal seizures 2. Infantile spasms	

9.3 PARKINSON'S DISEASE

In 1817, British Physician Dr. James Parkinson published a case series describing six patients afflicted with the "shaking palsy" (paralysis agitans), a chronic and progressive neurologic disorder called Parkinsonism i.e. loss of control of movement. Parkinson's occurs when certain nerve cells in a part of the brain called the substantia nigra die or become impaired. Normally, these cells produce a vital chemical known as dopamine. Dopamine allows smooth, coordinated function of the body's muscles and movement. When approximately 70% of the dopamine producing cells is damaged, the symptoms of Parkinson disease appear. Parkinson disease (PD) is recognized as one of the most common neurologic disorders, affecting approximately 1% of individuals older than 60 years. It is a progressive movement disorder marked by tremors, rigidity, slow movement (bradykinesia), and posture instability.

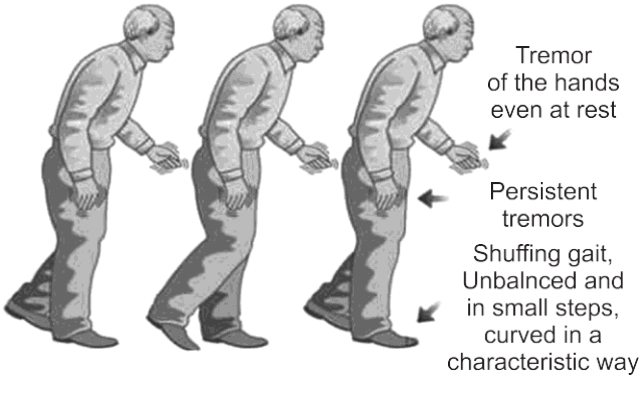


Fig. 9.3 : Parkinson's disease

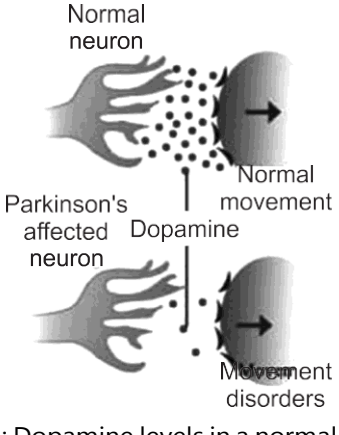


Fig. 9.4 : Dopamine levels in a normal and a Parkinson's affected neuron

The motor symptoms of parkinson's disease result from the death of dopamine-generating cells in the substantia nigra, a region of the midbrain; the cause of this cell death is unknown. Sometimes it is genetic, but most cases do not seem to run in families. Exposure to chemicals in the environment might play a role.

It usually begin in a person's late fifties or early sixties. Parkinson disease causes progressive decline in movement controls, affecting the ability to control initiation, speed and smoothness of motion. Symptoms of parkinson's disease are seen in 15% of the people in the age 65-74 and almost 30% of people in age 75-84.

Most cases of parkinson's disease are sporadic. In that, there is a spontaneous and permanent change in nucleotide sequences. Sporadic mutations also involve unknown environmental factors in combination with genetic defects. The abnormal gene (mutated gene) will form an altered end product or protein. This will cause abnormalities in specific areas in the body where the protein is used. Some evidence suggests that the disease is transmitted by autosomal dominant inheritance. This implies that an affected parent has a 50% chance of transmitting the disease to any child.

This type of inheritance is not commonly observed. The most recent evidence is

linking parkinson's disease with a gene that codes for a protein called α-synuclein.

Causes

The immediate cause of PD is degeneration of brain cells in the area known as the substantia nigra, one of the movement control centers of the brain. Damage to this area leads to the cluster of symptoms known as "Parkinsonism".

The substantia nigra is one of the principal movement control centers in the brain. By releasing the neurotransmitter known as dopamine, it helps to refine movement patterns throughout body. The dopamine released by nerve cells of substantia nigra stimulates another brain region, the corpus striatum. Without enough dopamine, the corpus striatum cannot control its targets, and so on down the line. Ultimately, the movement patterns of walking, writing, reaching for objects, and other basic programs cannot operate properly and the symptoms of parkinsonism are the result. The cause of parkinson's disease is unknown, but several factors appear to play a role, including:

Genetic: Researchers have identified specific genetic mutations such as *α–synuclein* and *parkin,* that can cause Parkinson's disease, but these are uncommon except in rare cases with many family members affected by Parkinson's disease. Recent studies suggest that dysfunction of the ubiquitin–proteasome system (UPS) and the resultant accumulation of misfolded proteins and endoplasmic reticulum stress may cause the death of Dopaminergic (DA) neurons.

In parkinson's disease, degenerating brain cells contain Lewy bodies, which help to identify the disease.

The presence of Lewy bodies: Clumps of specific substances within brain cells are microscopic markers of Parkinson's disease. These are called Lewy bodies, and researchers believe these Lewy bodies hold an important clue to the cause of Parkinson's disease.

A synuclein is found within Lewy bodies: Although many substances are found within Lewy bodies, scientists believe the most important of these is the natural and widespread protein called α-synuclein. It is found in all Lewy bodies in a clumped form that cells cannot break down. This is currently an important focus among Parkinson's disease researchers.

The cell death leading to Parkinsonism may be caused by a number of conditions, including infection, trauma and poisoning.

Some drugs given for psychosis, such as haloperidol or chlorpromazine, may cause parkinsonism. When no cause for nigral cell degeneration can be found, the disorder is called idiopathic Parkinsonism.

Parkinsonism may be seen in other degenerative conditions, known as the "Parkinsonism plus" syndromes, such as progressive supranuclear palsy.

There are some known toxins that can cause parkinsonism, most notoriously a chemical called MPTP, (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) is a neurotoxin precursor to MPP^+, which causes permanent symptoms of Parkinson's disease by destroying dopaminergic neurons in the substantia nigra of the brain, found as an impurity in some illegal drugs. Parkinsonian symptoms appear within hours of ingestion and are permanent. MPTP may exert its effects through generation of toxic molecular fragments called free radicals, and

reducing free radicals has been a target of several experimental treatments for parkinson's disease using antioxidants.

It is possible that early exposure to some unidentified environmental toxin or virus leads to undetected nigral cell death, and manifests as normal age related decline brings the number of functioning nigral cells below the threshold, needed for normal movement. It is also possible that, for genetic reasons, some people are simply born with fewer cells in their substantia nigra than others, they develop parkinson's disease as a consequence of normal decline.

Risk Factors

Age: Young adults rarely experience Parkinson's disease. It ordinarily begins in middle or late life, and the risk increases with age. People usually develop the disease around age 60 or older.

Heredity: Having a close relative with Parkinson's disease increases the chances to develop the disease. However, risks are still small unless many relatives in family with Parkinson's disease.

Sex: Men are more likely to develop Parkinson's disease than are women.

Exposure to toxins: Ongoing exposure to herbicides and pesticides may slightly increase risk of Parkinson's disease.

Pathophysiology

No specific, standard criteria exist for the neuropathologic diagnosis of Parkinson disease, as the specificity and sensitivity of its characteristic findings have not been clearly established. However, the following are the 2 major neuropathologic findings in Parkinson disease:

- Loss of pigmented dopaminergic neurons of the substantia nigra pars compacta.
- The presence of Lewy bodies and Lewy neurites.

The loss of dopamine neurons occurs most prominently in the ventral lateral substantia nigra. Approximately 60-80% of dopaminergic neurons are lost before the motor signs of parkinson's disease emerge.

Some individuals who were thought to be normal neurologically at the time of their deaths are found to have Lewy bodies on autopsy examination. These incidental Lewy bodies have been hypothesized to represent the presymptomatic phase of Parkinson disease. The prevalence of incidental Lewy bodies increases with age. Nonetheless, they are a characteristic pathology finding of Parkinson disease.

Symptoms

Parkinson's disease symptoms and signs may vary from person to person. Early signs may be mild and may go unnoticed. Symptoms often begin on one side of body and usually remain worse on that side, even after symptoms begin to affect both sides.

Parkinson's signs and symptoms may include:

Tremors: Usually begins in a limb, often hand or fingers. The classic tremor of parkinson's disease is called as “Pill-rolling tremor”, because the movement resembles rolling a pill between the thumb and fore finger. This tremor occurs at a frequency of about three per second.

Slowed movement (Bradykinesia): It may involve slowing down or stopping in the middle of familiar tasks such as walking, eating or shaving, this may include freezing in place during movements (akinesia).

Rigid muscle: Muscle rigidity or stiffness, occuring with jerky movements

replacing smooth motion. The stiff muscles can limit range of motion and cause pain.

Impaired posture and balance: Postural instability or balance difficulty occurs. This may lead to a rapid, shuffling gait (festination) to prevent falling.

Loss of automatic movements: In Parkinson's disease, ability to perform unconscious movements, including blinking, smiling or swinging arms when walking may decrease. In most cases, there is a "masked face", with little facial expression and decreased eye blinking.

Speech changes: Speech may be more of a monotone rather than with the usual inflections. Patient may speak softly, quickly, slur or hesitate before talking.

Writing changes: Handwriting changes, with letters becoming smaller across the page (micrographia) and become difficult. Progressive problems with intellectual function (dementia).

Bladder problems: Parkinson's disease may cause bladder problems, including being unable to control urine or having difficulty urinating.

Constipation: Many people with Parkinson's disease develop constipation, mainly due to a slower digestive tract.

Smell dysfunction: Problems with sense of smell, may have difficulty identifying certain odours or the difference between odours.

Fatigue: Many people with Parkinson's disease lose energy and experience fatigue, and the cause is not always known.

Pain: Many people with Parkinson's disease experience pain, either in specific areas of their bodies or throughout their bodies.

Sexual dysfunction: Some people with Parkinson's disease notice a decrease in sexual desire or performance.

In addition, a wide range of other symptoms may often be seen, some beginning earlier than others: Depression, problems with sleep, including restlessness and nightmares. Emotional changes including fear, irritability and insecurity.

Tests and Diagnosis

The diagnosis of Parkinson disease involves a careful medical history and a neurological exam to look for characteristic symptoms.

There are no definitive tests for parkinson's disease, although a variety of lab tests may be done to rule out other causes of symptoms, especially if only some of the identifying symptoms are present.

Test for other causes of Parkinsonism may include brain scans, blood tests, lumbar puncture and X-rays.

Treatment and Drugs

No known treatment can stop or reverse the breakdown of nerve cells that causes Parkinson's disease. But there are many treatments that can help your symptoms and improve your quality of life. Treatments for Parkinson's include:

Medicines: Medicines, such as levodopa and dopamine agonists. The goal is to correct the shortage of the brain chemical dopamine, which causes the symptoms of Parkinson's. Several medicines may be used at different stages of the disease are:

- Levodopa and carbidopa: Levodopa is precursor of dopamine. Levodopa is combined with carbidopa, which protects levodopa from premature conversion to dopamine outside brain, which prevents or lessens side effects

such as nausea. L-dopa therapy usually remains effective for five years, as disease progresses, many patients develop motor fluctuations including dyskinesias (abnormal movements such as twisting, restlessness), rapid loss of response after dosing ("on-off phenomenon) even after taking of high doses of levodopa.

- Dopamine agonists (for example, pramipexole or ropinirole): Dopamine agonists may be used before L-dopa therapy or added on to avoid requirements for higher L-dopa doses late in the disease.
- COMT inhibitors: Entacapone and tolcapone are inhibitors of another enzyme system called catechol-o-methyl transferase are effectively treating Parkinson's disease. This medication mildly prolongs the effect of levodopa therapy by blocking an enzyme that breaks down dopamine.
- MAO-B inhibitors (rasagiline, selegiline): These can prevent the breakdown of brain dopamine by inhibiting the brain enzyme monoamine oxidase B (MAO-B) and prolong the effects of dopamine. This enzyme metabolizes brain dopamine.
- Amantadine: Amantadine is sometimes used alone to provide short-term relief of symptoms of mild, early-stage parkinson's disease. It may also be given with carbidopa-levodopa therapy during the later stages of Parkinson's disease to control involuntary movements (dyskinesias) induced by carbidopa-levodopa.
- Anticholinergic agents: These medic-ations were used for many years to help control the tremor associated with Parkinson's disease. Example: Benztropine or Trihexyphenidyl.
- Apomorphine: A short-acting injectable dopamine agonist, apomorphine is used for quick relief.
- Home treatment: There are many steps can be taken at home to make dealing with the symptoms of Parkinson's disease easier, such as getting regular exercise and eating a healthy diet including plenty of fruits, vegetables, grains, cereals, legumes, poultry, fish, lean meats, and low-fat dairy products.
- Surgery: Brain surgery, for example deep brain stimulation (DBS), may be considered when medicine fails to control symptoms of Parkinson's disease or causes severe or disabling side effects.
- Speech therapy: Speech therapists use breathing and speech exercises to help overcome the soft, imprecise speech and monotone voice that develop in advanced Parkinson's disease.
- Physical therapy and Occupational therapy: Therapists may help improve walking and reduce risk of falling.

Alternative Treatment:

Alternative therapies, including acupuncture, massage and yoga can help relieve some symptoms of the disease and loosen tight muscles. Alternative treatment also include herbal and dietary therapies, including amino acid supplementation, antioxidant (vitamins A, C, E, selenium and zinc) therapy, B vitamin supplementation and calcium and magnesium supplementation to treat Parkinson's disease.

Prevention

Because the cause of Parkinson's is unknown, there is no known way to prevent Parkinson's disease. However, some research has shown that caffeine found in coffee, tea and cola may reduce the risk of developing Parkinson's disease. Green tea also may reduce the risk of developing Parkinson's disease. Some research has shown that regular aerobic exercise may reduce the risk of Parkinson's disease.

9.4 STROKE

A stroke is a "brain attack". It occurs when blood flow to an area of brain is cut off. When this happens, brain cells are deprived of oxygen and begin to die. When brain cells die during a stroke, abilities controlled by that area of the brain such as memory and muscle control are lost. Stroke also known as cerebrovascular accident (CVA). The effect of stroke depends on where the stroke occurs in the brain and how much the brain is damaged. For example, someone who had a small stroke may only have minor problems such as temporary weakness of an arm or leg. People who have larger strokes may be permanently paralyzed on one side of their body or lose their ability to speak. Some people recover completely from strokes, but more than 2/3 of survivors will have some type of disability.

Types of Stroke

There are three main kinds of stroke:

- Ischemic strokes,
- Hemorrhagic strokes,
- Transient ischemic attacks (TIAs), also referred to as mini-strokes.

Causes

The different forms of stroke have different specific causes.

Causes of Ischemic Stroke: Ischemic stroke is the most common form, accounting for around 85 % of strokes. This type of stroke is caused by blockages or narrowing of the arteries that provide blood to the brain, resulting in ischemia - severely reduced blood flow that damages brain cells. These blockages are often caused by blood clots, which can form either in the arteries within the brain, or in other blood vessels in the body before being swept through the bloodstream and into narrower arteries within the brain. Fatty deposits within the arteries called plaque can cause clots that result in ischemia.

Causes of Hemorrhagic Stroke: Hemorrhagic strokes are caused by arteries in the brain either leaking blood or bursting open. The leaked blood puts pressure on brain cells and damages them. It also reduces the blood supply reaching the brain tissue after the hemorrhage point. Blood vessels can burst and spill blood within the brain or near the surface of the brain, sending blood into the space between the brain and the skull. The ruptures can be caused by conditions such as hypertension, trauma, blood-thinning medications, and aneurysms (weaknesses in blood vessel walls). Intracerebral hemorrhage is the most common type of hemorrhagic stroke and occurs when brain tissue is flooded with blood after an artery in the brain bursts. Subarachnoid hemorrhage is the second type of hemorrhagic stroke and is less common. In this type of stroke, bleeding occurs in an artery in the subarachnoid space - the area between the brain and the thin tissues that cover it.

Causes of Transient Ischemic Attack (TIA): TIAs are different from the kinds above because the flow of blood to the brain is only briefly interrupted. TIAs are similar to ischemic strokes. In that, they are often caused by blood clots or other clots. TIAs should be regarded as medical emergencies just like the other kinds of stroke, even if the blockage of the artery and symptoms are temporary. They serve as warning signs for future strokes and indicate that there is a partially blocked artery or clot source in the heart.

Risk Factors

- Uncontrolled hypertension,
- Diabetes mellitus,
- Smoking,
- Cardiac disease,
- Hyperlipidemia,
- Excessive alcohol intake.

Epidemiology

Stroke is one of the leading causes of death and disability in India. The estimated adjusted prevalence rate of stroke range, 84-262/100,000 in rural and 334-424/ 100,000 in urban areas. The incidence rate is 119-145/100,000 based on the recent population based studies. There is also a wide variation in case of fatality rates with the highest being 42% in Kolkata. Stroke units are predominantly available in urban areas that too in private hospitals. Intravenous (IV) and intra-arterial thrombolysis (IA) are commonly used in India.

Pathophysiology

The pathophysiology of stroke is complex and involves numerous processes, including: energy failure, loss of cell ion homeostasis, acidosis, increased intracellular calcium levels, excitotoxicity, free radical-mediated toxicity, generation of arachidonic acid products, cytokine mediated cytotoxicity, complement activation, disruption of the blood-brain barrier (BBB), activation of glial cells, and infiltration of leukocytes.

Glutamate excitotoxicity: A significant portion of ischemia-induced neuronal damage is mediated by excessive accumulation of excitatory amino acids, leading to toxic increase in intracellular calcium. Although this is an intrinsic defensive response to protect against ischemia by activating a reaction to severe cell stress, paradoxically, this increase in intracellular calcium activates multiple signaling pathways, which ultimately leads to cell death. The reduction or termination of cerebral blood flow, energy dependent cellular pumps fail due to a fall in glucose dependent ATP generation, resulting in the flow of numerous ionic species into the cell. This results in cellular swelling through osmosis and cellular depolarization. Calcium ions (Ca^{2+}) enter the cell through voltage-dependent and ligand-gated ion channels, resulting in activation of a number of proteases, kinases, lipases, and endonucleases, triggering of the intrinsic apoptotic pathway and thus ending in cell death by Glutamate, which is the major excitatory neurotransmitter in the brain, accumulates in the extracellular space following ischemia, and activates its receptors.

Oxidative stress: The oxidative stress and apoptosis are closely linked phenomena in the pathophysiology of ischemic stroke. Neurons are normally exposed to a baseline level of oxidative stress from both exogenous and endogenous sources, as are

all cells in the body. Free radicals like superoxide anion radical, hydroxyl radical and nitric oxide (NO) produced by mitochondria are involved in stroke induced brain injury. Free radicals can react with DNA, proteins and lipids, causing varying degrees of damage and dysfunction.

Oxygen free radicals can also be generated by activated microglia and infiltrating peripheral leukocytes via the NADPH oxidase system following reperfusion of ischemic tissue. This oxidation causes further tissue damage, and is thought to be an important trigger molecule for apoptosis after ischemic stroke.

Lipid peroxidation: Lipid peroxidation plays a prominent role in the pathogenesis of stroke. The mechanism, whereby membrane lipid peroxidation induces neuronal apoptosis, involves generation of an aldehyde called 4-hydroxynonenal (4-HNE), which covalently modifies membrane transporters such as the Na^+ /K^+ ATPase, glucose transporters and glutamate transporters, thereby impairing their function.

Inflammation and Leucocyte Infiltration: Inflammation in stroke is characterized by the accumulation of leukocytes and activation of resident microglial cells. Inflammatory cells can contribute to stroke pathology through two basic mechanisms. They form aggregates in the venules after reperfusion, or, enter infarcted tissue and exacerbate cell death through production of free radicals and cytokines. Cell adhesion molecules such as selectins, integrins, and ICAMs permit endothelial-inflammatory cell interactions.

Symptoms

Strokes occur quickly, so symptoms often appear suddenly and without warning. The main symptoms of stroke are:

Muscular: Difficulty walking, paralysis with weak muscles, problems with co-ordination, stiff muscles, overactive reflexes, or paralysis of one side of the body.

Whole body: Balance disorder, fatigue, light-headedness, or vertigo.

Visual: Blurred vision, double vision, sudden visual loss, or temporary loss of vision in one eye.

Speech: Difficulty in speaking, slurred speech, or speech loss.

Sensory: Reduced sensation of touch, even by applying pins and needles.

Facial: Muscle weakness or numbness.

Limbs: Numbness or weakness.

Common: Difficulty in swallowing, headache, inability to understand, mental confusion, or rapid involuntary eye movement.

Facts on Stroke

- During a stroke, the brain does not receive enough oxygen or nutrients, causing brain cells to die.
- Ischemic strokes are caused by a narrowing or blocking of arteries to the brain.
- Hemorrhagic strokes are caused by blood vessels in and around the brain bursting or leaking.
- Strokes need to be diagnosed and treated as quickly as possible to minimize brain damage.
- Treatment depends on the type of stroke.
- The most effective way to prevent strokes is through maintaining a healthy lifestyle and treating underlying conditions that are a risk factor.

Diagnosis

There are several different types of diagnostic tests that can be used to determine which type of stroke has occurred:

- Physical examination: It consists of measurement of blood pressure, listen to the carotid arteries in the neck, and examine the blood vessels at the back of the eyes, all to check for indications of clotting.
- Blood tests: A doctor may perform blood tests to find out how quickly the patient's blood clots. The levels of particular substances (including clotting factors) in the blood, and whether or not the patient has an infection.
- CT scan: A series of X-rays that can show haemorrhages, strokes, tumors, and other conditions within the brain.
- MRI scan: Radio waves and magnets create an image of the brain to detect damaged brain tissue.
- Carotid ultrasound: An ultrasound scan to check the blood flow in the carotid arteries and to see if there is any plaque present.
- Cerebral angiogram: Dyes are injected into the brain's blood vessels to make them visible under X-ray, to give a detailed view of the brain and neck blood vessels.
- Echocardiogram: A detailed image of the heart is created to check for any sources of clots that could have travelled to the brain to cause a stroke.

Prevention

- Eating a healthy diet.
- Maintaining a healthy weight.
- Exercise regularly.
- Do not smoke.
- Avoiding alcohol or drink moderately.
- Keeping blood pressure under control.
- Managing diabetes.
- Treating obstructive sleep apnea (if present).

Treatment

Drug Treatment: There is only one Food and Drug Administration (FDA) approved drug treatment for acute ischemic stroke. Tissue plasminogen activator (tPA) is given via intravenous therapy (IV) and works by dissolving the clot and improving blood flow to the part of the brain being deprived of blood flow. tPA should be given within three hours (and upto 4.5 hours in certain eligible patients) of the time symptoms first started.

Mechanical Devices: Some ischemic strokes are treated with small mechanical devices that remove or break up blood clots. If clot-busting drugs are ruled out, another option one of the many FDA approved mechanical devices. A surgeon inserts a small mechanical device into the blocked artery using a thin tube. Once inside, the tool traps the clot, and either breaks it up or the surgeon pulls it out of the brain, reopening the blocked blood vessel in the process.

A hemorrhagic stroke (sometimes called a bleed) occurs if an artery in a brain leaks blood or ruptures (breaks open). The first step in treating a hemorrhagic stroke is to find the cause of bleeding in the brain and then control it. Some of the options for treatments include surgical clips or coils inserted in aneurisms (weaknesses in the blood vessel wall), controlling high blood pressure, and surgery to remove the bleeding vessel and blood that has spilled into the brain.

9.5 DEPRESSION

Depression is a common mental disorder, characterized by sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, feelings of tiredness and poor concentration. It can be long lasting or recurrent, substantially impairing a person's ability to function at work or school, or cope with daily life. There are many different types of depression caused by certain events in life and chemical changes in brain.

Major depression: Major depression is the presence of depressed mood or loss of pleasure for at least two consecutive weeks along with changes in appetite or weight, changes in sleep pattern, retardation, fatigue, feeling of worthlessness, excessive guilt, difficulty concentrating, and thoughts of suicide and can lead to a variety of emotional and physical problems.

Chronic major depression: Depressed mood for at least two years along with appetite disturbance, sleep disturbance, fatigue, low self-esteem, poor concentration and difficulty in making decision and feeling of hopelessness.

Dysthymia (recurrent, mild depression): Dysthymia is a type of chronic "low-grade" depression. More days than not, person feel mildly or moderately depressed, although person may have brief periods of normal mood.

The symptoms of dysthymia are not as strong as the symptoms of major depression, but they last a long time (at least two years). These chronic symptoms make it very difficult to live life to the fullest or to remember better times. Some people also experience major depressive episodes on top of dysthymia, a condition known as "double depression".

Seasonal affective disorder (SAD): Some people get depressed in the fall or winter, when overcast days are frequent and sunlight is limited. This type of depression is called seasonal affective disorder (SAD). Seasonal affective disorder is more common in northern climates and in younger people. Like depression, seasonal affective disorder is treatable. Light therapy, a treatment that involves exposure to bright artificial light, often helps relieve symptoms.

Bipolar disorder: When depression is just one side of the coin, it is bipolar disorder, also known as manic depression and it is characterized by cyclic mood changes. Episodes of depression alternate with manic episodes, which can include impulsive behaviour, hyperactivity, rapid speech and little to no sleep.

Typically, the switch from one mood extreme to the other is gradual, with each manic or depressive episode lasting for at least several weeks. When depressed, a person with bipolar disorder exhibits the usual symptoms of major depression. However, the treatments for bipolar depression are very different. In fact, antidepressants can make bipolar depression worse.

Depression affects each person in different ways; therefore symptoms caused by depression vary from person to person. Depression with specific features, such as:

Atypical features: An ability to be cheered by happy events, increased appetite, little need for sleep, sensitivity to rejection, and a heavy feeling in arms or legs.

Mixed features: Simultaneous depression and mania, which includes elevated self-esteem, talking too much, and racing thoughts and ideas.

Psychotic features: Depression accompanied by delusions or hallucinations, which may involve themes of personal inadequacy or negative themes.

Catatonia: Include motor activity that involves either uncontrollable and purposeless movement or fixed and inflexible posture.

Peripartum onset: It occurs during pregnancy or in the weeks or months after delivery.

Epidemiology

Depression is a major cause of morbidity worldwide. Lifetime prevalence varies widely, from 3% in Japan to 17% in the US. In most countries the number of people who would suffer from depression during their lives falls within 8–12% range.

In India, depression is a disorder of major public health importance, in terms of its prevalence and the suffering, dysfunction, morbidity, and economic burden. Depression is more common in women than men. It occurs in about 6% adult population because of stressful life events, prior suicidal attempts, age less than 40 years, family history of depression, recent childbirth, lack of social support and current substance abuse.

Causes

The causes of depression are not fully understood and may not be down to a single source. Depression is likely to be due to a complex combination of factors that include:

- Genetics
- Biological: Changes in neurotransmitter levels
- Environmental
- Psychological and social (psychosocial)

Some people are at higher risk of depression than others; risk factors include:

- Life events: Including bereavement, divorce, work issues, relationships with friends and family, financial problems, medical concerns, or acute stress.
- Personality: Those with less successful coping strategies, or previous life trauma.
- Genetic factors: First-degree relatives of depressed patients are at higher risk.
- Childhood trauma.
- Some prescription drugs: Including corticosteroids, some β-blockers, interferon, and other prescription drugs.
- Abuse of recreational drugs (including alcohol and amphetamines): Can accompany depression or result in it. There are strong links between drug abuse and depression.
- A past head injury.
- People who have had an episode of major depression are at higher risk of a subsequent one.
- Chronic pain syndromes in particular, but also other chronic conditions, such as diabetes, chronic obstructive pulmonary disease, and cardiovascular disease.

Pathophysiology

Exact pathophysiology of depression is unknown but hypothesis is monoamine deficiency (e.g. norepinephrine and serotonin) and this may represent a final common pathway triggered by initial disorder involving other neurotransmitters or their receptor.

Autopsy examination of neural tissue revealed that, significant low concentration of serotonin metabolites and reduced serotonin uptake by platelet in depressed people.

Dietary restriction of L-tryptophan, an amino acid that is serotonin precursor.

Deregulation of Serotonin (5HT) and Norepinephrine (NE) in the brain are strongly associated with depression. Deregulation of 5HT and NE in the spinal cord may explain an increased pain perception among depressed patients. Decreased levels of 5HT and NE may explain the presence of both emotional and physical symptoms of depression.

Serotonin:

As a neurotransmitter, serotonin helps to relay messages from one area of the brain to another. Because of the widespread distribution of its cells, it is believed to influence a variety of psychological and other body functions. Approximately 40 million brain cells, most are influenced either directly or indirectly by serotonin.

This includes brain cells related to mood, sexual desire and function, appetite, sleep, memory and learning, temperature regulation, and some social behaviour.

In terms of body function, serotonin can also affect the functioning of cardiovascular system, muscles and various elements in the endocrine system.

Serotonin is made via a unique biochemical conversion process. It begins with tryptophan, a building block to proteins. Cells that make serotonin use tryptophan hydroxylase, a chemical reactor which, when combined with tryptophan, forms 5-hydroxytryptamine, otherwise known as serotonin.

Link between serotonin and depression:

Researchers believe that an imbalance in serotonin levels may influence mood in a way that leads to depression. Possible problems include low brain cell production of serotonin, a lack of receptor sites able to receive the serotonin that is made, inability of serotonin to reach the receptor sites, or a shortage in tryptophan. If any of these biochemical glitches occur, it can lead to depression.

Although it is widely believed that a serotonin deficiency plays a role in depression, there is no way to measure its levels in the living brain. Therefore, there have not been any studies proving that brain levels of this or any neurotransmitter are in short supply when depression or any mental illness develops.

Blood levels of serotonin are measurable and have been shown to be lower in people who suffer from depression but researchers do not know if blood levels reflect the brain's level of serotonin. Also, researchers do not know whether the drop in serotonin causes the depression, or the depression causes serotonin levels to drop.

Symptoms

People with depressive illnesses do not all experience the same symptoms. The severity, frequency and duration of depression depending on the individual's particular illness. Although depression may occur only one time during life, usually people have multiple episodes of depression. During these episodes, symptoms occur most of the day, nearly every day and may include:

- Feelings of sadness, emptiness or unhappiness.

- Angry outbursts, irritability or frustration, even over small matters.
- Loss of interest or pleasure in normal activities, such as sex.
- Sleep disturbances, including insomnia or sleeping too much.
- Tiredness and lack of energy, so that even small tasks take extra effort.
- Changes in appetite often reduced appetite and weight loss, but increased cravings for food and weight gain in some people.
- Anxiety, agitation or restlessness, e.g., excessive worrying, pacing, hand-wringing or an inability to sit still.
- Slowed thinking, speaking or body movements.
- Feelings of worthlessness or guilt, fixating on past failures or blaming for the things that, they are not responsible.
- Trouble thinking, concentrating, making decisions and remembering things.
- Frequent thoughts of death, suicidal thoughts, suicide attempts or suicide.
- Unexplained physical problems, such as back pain or headaches.

Depression symptoms in children and teens:

Common symptoms of depression in children and teens are similar to those of adults, but there can be some differences.

In younger children, symptoms of depression may include sadness, irritability, clinginess, worry, aches and pains, refusing to go to school, or being underweight.

In teens, symptoms may include sadness, irritability, feeling negative and worthless, anger, poor performance or poor attendance at school, feeling misunderstood and extremely sensitive, using drugs or alcohol, eating or sleeping too much, self-harm, loss of interest in normal activities, and avoidance of social interaction.

Depression may occur with other mental health conditions, such as anxiety, eating disorders and substance abuse.

Depression symptoms in older adults:

Symptoms of depression may be different or less obvious in older adults, including: Memory difficulties or personality changes, fatigue, loss of appetite, sleep problems, aches or loss of interest in sex, which are not caused by a medical condition or medication. Often wanting to stay at home, rather than going out to socialize or doing new things, suicidal thinking or feelings, especially in older men.

Depression can appear as anger and discouragement, rather than feelings of sadness.

If depression is very severe, there may also be psychotic symptoms, such as hallucinations and delusions.

Complications

Depression is a serious disorder that can take a terrible toll on individuals and families. Untreated depression can result in emotional, behavioural and health problems that affect every area of life. Complications associated with depression may include:

- Excess weight or obesity, which can lead to heart disease and diabetes.
- Alcohol or substance abuse.
- Anxiety, panic disorder or social phobia.
- Family conflicts, relationship difficulties, and work or school problems.
- Social isolation.
- Suicidal feelings, suicide attempts or suicide.
- Premature death from other medical conditions.

Tests and Diagnosis

These exams and tests can help to rule out other problems that could be causing symptoms, pinpoint a diagnosis and check for any related complications:

Physical examination: There are no definitive findings of depression on physical examination, although most patients will have a depressed affect, as well as a downcast gaze, furrowed brow, psychomotor slowing, speech latency, and expressions of guilt or self-blame. The physical examination and cognitive screening may be useful in ruling out common conditions that are often confused with depression (i.e., hypothyroidism, dementia) and in looking for commonly co-occurring illnesses (i.e., obesity, cancer, stroke). In some cases, depression may be linked to an underlying physical health problem.

Lab tests: Simple laboratory tests should be performed in the work-up to exclude other causes of depression symptoms. Adults diagnosed with depression and with negative findings on physical examination do not routinely need further testing. Certain lab tests include a complete blood count, basic metabolic panel and thyroid function tests to rule out anemia and thyroid disease and to assess general nutritional status.

Psychological evaluation: To check for signs of depression, mental health provider asks about symptoms, thoughts, feelings and behaviour patterns.

Other tests may include:

- CT scan or MRI of the brain to rule out serious illnesses such as a brain tumor.
- Electrocardiogram (ECG), which is used to diagnose some heart problems.
- Electroencephalogram (EEG), which is used for recording electrical activity of the brain.

Treatments And Drugs

Numerous depression treatments are available. Medications and psychological counseling (psychotherapy) or other mental health counselor are very effective for most people.

Medications: Many types of antidepressant medications are available to treat depression, including those below. The more commonly used medications are from the following classes:

- Selective serotonin reuptake inhibitors (SSRIs): SSRIs include Fluoxetine, Paroxetine, Sertraline, Citalopram and Escitalopram.
- Serotonin-norepinephrine reuptake inhibitors (SNRIs): SNRI medications include Duloxetine, Venlafaxine and Desvenlafaxine.
- Atypical antidepressants: Trazodone and Mirtazapine
- Serotonin modulators.

Older, less commonly used, antidepressants include:

- Tricyclic antidepressants: Tricyclic antidepressants such as Imipramine and Nortriptyline tend to cause more severe side effects than do newer antidepressants.
- Monoamine oxidase inhibitors (MAOIs): Commonly used MAOIs are Tranylcypromine and Phenelzine. Taking MAOIs should avoid or limit certain foods, which can interact with the medication and cause serious health problems.

Psychotherapy:

Psychotherapy treatment is focused on improving positive changes in depressive patients. There are many specific types of psychotherapy that are used to treat depression. Each works in a slightly different way, but all have been proven to help improve the symptoms of depression.

- Cognitive-behavioural therapy (CBT): In CBT, the therapist is to identify and reshape the thought and behaviour patterns that contribute to depression.
- Interpersonal psychotherapy: In interpersonal psychotherapy, focus is on improvement of relationships, the way that depressive patients interact with other people in their life.
- Family and couples therapy: In family and couples therapy, the therapist shall improve interaction of patient with family members so that depressive patients can work together on the issues that are contributing depression.
- Problem solving therapy: In problem-solving therapy, the therapist have to develop practical and systematic approach to the problems in life and find effective ways to solve them.
- Psychodynamic psychotherapy: In psychodynamic therapy, therapist might explore childhood or historic life events and work to reduce their influence by gaining insight into how they may be shaping current behaviour.

Prevention

Avoid alcohol drinking or use of illegal drugs. These substances can make depression worse and might lead to thoughts of suicide. Take medication exactly as instructed.

There is no sure way to prevent depression. However, the following strategies may help feel better:

Get more exercise, maintain good sleep habits, seek out activities that bring pleasure, volunteer or get involved in group activities, try to be around people who are caring and positive, intervening with a depressed friend, be empathetic and understanding, avoid critical or shaming statements and challenge expressions of hopelessness

9.6 SCHIZOPHRENIA

Schizophrenia is a severe mental disorder, characterized by profound disruptions in thinking, affecting language, perception, and the sense of self. It often includes psychotic experiences, such as hearing voices or delusions. It can impair functioning through the loss of an acquired capability to earn a livelihood, or the disruption of studies. Schizophrenia typically begins in late adolescence or early adulthood. Schizophrenia is a serious brain disorder that distorts the way a person thinks, acts, expresses emotions, perceives reality, and relates to others. Schizophrenia can leave its sufferer frightened and withdrawn. It is a life-long disorder that cannot be cured, but usually can be controlled with proper treatment. Contrary to popular belief, schizophrenia is not a split personality or multiple personality. The word "schizophrenia" does mean "split mind," but it refers to a disruption of the usual balance of emotions and thinking. The behaviour of people with schizophrenia may be very strange and even shocking. A sudden change in personality and behaviour, which occurs when schizophrenia sufferers lose touch with reality, is called a psychotic episode. Schizophrenia varies in severity from person to person. Some people have only one psychotic

episode while others have many episodes during a lifetime but lead relatively normal lives between episodes. Schizophrenia symptoms seem to worsen and improve in cycles known as relapses and remissions.

Epidemiology

Schizophrenia affects around 0.3–0.7% of people at some point in their life. It occurs 1.4 times more frequently in males than females and typically appears earlier in men but the peak ages of onset are 25 years for males and 27 years for females. Onset in childhood it is much rarer, as is onset in middle or old age.

The prevalence rate for schizophrenia is approximately 1.1% of the population over the age of 18.

Types of Schizophrenia

Schizophrenia is a term given to a complex group of mental disorders. However, different types of schizophrenia may have some of the same symptoms. There are several subtypes of schizophrenia based on symptoms:

Paranoid schizophrenia: People with this type, are preoccupied with false beliefs (delusions) about being persecuted or being punished by someone. Their thinking, speech and emotions, however, remain fairly normal.

Disorganized schizophrenia: People with this type often are confused and incoherent and have jumbled speech. Their outward behaviour may be emotionless or flat or inappropriate, even silly or childlike. Often they have disorganized behavior that may disrupt their ability to perform normal daily activities such as showering or preparing meals.

Catatonic schizophrenia: The most striking symptoms of this type are physical. People with catatonic schizophrenia are generally immobile and unresponsive to the world around them. They often become very rigid and stiff and unwilling to move. Occasionally, these people have peculiar movements like grimacing or assume bizarre postures or they might repeat a word or phrase just spoken by another person. At times, the opposite may be true and these individuals appear to engage in restless ongoing activity with no specific purpose or desired outcome for example, walking a straight line over and over; repeatedly jumping in place. People with catatonic schizophrenia generally go back and forth between more sedentary behaviours, the restless, purposeless behaviours and are at increased risk of malnutrition, exhaustion, or self-inflicted injury.

Undifferentiated schizophrenia: This subtype is diagnosed when the person's symptoms do not clearly represent one of the other three subtypes.

Residual Schizophrenia: In this type of schizophrenia, the severity of schizophrenia symptoms has decreased. Hallucinations, delusions, or other symptoms may still be present but are considerably less than when the schizophrenia was originally diagnosed. In addition, there must still be evidence of the disturbance as indicated by the presence of some negative symptoms (for example, inexpressive faces, blank looks, monotone speech, seeming lack of interest in the world and other people, inability to feel pleasure).

Causes

The exact cause of schizophrenia is not yet known. It is known, however, that

schizophrenia like cancer and diabetes is a real illness with a biological basis. It is not the result of bad parenting or personal weakness. But researchers believe that a combination of genetics and environment contributes to development of the disorder.

Genetics (heredity): Schizophrenia tends to run in families, which means a greater likelihood to develop schizophrenia may be passed on from parents to their children.

Brain chemistry: People with schizophrenia may have an imbalance of certain chemicals in the brain. They may be either very sensitive to or produce too much of a brain chemical called dopamine.

Dopamine is a neurotransmitter, a substance that helps nerve cells in the brain to send messages to each other. An imbalance of dopamine affects the way the brain reacts to certain stimuli, such as sounds, smells, and sights, and can lead to hallucinations and delusions.

Brain abnormality: Research has found abnormal brain structure and function in people with schizophrenia. However, this type of abnormality does not happen in all schizophrenics and can occur in people without the disease.

Environmental factors: Evidence suggests that certain environmental factors, such as a viral infection, extensive exposure to toxins like marijuana, or highly stressful situations, may trigger schizophrenia in people who have inherited a tendency to develop the disorder. Schizophrenia more often surfaces when the body is undergoing hormonal and physical changes, such as those that occur during the teen and young adult years.

Risk Factors

Although the precise cause of schizophrenia is unknown, certain factors seem to increase the risk of developing or triggering schizophrenia, including:

- Having a family history of schizophrenia,
- Exposure to viruses, toxins or malnutrition while in the womb, particularly in the first and second trimesters,
- Increased immune system activation, such as from inflammation or autoimmune diseases,
- Taking mind-altering (psychoactive or psychotropic) drugs during teen years and young adulthood.

Dopamine Theory of Schizophrenia: The exact cause of schizophrenia is unknown, though genetics and environmental factors may play a role. For example, altered brain structures, such as having less gray matter than average, may contribute to the onset of the disorder. Altered brain chemistry, specifically due to the neurotransmitter dopamine, also may be a factor.

Pharmacological treatments support the idea that, an overactive dopamine system may result in schizophrenia: Medications that block dopamine receptors, specifically D_2 receptors, reduce schizophrenia symptoms.

Dopamine: It is a catecholamine neurotransmitter present in a wide variety of animals. In the brain, this function as a neurotransmitter, activating the five known types of dopamine receptor – D_1, D_2, D_3, D_4 and D_5.

Dopamine is also a neurohormone released by the hypothalamus. Its main function as a hormone is to inhibit the

release of prolactin from the anterior lobe of the pituitary.

Evidence for the dopamine hypothesis:

Amphetamine, cocaine and similar drugs increase levels of dopamine in the brain and can cause symptoms which resemble those present in psychosis.

Similarly, those treated with dopamine enhancing levodopa for Parkinson's disease can experience psychotic side effects mimicking the symptoms of schizophrenia.

Upto 75% of patients with schizophrenia have increased signs and symptoms of their psychosis upon challenge with moderate doses of methylphenidate or amphetamine or other dopamine like compounds.

Some functional neuroimaging studies have also shown that, after taking amphetamine, patients diagnosed with schizophrenia show greater levels of dopamine release than non-psychotic individuals.

However, the acute effects of dopamine stimulants include euphoria, alertness and over-confidence; these symptoms are more reminiscent of mania than schizophrenia.

Symptoms

In men, schizophrenia symptoms typically start in the early to mid-20s. In women, symptoms typically begin in the late 20s. It is uncommon for children to be diagnosed with schizophrenia and rare for those older than 45.

Schizophrenia involves a range of problems with thinking (cognitive), behaviour or emotions. Signs and symptoms may vary, but they reflect an impaired ability to function.

The most common symptoms of schizophrenia can be grouped into three categories:

- Positive symptoms
- Disorganized symptoms and
- Negative symptoms

Positive symptoms are disturbances that are "added" to the person's personality.

- Delusions: "False ideas" individuals may believe that someone is spying on him or her, or that they are someone famous (or a religious figure).
- Hallucinations: These usually involve seeing, feeling, tasting, hearing or smelling something that does not really exist. The most common experience is hearing imaginary voices that give commands or comments to the individual.
- Disordered thinking and speech: Moving from one topic to another, in a nonsensical fashion. Individuals may also make up their own words or sounds, rhyme in a way that does not make sense, or repeat words and ideas.
- Disorganized behaviour: This can range from having problems with routine behaviors like hygiene or choosing appropriate clothing for the weather, to unprovoked outbursts, to impulsive and uninhibited actions. A person may also have movements that seem anxious, agitated, tense or constant without any apparent reason.

Negative symptoms are capabilities that are "lost" from the person's personality.

- Social withdrawal,
- Extreme apathy (lack of interest or enthusiasm),
- Lack of drive or initiative,

- Emotional flatness,
- Loss of pleasure and lack of ability to experience pleasure,
- Decreased talking and neglect of personal hygiene, poor hygiene and grooming habits or have a loss of interest in everyday activities,
- Speaking without inflection or monotone or not adding hand or head movements that normally provide the emotional emphasis in speech.

Tests and Diagnosis

There is no single test for schizophrenia. The condition is usually diagnosed after assessment by a specialist in mental health.

A psychiatrist or other mental health professional should be involved in making a schizophrenia diagnosis. Some people with schizophrenia are afraid of their symptoms. They may be suspicious of others (paranoid). This can make it more difficult to confirm a schizophrenia diagnosis.

A schizophrenia diagnosis can be made when all of the following are true about a patient:

- Schizophrenia symptoms have been present for at least six months.
- Patient is significantly impaired by the symptoms. For example, has serious difficulty in working or with social relationships, compared to the period before symptoms began.
- Symptoms cannot be explained by another diagnosis, such as drug use or another mental illness.

If symptoms of schizophrenia are present or when psychiatrist suspects someone has schizophrenia, they typically ask for medical and psychiatric histories, conduct a physical exam, and run medical and psychological tests, including:

Tests and screenings: These may include complete blood count (CBC), other blood tests that may help rule out conditions with similar symptoms, and screening for alcohol and drugs. Other tests may include imaging studies, such as an MRI or CT scan.

Psychological evaluation: A psychiatrist or mental health provider will check mental status by observing appearance, attitude and asking about thoughts, moods, delusions, hallucinations, substance abuse, and potential for violence or suicide.

For a psychiatrist to make a confident schizophrenia diagnosis, some of these symptoms must be present:

- Hallucinations.
- Delusions.
- Disorganized speech and behaviour (talking and acting strangely).
- Lack of motivation and emotional expression.
- Lack of energy.
- Poor grooming habits.

Specific types of psychotic symptoms (called first-rank symptoms), when present, make a schizophrenia diagnosis more likely:

- Hearing own thoughts spoken aloud.
- Feeling that thoughts are being inserted into mind, or removed from it, by an outside force.
- Feeling like other people can read mind.

A person with schizophrenia may describe these symptoms openly or a psychiatrist may deduce as they are likely present, based on observations of a person's speech and behaviour.

Treatment

Schizophrenia requires lifelong treatment, even when symptoms have subsided. Treatment with medications and psychosocial therapy can help to manage the condition. During crisis periods or times of severe symptoms, hospitalization may be necessary to ensure safety, proper nutrition, adequate sleep and basic hygiene.

A psychiatrist experienced in treating schizophrenia usually guides treatment. The treatment team also may include a psychologist, social worker, psychiatric nurse and possibly a case manager to co-ordinate care. The full-team approach may be available in clinics with expertise in schizophrenia treatment.

Medications:

Second-generation antipsychotics: These newer, second-generation medications are generally preferred because they pose a lower risk of serious side effects than do first-generation antipsychotics. Second-generation antipsychotics include:

- Aripiprazole (Abilify)
- Asenapine (Saphris)
- Brexpiprazole (Rexulti)
- Cariprazine (Vraylar)
- Clozapine (Clozaril)
- Iloperidone (Fanapt)
- Lurasidone (Latuda)
- Olanzapine (Zyprexa)
- Paliperidone (Invega)
- Quetiapine (Seroquel)
- Risperidone (Risperdal)
- Ziprasidone (Geodon)

First-generation antipsychotics: These first-generation antipsychotics have frequent and potentially significant neurological side effects, including the possibility of developing a movement disorder (tardive dyskinesia) that may or may not be reversible.

First-generation antipsychotics include:

- Chlorpromazine
- Fluphenazine
- Haloperidol
- Perphenazine

Psychosocial interventions: Once psychosis recedes, in addition to continuing on medication, psychological and social (psychosocial) interventions are important. These may include:

- Individual therapy: Psychotherapy may help to normalize thought patterns. Also, learning to cope with stress and identify early warning signs of relapse can help people with schizophrenia manage their illness.
- Social skills training: This focuses on improving communication and social interactions and improving the ability to participate in daily activities.
- Family therapy: This provides support and education to families dealing with schizophrenia.
- Vocational rehabilitation and supported employment: This focuses on helping people with schizophrenia prepare for, find and keep jobs.

Electroconvulsive therapy (ECT): This is a procedure in which a series of electric shocks are delivered to the brain. The shocks induce seizures, causing the release of neurotransmitters in the brain. This form of treatment is rarely used today in the treatment of schizophrenia. ECT may be useful when all medications fail or if severe depression or catatonia makes treating the illness difficult.

Complications

Left untreated, schizophrenia can result in severe emotional, behavioral and health problems, as well as legal and financial problems that affect every area of life. Complications that schizophrenia may cause or be associated with include:

- Suicide,
- Any type of self-injury,
- Anxiety and phobias,
- Depression,
- Abuse of alcohol, drugs or prescription medications,
- Poverty,
- Homelessness,
- Family conflicts,
- Inability to work or attend school,
- Social isolation,
- Health problems, including those associated with antipsychotic medications, smoking and poor lifestyle choices,
- Being a victim of aggressive behaviour.

Aggressive behaviour, although it is uncommon and typically related to lack of treatment, substance misuse or a history of violence.

Prevention

There is no sure way to prevent schizophrenia. However, early treatment may help get symptoms under control before serious complications develop and may help improve the long-term outlook.

Sticking with the treatment plan can help to prevent relapses or worsening of schizophrenia symptoms.

9.7 ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a progressive, degenerative disorder that attacks the brain's nerve cells, or neurons especially in the cerebral cortex, resulting in loss of memory, thinking and language skills, and behavioural changes. A degenerative brain disease of unknown cause that is the most common form of dementia or loss of intellectual function, is generally found among people aged 65 and older. A common form of dementia of unknown cause, begin in late middle age, characterized by progressive memory loss and mental deterioration associated with brain damage. A disease marked by the loss of cognitive ability, generally over a period of 10 to 15 years and associated with the development of abnormal tissues and protein deposits in the cerebral cortex. Alzheimer's disease is a condition in which nerve cells in the brain die, making it difficult for the brain's signals to be transmitted properly. Alzheimer's symptoms may be hard to distinguish early on. A person with Alzheimer's disease has problems with memory, judgment, and thinking, which makes it hard for the person to work or take part in day-to-day life. The death of the nerve cells occurs gradually over a period of years.

Causes

Like all types of dementia, Alzheimer's disease is a neurodegenerative disease which results from a combination of genetic, lifestyle and environmental factors that affect progressive brain cell death over a course of time.

Although the causes of Alzheimer's are not yet fully understood, its effect on the brain is clear. Alzheimer's disease damages and kills brain cells. A brain affected by Alzheimer's disease has many fewer cells

and many fewer connections among surviving cells than does a healthy brain. As more and more brain cells die, Alzheimer's leads to significant brain shrinkage.

Plaques: These clumps of a protein called β-amyloid may damage and destroy brain cells in several ways, including interfering with cell-to-cell communication. Although the ultimate cause of brain-cell death in Alzheimer's is not known, the collection of β-amyloid on the outside of brain cells is a prime suspect.

Tangles: Brain cells depend on an internal support and transport system to carry nutrients and other essential materials throughout their long extensions. This system requires the normal structure and functioning of a protein called tau.

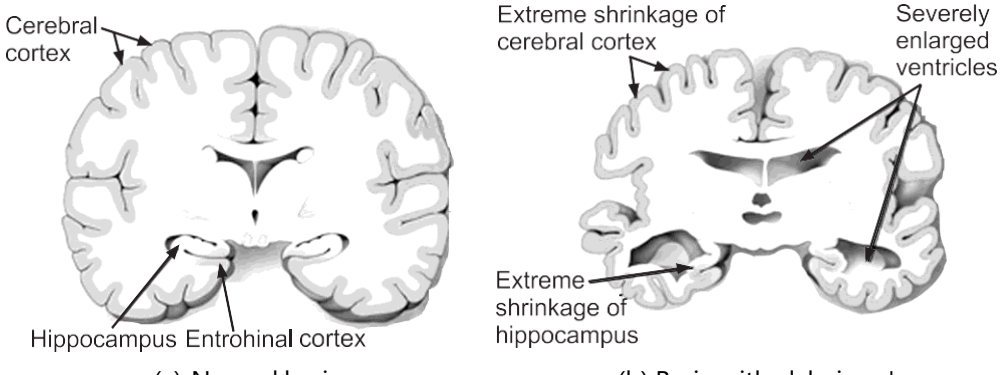
Loss of nerve cell connections: The tangles and plaques cause neurons to lose their connection to one another and die off. As the neurons die, brain tissue shrinks (atrophies).

In Alzheimer's, threads of tau protein twist into abnormal tangles inside brain cells, leading to failure of the transport system. This failure is also strongly implicated in the decline and death of brain cells.

Types of AD

Early onset AD: Symptoms appear before age 60. This type is much less common than late onset. However, it tends to get worse quickly. Early onset disease can run in families. Several genes have been identified.

Late onset AD: This is the most common type. It occurs in people after age 60 and older. It may run in some families, but the role of genes is less clear.



(a) Normal brain (b) Brain with alzheimer's

Fig. 9.5 : Features of alzheimer's disease

Symptoms

In most people with Alzheimer's, the disease progresses slowly, usually over a number of years. Dementia symptoms include difficulty with many areas of mental function, including: Emotional behaviour or personality.

Common symptoms of Alzheimer's disease include:

Impaired memory and thinking: The person has difficulty in remembering things or learning new information. In the later stages of the disease, long-term memory loss occurs, the person cannot remember personal information, such as place of birth

or occupation, or names of close family members. Forgetting details about current events and forgetting events of own life history.

Disorientation and confusion: People with Alzheimer's disease may get lost when out on their own and may not be able to remember where they are or how they got there. They may not recognize previously familiar places and situations. They also may not recognize familiar faces or know what time of the day it is, or even what year it is.

Misplacing items: The person forgets where they put items used every day, such as glasses, a hearing aid, keys etc. The person may also put things in strange places, such as leaving their glasses in the refrigerator.

Abstract thinking: Difficulty performing tasks that take some thought, but used to come easily, such as balancing a check book, playing complex games (such as bridge), and learning new information or routines.

Trouble performing familiar tasks: Difficulty in performing basic tasks, such as preparing meals, choosing proper clothing, grooming and driving. Planning for normal day-to-day tasks are also impaired.

Hallucinations, arguments, striking out, and violent behaviour: The person becomes unusually angry, irritable, restless, or quiet. At times, people with Alzheimer's disease can become confused, paranoid, or fearful.

Poor or decreased judgment: People with Alzheimer's disease may leave the house on a cold day without a coat or shoes or could go to the store wearing pajamas.

Inability to follow directions: The person has difficulty understanding simple commands or directions. The person may get lost easily and begin to wander.

Problems with language and communication: The person cannot recall words, name and objects (even ones that are very familiar, like a pen), or understand the meaning of common words.

Impaired visual and spatial skills: The person loses spatial abilities (the ability to judge shapes and sizes and the relationship of objects in space) and cannot arrange items in a certain order or recognize shapes.

Loss of motivation or initiative. The person may become very passive and require prompting to become involved and interact with others.

Loss of normal sleep patterns. The person may sleep during the day and be wide-awake at night.

Risk Factors

Increasing age is the greatest known risk factor for Alzheimer's. Alzheimer's is not a part of normal aging, but risk increases greatly after age 65. Nearly half of those older than age 85 have Alzheimer's.

Family history and genetics: Risk of developing Alzheimer's appears to be somewhat higher if a first-degree relative (parent or sibling) has the disease. Scientists have identified rare changes (mutations) in three genes that virtually guarantee a person who inherits them will develop Alzheimer's. But these mutations account for less than 5 % of Alzheimer's disease.

Sex: Women may be more likely than are men to develop Alzheimer's disease. Mild cognitive impairment have an increased risk.

Past head trauma: People who have had a severe head trauma or repeated head

trauma appear to have a greater risk of Alzheimer's disease.

Lifestyle and heart health: Some evidence suggests that the same factors that put at risk of heart disease also may increase the chance to develop Alzheimer's. Examples include: Lack of exercise, Smoking, High blood pressure, High blood cholesterol, Elevated homocysteine levels, poorly controlled diabetes and a diet lacking in fruits and vegetables.

Diagnosis

There is no specific test that confirms Alzheimer's disease. Alzheimer's disease can be diagnosed with complete accuracy only after death, when microscopic examination of the brain reveals the characteristic plaques and tangles. To help distinguish Alzheimer's disease from other causes of memory loss, doctors now typically rely on the following types of tests. A skilled health care provider can often diagnose alzheimer's disease with the following steps:

Complete physical exam: It includes neurological exam, medical history and symptoms which includes, reflexes, muscle tone and strength, ability to get up from a chair and walk across the room, sense of sight and hearing, co-ordination and balance.

A mental status examination: A brief mental status test to assess memory and other thinking skills.

A diagnosis of alzheimer's disease is made when certain symptoms are present, and by making sure other causes of dementia are not present.

Tests may be done to rule out other possible causes of dementia, including:

- Anemia,
- Brain tumor,
- Chronic infection,
- Intoxication from medication,
- Severe depression,
- Stroke,
- Thyroid disease,
- Vitamin deficiency.

Brain imaging: Images of the brain are now used chiefly to pinpoint visible abnormalities related to conditions other than Alzheimer's disease such as strokes, trauma or tumors, that may cause cognitive change.

Brain-imaging technologies include:

Computed tomography (CT) or magnetic resonance imaging (MRI) of the brain may be done to look for other causes of dementia, such as a brain tumor or stroke.

In the early stages of dementia, brain image scans may be normal. In later stages, an MRI may show a decrease in the size of different areas of the brain.

While the scans do not confirm the diagnosis of Alzeimer’s disease, they do exclude other causes of dementia (such as stroke and tumor).

Alzheimer's disease can be diagnosed with complete accuracy only after death, when microscopic examination of the brain reveals the characteristic plaques and tangles.

The following changes are more common in the brain tissue of people with alzheimer's disease:

"Neurofibrillary tangles" (twisted fragments of protein within nerve cells that clog up the cell).

"Neuritic plaques" (abnormal clusters of dead and dying nerve cells, other brain cells, and protein).

"Senile plaques" (areas where products of dying nerve cells have accumulated around protein).

Treatment

Although there is no cure, Alzheimer's medications can temporarily slow the worsening of symptoms and improve quality of life for those with Alzheimer's and their caregivers. The U.S. Food and Drug Administration (FDA) has approved five medications (listed below) to treat the symptoms of Alzheimer's disease.

Exercise: Regular exercise has known benefits for heart health and may also help prevent cognitive decline. Exercise may also help improve mood.

Nutrition: People with Alzheimer's may forget to eat, lose interest in preparing meals or not eat a healthy combination of foods. They may also forget to drink enough water, leading to dehydration and constipation.

Prevention

Although there is no proven way to prevent alzheimer's disease, there are some practices that may be worth incorporating into daily routine, particularly with family history of dementia.

Consume a low-fat diet, eat cold-water fish (like tuna, salmon and mackerel) rich in ω-3 fatty acids, at least 2 to 3 times per week, reduce intake of linoleic acid found in margarine, butter, and dairy products, increase antioxidants like carotenoids, vitamin E and vitamin C by eating plenty of darkly coloured fruits and vegetables, maintain a normal blood pressure and stay mentally and socially active throughout life.

Table 9.4 : The U.S. Food and Drug Administration (FDA) approved medications for Alzheimer's disease

Sr. No.	Drug name	Brand name	Approved For	FDA Approved
1.	Donepezil	Aricept	All stages	1996
2.	Galantamine	Razadyne	Mild to moderate	2001
3.	Memantine	Namenda	Moderate to severe	2003
4.	Rivastigmine	Exelon	All stages	2000
5.	Donepezil and memantine	Namzaric	Moderate to severe	2014

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Chapter...10

GASTROINTESTINAL SYSTEM

10.1 INTRODUCTION TO GASTROINTESTINAL TRACT

The human gastrointestinal tract (GIT) is an organ system responsible for consuming and digesting foodstuffs, absorbing nutrients, and expelling waste. The whole system is under hormonal control, with the presence of food in the mouth triggering off a cascade of hormonal actions; when there is food in the stomach, different hormones activate acid secretion, increased gut motility, enzyme release etc.

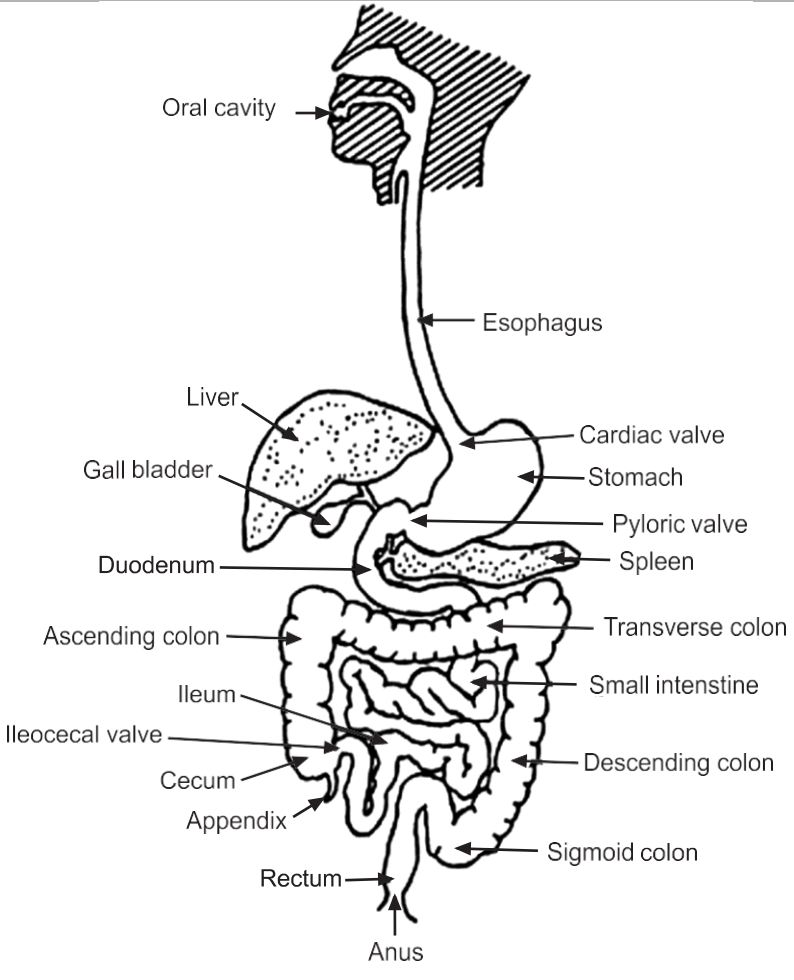

Fig. 10.1 : Parts of gastrointestinal tract

The upper gastrointestinal tract consists of the oesophagus, stomach, and duodenum. The lower gastrointestinal tract includes most of the small intestine and all of the large intestine. Other accessory organs include liver, pancreas, gall bladder, salivary gland, teeth and tongue.

Nutrients from the GI tract are not processed on-site; they are taken to the liver to be broken down further, stored, or distributed.

Mouth: The digestive process begins in the mouth. Food is partly broken down by the process of chewing and by the chemical action of salivary enzymes (these enzymes are produced by the salivary glands and break down starches into smaller molecules).

Esophagus: After being chewed and swallowed, the food enters the esophagus. The esophagus is a long tube that runs from the mouth to the stomach. It uses rhythmic, wave-like muscle movements (called peristalsis) to force food from the throat into the stomach. This muscle movement gives us the ability to eat or drink even when we are upside-down.

Stomach: It is usually "J" shaped situated at left side of body, anterior to the spleen and it connects esophagus to duodenum. It is mixing chamber and holding reservoir.

The stomach is a large, sack-like organ that churns the food and bathes it in a very strong acid (gastric acid). Food in the stomach that is partly digested and mixed with stomach acids is called chyme.

The parts of the stomach are cardia, fundus, body and pylorus. Pyloric sphincter communicate with duodenum.

Layers of stomach are mucosa, submucosa, muscularis and serosa.

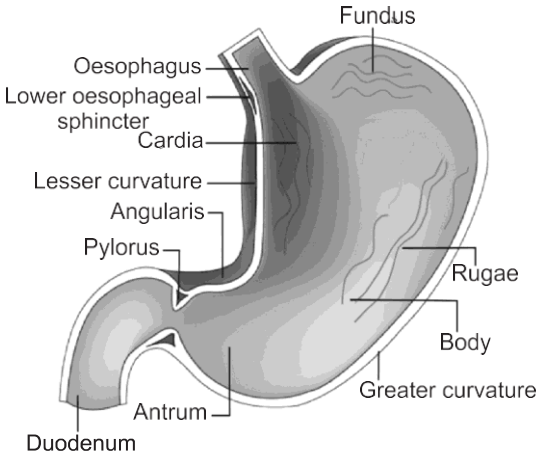

Fig. 10.2 : Structure of stomach

Mucous membrane consist of gastric glands. Gastric pits are the numerous small indentations in the mucous membrane of the stomach which are the mouths of the gastric glands. Secretions of gastric glands flow into each gastric pit and then into the lumen of the stomach. The gastric glands contain three types of exocrine gland cells that secrete their products into the stomach lumen.

- Goblet cells secrete mucous.
- Parietal cells secrete HCl and intrinsic factor.
- Gastric chief cells secrete pepsin, and gastric lipase.

The secretion from these cells are called gastric juice.

In addition, gastric gland include a type of enteroendocrine cells, the G cells, which are located mainly in the pyloric antrum and secrete hormone gastrin into blood stream.
The stomach has five major functions:

- Temporary food storage.

- Control the rate at which food enters the duodenum.
- Acid secretion and antibacterial action.
- Fluidization of stomach contents.
- Preliminary digestion with pepsin, lipases etc.

The process of gastric secretion is divided into three phases.

Cephalic Phase: The cephalic phase of gastric secretion occurs in response to stimuli received by the senses, such as taste, smell, sight and sound. This phase of gastric secretion is entirely reflex in origin and is mediated by the vagus nerve.

Gastric Phase: It is stimulated by the presence of food in the stomach to secrete gastrin. The gastric phase is mediated by the vagus nerve and by the release of gastrin. The acidity of the gastric contents after a meal is buffered by proteins so that overall it remains around pH-3 (acidic) for approximately 90 minutes.

Intestinal Phase: The intestinal phase is not fully understood, because of a complex stimulatory and inhibitory process. Amino acids and small peptides that promote gastric acid secretion are infused into the circulation, however, at the same time chyme inhibits acid secretion. The secretion of gastric acid is an important inhibitor of gastrin release. If the pH of the antral contents falls below 2.5, gastrin is not released. Some of the hormones that are released from the small intestine by products of digestion (especially fat), in particular glucagon and secretin, also suppress acid secretion.

Small Intestine: The small intestine is the site where most of the chemical and mechanical digestion is carried out, and where virtually all of the absorption of useful materials is carried out. The whole of the small intestine is lined with an absorptive mucosal type, with certain modifications for each section. The intestine also has a smooth muscle wall with two layers of muscle; rhythmical contractions force the products of digestion through intestine (peristalisis).

There are three main sections to the small intestine:

Duodenum: It forms a 'C' shape around the head of the pancreas. Its main function is to neutralize the acidic gastric contents called 'chyme' and to initiate further digestion; Brunner's glands in the submucosa secrete alkaline mucus which neutralizes the chyme and protects the surface of the duodenum.

Jejunum: This is the midsection of the small intestine, connecting the duodenum to the ileum. It is about 2.5 m long, and contains the plicae circulares (also called circular folds or valves of Kerckring), and villi that increase the surface area of this part of the GI Tract. Products of digestion (sugars, amino acids and fatty acids) are absorbed into the bloodstream here.

Ileum: The jejunum and the ileum are the greatly coiled parts of the small intestine, and together are about 4-6 metres long; the junction between the two sections is not well-defined. The mucosa of these sections is highly folded (the folds are called plicae), increasing the surface area available for absorption dramatically.

Liver and Gallbladder: The liver is a roughly triangular accessory organ of the digestive system located to the right of the stomach, just inferior to the diaphragm and superior to the small intestine. The liver weighs about 3 pounds and is the second

largest organ in the body. The liver has many different functions in the body, but the main function of the liver in digestion is the production of bile and its secretion into the small intestine. The gallbladder is a small, pear-shaped organ located just posterior to the liver. The gallbladder is used to store and recycle excess bile from the small intestine so that it can be reused for the digestion of subsequent meals.

Pancreas: The pancreas is a large gland located just inferior and posterior to the stomach. It is about 6 inches long and shaped like short, lumpy snake with its "head" connected to the duodenum and its "tail" pointing to the left wall of the abdominal cavity. The pancreas secretes digestive enzymes into the small intestine to complete the chemical digestion of foods.

Large Intestine: The large intestine consists of the cecum, colon, rectum, and anal canal. It also includes the vermiform appendix, which is attached to the cecum. The colon is further divided into:

1. Ascending colon (ascending in the back wall of the abdomen)
2. Transverse colon (passing across the back wall).
3. Descending colon (descending down the left side of the abdomen).
4. Sigmoid colon the main function of the large intestine is to absorb water.

By the time digestive products reach the large intestine, almost all of the nutritionally useful products have been removed. The large intestine removes water from the remainder, passing semi-solid faeces into the rectum to be expelled from the body through the anus. The mucosa is arranged into tightly-packed straight tubular glands which consist of cells specialized for water absorption and mucus-secreting goblet cells to aid the passage of faeces. The large intestine also contains areas of lymphoid tissue. These can be found in the ileum too (called Peyer's patches), and they provide local immunological protection of potential weak-spots in the body's defenses. As the gut is teeming with bacteria, reinforcement of the standard surface defenses seems only sensible.

10.2 PEPTIC ULCER

Peptic ulcers are open sores that develop in the inside lining of the esophagus, stomach and upper portion of small intestine (duodenum) as a result of erosion from stomach acids. A peptic ulcer of the stomach is called a gastric ulcer of the duodenum, a duodenal ulcer; and of the esophagus, an esophageal ulcer. Peptic ulcers occur when the lining of these organs is corroded by the acidic digestive (peptic) juices which are secreted by the cells of the stomach. A peptic ulcer differs from erosion because it extends deeper into the lining of the esophagus, stomach, or duodenum and excites more of an inflammatory reaction from the tissues that are eroded. It is an ulcer of gastrointestinal tract at an area exposed to the acid pepsin mixture (APM). The mucosa of gastrointestinal tract (GIT) in this area is digested by pepsin (peptic digestion). It is most often caused by Helicobacter pylori infection.

Vast majority of peptic ulcer occurs in

1. Stomach (Gastric ulcer).
2. First part of duodenum (Duodenal ulcer).
3. Lower end of esophagus (as a result of reflux from the stomach into the esophagus).

The ratio of incidence in duodenal ulcer and peptic ulcer is 4:1.

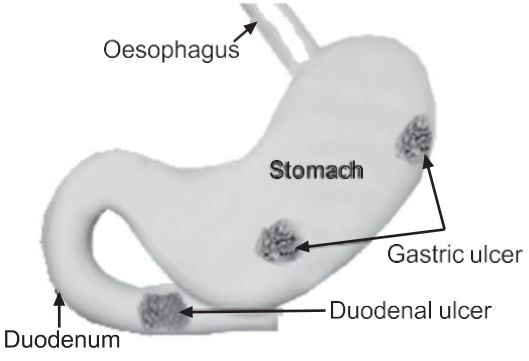

Fig 10.3 : Peptic ulcer development

Components of Gastric Defense Mechanism:

A. Gastric mucus and bicarbonate secretion by gastric mucosal cells: Gastric mucus forms a layer over the epithelium of mucosa. Mucosal cells of pyloric region secrete bicarbonate ions which remain in between the epithelial cells and the mucus and pH at this region is 6 or 7. In the luminal surface of the mucus, the pH is low i.e. 2-3, therefore the peptic activity is high, digestion is possible. Near the epithelium, deep to the mucus layer, the pH is high therefore pepsin loses its activity.

Mechanical barrier offered by mucus present over the surface of gastric epithelium is an important component of defense. The mucus is thick and sticky, APM fails to penetrate it and no digestion of epithelial cells. Pepsin is big molecule and it requires good deal of space through which it transverse. Aspirin and non-steroidal anti-inflammatory agent can depolymerizes and causes loss of their stickiness and increases permeability to pepsin.

B. Presence of tight junction between epithelial cells of stomach and duodenum: Presence of tight junction between epithelial cells of stomach and duodenum restrict the entry of material but high acidity of aspirin is better absorbed in stomach and damage the tight junction leads to peptic ulceration.

Components of Aggressive Mechanism:

1. Helicobacter pylori (H. Pylori): It is gram –ve bacteria found in gastric and duodenal mucosa of most person, particularly elderly. They, while in the mucosa, split urea into ammonia and thus elevate the local pH and damage the local region of the mucosa by high alkalinity. In this way, they strongly help the peptic ulcer development (PUD).

2. Acid: Hydrochloric acid (HCl) is secreted by the parietal cells of the gastric glands. Excess acid production from gastrinomas (it is a tumor in the pancreas or duodenum that secretes excess of gastrin leading to ulceration), tumors of parietal cells of stomach increases acid output.

3. Non-steroidal anti-inflammatory drugs (NSAID): Non-steroidal anti-inflammatory drugs, such as aspirin, naproxen, ibuprofen, and many pain medications can irritate or inflame the lining of stomach and small intestine. Even safety coated aspirin and aspirin in powered form can frequently cause ulcers.

4. Stress: Emotional stress is no longer thought to be a cause of ulcers, however, people with ulcers often report that emotional stress increases ulcer pain.

Physical stress may increase the risk of developing ulcers, particularly in the stomach. For example, people with injuries, such as severe burns, and people undergoing major surgery often require

treatment to prevent ulcers and ulcer related complications, such as bleeding.

5. Genetics: A significant number of individuals with peptic ulcers have close relatives with the same problem, suggesting that genetic factors may also be involved. The genetic disorder Zollinger-Ellison syndrome (ZES) is responsible for some ulcers. Zollinger-Ellison syndrome is a rare disorder in which tumors secrete large amounts of the hormone gastrin. This hormone causes the stomach to produce excess acid which attack the lining of the stomach and cause ulcers.

6. Smoking: People who regularly smoke tobacco are more likely to develop peptic ulcers compared to non-smokers.

7. Alcohol consumption: Regular heavy drinkers of alcohol have a higher risk of developing peptic ulcers.

In normal person, the defense mechanism is adequate, no ulcer develops. Where the defense mechanism is weakened, or, is the aggressive mechanism, i.e. APM strengthened, peptic ulcer develops.

Stimulants/Inhibitors of HCl Secretion: Parietal cells are supplied by vagal fibers. Stimulation of vagus causes HCl secretion from parietal cells. Parietal cell also contains gastrin receptors on their surface. Combination of gastrin with these receptors causes parietal cell stimulation and production of HCl. Histamine produced by mast cells is situated very close to parietal cells. Histamine stimulates HCl secretion by stimulating histamine receptors on parietal cells.

Other notable factors influencing HCl secretion include, calcium, alcohol, coffee, acidity and food fat.

Parietal cells also contain Somatostatin and Prostaglandin receptors. Both are inhibitors of HCl secretion. Somatostatin is secreted by D cells of the gastric antral mucosa. D and G cells lie side by side and exert a paracrine effect on each other.

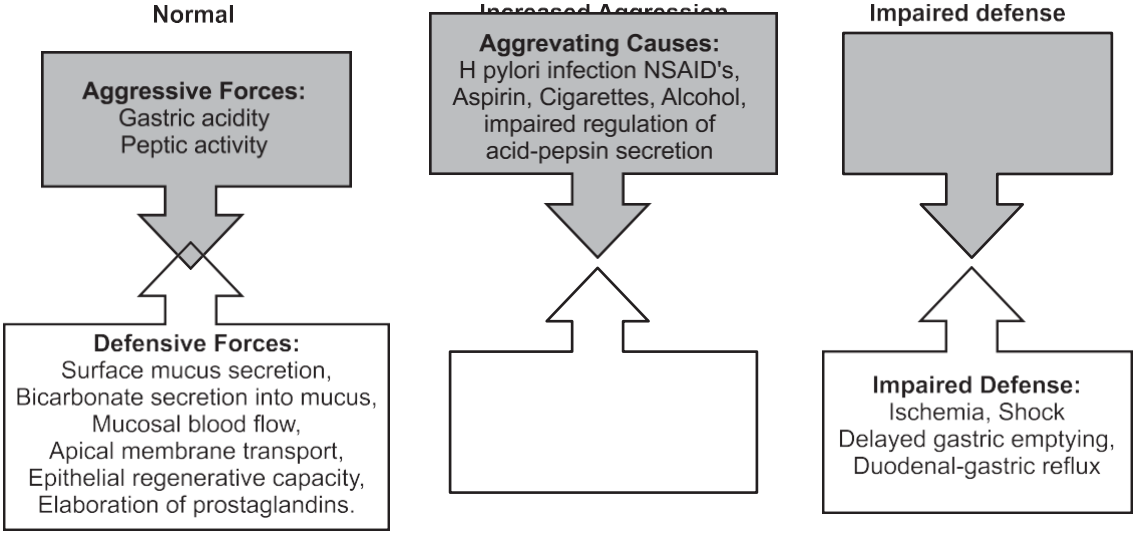

Fig. 10.4 : Components of gastric defense and aggressive mechanism

Epidemiology

Higher prevalence of peptic ulcer is in developing countries. Helicobactor Pylori is sometimes associated with socioeconomic status and poor hygiene.

According to latest WHO data, peptic ulcer disease death in India reached to 1.20% of total death. The age adjusted death rate is 12.37 per 1,00,000 of population ranks India 5th in the world.

Mortality rate has decreased dramatically in the past 20 years.

Pathophysiology

The normal stomach maintains a balance between the protective factors (i.e.: mucus and bicarbonate secretion, blood flow) and aggressive factors (i.e. acid secretion, pepsin). Gastric ulcers develop when aggressive factors overcome the protective mechanism.

In addition to an increase in acid secretion, H. pylori also predisposes patients to PUD by disrupting mucosal integrity. The bacterium's spiral shape, flagella and mucolytic enzymes, which it produces facilitate its pasage through mucous layer to gastric surface epithelium. Subsequently, it releases phospholipase and proteases, which cause further mucosal damage. A cytotoxin-associated gene (cag A) has been isolated in approximately 65% of the bacteria. The products of this gene are associated with more severe gastritis, gastric ulcer, gastric cancer and lymphoma.

NSAID-induced ulcers account for approximately 26% of gastric ulcers, and they are believed to be secondary to a decrease in prostaglandin production resulting from the inhibition of cyclo-oxygenase. The topical effects of NSAIDs are superficial gastric erosions and petechial lesions. However, the risk of gastroduodenal ulcer is not diminished with parental or rectal use of NSAIDs indicating injury occurring from the systemic effect of NSAIDs on the gastrointestinal mucosa. The greatest risk of developing an ulcer occurs during the first three months of NSAID use; thereafter, the risk decreases but continues to be present. Whether concurrent H pylori infection and NSAID use are synergistic in producing gastric ulcers, it remains unclear.

Cigarette smoking can affect gastric mucosal defense adversely. Cigarette smoking is believed to play a facultative role in H pylori infection, that is, people who smoke tend to develop frequent and recurrent ulcers and their ulcers are more resistant to therapy.

There are two different types of peptic ulcer.

- Gastric ulcer, which form in the lining of the stomach.
- Duodenal ulcer, which form in the upper small intestine.

Both types of peptic ulcers are most commonly caused either by infection with Helicobactor pylori bacteria or by frequent use of nonsteroidal anti-inflammatory drugs.

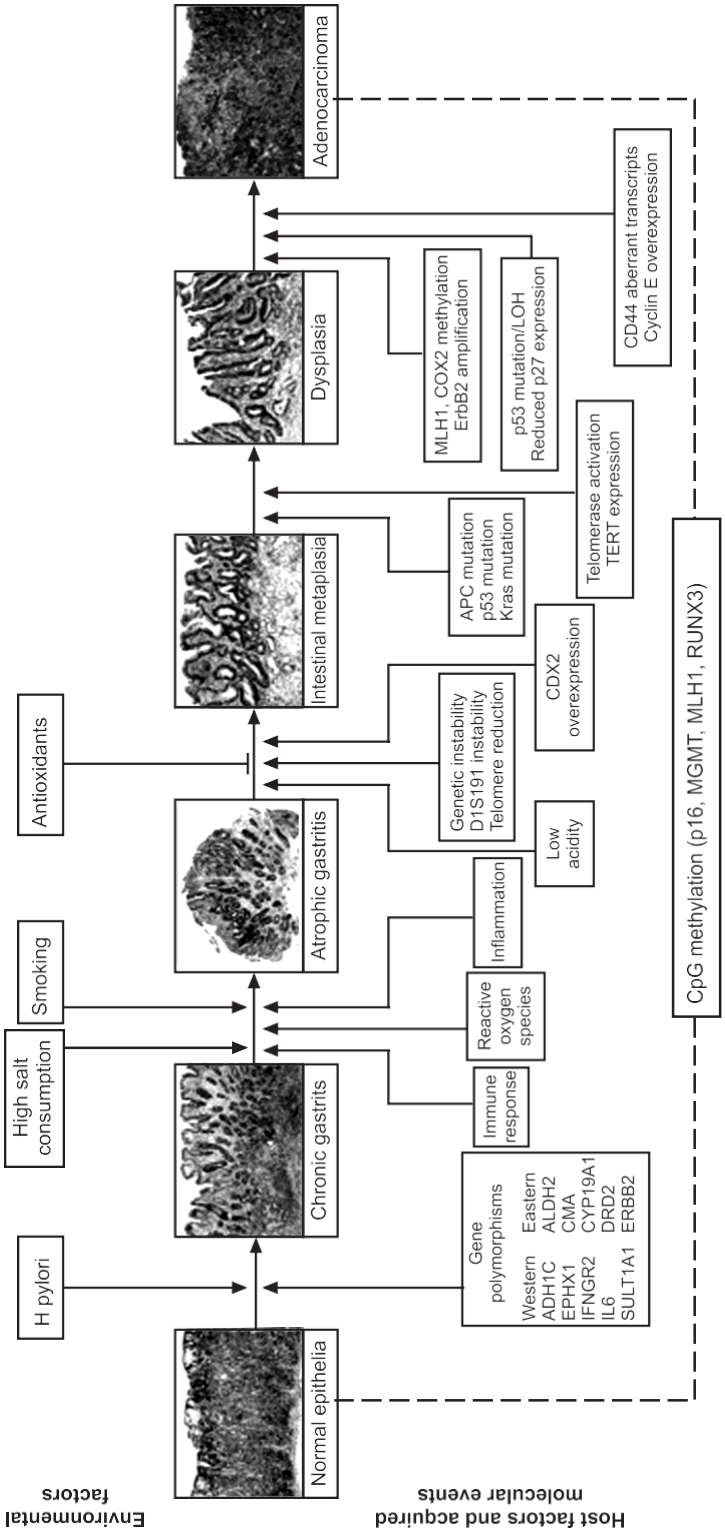

Fig 10.5 : Destruction of gastric mucosa

Clinical Manifestations

Mild inflammation due to small ulcers may not cause any major symptoms and may heal on their own like mouth ulcers do. However, some ulcers can cause serious symptoms.

Stomach pain is the most common symptom. The type of pain can vary from mild to severe and may occur typically at night. It may become severe as the stomach empties and in some cases may be relieved after having food. In some cases, pain may disappear for a few days and then reappear.

Other less common signs include:

- Bloating,
- Heartburn,
- Nausea or vomiting.

In severe cases, symptoms can include:

- Dark or black stool (due to bleeding),
- Vomiting blood,
- Weight loss,
- Severe pain in the mid to upper abdomen.

Complications

Gastrointestinal bleeding is the most common complication. Sudden large bleeding can be life-threatening. It occurs when the ulcer erodes one of the blood vessels, such as the gastroduodenal artery.

Perforation (a hole in the wall of the GIT) often leads to catastrophic consequences if left untreated. Erosion of the gastro-intestinal wall by the ulcer leads to spillage of stomach or intestinal content into the abdominal cavity. Perforation at the anterior surface of the stomach leads to acute peritonitis, initially chemical and later bacterial peritonitis.

Gastric outlet obstruction is the narrowing of pyloric canal by scarring and swelling of gastric antrum and duodenum due to peptic ulcers.

Cancer is included in the differential diagnosis elucidated by biopsy. Helico-bacter pylori as the etiological factor make it 3 to 6 times more likely to develop stomach cancer from the ulcer.

Tests and Diagnosis

Diagnosis is mainly depend on characteristic symptoms and the severity of ulcer. Stomach pain is usually the first signal of a peptic ulcer. Some tests will be ordered so that diagnosis can be confirmed, such as:

General Investigation:

Physical examination and recording of patient's history.

There are no established blood tests that can reliably predict the presence of peptic ulcer disease. However, a complete blood count and blood chemistries (including liver function tests, amylase, lipase and serum calcium levels) are generally obtained.

H. Pylori can be diagnosed by urea breath test, blood test, stool antigen assays, and rapid urease test on a biopsy sample.

Table 10.1 : Comparison of duodenal and gastric ulcers

Duodenal Ulcers	Gastric Ulcers
(i) Most common in middle age and peak level is 30-50 years.	(i) Common in late middle age but incidence increases with age.
(ii) The male to female ratio is 4:1.	(ii) The male to female ratio is 2:1
(iii) It is more common in patients with blood group O.	(iii) More common in patients with blood group A.
(iv) It is associated with increased serum pepsinogen.	(iv) Use of Non-steroidal anti-inflammatory drugs is associated with a three to four fold increase in risk of gastric ulcer
(v) H. pylori infection is common and seen in up to 95% patients. In other cases smoking is twice as common.	(iv) It is less related to H. pylori than duodenal ulcers and found in about 80% patients. 10 - 20% of patients with a gastric ulcer have a concomitant duodenal ulcer.
(vi) Genetic link is more common in 1st degree relatives.	

Blood, urea breath, and stomach tissue tests: These tests are performed to detect the presence of H. pylori. Although some of the tests for H. pylori may occasionally give false-positive results, or may give false-negative results in people who have recently taken antibiotics, omeprazole or bismuth. These tests can be helpful in detecting the bacteria and guiding treatment.

Radiology: Upper GI series (also called barium swallow): A diagnostic test that examines the organs of the upper part of the digestive system: the esophagus, stomach, and duodenum. Fluid called barium (a metallic, chemical, chalky, liquid used to coat the inside of organs so that they will show up on an X-ray) is swallowed. X-rays are then taken to evaluate an ulcer, scar tissue, or a blockage that is preventing food from passing through the digestive organs normally.

Endoscopy: Endoscopy is the most accurate diagnostic test for peptic ulcer disease. It involves inserting a small, lighted tube (endoscope) through the throat and into the stomach to look for abnormalities. Endoscopies are also performed if the patient has other signs or symptoms, such as weight loss, vomiting (especially if blood is present), black stools, anemia, and swallowing difficulties.

Endoscopic biopsy: During the endoscopy, a piece of stomach tissue is removed, so that it can later be analyzed for exact cause of peptic ulcer development. This type of test is typically used for older people, or those that have experienced weight loss or bleeding.

Other differential diagnosis:

- Neoplasm of the stomach,
- Pancreatitis,
- Pancreatic cancer,
- Nonulcer dyspepsia (also called functional dyspepsia),
- Cholecystitis,
- Gastritis,
- GERD - Gastroesophageal Reflux Disease,
- MI (myocardial infarction, not to be missed if having chest pain).

Treatment

The type of treatment is usually determined by what caused the peptic ulcer. Treatment is focused on either lowering stomach acid levels so that the ulcer can heal, or eradicating the Helicobactor pylori infection.

Treatments can include:

Antibiotic medications to kill H. pylori: Antibiotic combination drug therapy regimen commonly used to treat if H. pylorus is found in digestive tract. It likely needs to take antibiotics for two weeks, as well as additional medications to reduce stomach acid. eg. Metronidazole, Amoxycillin, tetracycline etc.

Medications that block acid production and promote healing: Proton pump inhibitors reduce stomach acid by blocking the action of the parts of cells that produce acid and include: Omeprazole, Lansoprazole, Rabeprazole, Esomeprazole, and pantoprazole.

Medications to reduce acid production: Acid blockers, also called histamine (H_2) blockers, they reduce the amount of stomach acid released into digestive tract, which relieves ulcer pain and encourages healing include: Ranitidine, Famotidine, Cimetidine and Nizatidine.

Antacids that neutralize stomach acid: Antacids neutralize existing stomach acid and can provide rapid pain relief include: Aluminum hydroxide, Magnesium hydroxide, Calcium carbonate and Sodium bicarbonate.

Medications that protect the lining of stomach and small intestine: In some cases, medications called cytoprotective agents that help to protect the tissues that line stomach and small intestine include: Sucralfate and misoprostol. Another non-prescription cytoprotective agent is bismuth subsalicylate can also be used.

Prophylactic regimens that have been shown to dramatically reduce the risk of NSAID-induced gastric and duodenal ulcers include the use of a prostaglandin analogue or a proton pump inhibitors.

Surgery: In very rare cases, a complicated stomach ulcer will require surgery, especially people who do not respond to medication, or who develop complications.

Surgery may include: Removal of the entire ulcer, taking tissue from another part of the intestines and sewing it over the ulcer site, tying off a bleeding artery and cutting off nerve supply to stomach to reduce the production of stomach acid.

Vagotomy: It involves cutting the vagus nerve to interrupt messages sent from the brain to the stomach to reduce acid secretion.

Antrectomy: It involves the removing of lower part of the stomach (antrum), which produces a hormone that stimulates the stomach to secrete digestive juices. A Vagotomy is usually done in conjunction with an antrectomy.

Pyloroplasty: Pyloroplasty is an elective surgical procedure in which the lower portion of stomach, the pylorus, cut and resutured, to relax the muscle and widen the opening into small intestine, enabling contents to pass more freely from the stomach. It may be performed along with a Vagotomy.

Prevention

Peptic ulcers can be prevented by avoiding things that break down the stomach's protective barrier and increase stomach acid secretion. These include alcohol, smoking, aspirin, non-steroidal anti-inflammatory drugs and caffeine.

Preventing infection with H. pylori is a matter of avoiding contaminated food and water and adhering to strict standards of personal hygiene. Wash hands carefully with warm water and soap every time the bathroom is used, diaper changed, and before and after preparing food.

Certain lifestyle changes can reduce risk of developing peptic ulcers by properly managing emotional and physical stress.

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UNIT IV

Chapter...11

INFLAMMATORY BOWEL AND LIVER DISEASES

11.1 INFLAMMATORY BOWEL DISEASE (IBD)

11.1.1 Introduction

Inflammatory bowel disease (IBD) is an idiopathic disease caused by a dysregulated immune response to host intestinal microflora. The term IBD is commonly used to two bowel disease having many similarities but the conditions usually have distinctive morphological appearance. These two conditions are ulcerative colitis and Crohn's disease.

- Ulcerative colitis: This condition causes long-lasting inflammation and sores (ulcers) in the innermost lining of large intestine (colon) and rectum. Classically, ulcerative colitis begins in the rectum, and in continuity extends upwards into the sigmoid colon, descending colon, transverse colon, and sometimes may involve the entire colon. The colonic contents may rarely back flow in the terminal ileum in continuity, causing 'back wash ileitis' in about 10% of cases.
- Crohn's disease: Crohn's disease may involve any portion of the gastrointestinal tract but affect most commonly 15-25 cm of the terminal ileum which may extend into the caecum and sometimes into the ascending colon. Both ulcerative colitis and Crohn's disease usually involve severe diarrhoea, abdominal pain, and fatigue and weight loss.

CAUSES

1. Immunological factors:

The exact cause of IBD is unknown, but IBD is the result of a defective immune system. A properly functioning immune system attacks foreign organisms, such as viruses and bacteria, to protect the body. In IBD, the immune system responds incorrectly to environmental triggers, which causes inflammation of the gastrointestinal tract.

2. Genetic factors:

- There is about 3 to 20 time higher incidence of occurrence of IBD in first degree relatives. This is due to genetic defect causing diminished epithelia barrier function.
- There is approximately 50% chance of development of IBD (Crohn's disease about 60%, ulcerative colitis about 6%) in monozygotic twins. However there is no clear link between the abnormal genes and IBD.

3. Exogenous factors:

i) Microbial factors: Microbial factors (bacteria, viruses, protozoa and fungi) have been suspect but without definite evidence.

ii) Psychosocial factors: It has been observed that individuals who are unduly sensitive, dependent on others and unable to express themselves, or some major life events such as illness or death in the family, divorce, interpersonal conflicts etc. suffer from irritable colon or have exacerbation of symptoms.

iii) Smoking: Role of smoking in causation of Crohn's disease has been reported.

iv) Oral contraceptives: An increased risk to develop Crohn's disease with long term use of oral contraceptive has been found in some studies but there is no such increased risk of ulcerative colitis.

Pathophysiology of Inflammatory Bowel Disease

The location and appearance of inflammatory lesions differs between the two forms. In Crohn's disease, inflammatory lesions extend through the bowel wall and develop simultaneously in separate areas. Granuloma formation occurs first, followed by ulceration and abscess formation, fistula may form between the affected areas and the bladder, vagina or rectum. With repeated episodes, the gut wall assumes a cobblestone appearance, with permanent scarring and constriction. The characteristic lesion of UC is the crypt abscess, pus filled, necrotic lesion that starts at the bases of any of the tubular glands of the intestinal mucous membrane. These lesions ulcerate and bleed during flares, then heal with scarring and constriction.

In a normal individual, there is lack of immune responsiveness to dietary antigens and commersal flora in the intestinal lumen. The mechanism responsible for this is by activation of CD_4+T cell secreting cytokines inhibitory to inflammation (IL-10, TGF-β) which suppress inflammation in the gut wall. In IBD, this immune mechanism of suppression of inflammation is defective and thus results in uncontrolled inflammation. In both types of IBD, activated CD_4+T cells are present in the lamina propria and in the peripheral blood. These cells either activate other inflammatory cells macrophages and B cells. There are two main types of CD_4+T cells in IBD.

- TH1 cells secrete proinflammatory y cytokines IFN-γ and TNF which induce transmural granulomatous inflammation seen in Crohn's disease. IL-12 initiates TH1 cytokine pathway.
- TH2 cells secrete IL-4, IL-5 and IL-13 which induce superficial mucosal inflammation characteristically seen in ulcerative colitis.

Crohn's disease begins with crypt inflammation and abscesses, which progress to tiny focal aphthoid ulcers. These mucosal lesions may develop into deep longitudinal and transverse ulcers with intervening mucosal edema, creating a characteristic cobblestoned appearance to the bowel.

Transmural spread of inflammation leads to lymphedema and thickening of the bowel wall and mesentery. Mesenteric fat typically extends onto the serosal surface of the bowel. Mesenteric lymph nodes often enlarge. Extensive inflammation may result

in hypertrophy of the muscularis mucosae, fibrosis, and stricture formation, which can lead to bowel obstruction. Abscesses are common, and fistulas often penetrate into adjoining structures, including other loops of bowel and the bladder. Fistulas may even extend to the skin of the anterior abdomen or flanks. Independently of intra-abdominal disease activity, perianal fistulas and abscesses occur in 25 to 33% of cases; these complications are frequently the most troublesome aspects of Crohn's disease.

Non-caseating granulomas can occur in lymph nodes, peritoneum, the liver, and all layers of the bowel wall. Although pathognomonic (a characteristic sign or symptom of a disease that can be used to diagnosis) when present, granulomas are not detected in about half of patients with Crohn's disease. The presence of granulomas does not seem to be related to the clinical course.

Sign and Symptoms

Inflammatory bowel disease symptoms vary, depending on the severity of inflammation and where it occurs. Symptoms may range from mild to severe. Signs and symptoms that are common to both Crohn's disease and ulcerative colitis include: Diarrhoea, fever and fatigue, abdominal pain and cramping, blood in stool, reduced appetite, unintended weight loss. Other symptoms may include: Constipation, sores or swelling in the eyes, draining of pus, mucus, or stools from, around the rectum or anus (fistula), joint pain and swelling, mouth ulcers, rectal bleeding and bloody stools, swollen gums, tender, red bumps (nodules) under the, skin which may turn into skin ulcers.

Diagnosis

Crohn's disease is diagnosed through a medical history, physical exam, imaging tests to look at the intestines, and lab tests. General investigation: Physical examination include, checking for signs such as paleness (caused by anemia) or tenderness in the abdomen, skin rash, swollen joints, or mouth ulcers and tenderness in stomach (caused by inflammation) and recording of patient's history.

Blood tests: To look for changes in

- Red blood cells: When red blood cells are fewer or smaller than normal, a patient may have anemia.
- White blood cells: When the white blood cell count is higher than normal, a person may have inflammation or infection somewhere in body.
- Blood tests are also helpful to find antibodies. The presence of certain antibodies can sometimes help diagnose type of inflammatory bowel disease i.e. Crohn's disease or ulcerative colitis.
- Stool tests: A stool test is the analysis of a sample of stool, to rule out other causes of GI diseases.
- Upper gastrointestinal (UGI) series: It examines the upper part of the digestive tract.
- Upper gastrointestinal endoscopy: It looks at the interior lining of esophagus, stomach and duodenum.
- Colonoscopy or flexible sigmoido-scopy: Colonoscopy is often the preferred test because it can be used to examine the entire colon. Sigmoidoscopy reaches only the lowest part of the colon.

- Abdominal X-ray: This test can show possible obstructions in the abdomen.
- Barium enema: This test looks at the large intestine (colon).
- Computed tomography (CT) scan: Computerized tomography scans use a combination of X-rays and computer technology to create images. CT scans can diagnose both Crohn's disease and the complications seen with the disease.
- Magnetic resonance imaging (MRI): MRI uses a magnetic field and pulses of radio wave energy to provide pictures of organs and structures inside the body. The pathologic entities of a fistula, a sinus tract, and an abscess can be detected in the static anorectal region by using MRI.
- Barium enema: This diagnostic test allows evaluating entire large intestine with an X-ray. Barium, a contrast solution, is placed into bowel using an enema. Sometimes air is added as well. The barium coats the lining, creating a features of rectum, colon and a portion of small intestine. This test is rarely used anymore, and it can be dangerous because the pressure required to inflate and coat the colon can lead to rupture of the colon. For people with severe symptoms, flexible sigmoidoscopy combined with a CT scan is a better alternative.

Treatment

Treatment for IBD depends on the seriousness of the disease. Most people are treated with medication. Some people whose symptoms are triggered by certain foods are able to control the symptoms by avoiding foods that upset their intestines, like highly seasoned foods or dairy products. Each person may experience ulcerative colitis differently, so treatment is adjusted for each individual. Emotional and psychological support is also important.

The main aims of treatment are to:

- Reduce symptoms, known as inducing remission (a period without symptoms),
- Maintain remission.

Anti-inflammatory Drugs:

Anti-inflammatory drugs are often the first step in the treatment of inflammatory bowel disease. They include:

(i) Aminosalicylates (ASAs): Such as Sulfasalazine, Mesalamine, Balsalazide and Olsalazine are medications that help to reduce inflammation and effective in ulcerative colitis.

(ii) Corticosteroids: These drugs, which include prednisone and hydrocortisone are a more powerful type of medications used to reduce inflammation. They can be used with or instead of ASAs to treat a flare-up if ASAs alone are not effective.

(iii) Immunosuppressants: Immunosuppressants such as Azathioprine, 6-mercaptopurine, methot-rexate, cyclosporine are often used and can make a marked improvement at a low dose with few side effects. Other drugs may be given to relax the patient or to relieve pain, diarrhoea, or infection. Occasionally, symptoms are severe enough that the person must be hospitalized.

Other Medications:

Additional medications are required to manage specific symptoms of ulcerative colitis.

(i) Antibiotics: People with ulcerative colitis who run fevers will likely take antibiotics to help prevent or control infection. (e.g., Metronidazole, Ciprofloxacin, Rifaximin etc.)

(ii) Antidiarrhoeal medications: For severe diarrhoea, loperamide may be effective. Use antidiarrhoeal medications with great caution, however, because they may increase the risk of toxic megacolon.

(iii) Iron supplements: In chronic intestinal bleeding, person may develop iron deficiency anemia and be given iron supplements.

(iv) Bowel rest: Sometimes Crohn's disease symptoms are severe and a person may need to rest bowel for a few days to several weeks. Bowel rest involves drinking only clear liquids or having no oral intake. Nutritions are provided to the patient intravenosly through a special catheter, or tube, inserted into a vein in the patient's arm.

(v) Surgery: Even with medication treatments, up to 20% of people will need surgery to treat their Crohn's disease. Although surgery will not cure Crohn's disease, it can treat complications and improve symptoms.

Table 11.1 : Different clinical features

Features	UC	Crohn's disease
Blood in stool	Yes	Occasionally
Mucus	Yes	Occasionally
Systemic symptoms	Occasionally	Frequently
Pain	Occasionally	Frequently
Abdominal- mass	Rarely	Yes
Perineal disease	No	Frequently
Fistulas	No	Yes
Small intestine obstruction	No	Frequently
Colonic obstruction	Rarely	Frequently
Response to antibiotic	No	Yes
Recurrence after surgery	No	Yes

11.2 JAUNDICE

Jaundice is a condition in which a person's skin and the whites of the eyes are discoloured yellow due to an abnormally increased level of bile pigments, bilirubin in the blood and body tissue resulting from liver diseases such as cirrhosis, hepatitis or gallstones.

Causes of Jaundice

The liver breaks down old, inefficient red blood cells in a process (hemolysis) and releases large amounts of bilirubin. The excess amount of bilirubin results in toxic and can cause jaundice. The liver also manufactures the other components of bile. Normally, the liver metabolizes and excretes the bilirubin in the form of bile. However, if there is a disruption due to infection or damage in this normal metabolism and production of bilirubin, jaundice may result.

The excess amount of bilirubin can be toxic and it is important to eliminate from the body as fast as it is produced. There are three basic ways this process can go wrong and can cause jaundice:

- The liver itself can be temporarily or permanently damaged, reducing its ability to break down bilirubin (mix it with bile) and move it into the gallbladder.
- The gallbladder or its bile ducts can become blocked, preventing excretion of bilirubin into the intestine. Bilirubin will then back up into the liver and then into the bloodstream.
- Any condition that leads to very rapid destruction of red blood cells can create too much bilirubin for even a healthy liver to handle. Again, the excess is carried into the bloodstream.

Some Causes of Jaundice due to Poor Liver Function include:

Viral hepatitis: Hepatitis A, B, C, D and E can all cause temporary liver inflammation. Types B and C can also cause chronic, lifelong inflammation.

Medication-induced hepatitis: This may be caused by alcohol, erythromycin, methotrexate, amiodarone, statins (e.g., lovastatin, pravastatin, rosuvastatin), nitrofurantoin, testosterone, oral contraceptives, acetaminophen and many other medications.

Autoimmune hepatitis: In this condition, the body's immune system attacks its own liver cells. Autoimmune hepatitis is more common in people and families with other autoimmune diseases, such as lupus, thyroid disease, diabetes, or ulcerative colitis. Primary biliary cirrhosis is another autoimmune condition of the liver and involves inflammation of the bile ducts.

Gilbert's syndrome: This harmless inherited condition is quite common, affecting about 2% of the population. Minor defects in the liver's metabolism of bilirubin cause jaundice to appear in times of stress, exercise, hunger or infection.

Some Causes of Jaundice due to Obstruction (Blockage) include:

Gallstones: Formed in the gallbladder, gallstones can block the bile ducts, preventing bile (and bilirubin) from reaching the intestine. Sometimes, the bile ducts may become infected and inflamed.

Cholestasis: A condition in which the flow of bile from the liver is interrupted. The bile containing conjugated bilirubin remains in the liver instead of being excreted.

Newborn jaundice: Jaundice in newborn babies can be caused by several different conditions, although it is often a normal physiological consequence of the newborn's immature liver. Even though it is usually harmless under these circumstances, newborns with excessively elevated levels of bilirubin from other medical conditions (pathologic jaundice) may suffer devastating brain damage (kernicterus) if the underlying problem is not addressed. Newborn jaundice is the most common condition requiring medical evaluation in newborns.

The following are some common causes of newborn jaundice:

Physiological jaundice: This form of jaundice is usually evident on the second or third day of life. It is the most common cause of newborn jaundice and is usually a transient and harmless condition. Jaundice is caused by the inability of the newborn's immature liver to process bilirubin from the accelerated breakdown of red blood cells that occurs at this age. As the newborn's liver matures, the jaundice eventually disappears.

Maternal-fetal blood group incompatibility (Rh, ABO): This form of jaundice occurs when there is incompatibility between the blood types of the mother and the fetus. This leads to increased bilirubin levels from the breakdown of the fetus' red blood cells (hemolysis).

Breast milk jaundice: This form of jaundice occurs in breastfed newborns and usually appears at the end of the first week of life. Certain chemicals in breast milk are thought to be responsible. It is usually a harmless condition that resolves spontaneously.

Types of Jaundice

Jaundice is classified into three categories, depending on which part of the physiological mechanism the pathology affects. The three categories are:

Pre-hepatic jaundice: If an infection or medical condition makes the red blood cells break down sooner than usual, bilirubin levels rise. This is known as pre-hepatic jaundice. Conditions which may trigger this include malaria, sickle cell anaemia, thalassaemia, Gilbert's syndrome, hereditary spherocytosis and Crigler-Najjar syndrome.

Table 11.2 : Type of jaundice

Category	Definition
Pre-hepatic/ hemolytic	The pathology is occurring prior to the liver.
Hepatic/ hepatocellular	The pathology is located within the liver.
Post-hepatic/ Cholestatic	The pathology is located after the conjugation of bilirubin in the water

Intra-hepatic jaundice: If the liver is damaged, it may be less able to process bilirubin and reduces the liver's ability to metabolize and excrete bilirubin leading to a buildup of unconjugated bilirubin in the blood which causes intra-hepatic jaundice. The liver damage may be a result of causes that include hepatitis, alcoholic liver disease, glandular fever, liver cancer, illegal drug use, and paracetamol overdose. Obesity and non-alcoholic fatty liver disease can be a cause of cirrhosis of the liver and jaundice.

Post-hepatic jaundice: Gallstones, pancreatitis, pancreatic cancer and cancers of the gallbladder or bile duct may also

disrupt the bilirubin removal process leading to jaundice. This is called post-hepatic jaundice.

Eating a high-fat diet can raise cholesterol levels and increase the risk of gallstones.

Pathophysiology

Conjugated hyperbilirubinemia results from reduced secretion of conjugated bilirubin into the bile, such condition occurs in patients with hepatitis, or it results from impaired flow of bile into the intestine, such condition occurs in patients with biliary obstruction. Bile formation is sensitive to various hepatic insults, including high levels of inflammatory cytokines, such as may occur in patients with septic shock.

High levels of conjugated bilirubin may secondarily elevate the level of unconjugated bilirubin. Although the mechanism of this effect is not fully defined, one likely cause is reduced hepatic clearance of unconjugated bilirubin that results from competition with conjugated bilirubin for uptake or excretion.

Symptoms

Common signs and symptoms seen in individuals with jaundice include:

- Yellow discolouration of the skin, mucous membranes, and the whites of the eyes,
- Light-colored stools,
- Dark-colored urine,
- Itching of the skin,
- Nausea and vomiting,
- Abdominal pain,
- Fever,
- Weakness,
- Loss of appetite,
- Confusion,
- Swelling of the legs and abdomen.

Newborn jaundice: In newborn's, as the bilirubin level rises, jaundice will typically progress from the head to the trunk, and then to the hands and feet.

Additional signs and symptoms that may be seen in the newborn include:

- Poor feeding,
- Lethargy,
- Changes in muscle tone,
- High-pitched crying and seizures.

Diagnosis

Physical Examination: The physical examination should focus primarily on signs of liver disease other than jaundice, including bruising, spider angiomas, gynecomastia, testicular atrophy, and palmar erythema. An abdominal examination to assess liver size and tenderness is important. The presence or absence of ascites also should be noted.

Urine Test: Urine can be tested for urobilinogen, which is produced when bilirubin is broken down. Finding high or low levels can help pinpoint the type of jaundice.

Serum Testing: First-line serum testing in a patient presenting with jaundice should include a complete blood count (CBC) and determination of bilirubin (total and direct fractions), aspartate transaminase (AST), alanine transaminase (ALT), γ-glutamyl transpeptidase, and alkaline phosphatase levels.

Imaging Studies:

Ultrasound: It is very useful for detecting gallstones and dilated bile ducts. It can also detect abnormalities of the liver and the pancreas.

Computerized tomography (CT) scan: A CT scan is an imaging study which provides more details of all the abdominal

organs, useful in distinguishing an obstructing lesion from hepatocellular disease in the evaluation of a jaundiced patient.

Magnetic resonance imaging (MRI): MRI is an imaging study that uses a magnetic field to examine the organs of the abdomen. It can be useful for detailed imaging of the bile ducts.

Endoscopic retrograde cholangiopancreatography (ERCP): ERCP is a procedure that involves the introduction of an endoscope (a tube with a camera at the end) through the mouth and into the small intestine. A dye is then injected into the bile ducts while X-rays are taken. It can be useful for identifying stones, tumors or narrowing of the bile ducts.

Liver Biopsy: Liver biopsy can be particularly helpful in diagnosing autoimmune hepatitis or biliary tract disorders. Patients with primary biliary cirrhosis are almost always positive for antimitochondrial antibody, and the majority of those affected by primary sclerosing cholangitis have antineutrophil cytoplasmic antibodies.

Laparoscopy (peritoneoscopy): It allows direct inspection of the liver and gallbladder, without the trauma of a full laparotomy. Unexplained cholestatic jaundice warrants laparoscopy occasionally and diagnostic laparotomy rarely.

Treatment

Treatment of jaundice typically requires a diagnosis of the specific cause in order to select suitable treatment options. Treatment would target the specific cause, rather than the jaundice itself.

Pre-hepatic jaundice: In treating pre-hepatic jaundice, the objective is to prevent the rapid breakdown of red blood cells that is causing bilirubin levels to build up in the blood.

In cases of infections, such as malaria, the use of medication to treat the underlying infection is usually recommended. For genetic blood disorders, such as sickle cell anaemia or thalassaemia, blood transfusions may be required to replace the red blood cells.

Intra-hepatic jaundice: In cases of intra-hepatic jaundice, the objective is to repair any liver damage, although the liver can often repair itself over time. The treatment is therefore to prevent any furtherliver damage occurring.

If the damage is caused by exposure to harmful substances such as alcohol or chemicals, avoiding any further exposure to the substance is recommended.

In severe cases of liver disease, a liver transplant is another possible option.

Post-hepatic jaundice: In most cases of post-hepatic jaundice, surgery is recommended to unblock the bile duct system. During surgery, it may also be necessary to remove:

- the gallbladder,
- a section of the bile duct system,
- a section of the pancreas to prevent further blockages occurring.

In certain cases of newborn jaundice, exposing the baby to special coloured lights (phototherapy) or exchange blood transfusions may be required to decrease elevated bilirubin levels.

Complication

Complications of jaundice include sepsis especially cholangitis, biliary cirrhosis, pancreatitis, coagulopathy, renal and liver failure.

The itching associated with jaundice and cholestasis can sometimes be so severe that it causes patients to scratch their skin "raw", have trouble sleeping, and, rarely, even to commit suicide.

Most complications that arise are a result of the underlying cause of jaundice, not from jaundice itself. For example, jaundice caused by a bile duct obstruction may lead to uncontrolled bleeding due to a deficiency of vitamins needed for normal blood clotting.

11.3 HEPATITIS

Hepatitis means injury to the liver with inflammation of the liver cells. Toxins, certain drugs, some diseases, heavy alcohol use, bacterial and viral infections can all cause hepatitis. Hepatitis is also the name of a family of viral infections that affect the liver; the most common types in the India and Asian countries are hepatitis A, hepatitis B and hepatitis C.

Types of Viral Hepatitis:

A group of viruses known as the hepatitis viruses cause most cases of liver damage worldwide. Common viruses cause hepatitis include A, B, C, D, E and G (95% cause of viral hepatitis). Other viruses include, Herpes simplex virus, Cytomegalovirus, Epstein-Barr virus, Yellow fever virus and Adenoviruses also cause hepatitis.

HCV infection in India has a population prevalence of around 1%, and occurs predominantly through blood transfusion and the use of unsterile glass syringes.

Table 11.3 : Risk factors and modes of transmission in viral hepatitis

	A	B	C	D	E
Source of virus	Feces	Blood/blood-derived body fluids	Blood/blood-derived body fluids	Blood/blood-derived body fluids	Feces
Route of transmission	Fecal-oral	Percutaneous permucosal	Percutaneous permucosal	Percutaneous permucosal	Fecal-oral
Chronic infection	No	Yes	Yes	Yes	No
Prevention	Pre/post-exposure immunization	Pre/post-exposure immunization	Blood donor screening; Risk behaviour modification	Pre/post-exposure immunization; Risk behaviour modification	Ensure safe drinking water

Etiology

Most common cause of all viral hepatitis includes —

- Use of infected needle and syringes,
- Intravenous drug users,
- Transfusion of infected blood and blood products,
- Unprotected sexual contact with an infected partner.

Hepatitis A virus: Infection causes due to eating raw shellfish from water polluted with sewage and contaminated food and water. Travel or work in regions with high rates of hepatitis A.

Carrier of Hepatitis B virus: Some people with Hepatitis B never fully recover from the infection (chronic infection), they still carry the virus and can infect others for the rest of their lives. HBV can be transmitted between family members within households by contact of non-intact skin or mucous membrane with secretions or saliva containing HBV.

Causes of Hepatitis C virus: Occurs as the result of percutaneous transmission of the hepatitis C virus through infectious blood. It can be passed from an infected mother to her baby. HCV can also be transmitted through household contact (sharing of personal items such as razors, toothbrushes, scissors and manicuring equipment within the same household).

Causes of Hepatitis D virus: HDV is transmitted parenterally, it can replicate independently within the hepatocyte, but it requires HBs Ag for propagation. Sexual transmission is less efficient than with HBV. Perinatal transmission is rare.

Causes of Hepatitis E virus: Infection spread by fecally contaminated water within endemic areas. On the other hand, in non-endemic areas, the major mode of the spread of HEV is food borne, especially undercooked pork.

Causes of Hepatitis G virus: It has been identified in all ethnicities, and 1% - 4% of worldwide blood donors are carriers of the virus at the time of blood donation.

Pathophysiology of Hepatitis

[I] Hepatitis A

Hepatitis A is a highly contagious liver infection caused by the hepatitis A virus. The hepatitis A virus is one of several types of hepatitis viruses that cause inflammation that affects liver's ability to perform normal function. Nearly everyone who develops Hepatitis A makes a full recovery; it does not lead to chronic disease. Mild cases of hepatitis A do not require treatment, and most people who are infected recover completely with no permanent liver damage. It is small sized (27 nm), non-enveloped, single stranded RNA virus. Related to enteroviruses, (Enteroviruses are a genus of positive sense single-stranded RNA viruses) formerly known as enterovirus 72, now put in its own family heptovirus. It is very difficult to grow in cell culture:

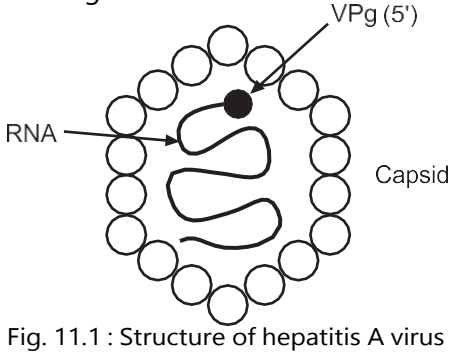


Fig. 11.1 : Structure of hepatitis A virus

Pathophysiology

After oral inoculation the virus is transported across the intestinal epithelium. After travelling through the mesenteric veins to the liver, the virus enters hepatocytes, where replication of hepatitis A virus (HAV) occurs exclusively within the cytoplasm via RNA-dependent polymerase.

The liver damage is due to direct killing of hepatocytes and by the host's immune system response to infected hepatocytes indicates inflammation of liver. Microscopically there is spotty parenchymal cell degeneration, with necrosis of hepatocytes, with disruption of liver cell cords.

[II] Hepatitis B

Hepatitis B is a serious liver infection caused by the hepatitis B virus (HBV), which infects the liver and causes an inflammation called hepatitis, originally known as "serum hepatitis". It ranges in severity from a mild illness, lasting a few weeks (acute), to a serious long-term (chronic) illness that can lead to liver cancer or cirrhosis (a condition that causes permanent scarring of the liver). Most people infected with hepatitis B as adults recover fully, even if their signs and symptoms are severe. Infants and children are much more likely to develop a chronic hepatitis B infection. Although no cure exists for hepatitis B, a vaccine can prevent the disease.

Hepatitis B Virus: Hepatitis B virus is a hepadna virus – 'hepa' from hepatotrophic (attracted to the liver) and 'dna' because it is a DNA virus and it has a circular genome composed of partially double-stranded DNA. The viruses replicate through an RNA intermediate form by reverse transcription and in this respect they are similar to retroviruses. Although replication takes place in the liver, the virus spreads to the blood where virus-specific proteins and their corresponding antibodies are found in infected people. Blood test for these proteins and antibodies are used to diagnose the infection. It has long incubation period i.e. 30 to 180 days. Virus does not kill hepatocytes but the infected cells die itself as a result of immune system attack after recognition of viral antigen on cell surface.

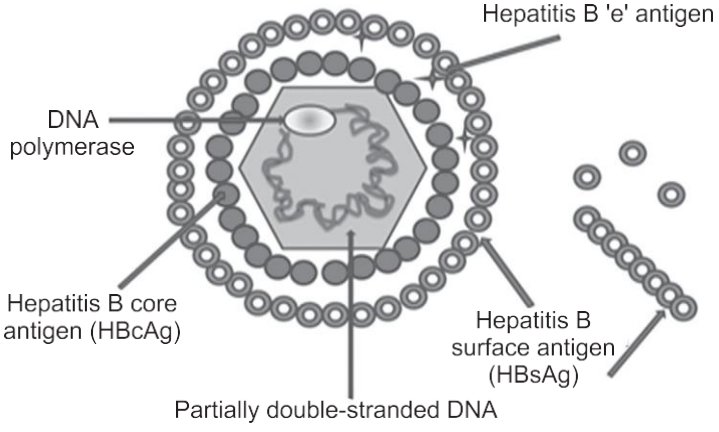


Fig. 11.2 : Structure of hepatitis B virus

The outer shell called HbsAg, these particles are not infectious and are composed of the lipid and protein (devoid of nucleic acid and not infectious) that forms part of the surface of the virion, and is produced in excess during the life cycle of the virus. The nucleocapsid encloses the viral DNA and a DNA polymerase that has reverse transcriptase activity.

The outer envelope contains embedded proteins which are involved in viral binding and enter into susceptible cell.

HBc-Ag is present only in the hepatocyte indicating its replication in liver while HB 'e' Ag is present in the blood within 2-6 weeks. Persistent presence of HBeAg indicates chronic carrier state and a period of highest infectivity (blood test for these proteins and antibodies are used to diagnose the infection).

Pathophysiology

HBV infection in itself does not lead to the death of infected hepatocytes. The host's immune response to viral antigens is thought to be the cause of the liver injury in HBV infection. Liver damage arises from cytolytic effects of the immune system's cytotoxic T lymphocytes (CTL) which attempt to clear infection by killing infected cells. The cellular immune response, rather than the humoral immune response, seems to be primarily involved in disease pathogenesis. Induction of antigen-specific T-lymphocyte response is thought to occur when host T lymphocytes are presented with viral epitopes by antigen-presenting cells in lymphoid organs. These antigen-specific T cells mature, expand and then migrate to the liver. In acute HBV infection, most HBV DNA is cleared from hepatocytes through non-cytocidal effects of inflammatory byproducts of CD8+ T lymphocytes, stimulated by CD4+ T lymphocytes, notably interferon-gamma and tumour necrosis factor-alfa. These cause down-regulation of viral replication, and trigger direct lysis of infected hepatocytes by HBV-specific CD8+ cytotoxic T cells. In contrast, people with chronic HBV infection display weak, infrequent, and narrowly focused HBV-specific T-cell responses, and the majority of mononuclear cells in livers of chronic HBV-infected people are non-antigen-specific.

In addition, the integration of HBV DNA to the hepatocyte nucleus during replication process may lead to increased risk for hepatocellular carcinoma. Furthermore, co-infection with hepatitis C virus (HCV) can synergistically increase the rate of fibrosis, cirrhosis, and hepatocellular cancer, since both HBV and HCV occupy the same hepatocyte independently.

[III] Hepatitis C

Hepatitis C is a liver disease caused by the hepatitis C virus (HCV). The virus can cause both acute and chronic hepatitis infection, ranging in severity from a mild illness lasting a few weeks to a serious, lifelong illness. Hepatitis C is usually spread through direct contact with the blood of infected person. The liver can swell and become damaged. In hepatitis C, unlike hepatitis B, liver cancer risk is only increased in people with cirrhosis and only 20% of hepatitis C patients get cirrhosis. The infection is often asymptomatic, but once established, chronic infection can progress to scarring of the liver (cirrhosis) and liver cancer.

Hepatitis 'C' virus: The virus was earlier known as non-A, non-B virus. The Hepatitis C virus (HCV) is a small (50 nm in size), enveloped, single-stranded, RNA virus. It is the only known member of the hepacivirus genus in the family Flaviviridae.

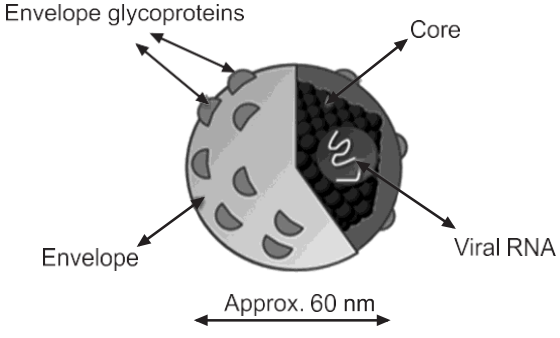


Fig. 11.3 : Structure of hepatitis C virus

Pathophysiology

The natural targets of HCV are hepatocytes and possibly, B lymphocytes. Viral clearance is associated with the development and persistence of strong virus-specific responses by cytotoxic T

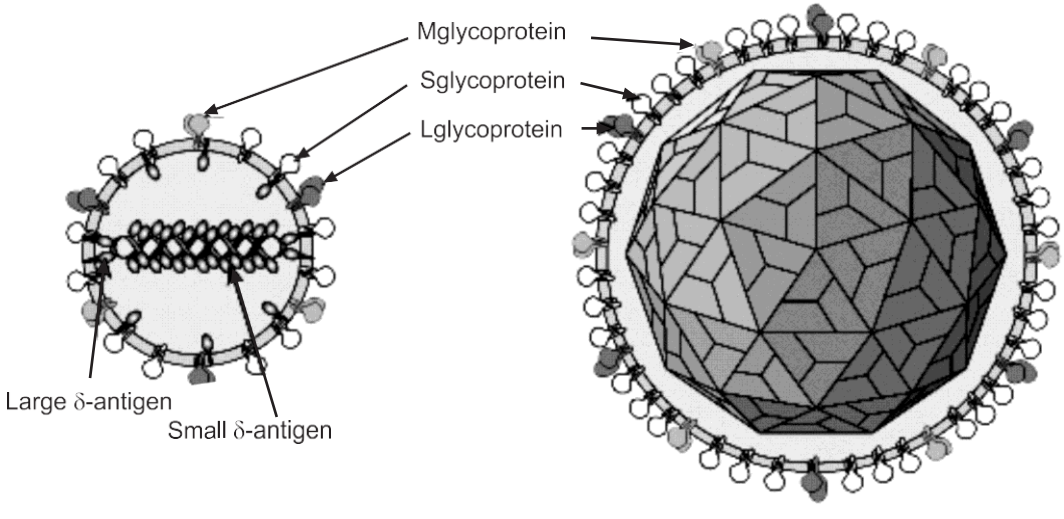
lymphocytes and helper T cells. In most infected people, viremia persists and is accompanied by variable degrees of hepatic inflammation and fibrosis.

[IV] Hepatitis D

Hepatitis D is a serious liver disease caused by the hepatitis D virus (HDV) and relies on HBV to replicate. Hepatitis D virus (HDV) is an RNA virus and causes a unique infection that requires the assistance of viral particles from hepatitis B virus (HBV) to replicate and infect other hepatocytes. Its clinical course is varied and ranges from acute, self-limited infection to acute, fulminant liver failure. Chronic liver infection can lead to end-stage liver disease and associated complications.

Simultaneous infection with HBV and HDV is known as coinfection and results in fulminant liver failure in 1% of patients. Complete clinical recovery and clearance of HBV and HDV coinfection, is the most common outcome. Chronic infection with HBV and HDV occurs in less than 5% of patients. Infection with HDV in a patient who is already positive for the hepatitis B surface antigen (HBsAg) is known as superinfection and results in fulminant liver failure in 5% of patients. Approximately 80-90% develops chronic HDV infection. These patients progress more rapidly to develop cirrhosis and may develop hepatocellular carcinoma.

The agent consists of a particle 35 nm in diameter consisting of the δ-antigen surrounded by an outer coat of HBsAg. The genome of the virus is very small and consists of a single-stranded RNA.



(a) HDV virion **(b) HBV helper virus**

Fig. 11.4 : Structure of hepatitis D virus

Co-infection and Super-infection:

Simultaneous HBV and HDV Infection:

In the patient who is co-infected with HBV and HDV, clinical illness is usually moderate, but it can be severe with acute liver failure. Clinical illness may be biphasic, with two aminotransferase peaks; first from HBV and then HDV, although a monophasic illness with single peak of enzyme levels may also be observed. Co-infection is

usually self-limited, and clearance of HBV results in clearance of HDV. Chronic HBV/HDV infection occurs in less than 5% of patients with co-infection.

Infection with HDV after HBV:

The patient with previous chronic HBV infection provides a potential environment for superinfection with HDV after exposure to someone infected with both HBV and HDV. This may be observed as an acute flare of hepatitis and sometimes leads to initial discovery of the underlying HBV infection, with misidentification of the illness as acute HBV infection. Measurement of the IgM anti-HBc titer can assist in differentiating chronic from acute HBV disease; circulating titers are typically low (or negative) in chronic HBV carriers but high in patients with acute HBV infection. Testing for HDV should be considered in any patient with HBV who has an acute flare of hepatitis and risk factors for HDV infection.

Most patients with superinfection develop a progressive form of chronic hepatitis. Superinfection is often seen as a worsening clinical illness in a previously stable chronic carrier of HBV. Clinical illness with superinfection can be rapidly progressive, leading to cirrhosis within 2 years in 10%-15% of patients. The genotype of HBV may also play a role in the rapidity and severity of progressive disease. HDV will suppress HBV replication in simultaneously infected patients. Even HBV/HDV infected patients with coexisting hepatitis C virus (HCV) infection will have reduced HCV replication.

[V] Hepatitis E

It is a serious liver disease caused by the hepatitis E virus (HEV), usually results in an acute infection. It does not lead to a chronic infection.

Hepatitis E is an enterically transmitted infection typically self-limited. Hepatitis E has many similarities with hepatitis A. Hepatitis E has been associated with chronic hepatitis in solid organ transplant recipients, patients infected by HIV, and an individual on rituximab treatment for non-Hodgkin lymphoma.

Etiology and Pathophysiology

The hepatitis E virus (HEV) genome contains 3 open reading frames (ORFs). The largest, ORF-1, codes for the non-structural proteins responsible for viral replication. ORF-2 contains genes encoding the capsid. The function of ORF-3 is unknown, but the antibodies directed against ORF-3 epitopes have been identified.

HEV is an RNA virus of the genus Hepevirus. The virus is icosahedral and non-enveloped. It has a diameter of approximately 34 nanometres, and it contains a single strand of RNA approximately 7.5 kilobases in length. Four HEV genotypes have been identified. Genotypes 1 and 2 are considered human viruses; genotypes 3 and 4 are zoonotic and have been isolated from humans and animals.

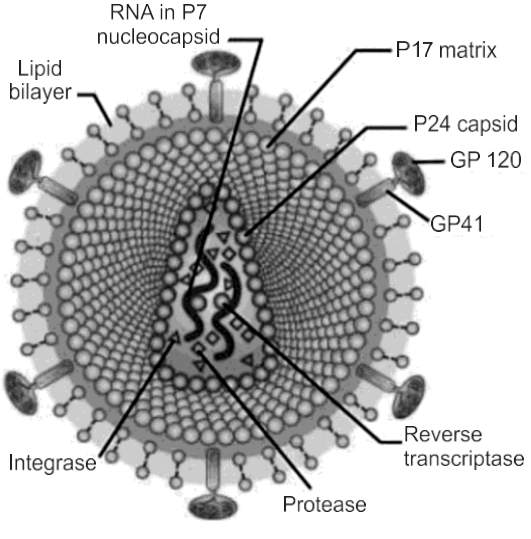


Fig. 11.5 : Structure of hepatitis E virus

[VI] Hepatitis G

A new virus recently identified in humans.

GB virus C (GBV-C), formerly known as hepatitis G virus (HGV) and also known as HPgV is a virus in the flaviviridae family and a member of the Pegivirus genus, is known to infect humans, but is not known to cause human disease.

Hepatitis G virus and GB virus C (GBV-C) are RNA viruses that were independently identified in 1995, and were subsequently found to be two isolates of the same virus.

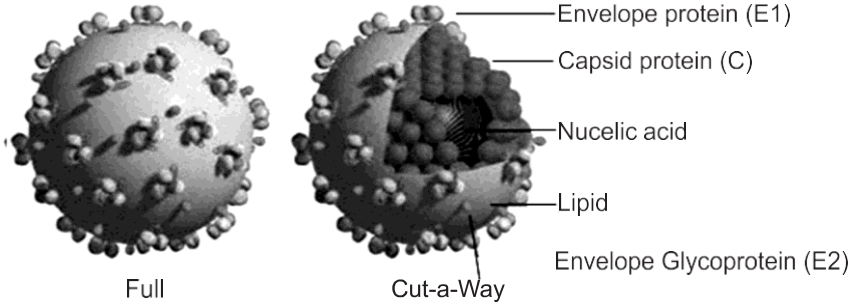


Fig. 11.6 : Structure or model of hepatitis G virus (GB virus-C)

Virus Structure:

GBV-C belongs to the flaviviridae family of viruses, which includes GBV-A, GBV-B, and HCV. GBV-C is an enveloped RNA virus with a single chain RNA structure of positive polarity. It is composed of approximately 9300 nucleotides with structural genes at the 52 end, an open reading frame, and non-structural genes at the 32 end. It is similar to HCV in structural organization, with approximately 25% homology to HCV in nucleotide sequences.

The site of GBV-C viral replication remains unclear. GBV-C virus is found in low titer in the liver cells in most, but not all patients. Viral replication seems to occur in mononuclear cells, including CD4 and CD8 T cells and B cells.

Symptoms

Common symptoms of all viral hepatitis includes —

- Nausea and vomiting
- Loss of appetite
- Weakness and fatigue
- Fever
- Dark urine
- Pale stool
- Jaundice
- Stomach pain and side pain.
- Abdominal pain

Symptoms of Hepatitis A: In rare cases, hepatitis A can cause acute liver failure, which is a loss of liver function that occurs suddenly. People with the highest risk of this complication include those with chronic liver diseases and older adults.

Symptoms of Hepatitis B: Most infants and children with hepatitis B never develop signs and symptoms. Chronic infection with hepatitis B virus either may be asymptomatic or may be associated with a chronic inflammation of the liver failure (chronic hepatitis), leading to cirrhosis over a period of several years, kidney problems and sometimes chronically infected with HBV is also susceptible to infection with another strain of viral hepatitis (i.e. hepatitis

D). Person cannot become infected with hepatitis D unless he is already infected with HBV. Having both hepatitis B and hepatitis D makes it more likely may develop complications of hepatitis.

Symptoms of Hepatitis C: Generalized signs and symptoms associated with chronic hepatitis C include fatigue, marked weight loss, flu-like symptoms, muscle pain, joint pain, intermittent low-grade fevers, itching, sleep disturbances, nausea, diarrhoea, dyspepsia, cognitive changes, depression, headaches and mood swings.

Once chronic hepatitis C has progressed to cirrhosis, possible signs and symptoms include ascites, bruising and bleeding tendency, bone pain, varices, fatty stools (steatorrhoea), jaundice, and a syndrome of cognitive impairment known as hepatic encephalopathy.

Symptoms of Hepatitis D: The symptoms of hepatitis B and hepatitis D are similar, so it can be difficult to determine which disease is causing symptoms. In some cases, hepatitis D can make the symptoms of hepatitis B worse. It can also cause symptoms in people who have hepatitis B but who never had symptoms.

Symptoms of Hepatitis E: Other feature includes, malaise, arthritis, pancreatitis, aplastic anemia, thrombocytopenia etc. Some neurologic symptoms includes polyradiculopathy, Guillain–Barré syndrome, Bell palsy, peripheral neuropathy, ataxia and mental confusion.

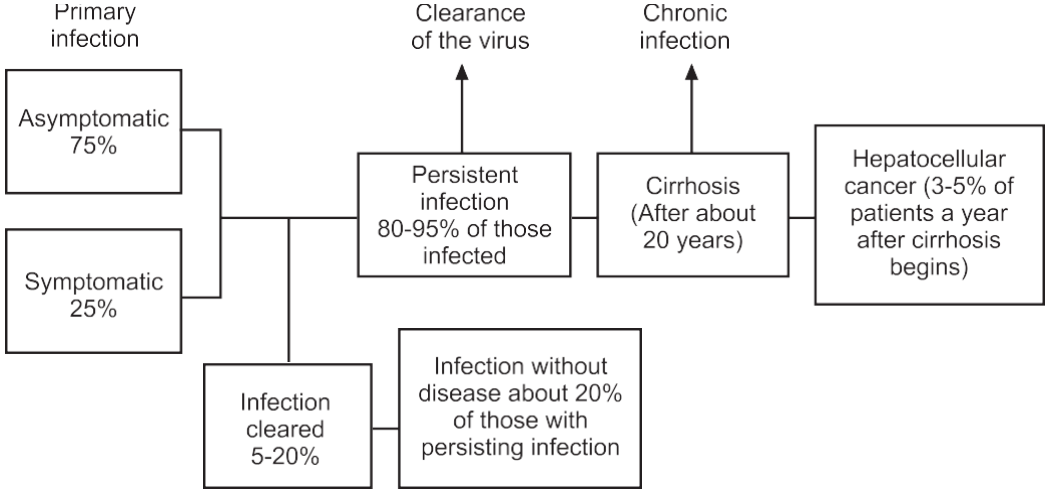


Fig. 11.7 : Epidemiology/Natural history of HCV infection

Diagnosis

Blood test: Blood test used to detect antibodies made by the body in response to the virus that causes viral hepatitis.

Liver function tests: When hepatocytes become damaged by Hepatic virus, regular blood tests are helpful to measure the levels of liver enzymes. These enzymes can become elevated and releases into the blood. Liver function test includes: Alanine aminotransferase (ALT or "SGPT, Aspartate aminotransferase (AST or "SGOT"), Alkaline phosphatase and γ glutamyl transpeptidase (GGT or GGTP).

An acute viral hepatitis panel is used to help detect and diagnose acute liver infection and inflammation due to one of the three most common hepatitis viruses: Hepatitis A virus (HAV), Hepatitis B virus (HBV), or Hepatitis C virus (HCV).

There are several causes of hepatitis and the accompanying symptoms, so these tests are used to determine if symptoms are due to a current infection with a virus and to identify which virus in particular is causing the disease. These tests may also help determine if someone has been exposed to one of the viruses even before symptoms develop.

An acute viral hepatitis panel typically consists of the following tests:

Hepatitis A antibody, IgM: These antibodies typically develop 2 to 3 weeks after first being infected and persist for about 2 to 6 months. Hepatitis A IgM antibodies develop early in the course of infection, so a positive hepatitis A IgM test is usually considered diagnostic for acute hepatitis A in a person with signs and symptoms.

Hepatitis B core antibody IgM: This is an antibody produced against the hepatitis B core antigen. It is the first antibody produced in response to a hepatitis B infection and, when detected, may indicate an acute infection. It may also be present in people with chronic hepatitis B when flares of disease activity occur.

Hepatitis B surface Ag: This is a protein present on the surface of the hepatitis B virus. It is the earliest indicator of an acute infection but may also be present in the blood of those chronically infected.

Hepatitis C antibody: This test detects antibodies produced in response to an HCV infection. It cannot distinguish between an active or previous infection. If positive, it is typically followed up with other tests to determine if the infection is a current one. (See the article on Hepatitis C for more on this.)

There are some other tests that may be offered as part of a hepatitis panel, depending on the laboratory performing the tests. These may include:

HAV antibody and HBV core antibody: These tests detect both IgM and IgG antibodies and may be used as part of the panel to determine if someone has had a previous infection.

HBV surface antibody: The test for this antibody may sometimes be included in a panel to help determine if an infection has resolved or if a person has developed the antibody after receiving the hepatitis B vaccine and achieved immunity for protection against HBV.

HDV Antibody Testing: IgM anti-HDAg antibody develops with acute HDV infection, becoming positive 7-15 days after onset of clinical illness and decline with recovery and resolution of HDV infection. During acute infection, HDV RNA can also be detected by polymerase chain reaction. After clearance of HDV, IgG anti-HDAg becomes positive.

HDV RNA Detection: With chronic HBV/HDV infection, both serum IgM and IgG anti-HDAg can be present in conjunction with detectable circulating HDV RNA.

Hepatitis E: Acute hepatitis E virus (HEV) infection is diagnosed in immunocompetent individuals based on detection of anti-HEV immunoglobulin M (IgM). The anti-HEV IgM usually starts rising 4 weeks after infection and remains

detectable for 2 months after the onset of illness.

Hepatitis GBV-C: GBV-C RNA can be identified in the blood of infected individuals by use of reverse transcriptase polymerase chain reaction. According to this technique, viral particles are present in liver cells, endothelial cells, monocytes, and lymphocytes. With clearance of infection, antibody to the envelope glycoprotein E2 develops and may be recovered from the serum. Most patients will develop detectable anti-E2 antibody after clearance of the virus. Co-existence of circulating GBV-C virus and anti-E2 antibody is infrequent, occurring in less than 5% of patients.

Liver Biopsy: A procedure in which a small needle is inserted into the liver to collect a tissue sample and tissue is then analyzed to help diagnose a variety of disorders and diseases in the liver. A liver biopsy is most often performed to help identify the cause of persistent abnormal liver enzymes, jaundice, liver abnormality found on ultrasound, CT scan, or nuclear scan and unexplained enlargement of the liver. A liver biopsy can also be used to estimate the degree of liver damage, to grade and stage hepatitis B and C, and to determine the best treatment for the damage or disease.

Treatment

Hepatitis A:

No specific treatment exists for hepatitis A. Body will clear the hepatitis A virus on its own. No complementary or alternative medicine treatments have proved helpful in preventing or treating hepatitis A infection.

One herb that continues to attract attention for its liver health properties is milk thistle. Proponents of milk thistle recommend the herb to treat jaundice and other liver disorders. Milk thistle seeds consumed as a powder, tea, tincture or standardized extract or infusion, tablets or capsules.

Hepatitis B:

Acute infection with hepatitis B usually does not require treatment because most adults clear the infection spontaneously.

Antiviral medications: Several antiviral medications including lamivudine, adefovir, telbivudine and entecavir can help fight the virus and slow its ability to damage liver.

Other medications in current use for chronic hepatitis B include the interferons (interferon α-2a and pegylated interferon α-2a) and nucleoside/ nucleotide analogues.

Liver transplant: If liver has been severely damaged, a liver transplant may be an option.

Prevention: Several vaccines have been developed for the prevention of hepatitis B virus infection. These rely on the use of one of the viral envelope proteins (hepatitis B surface antigen or HBsAg). Hepatitis B vaccination is recommended for all infants, older children and adolescents who were not vaccinated previously, and adults at risk for HBV infection.

Hepatitis C:

The goal of HCV treatment is to cure the virus, which can be done with a combination of drugs. There are a number of approved therapies to treat HCV, such as sofosbuvir/ledipasvir, sofosbuvir and simeprevir. Sofosbuvir and Simeprevir may be given together, or each may be separately combined with ribavirin and in some cases peginterferon as well. The current standard treatment for hepatitis C is combination antiviral therapy with interferon

and ribavirin, which are effective against all the genotypes of hepatitis viruses.

Vaccination: There is no vaccine for hepatitis C. Current guidelines strongly recommend that hepatitis C patients be vaccinated for hepatitis A and B if they have not yet been exposed to these viruses.

Hepatitis D:

Current treatment regimens for HDV still use unapproved interferon-based, high-dose, long-term therapy for 48 weeks with interferon alpha, 5 million U/day, or pegylated interferon alpha, 9 million U 3 times weekly. These regimens can reduce aminotransferase levels and possibly improve survival, although viral HDV RNA can persist. Successful immunization against HBV with subsequent immunity to HBV can prevent HDV infection. No specific HDV vaccine is yet available.

Liver transplantation: Liver transplantation is indicated in patients with fulminant liver failure. The 5-year survival of patients who undergo transplantation for end stage liver disease from HBV/HDV is similar to that of patients coinfected with HBV and HCV.

Hepatitis E:

Acute hepatitis E in immunocompetent persons usually only requires symptomatic treatment, as almost all of them are able to clear the virus spontaneously. Ribavirin may improve liver enzymes and functions in severe acute hepatitis E.

Treatment with pegylated interferon alfa for 3-12 months has led to sustained clearance of HEV RNA in patients with chronic hepatitis E in liver transplantations.

Prevention

Management should be predominantly preventive, relying on clean drinking water, good sanitation, and proper personal hygiene. Travelers to endemic areas should avoid drinking water or other beverages that may be contaminated and should avoid eating uncooked shellfish.

11.4 ALCOHOLIC LIVER DISEASE

Alcoholic Liver Disease is a syndrome of progressive inflammatory liver injury associated with long-term heavy intake of alcohol. The pathogenesis is not completely understood.

Though alcoholic liver disease is most likely to occur in people who drink heavily over many years, the relationship between drinking and alcoholic liver disease is complex. Not all heavy drinkers develop alcoholic liver disease, and the disease can occur in people who drink only moderately.

Patients who are severely affected present with subacute onset of fever, hepatomegaly, leukocytosis, marked impairment of liver function (e.g., jaundice, coagulopathy), and manifestations of portal hypertension (e.g., ascites, hepatic encephalopathy, variceal hemorrhage). However, milder forms of alcoholic liver disease often do not cause any symptoms.

Alcoholic liver disease usually persists and progresses to cirrhosis if heavy alcohol use continues. If alcohol use ceases, alcoholic liver disease resolves slowly over weeks to months, sometimes without permanent sequelae but often with residual cirrhosis. Of all chronic heavy drinkers, only 15–20% develops hepatitis or cirrhosis, which can occur concomitantly or in succession.

Epidemiology

Alcohol abuse is the most common cause of serious liver disease in Western societies. The true prevalence of alcoholic liver disease, especially of its milder forms, is unknown, because patients may be asymptomatic and never seek medical attention.

Causes

Alcoholic liver disease occurs when the liver is damaged by the excessive consumption of alcohol. How alcohol damages the liver and why it does so only in a minority of heavy drinkers is not clear. It is known that the process of breaking down ethanol; the alcohol in beer, wine and liquor produces highly toxic chemicals, such as acetaldehyde. These chemicals trigger inflammation that destroys liver cells. Over time, web-like scars and small knots of tissue replace healthy liver tissue, interfering with the liver's ability to function. This irreversible scarring, called cirrhosis, is the final stage of alcoholic liver disease.

Heavy alcohol use can lead to liver disease, and the risk increases with the length of time and amount of alcohol drink. But because many people who drink heavily or binge drink never develop alcoholic liver disease or cirrhosis, it is likely that factors other than alcohol play a role. These include:

Other types of hepatitis: Long-term alcohol abuse worsens the liver damage caused by other types of hepatitis, especially hepatitis C.

Malnutrition: Many people who drink heavily are malnourished, either because they eat poorly or because alcohol and its toxic by-products prevent the body from properly absorbing and breaking down nutrients, especially protein, certain vitamins and fats. In both cases, the lack of nutrients contributes to liver cell damage.

Sex: Women have a higher risk of developing alcoholic liver disease than men do. This disparity may result from differences in the way alcohol is processed by women.

Genetic factors: A number of genetic mutations have been identified that affect the way alcohol is broken down in the body. Having one or more of these mutations may increase the risk of alcoholic liver disease.

Other factors which may increase risk include:

- Type of beverage (beer or spirits are riskier than wine)
- Binge drinking
- Obesity - Alcohol and obesity may have a synergistic effect on the liver; that is, their combined effect is worse than the effect of either of them alone.

Pathophysiology

Some signs and pathological changes in liver histology include:

Alcoholic liver disease is characterized by the inflammation of hepatocytes. Between 10% and 35% of heavy drinkers develop alcoholic liver disease. While development of hepatitis is not directly related to the dose of alcohol, some people seem more prone to this reaction than others. This is called alcoholic steato necrosis and the inflammation appears to predispose to liver fibrosis. Inflammatory

cytokines (TNF-alpha, IL6 and IL8) are thought to be essential in the initiation and perpetuation of liver injury by inducing apoptosis and necrosis. One possible mechanism for the increased activity of TNF-alpha is the increased intestinal permeability due to liver disease. This facilitates the absorption of the gut-produced endotoxin into the portal circulation. The Kupffer cells of the liver then phagocytose endotoxin, stimulating the release of TNF-alpha. TNF-alpha then triggers apoptotic pathways through the activation of caspases, resulting in cell death.

Mallory's hyaline body: A condition where pre-keratin filaments accumulate in hepatocytes. This sign is not limited to alcoholic liver disease, but is often characteristic.

Ballooning degeneration: Hepatocytes in the setting of alcoholic change often swell up with excess fat, water and protein; normally these proteins are exported into the bloodstream. Accompanied with ballooning, there is necrotic damage. The swelling is capable of blocking nearby biliary ducts, leading to diffuse cholestasis.

Inflammation: Neutrophilic invasion is triggered by the necrotic changes and presence of cellular debris within the lobules. Ordinarily the amount of debris is removed by Kupffer cells, although in the setting of inflammation they become overloaded, allowing other white cells to spill into the parenchyma.

Chronic liver disease also shows the conditions, such as fibrosis and cirrhosis.

Fibrosis: Fibrosis of the liver is excessive accumulation of scar tissue that results from ongoing inflammation and liver cell death that occurs in most types of chronic liver diseases. Nodules, an abnormal spherical areas of cells, form as dying liver cells are replaced by regenerating cells. This regeneration of cells causes the liver to become hard. Fibrosis refers to the accumulation of tough, fibrous scar tissue in the liver.

Cirrhosis: A progressive and permanent type of fibrotic degeneration of liver tissue. Cirrhosis is a late stage of serious liver disease marked by inflammation (swelling), fibrosis (cellular hardening) and damaged membranes preventing detoxification of chemicals in the body, ending in scarring and necrosis (cell death). Between 10% to 20% of heavy drinkers will develop cirrhosis of the liver. Acetaldehyde may be responsible for alcohol-induced fibrosis by stimulating collagen deposition by hepatic stellate cells.

Symptoms

It may not have symptoms in the early stages. Symptoms tend to be worse after a period of heavy drinking. Digestive symptoms include:

- Pain and swelling in the abdomen and tenderness,
- Decreased appetite and weight loss,
- Nausea and vomiting,
- Fatigue,
- Dry mouth and increased thirst,
- Bleeding from enlarged veins in the walls of the lower part of the esophagus.

Skin problems such as:

- Yellow colour in the skin, mucus membranes, or eyes (jaundice).

- Small, red spider-like veins on the skin.
- Very dark or pale skin.
- Redness on the feet or hands.
- Itching.

Just about everyone who has alcoholic liver disease is malnourished. Drinking large amounts of alcohol suppresses the appetite, and heavy drinkers get most of their calories in the form of alcohol.

Complications

Complications of alcoholic liver disease include:

Increased blood pressure in the portal vein: Blood from the intestine, spleen and pancreas enters the liver through the portal vein. If scar tissue slows normal circulation through the liver, this blood backs up, leading to increased pressure within the vein (portal hypertension).

Enlarged veins (varices): When circulation through the portal vein is blocked, blood may back up into other blood vessels in the stomach and esophagus. Massive bleeding in the upper stomach or esophagus from these blood vessels is a life-threatening emergency that requires immediate medical care.

Jaundice: It occurs when liver is not able to remove bilirubin; the residue of old red blood cells from blood. Bilirubin builds up and is deposited in skin and the whites of eyes, causing a yellow colour.

Hepatic encephalopathy: A liver damaged by alcoholic liver disease has trouble removing toxins from body normally one of the liver's key tasks. The buildup of toxins can damage brain, leading to changes in mental state, behaviour and personality (hepatic encephalopathy). Signs and symptoms of hepatic encephalopathy include forgetfulness, confusion and mood changes, and in the most severe cases, coma.

Diagnosis

Common considerations in alcoholic patients with jaundice include chronic pancreatitis with biliary strictures and pancreaticobiliary neoplasms.

Changes in the mental status of patients with alcoholic liver disease do not always imply the presence of hepatic encephalopathy. Entities (e.g. subdural hematomas) should be excluded by obtaining a computed tomography (CT) scan of the brain.

CBC Count:

A complete blood cell (CBC) count commonly reveals some degree of neutrophilic leukocytosis with bandemia. Usually, this is moderate; however, rarely, it is severe enough to provide a leukemoid picture.

Alcohol is a direct marrow suppressant, and moderate anemia may be observed. In addition, alcohol use characteristically produces a moderate increase in mean corpuscular volume.

Thrombocytosis may be observed as part of the inflammatory response; conversely, myelosuppression or portal hypertension with splenic sequestration may produce thrombocytopenia.

Screening Blood Tests: Screening blood tests to exclude other conditions (appropriate in any patient with alcoholic liver disease) may include the following:

Hepatitis B surface antigen (HBsAg) detects hepatitis B.

Anti–hepatitis C virus by enzyme-linked immunosorbent assay (ELISA) detects hepatitis C.

Ferritin and transferrin saturation detect hemochromatosis.

Jaundice with fever can be caused by gallstones producing cholangitis and is suggested by a disproportionate elevation of the alkaline phosphatase (ALP) level.

Liver Function Tests: Liver enzyme levels exhibit a characteristic pattern. In most patients, the aspartate aminotransferase (AST) level is moderately elevated, whereas the alanine aminotransferase (ALT) level is in the reference range or only mildly elevated. This is the opposite of observed in most other liver diseases.

Ultrasonography: Ultrasonography is the preferred imaging study in evaluating patients with suspected alcoholic liver disease. This modality provides a good evaluation of the liver and other viscera, and it permits guided liver biopsy.

Liver Biopsy: Liver biopsy is not always required in the evaluation of alcoholic liver disease, but it may be useful in establishing the diagnosis, in determining the presence or absence of cirrhosis, and in excluding other causes of liver disease.

Treatment

In most patients with alcoholic liver disease, the illness is mild. Their short-term prognosis is good, and no specific treatment is required. Hospitalization is not always necessary. Alcohol use must be stopped, and care should be taken to ensure good nutrition; providing supplemental vitamins and minerals, including folate and thiamine, is reasonable. Patients who are coagulopathic should receive vitamin K parenterally. Anticipate symptoms of alcohol withdrawal, and manage them appropriately.

Patients with severe alcoholic liver disease may benefit over the short term from specific therapies directed toward reducing liver injury, enhancing hepatic regeneration, and suppressing inflammation. For the long term, goals include improvement of liver function, prevention of progression to cirrhosis, and reduction of mortality.

Cessation of Alcohol Intake: Cessation of alcohol use is the mainstay of treatment of alcoholic liver disease.

Liver Transplantation: Orthotopic liver transplantation is widely used in patients with end-stage liver disease. Most patients with active alcoholic liver disease are excluded from transplantation because of ongoing alcohol abuse. In most liver transplantation programs, patients must abstain from alcohol for at least 6 months before they can be considered for transplantation, and a thorough psychosocial evaluation must demonstrate that patients have a low likelihood of reverting to alcohol abuse.

Surgical Considerations:

Patients with acute alcoholic liver disease are at high risk of developing hepatic failure following general anesthesia and major surgery. Because postoperative mortality rates are high, surgery should be avoided in the setting of acute alcoholic liver disease unless it is absolutely necessary. If patients remain abstinent, alcoholic liver disease usually resolves over time, permitting surgery to be undertaken with a substantially reduced risk.

Herbal Agents:

Milk thistle: Herbal agents have also been tried in alcoholic liver disease. Silymarin is the active ingredient in milk thistle, is a member of the flavonoids. The precise mechanism of its hepatoprotective mediation is not known, but it is probably related to its antioxidant properties. In humans with mild alcoholic liver disease, silymarin improves liver chemistry test results. Milk thistle is generally safe, but can cause diarrhoea and nausea.

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Chapter...12

DISEASES OF BONES AND JOINTS

12.1 INTRODUCTION TO HUMAN SKELETON

The human skeleton is the internal framework of the body. It is composed of 270 bones at birth. This total decreases to 206 bones by adulthood after some bones have fused together. The bone mass in the skeleton reaches maximum density around age 30. The human skeleton can be divided into the axial skeleton and the appendicular skeleton. The axial skeleton is formed by the vertebral column, the rib cage and the skull. The appendicular skeleton, which is attached to the axial skeleton, is formed by the pectoral girdles, the pelvic and the bones of the upper and lower limbs.

The individual bones are attached in such a way that a large variety of co-ordinate movements are made possible in different parts of the body. These movements are made possible by skeletal muscles, the fact that the bones act as levers, cartilage which reduces friction and ligaments which prevent dislocation and the presence of movable joints. The site or place where two or more bones of the skeleton are attached to each other is called a joint or place of articulation.

Structure & Function of Joints

A joint is formed where two or more bones come in close contact in the body and are attached to each other by ligaments or cartilage.

Types of Joints:

Joints can be classified according to the degree and type of movement they allow. The following types of joints can be recognized:

a) Fibrous (or immovable) Joints: These joints are firmly held together by a thin layer of strong connective tissue. There is no movement between the bones such as the sutures of the skull and the teeth in their sockets.

b) Cartilagenous Joints: Cartilagenous joints are joints where the articular surfaces of the bones forming the joints are attached to each other by means of white fibro-cartilaginous discs and ligaments which allow only a limited degree of movement. Examples are the cartilaginous joint between the vertebrae, the cartilage in the symphysis which binds the pubic bones together at the front of the pelvic girdle, and the cartilage in the joint between the sacrum and the hip bone.

c) Synovial Joints: Synovial joints are freely movable joints and shows free movement including flexion (bending), extension (straightening or bending), abduction (away from the middle of the body), adduction (towards the midline), rotation, supination (turning the palm up, inversion (turning the sole of the foot inward) and eversion (turning the sole of the foot outward).

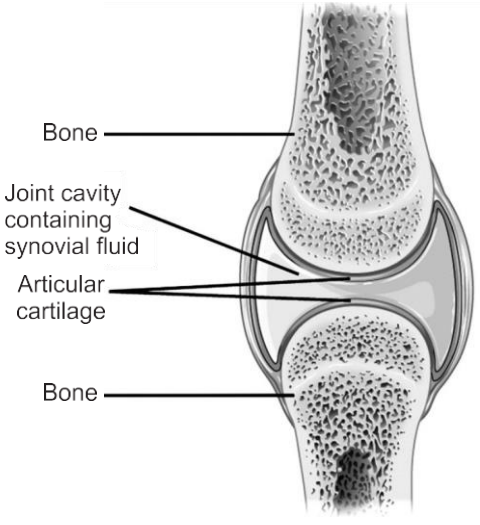

Fig. 12.1 : Synovial joints

Synovial joints are most evolved and therefore most mobile type of joints. They possess the following characteristic features:

- There articular surfaces are covered with hyaline cartilage. This articular cartilage is avascular, non-nervous and elastic. Lubricated with synovial fluid, the cartilage forms slippery surfaces for free movements.
- Between the articular surfaces there is a joint cavity filled with synovial fluid. The cavity may be partially or completely subdivided by an articular disc known as meniscus.
- The joint is surrounded by an articular capsule which is fibrous in nature and is lined by synovial membrane. Because of its rich nerve supply the fibrous capsule is sensitive to stretches imposed by movements.
- The synovial membrane lines the entire joint except the articular surfaces covered by hyaline cartilage. It is this membrane that secretes the slimy fluid called synovial fluid which lubricates the joint and nourishes the articular cartilage.

Synovial joints are the only joints that have a space between the adjoining bones. This space, referred to as the synovial (or joint) cavity, is filled with synovial fluid.

Synovial joints can be subdivided into the following groups according to the type of movement they carry out.

Functions of the Skeleton

1. Support: The skeleton is the framework of the body, it supports the softer tissues and provides points of attachment for most skeletal muscles.

2. Protection: The skeleton provides mechanical protection for many of the body's internal organs, reducing risk of injury to them.

For example, cranial bones protect the brain, vertebrae protect the spinal cord, and the ribcage protects the heart and lungs.

3. Assisting in Movement: Skeletal muscles are attached to bones, therefore when the associated muscles contract they cause bones to move.

4. Storage of Minerals: Bone tissues store several minerals, including calcium (Ca) and phosphorus (P). When required, bone releases minerals into the blood, facilitating the balance of minerals in the body.

5. Production of Blood Cells: The red bone marrow inside some larger bones produce blood cells (RBC, WBC and Platelets)

6. Storage of Chemical Energy: With increasing age some bone marrow changes from 'red bone marrow' to 'yellow bone marrow'.

Yellow bone marrow consists mainly of adipose cells, and a few blood cells. It is an important chemical energy reserve.

Bone Structure

Each bone in the skeleton contains two forms of tissue: compact (dense) bone that is relatively solid and spongy (cancellous) bone that forms an open network of struts and plates. Compact bone is found on the external surface of the bone. Spongy bone is located inside the bone. The proportion of compact and spongy bone varies with the shape of the bone. Compact bone is thickest where stresses arrive from a limited range of directions. Spongy bone is located where bones are not heavily stressed or where stresses arrive from many directions. Spongy bone is much lighter than compact bone, which helps to reduce the weight of the skeleton and makes it easier for muscles to move the bones.

- Tendons: These attach muscle to bone.
- Ligaments: These attach bone to bone.

Skeletal muscles:

These muscles contract to pull on tendons and move the bones of the skeleton. In addition to producing skeletal movement, muscles also maintain posture and body position, support soft tissues, guard entrances and exits to the digestive and urinary tracts, and maintain body temperature.

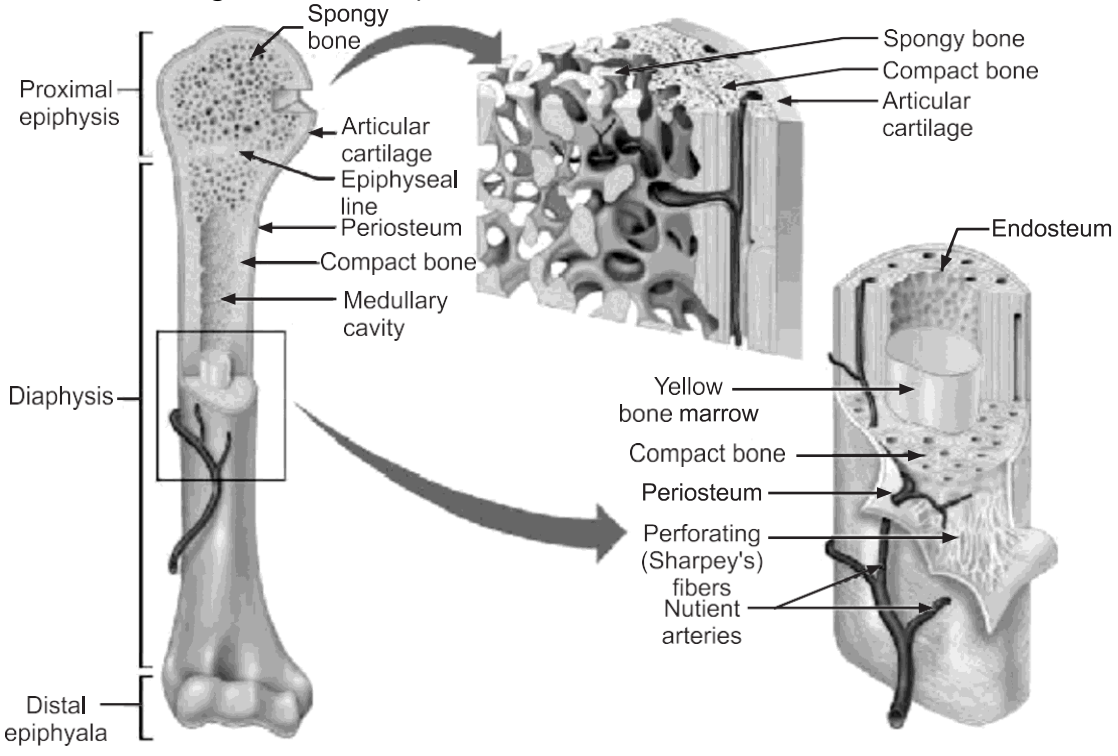

Fig. 12.2 : Structure of the bone nerves

Nerves control the contraction of skeletal muscles, interpret sensory information, and co-ordinate the activities of the body's organ systems.

Cartilage:

This is a type of connective tissue. It is a firm gel-like substance. The body contains three major types of cartilage: hyaline cartilage, elastic cartilage and fibrocartilage.

Hyaline cartilage: It is the most common type of cartilage. This type of cartilage provides stiff but somewhat flexible support. Examples in adults include the tips of ribs (where they meet the sternum) and part of the nasal septum. Another example is articular cartilage, which is cartilage that covers the ends of bones within a joint. The surfaces of articular cartilage are slick and smooth, which reduces friction during joint movement.

Elastic cartilage: It provides support but can tolerate distortion without damage and return to its original shape. The external flap of the ear is one place where elastic cartilage can be found.

Fibrocartilage resists: Fibrocartilage resists compression, prevents bone-to-bone contact, and limits relative movement. Fibrocartilage can be found within the knee joint, between the pubic bones of the pelvis, and between the spinal vertebrae.

Disease of Bones and Joints:

- Rheumatoid arthritis
- Osteoporosis
- Gout

12.2 RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is an autoimmune disease that results in a chronic, systemic inflammatory disorder that may affect many tissues and organs, but principally attacks flexible (synovial) joints. It can be a disabling and painful condition, which can lead to substantial loss of functioning and mobility if not adequately treated. The hallmark feature of this condition is persistent symmetric polyarthritis (synovitis) that affects the hands and feet, though any joint lined by a synovial membrane may be involved. Extra-articular involvement of organs such as the skin, heart, blood vessels, lungs and eyes can be significant. Although rheumatoid arthritis affects approximately 1% of world population. It can occur at any age, usually begins after age 40 (Peak incidence is between 4th and 6th decade). The disorder is much more common in women than in men. Genetic and autoimmune factors are mainly responsible for the initiation of disease process.

Juvenile Rheumatoid Arthritis (JRA)

Juvenile rheumatoid arthritis causes joint inflammation and stiffness for more than six weeks in a child aged 16 or younger. Even though infectious agents such as viruses, bacteria, and fungi have long been suspected, the cause of rheumatoid arthritis is unknown. Treatment focuses on controlling symptoms and preventing joint damage.

Epidemiology

Worldwide, the annual incidence of RA is approximately 3 cases per 10,000 populations, and the prevalence rate is approximately 1%, increasing with age and peaking between the ages of 35 and 50 years. In 2010, it resulted in about 49,000 deaths globally.

About 1.5 million people in the United State have RA. Nearly three times as many women have the disease as men. In women, RA most commonly begins between ages 30 and 60. In men, it often occurs later in life.

RA is a chronic disease, and although rarely, a spontaneous remission may occur. The natural course is almost invariably one of persistent symptoms, waxing and waning in intensity, and a progressive deterioration of joint structures leading to deformations and disability.

Etiology

The cause of RA is unknown. Genetic, environmental, hormonal, immunologic and infectious factors may play significant roles. Socioeconomic, psychological, and lifestyle factors (e.g., tobacco use, the main environmental risk) may influence disease outcome.

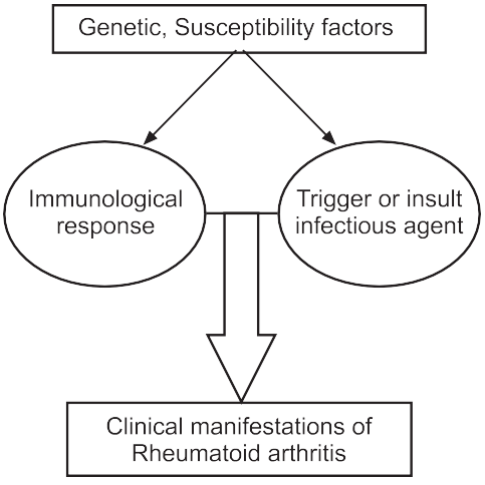

Fig. 12.3: Etiology of RA

Immunologic factors: Rheumatoid arthritis occurs when immune system attacks the synovium, the lining of the membranes that surround joints. All of the major immunologic elements play fundamental roles in the initiation, propagation and maintenance of the autoimmune process of RA. The exact orchestration of the cellular and cytokine events that lead to pathologic consequences, such as synovial proliferation and subsequent joint destruction is complex. It involves T and B lymphocytes, antigen-presenting cells (e.g., B cells, macrophages, dendritic cells), and numerous cytokines. Aberrant production and regulation of both pro-inflammatory and anti-inflammatory cytokines and cytokine pathways are found in RA. The resulting inflammation thickens the synovium, which can eventually destroy the cartilage and bone within the joint. The tendons and ligaments that hold the joint together weaken and stretch. Gradually, the joint loses its shape and alignment.

Genetic factors: Half of the risk for RA is believed to be genetic. It is strongly associated with the inherited tissue type major histocompatibility complex (MHC) antigen HLA-DR4 (most specifically DR0401 and 0404), and the genes PTPN 22 and PAD I4, hence family history is an important risk factor. Inheriting the PTPN22 gene has been shown to double a person's susceptibility to RA. PADI4 has been identified as a major risk factor in people of Asian descent, but not in those of European descent. First-degree relatives prevalence rate is 2–3% and disease genetic concordance in monozygotic twins is approximately 15–20%.

Infectious agents: For many decades, numerous infectious agents have been suggested as potential causes of RA, including Mycoplasma organisms, Epstein-Barr virus (EBV), and rubella virus.

Hormonal factors: Sex hormones may play a role in RA, as evidenced by the disproportionate number of females with this disease, its amelioration during pregnancy, its recurrence in the early postpartum period, and its reduced incidence in women using oral contraceptives. Hyperprolactinemia may be a risk factor for RA.

Other factors: Smoking is the most significant non-genetic risk with RA being up to three times more common in smokers than non-smokers, particularly in men. Vitamin D deficiency is more common in patients with rheumatoid arthritis than in the general population. However, whether

vitamin D deficiency is a cause or a consequence of the disease remains unclear.

Pathophysiology

The pathogenesis of RA is not completely understood. An external trigger (e.g., cigarette smoking, infection, or trauma) that triggers an autoimmune reaction, leading to synovial hypertrophy and chronic joint inflammation along with the potential for extra-articular manifestations, is theorized to occur in genetically susceptible individuals.

Synovial cell hyperplasia and endothelial cell activation are early events in the pathologic process that progresses to uncontrolled inflammation and consequent cartilage and bone destruction. Genetic factors and immune system abnormalities contribute to disease propagation.

CD4 T cells, mononuclear phagocytes, fibroblasts, osteoclasts, and neutrophils play major cellular roles in the pathophysiology of RA, whereas B cells produce autoantibodies (Rheumatoid factors). Abnormal production of numerous cytokines, chemokines and other inflammatory mediators (e.g., tumor necrosis factor alpha [TNF-α], interleukin [IL-1, IL-6, IL-8], transforming growth factor beta [TGF-β], fibroblast growth factor [FGF], and platelet-derived growth factor [PDGF]) has been demonstrated in patients with RA.

Ultimately, inflammation and exuberant proliferation of the synovium (pannus) leads to destruction of various tissues, including cartilage, bone, tendons, ligaments and blood vessels. Although the articular structures are the primary sites involved by RA, other tissues are also affected.

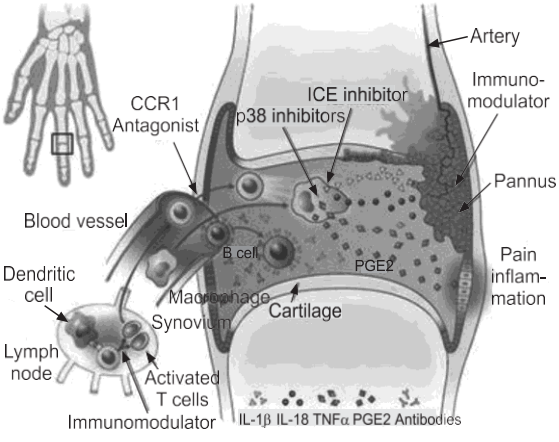

Fig. 12.4 : Pathogenesis of RA symptoms

Rheumatoid Arthritis and Joint Inflammation:

Joint inflammation is a hallmark of rheumatoid arthritis. That includes:

Stiffness: The joint is harder to use and might have a limited range of motion. "Morning stiffness" is one of the hallmark symptoms of rheumatoid arthritis. While many people with other forms of arthritis have stiff joints in the morning. People with rheumatoid arthritis take more than an hour (sometimes several hours) before their joints feel loose.

Swelling: Fluid enters into the joint and it becomes puffy; this also contributes to stiffness.

Pain: Inflammation inside a joint makes it sensitive and tender. Prolonged inflammation causes damage that also contributes to pain.

Redness and warmth: The joints may be somewhat warmer and more pink or red than neighbouring skin.

Other symptoms: RA can affect many areas of the body. These effects all result from the general process of inflammation,

leading to a wide variety of symptoms of rheumatoid arthritis:

- Fatigue,
- Malaise,
- Loss of appetite, which can lead to weight loss,
- Muscle aches.

These feelings have been compared to having the flu, although they are usually less intense and longer lasting. Rheumatoid arthritis may affect other areas of body. Involvement of multiple areas of the body occurs and is more common with moderate to severe rheumatoid arthritis.

Complications

Rheumatoid Arthritis Skin Problems: Rheumatoid arthritis (RA) is primarily a disease of the joints. But the disease and many of the medications used to treat it can also affect the skin, causing problems as diverse as sun sensitivity, rash, and firm lumps of tissue called nodules.

Lung involvement, due to either damage to the lungs or inflammation of the lining around the lungs, is common but sometimes causes no symptoms. If shortness of breath develops, it can be treated with drugs that reduce inflammation in the lungs.

Rheumatoid arthritis can even affect a joint in voice box or larynx (cricoarytenoid joint), causing hoarseness.

Rheumatoid arthritis can cause inflammation in the lining around the heart, but it usually has no symptoms. If symptoms do develop, it may cause shortness of breath or chest pain. In addition, people with rheumatoid arthritis are more likely to develop clogged arteries in their heart, which can lead to chest pain and heart attacks.

The eyes are affected in less than 5% of people with rheumatoid arthritis. When the eyes are affected, symptoms can include red, painful eyes or possibly dry eyes.

Early rheumatoid arthritis tends to affect smaller joints first, particularly the joints that attach fingers to hands and toes to feet. As the disease progresses, symptoms often spread to the knees, ankles, elbows, hips and shoulders. In most cases, symptoms occur in the same joints on both sides of body.

Tests and Diagnosis

Rheumatoid arthritis can be difficult to diagnose in its early stages because the early signs and symptoms mimic those of many other diseases. There is no one blood test or physical finding to confirm the diagnosis.

Physical exam: To check joints for swelling, redness, warmth and also check reflexes and muscle strength.

Laboratory studies: Routine viral screening by serologic testing neither significantly facilitate the diagnosis of RA in patients with early RA, nor it is helpful as a potential identifier of disease progression.

Potentially useful laboratory studies in suspected RA fall into 3 categories: markers of inflammation, hematologic parameters, and immunologic parameters and include the following:

- Erythrocyte sedimentation rate (ESR)
- C-reactive protein (CRP) level
- Complete blood count (CBC)
- Rheumatoid factor (RF) assay
- Antinuclear antibody (ANA) assay

Markers of inflammation: The ESR and the CRP level are associated with disease activity.

Hematologic parameters: People with rheumatoid arthritis tend to have an elevated erythrocyte sedimentation rate (ESR), which indicates the presence of an inflammatory process in the body. C-reactive protein (CRP) levels are an even better indication than ESR of the amount of inflammation present. In people with rheumatoid arthritis, if the CRP is high, it suggests that there is significant inflammation or injury in the body.

Both CRP and ESR levels are used to monitor disease activity and to monitor how well someone is responding to treatment.

The CBC commonly demonstrates anemia of chronic disease and correlates with disease activity; it improves with successful therapy. Hypochromic anemia suggests blood loss, commonly from the gastrointestinal (GI) tract (associated with the use of nonsteroidal anti-inflammatory drugs). Anemia may also be related to disease modifying antirheumatic drug (DMARD) therapy.

Thrombocytosis is common and also associated with disease activity. Thrombocytopenia may be a rare adverse event of therapy and may occur in patients with Felty syndrome. Leukocytosis may occur but is usually mild. Leukopenia may be a consequence of therapy or a component of Felty syndrome, which may then respond to DMARD therapy.

Immunologic parameters: Abnormal antibodies can be found in the blood of people with rheumatoid arthritis with simple blood testing. An antibody "rheumatoid factor" (RF) can be found in 80% of patients with rheumatoid arthritis. Patients who are felt to have rheumatoid arthritis and do not have positive rheumatoid factor testing are referred to as having "seronegative rheumatoid arthritis". Citrulline antibody (also referred to as anticitrulline antibody, anticyclic citrullinated peptide antibody, and anti-CCP antibody) is present in 50%-75% people with rheumatoid arthritis. It is useful in the diagnosis of rheumatoid arthritis when evaluating cases of unexplained joint inflammation. A test for citrulline antibodies is especially helpful in looking for the cause of previously undiagnosed inflammatory arthritis when the traditional blood test for rheumatoid arthritis, rheumatoid factor, is not present. Citrulline antibodies have been felt to represent the earlier stages of rheumatoid arthritis in this setting. Citrulline antibodies also have been associated with more aggressive forms of rheumatoid arthritis. Another antibody called the "antinuclear antibody" (ANA) is also frequently found in people with rheumatoid arthritis.

X-rays: X-rays of the hands and feet are generally performed in people with a polyarthritis. It may be applicable to help track the progression of rheumatoid arthritis in joints over time.

Other medical imaging techniques such as magnetic resonance imaging (MRI) and ultrasound are also used in RA.

Treatments and Drugs

There is no cure for rheumatoid arthritis. Medications can reduce inflammation in joints in order to relieve pain and prevent or slow joint damage. Occupational and physical therapy helps how to protect joints. If joints are severely damaged by rheumatoid arthritis, surgery may be necessary.

Medications: Many drugs used to treat rheumatoid arthritis have potentially serious side effects.

NSAIDs: NSAIDs can relieve pain and reduce inflammation. (e.g. Aspirin, Fenoprofen, Piroxicam, Indomethacin etc.)

Steroids: Corticosteroid medications, such as prednisone, reduce inflammation and pain and slow joint damage. Side effects may include thinning of bones, cataracts, weight gain and diabetes. Corticosteroids are used to relieve acute symptoms, with the goal of gradually tapering off the medication.

Disease modifying antirheumatic drugs (DMARDs): These drugs can slow the progression of rheumatoid arthritis and save the joints and other tissues from permanent damage. Common DMARDs include Gold,d-penicillamine, chloroquine or hydroxychloroquine, sulfasalazine, leflunomide etc. Side effects vary but may include liver damage, bone marrow suppression and severe lung infections.

Immunosuppressants: These medications act to suppress immune system, which is out of control in rheumatoid arthritis. Examples include cyclosporine, azothioprine, methotrexate. These medications can increase susceptibility to infection.

TNF-inhibitors: Tumor necrosis factor-alpha (TNF-α) is an inflammatory substance produced by body. TNF-inhibitors can help to reduce pain, morning stiffness and tender or swollen joints. Examples include etanercept, infliximab, adalimumab, golimumab and certolizumab. Potential side effects include nausea, diarrhoea, hair loss and an increased risk of serious infections.

Other drugs: Several other rheumatoid arthritis drugs target a variety of processes involved with inflammation in body. These drugs include anakinra, abatacept, rituximab, tocilizumab andtofacitinib. Side effects vary but may include itching, abdominal pain, headache, runny nose or sore throat.

Surgery: If medications fail to prevent or slow joint damage, surgery requires repairing damaged joints. Surgery may help restore ability to use joint. It can also reduce pain and correct deformities. Rheumatoid arthritis surgery may involve one or more of the following procedures:

- Total joint replacement
- Tendon repair
- Joint fusion

Table 12.1 : Drug therapy for rheumatoid arthritis

Category/Examples	Mechanism	Possible Toxicity
Non-steroidal anti-inflammatory drugs: Aspirin, Fenoprofen, Ibuprofen, Naproxen, Indomethacin Etodolac, Sulindac, Meclofenamate, Piroxicam	Inhibition of cyclooxygenase enzyme within arachidonic acid pathway, reducing production of inflammatory mediators (e.g., prostaglandins).	Gastrointestinal bleeding; interstitial nephritis; fluid retention; dizziness; anemia; thrombocytopenia; alterations in vision, taste, or hearing.

Contd...

Corticosteroids: Prednisone, Prednisolone	Inhibition of synthesis of inflammatory mediators; suppression of phagocyte infiltration and leukocytosis.	Decreased calcium absorption and bone mass; avascular necrosis with large doses; potential Cushing's syndrome with prolonged, systemic use.
Slow-acting or disease-modifying agents: Gold compounds, e.g., aurothioglucose, auranofin, Penicillamine, Hydroxy-chloroquine, Sulfasalazine	Altered production of cytokines such as interleukin-1 and tumor necrosis factor; some have weak immunosuppressive effects.	Gastrointestinal irritation; rash; flushing and dizziness (with gold); nephritis; bone marrow depression.
Cytotoxic agents: Methotrexate, Azathioprine, Cyclosporine	Inhibition of immune-mediated inflammation.	Nausea; mucosal ulcers; cytopenias and anemia; hepatotoxicity; pulmonary fibrosis; nephrotoxicity.

12.3 OSTEOARTHRITIS

Osteoarthritis (OA) is the most common form of arthritis, affecting millions of people around the world. It can be thought of as a degenerative disorder arising from the biochemical breakdown of articular (hyaline) cartilage in the synovial joints. However, the current view holds that osteoarthritis involves not only the articular cartilage but also the entire joint organ, including hands, neck, lower back, knees and hips.

There are two types of osteoarthritis:

Primary osteoarthritis:

It is mostly related to aging. With aging, the water content of the cartilage increases, and the protein makeup of cartilage degenerates.

Secondary osteoarthritis:

Secondary osteoarthritis is caused by another disease or condition. Conditions that can lead to secondary osteoarthritis include obesity, repeated trauma or surgery to the joint structures, abnormal joints at birth (congenital abnormalities), gout, diabetes, and other hormone disorders.

Epidemiology

Globally approximately 250 million people have osteoarthritis of the knee (3.6% of the population). Osteoarthritis affects nearly 27 million people in the United States. It is estimated that 80% of the population have radiographic evidence of osteoarthritis by age 65, although only 60% of those will have symptoms. Osteoarthritis globally causes moderate to severe disability in 43.4 million people.

Causes

Osteoarthritis occurs when the cartilage that cushions the ends of bones in joints deteriorates over time. Cartilage is a firm, slippery tissue that permits nearly frictionless joint motion. In osteoarthritis, the slick surface of the cartilage becomes rough.

The daily stresses applied to the joints, especially the weight-bearing joints

(e.g., ankle, knee and hip), play an important role in the development of osteoarthritis. Most investigators believe that degenerative or alterations in osteoarthritis primarily begin in the articular cartilage, as a result of either excessive loading of a healthy joint or relatively normal loading of a previously disturbed joint. External forces accelerate the catabolic effects of the chondrocytes and further disrupt the cartilaginous matrix.

Knee osteoarthritis is classified as either primary (idiopathic) or secondary. Among the various structures making up the knee joint, the hyaline joint cartilage is the main target of the harmful influences that cause osteoarthritis and the structure in which the disease begins. About 95% of hyaline cartilage consists of extracellular matrix.

Older age: The risk of osteoarthritis increases with age.

Sex: Women are more likely to develop osteoarthritis, though the reason is unknown.

Obesity: Carrying more body weight puts added stress on weight-bearing joints, such as knees.

Joint injuries: Injuries, such as those that occur when playing sports or from an accident, may increase the risk of osteoarthritis.

- Genetics (significant family history)
- Reduced levels of sex hormones
- Muscle weakness
- Repetitive use (jobs requiring heavy labour and bending)
- Infection
- Crystal deposition
- Acromegaly
- Previous inflammatory arthritis (e.g., burnt-out rheumatoid arthritis)
- Heritable metabolic causes (e.g., alkaptonuria, hemochromatosis, and Wilson disease)
- Hemoglobinopathies (e.g., sickle cell disease and thalassemia)
- Neuropathic disorders leading to a Charcot joint (e.g., syringomyelia, tabesdorsalis and diabetes)
- Underlying morphologic risk factors (e.g., congenital hip dislocation and slipped femoral capital epiphysis)
- Disorders of bone (e.g., Paget disease and avascular necrosis)
- Previous surgical procedures (e.g., meniscectomy)

Pathophysiology

Osteoarthritis is a degenerative joint disease that may cause gross cartilage loss and morphological damage to other joint tissues, more subtle biochemical changes occur in the earliest stages of osteoarthritis progression. The water content of healthy cartilage is finely balanced by compressive force driving water out and swelling pressure drawing water in. Collagen fibres exert the compressive force, whereas the Gibbs–Donnan effect and cartilage proteoglycans create osmotic pressure which tends to draw water in.

However during onset of osteoarthritis, the collagen matrix becomes more disorganized and there is a decrease in proteoglycan content within cartilage. The breakdown of collagen fibres results in a net increase in water content. This increase occurs because there is an overall loss of proteoglycans (and thus a decreased osmotic pull), it is outweighed by a loss of collagen. Without the protective effects of the proteoglycans, the collagen fibres of the cartilage can become susceptible to

degradation and thus exacerbate the degeneration. Inflammation of the surrounding joint capsule can also occur, though often mild (compared to rheumatoid arthritis). This can happen, as breakdown products from the cartilage are released into the synovial space, and the cells lining the joint attempt to remove them. New bone outgrowths, called "spurs" or osteophytes, can form on the margins of the joints, possibly in an attempt to improve the congruence of the articular cartilage surfaces. These bone changes, together with the inflammation, can be both painful and debilitating.

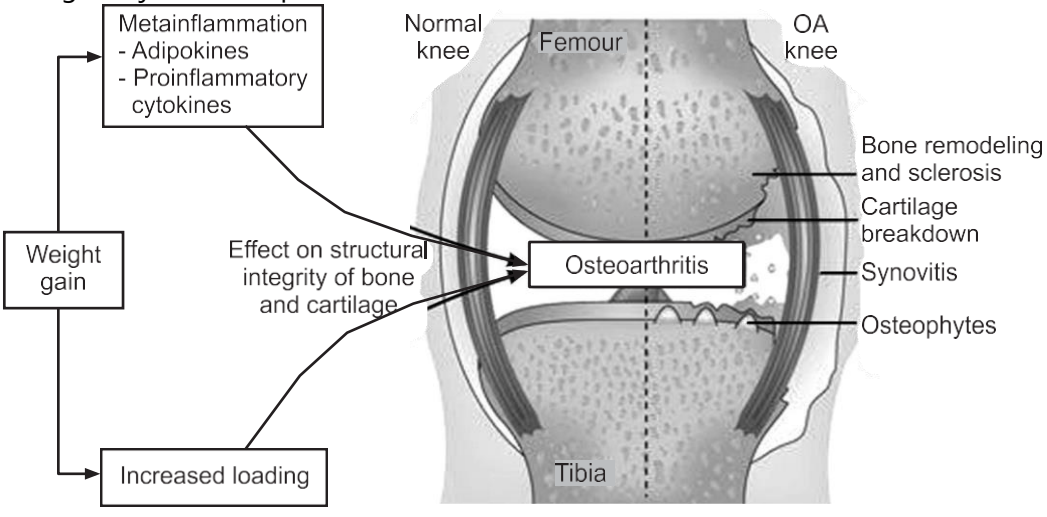

Fig. 12.5 : Pathogenesis of OA

Symptoms

Osteoarthritis symptoms often develop slowly and worsen over time. Signs and symptoms of osteoarthritis include:

Pain: Joint may hurt during or after movement.

Tenderness: Joint may feel tender, if light pressure is applied on it.

Stiffness: Joint stiffness may be most noticeable when wake up in the morning or after a period of inactivity.

Loss of flexibility: The joints are not able to move through its full range of motion.

Grating sensation: May hear or feel a grating sensation when use the joint.

Bone spurs: These extra bits of bone, which feel like hard lumps, may form around the affected joint.

Tests and Diagnosis

Physical exam: Physical examination of affected joint includes, checking for tenderness, swelling or redness.

Imaging tests: Pictures of the affected joint can be obtained during imaging tests. Examples include:

X-rays: An X-ray may also show bone spurs around a joint. Many people have X-ray evidence of osteoarthritis before they experience any symptoms.

Magnetic resonance imaging (MRI): MRI can be helpful in determining what exactly is causing pain.

Lab tests: Analyzing blood or joint fluid can help to pinpoint the diagnosis.

Blood tests: Blood tests may help to rule out other causes of joint pain, such as rheumatoid arthritis.

Joint fluid analysis: Draw fluid out of the affected joint for inflammation and pain is caused by gout or an infection.

Treatments and Drugs

There is no known cure for osteoarthritis, but treatments can help to reduce pain and maintain joint movement.

Medications: Osteoarthritis symptoms can be relieved by a variety of medications, including:

Acetaminophen: Acetaminophen can relieve pain, but it does not reduce inflammation.

NSAIDs: NSAIDs may reduce inflammation and relieve pain. NSAIDs include Ibuprofen, Indomethacin, Diclofenac sodium, Aceclofenac and Naproxen.

Narcotics: Narcotics like codeine and may provide relief from more severe osteoarthritis pain.

Lifestyle and home remedies: Lifestyle changes and home treatments also can help to reduce osteoarthritis symptoms.

Rest: Experiencing pain or inflammation in joint, rest it for 12 to 24 hours.

Exercise: Exercise can increase endurance and strengthen the muscles around joint, making joint more stable.

Lose weight: Being overweight or obese increases the stress on weight-bearing joints, such as knees and hips. Even a small amount of weight loss can relieve some pressure and reduce pain.

Use heat and cold to manage pain: Both heat and cold can relieve pain in joint. Heat also relieves stiffness, and cold can relieve muscle spasms and pain.

Table 12.2 : Difference between RA and OA

Rheumatoid arthritis (RA)	Osteoarthritis (OA)
• Inflammatory.	• Degenerative.
• Symmetric involvement of small joints first.	• Asymmetric involvement of large joint first.
• Polyarticular.	• Generally monoarticular.
• Other visceral organs also affected.	• Not affected.
• Erosion of adjacent bony surface.	• Sclerosis of adjacent bony surface with osteophyte formation.
• Morning stiffness > 1hr.	• Morning stiffness < 1hr.

12.4 OSTEOPOROSIS

Osteoporosis is a condition that weakens bones, making them fragile and more likely to break (Latin "porous bones"). The inside of a healthy bone has small spaces, like a honeycomb. Osteoporosis increases the size of these spaces, causing the bone to lose strength and density. In addition, the outside of the bone grows weaker and thinner. Osteoporosis can occur in people of any age, but it is more common in older adults, especially women. People with osteoporosis are at a high risk of fractures, or bone breaks, while doing routine activities such as standing or walking.

The most common injuries in people with osteoporosis are:

- Wrist fractures
- Hip fractures
- Fractures of the spinal bones (vertebrae)

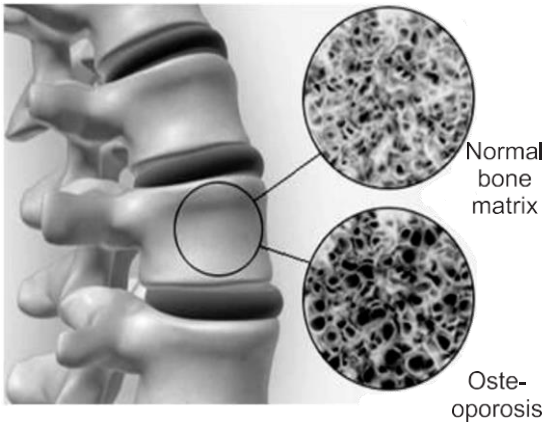

Fig. 12.6 : Normal and Osteoporosis bone

Causes

Losing bone is a normal part of the ageing process, but some people lose bone density much faster than normal. This can lead to osteoporosis and an increased risk of fractures.

Women also lose bone rapidly in the first few years after the menopause. Women are more at risk of osteoporosis than men, particularly if the menopause begins early (before the age of 45).

Many other factors can also increase the risk of developing osteoporosis, including:

- Long-term use of high-dose oral corticosteroids.
- Other medical conditions – such as inflammatory conditions, hormone-related conditions, or malabsorption problems.
- Family history of osteoporosis – particularly history of a hip fracture in a parent.
- Long-term use of certain medications which can affect bone strength or hormone levels.
- Low body mass index (BMI).
- Heavy drinking and smoking.
- Being female.
- Being an older adult.
- Poor nutrition.
- Physical inactivity.
- Small-boned frame.

Osteoporosis occurs when there is an imbalance between new bone formation and old bone resorption. The body may fail to form enough new bones, or too much old bones may be reabsorbed, or both. Two essential minerals for normal bone formation are calcium and phosphate. Throughout youth, the body uses these minerals to produce bones. Calcium is essential for proper functioning of the heart, brain, and other organs. To keep those critical organs functioning, the body reabsorbs calcium that is stored in the bones to maintain blood calcium levels. If calcium intake is not sufficient or if the body does not absorb enough calcium from the diet, bone production and bone tissue may suffer. Thus, the bones may become weaker, resulting in fragile and brittle bones that can break easily.

Usually, the loss of bone occurs over an extended period of years. Often, a person will sustain a fracture before becoming aware that the disease is present. By then, the disease may be in its advanced stages and damage may be serious.

The leading cause of osteoporosis is a lack of certain hormones, particularly estrogen in women and androgen in men. Women, especially those older than 60 years

of age, are frequently diagnosed with the disease. Menopause is accompanied by lower estrogen levels and increases a woman's risk for osteoporosis. Other factors that may contribute to bone loss in this age group include inadequate intake of calcium and vitamin D, lack of weight-bearing exercise, and other age-related changes in endocrine functions (in addition to lack of estrogen).

Other conditions that may lead to osteoporosis include overuse of corticosteroids (Cushing syndrome), thyroid problem, lack of muscle use, bone cancer, certain genetic disorders, use of certain medications, and problems such as low calcium in the diet.

Symptoms

Early in the course of the disease, osteoporosis may cause no symptoms or warning signs. Later, it may cause height loss or dull pain in the bones or muscles, particularly low back pain or neck pain.

If symptoms do appear, some of the earlier ones may include:

- Receding gums
- Weakened grip strength
- Weak and brittle nails

Severe Osteoporosis

Later in the course of the disease, sharp pains may come on suddenly. The pain may not radiate (spread to other areas); it may be made worse by activity that puts weight on the area, may be accompanied by tenderness, and generally begins to subside in one week. Pain may linger more than three months.

People with osteoporosis may not even recall a fall or other trauma that might cause a broken bone, such as in the spine or foot. Spinal compression fractures may result in loss of height with a stooped posture (called a dowager's hump).

Fractures at other sites, commonly the hip or bones of the wrist, usually result from a fall.

Diagnosis

- Diagnosis of osteoporesis begins with a careful family history of osteoporosis or a history of previous broken bones.
- Blood tests are used to measure calcium, phosphorus, vitamin D, testosterone, and thyroid and kidney function.
- Based on a medical examination, a specialized test called a bone mineral density test that can measure bone density in various sites of the body. The diagnosis of osteoporosis or osteopenia can be made based on the results of these tests. A bone mineral density test can detect osteoporosis before a fracture occurs and can predict future fractures. A bone mineral density test can also monitor the effects of treatment if the tests are performed a year or more apart and may help determine the rate of bone loss.
- The DXA (dual-energy X-ray absorptiometry) measures the bone density of the spine, hip, or total body.
- SXA (single-energy X-ray absorptiometry) is performed with a smaller X-ray machine that measure bone density at the heel, shinbone, and kneecap.

Treatment

There is no cure for osteoporosis, but proper treatment can help to protect and

strengthen bones. These treatments can help slow the breakdown of bone in body, and some treatments can spur the growth of new bone. The lifestyle changes can include increasing intake of calcium and vitamin D, as well as getting appropriate exercise.

- Diet: Young adults should be encouraged to achieve normal peak bone mass by getting enough calcium (1,000 mg daily) in their diet (drinking milk or calcium-fortified orange juice and eating foods high in calcium such as salmon), performing weight-bearing exercise such as walking or aerobics (swimming is aerobic but not weight-bearing), and maintaining normal body weight.
- Exercise: Lifestyle modification should also be incorporated into treatment. Regular exercise can reduce the likelihood of bone fractures associated with osteoporosis.

Medications

The most common drugs used to treat osteoporosis are called bisphosphonates which are used to prevent the loss of bone mass. They may be taken orally or by injection include:

- Alendronate
- Ibandronate
- Zoledronic acid

Other medications may be used to prevent bone loss or stimulate bone growth. They include:

- Testosterone: In men testosterone therapy may help to increase bone density.
- Hormone therapy: For women, estrogen used during and after menopause can help to stop bone density loss.
- Raloxifene: This medication has been found to provide the benefits of estrogen without many of the risks, although there is still an increased risk of blood clots.
- Denosumab: This drug is taken by injection and may prove even more promising than bisphosphonates at reducing bone loss.
- Teriparatide: This drug is also taken by injection and stimulates bone growth.
- Calcitonin salmon: This drug is taken as a nasal spray and reduces bone reabsorption.

12.5 GOUT

Gout is a metabolic disorder characterized by elevated serum uric acid levels and deposits of urate crystals in synovial fluids and surrounding tissues in joints. It is a type of arthritis that is characterized by sudden, severe attacks of joint pain with redness, warmth, and swelling in the affected area. It usually attacks only one joint at a time. It most often strikes the joint of the big toe, where it is also known as podagra, but other toes can also be involved.

Epidemiology

Gout affects around 1–2% of the Western population at some point in their lifetimes, and is becoming more common. Rates of gout have approximately doubled between 1990 and 2010. This rise is believed due to increasing life expectancy, changes in diet, and an increase in diseases associated

with gout, such as metabolic syndrome and high blood pressure. A number of factors have been found to influence rates of gout, including age, race, and the season of the year. In men over the age of 30 and women over the age of 50, prevalence is 2%.

Some studies have found that attacks of gout occur more frequently in the spring. This has been attributed to seasonal changes in diet, alcohol consumption, physical activity and temperature.

Causes

Gout is caused initially by an excess of uric acid in the blood (hyperuricemia). Uric acid is produced in the body through the breakdown of purines specific chemical compounds that are found in certain foods such as meat, poultry and seafood.

Normally, uric acid dissolves in the blood and is excreted from the body in urine via the kidneys. If too much uric acid is produced or not enough is excreted then it can build up and form the needle-like crystals that cause inflammation and pain in the joints and surrounding tissue.

There are a number of factors that can increase the likelihood of hyperuricemia, and therefore gout:

Age and gender: Men produce more uric acid than women. But after menopause, the uric acid level in women is equal to men.

Genetics: A family history of gout increases the likelihood of the condition developing.

Lifestyle Factors: Alcohol consumption interferes with the removal of uric acid from the body. Eating a high-purine diet also increases the amount of uric acid in the body.

Lead exposure: Chronic lead exposure has been linked in some cases to gout.

Medications: Certain medications can increase the levels of uric acid in the body, such as diuretics and drugs containing salicylate, Niacin etc.

Weight: Being overweight increases the risk as there is more tissue in the body for turnover or breakdown, leading to the production of excess uric acid.

Other health problems: If the kidneys are unable to eliminate waste products adequately (renal insufficiency) then uric acid levels can remain high. Other conditions that can contribute are high blood pressure (hypertension), diabetes and hypothyroidism.

People with Kelley-Seegmiller syndrome or Lesch-Nyhan syndrome have a partial or complete deficiency in an enzyme that helps to control uric acid levels.

Pathophysiology

Gout is a disorder of purine metabolism, and occurs when its final metabolite, uric acid, crystallizes in the form of monosodium urate, precipitating in joints, on tendons, and in the surrounding tissues. These crystals then trigger a local immune-mediated inflammatory reaction, with one of the key proteins in the inflammatory cascade being interleukin. An evolutionary loss of uricase, which breaks down uric acid, in humans and higher primates has made this condition common.

The triggers for precipitation of uric acid are not well understood. While it may crystallize at normal levels, it is more likely to do so as levels increase. Other factors believed important in triggering an acute

episode of arthritis include cool temperature, rapid changes in uric acid levels, acidosis, articular hydration and extracellular matrix proteins such as proteoglycans, collagens and chondroitin sulfate.

Rapid changes in uric acid may occur due to a number of factors, including trauma, surgery, chemotherapy, diuretics, and stopping or starting allopurinol. Calcium channel blockers are associated with a lower risk of gout as compared to other medications for hypertension.

Clinical Manifestations

The signs and symptoms of gout are almost always acute, occurring suddenly often at night and without warning.

Intense joint pain: Gout usually affects the large joint of big toe, but it can occur in feet, ankles, knees, hands and wrists. The pain is likely to be most severe within the first 12 to 24 hours after it begins.

Lingering discomfort: After the most severe pain subsides, some joint discomfort may last from a few days to a few weeks. Later attacks are likely to last longer and affect more joints.

Inflammation and redness: The affected joint or joints become swollen, tender and red.

Complications

People with gout can develop more-severe conditions, such as:

Recurrent gout: Some people may never experience gout signs and symptoms again. But others may experience gout several times each year. Medications may help prevent gout attacks in people with recurrent gout.

Advanced gout: Untreated gout may cause deposits of urate crystals to form under the skin in nodules called tophi. Tophi can develop in several areas such as fingers, hands, feet, elbows or achilles tendons along the back of ankle. Tophi usually are not painful, but they can become swollen and tender during gout attacks.

Kidney stones: Urate crystals may collect in the urinary tract of people with gout, causing kidney stones.

Symptoms

Symptoms of gout include sever pain, bone erosion, redness and swelling in joints, often the big toe.

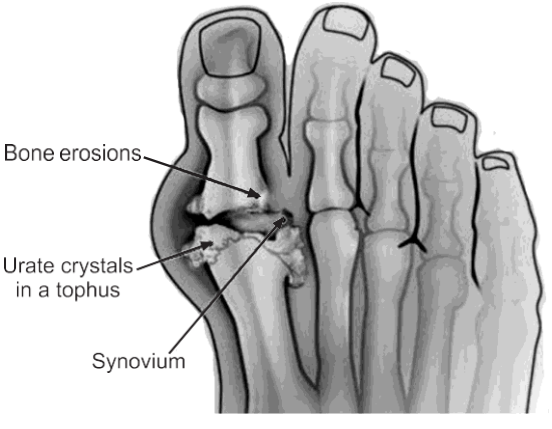

Fig. 12.7 : Gout

Diagnosis

Joint fluid test: Joint fluid test (arthrocentesis) is useful to see whether uric acid crystals are present. This is the only test for diagnosis of gout.

Blood test: To measure the uric acid level in blood. Blood test results can be misleading, though some people have high uric acid levels, but never experience gout.

And some people have signs and symptoms of gout, but do not have unusual levels of uric acid in their blood.

Urine Test: A test to measure levels of uric acid in urine.

X-ray: X-rays of extremities (hands and feet) are sometimes useful in the late stages of the disease; X-rays are not usually helpful in the early diagnosis. Pain often causes people to seek medical attention before any long-term changes can be seen on an X-ray. But X-rays may help to rule out other causes of arthritis.

Treatment

The goals of treatment for gout are fast pain relief and prevention of future gout attacks and long-term complications, such as joint destruction and kidney damage.

NSAIDs: NSAIDs may control inflammation and pain in people with gout. NSAIDs include indomethacin, ibuprofen, naproxen, and etoricoxib.

Colchicine: A type of pain reliever that effectively reduces gout pain, especially when started soon after symptoms appears.

Corticosteroids: Corticosteroid medications, such as the drug prednisone, may control gout inflammation and pain. Corticosteroids may be administered in pill form, or they can be injected into joint. Corticosteroids are generally reserved for people who cannot take either NSAIDs or colchicine.

Medications that block uric acid production: Xanthine oxidase inhibitors, including allopurinol and febuxostat, limit the amount of uric acid that body makes. This may lower blood's uric acid level and reduce risk of gout. Side effects of allopurinol include a rash and low blood counts. Febuxostat side effects include rash, nausea and reduced liver function.

If gout symptoms have occurred OFF and ON without treatment for more than 10 years, uric acid crystals may have built up in the joints to form gritty, chalky nodules called tophi. If tophi are causing infection, pain, pressure, and deformed joints, treatment includes: Xanthine oxidase inhibitors, which may shrink the tophi until they disappear.

Medication that improves uric acid removal: Probenecid improves kidney's ability to remove uric acid from body. This may lower uric acid levels and reduce risk of gout, but the level of uric acid in urine is increased.

Pegloticase: This medicine is for gout that has lasted a long time and has not responded to other treatment.

Prevention

During symptom free periods, these dietary guidelines may help protect against future gout attacks.

Drink 8 to 16 cups (about 2 to 4 litres) of fluid each day, with at least half being water.

Eat a moderate amount of protein, preferably from healthy sources, such as low-fat or fat-free dairy, eggs, and nut butters.

Limit daily intake of meat, fish and poultry to 4 to 6 ounces (113 to 170 grams). Maintain a desirable body weight.

Table 12.3 : Common forms of crystal-induced arthritis

Disorder	Etiology	Clinical features	Treatment
Gout (gouty arthritis)	Deposition of monosodium urate crystals, usually associated with hyperuricemia in males.	Typically affects one joint (big toe); intermittent flare ups occur suddenly, often at night; raised lesions (tophi) may develop after many years.	NSAIDs for acute attacks; urate lowering drugs; low purine diet.
Pseudogout (CPPD disease)	Deposition of calcium pyrophosphate dihydrate (CPPD) crystals; usually associated with aging; metabolic diseases; and previous joint trauma.	Typically affects knees, wrists, or hands.	NSAIDs for acute attacks; management of underlying disease.
Hydroxyapatite-associated arthritis	Deposition of calcium hydroxyapatite, a normal crystalline component of bone; may be associated with calcium or phosphate imbalance, as in renal failure; also seen in some connective tissue disorders'and after tissue injury or corticosteroid injections.	Usually causes inflammation of tendons or bursae, but may affect joints of shoulders, hips, elbows, wrists, and digits; may be asymptomatic.	NSAIDs; surgical aspiration.

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Chapter...13

PRINCIPLES OF CANCER

13.1 INTRODUCTION

When cells in some area of body duplicate without control, the excess of tissue that develops called tumor or neoplasm. The growth of neoplastic cells exceeds and is not co-ordinated with that of the normal tissues around it. The growth persists in the same excessive manner even after cessation of the stimuli. Tumors may be cancerous and sometime fatal or they may be quite harmless. A cancerous growth is called as malignant tumor or malignancy and noncancerous growth is called as benign growth. The study of tumor is called oncology.

13.1.1 Epidemiology

With the exception rare cases, cancer may be caused by inherited genetic defects and certain viruses. Specific cause is unknown. Several risk factors are associated with development of cancer.

All types of cancers are common, in that, the cancer cells are abnormal and multiply out of control. However, there are often great differences between different types of cancer. For example:

- Some grow and spread more quickly than others.
- Some are easier to treat than others, particularly if diagnosed at an early stage.
- Some respond much better than others to chemotherapy, radiotherapy, or other treatments.
- Some have a better outlook (prognosis) than others. For some types of cancer there is a very good chance of being cured. For some types of cancer the outlook is poor.

The incidence of cancer and cancer types are influenced by many factors such as age, sex, race, local environmental factors, diet, and genetics.

Table 13.1 : Risk factor and associated cancer

Risk factor	Associated cancer
Male	Prostate, bladder, liver, testicle
Female	Breast, cervix, ovary, endometrium
Infection (STD)	Cervix, bladder
Hepatitis B	Liver
HIV	Connective tissue

Contd...

Drug and hormone therapy	Bladder, skin, endometrium, breast, vagina
Reproductive history	Breast, ovary, endometrium
Family history	Breast, colon, lung, testicle, skin
Diet	Breast, colon, prostate
Obesity	Colon, endometrium
Cigarette smoking	Lung, bladder, mouth
Alcohol abuse	Breast, mouth, liver
Occupational exposure to carcinogen	Bladder, liver, lung, skin
Air pollution	Lung
Radiation (sunlight)	Skin

13.2 CLASSIFICATION OF CANCER

[I] Classification by Site of Origin

By primary site of origin, cancers may be of specific types like

- Breast cancer
- Lung cancer
- Prostate cancer
- Liver cancer
- Renal cell carcinoma (kidney cancer),
- Oral cancer
- Brain cancer etc.

[II] Classification by Tissue Types

Based on tissue types cancers may be classified into six major categories:

1. Carcinoma: This type of cancer originates from the epithelial layer of cells that form the lining of external parts of the body or the internal linings of organs within the body.

Carcinomas, malignancies of epithelial tissue, account for 80 to 90 % of all cancer cases since epithelial tissues are most abundantly found in the body from being present in the skin to the covering and lining of organs and internal passageways, such as the gastrointestinal tract. Carcinomas usually affect organs or glands capable of secretion including breast, lungs, bladder, colon and prostate.

2. Sarcoma: These cancers originate in connective and supportive tissues including muscles, bones, cartilage and fat. Bone cancer is one of the sarcomas termed as osteosarcoma. It affects the young most commonly. Sarcomas appear like the tissue in which they grow.

Other examples include Chondrosarcoma (of the cartilage), Leiomyosarcoma (smooth muscles), Rhabdomyosarcoma (skeletal muscles), Mesothelial sarcoma or mesothelioma (membranous lining of body cavities), Fibrosarcoma (fibrous tissue), Angiosarcoma or hemangioendothelioma (blood vessels), Liposarcoma (adipose or fatty tissue), Glioma or astrocytoma (neurogenic connective tissue found in the brain), Myxosarcoma (primitive embryonic connective tissue) and Mesenchymous or mixed mesodermal tumor (mixed connective tissue types).

3. Myeloma: These originate in the plasma cells of bone marrow. Plasma cells

are capable of producing various antibodies in response to infections. Myeloma is a type of blood cancer.

4. Leukemia: This group of cancers are grouped within blood cancers. These cancers affect the bone marrow which is the site for blood cell production. When cancerous, the bone marrow begins to produce excessive immature white blood cells that fail to perform their usual actions and the patient is often prone to infection.

Types of leukemia include:

- Acute myelocytic leukemia (AML)
- Chronic myelocytic leukemia (CML)
- Acute lymphatic, lymphocytic, or lymphoblastic leukemia (ALL)
- Chronic lymphatic, lymphocytic, or lymphoblastic leukemia (CLL)
- Polycythemia vera or erythremia

5. Lymphoma: These are cancers of the lymphatic system. Unlike the leukemias, which affect the blood and are called "liquid cancers", lymphomas are "solid cancers". These may affect lymph nodes at specific sites like stomach, brain, intestines etc. These lymphomas are referred to as extranodal lymphomas.

Lymphomas may be of two types – Hodgkin's lymphoma and Non-Hodgkin's lymphomas. In Hodgkin lymphoma there is characteristic presence of Reed-Sternberg cells in the tissue samples which are not present in Non-Hodgkin lymphoma.

6. Mixed types: These have two or more components of the cancer. Some of the examples include mixed mesodermal tumor, carcinosarcoma, adenosquamous carcinoma and teratocarcinoma. Blastomas are another type that involves embryonic tissues.

Central nervous system cancers: Cancers that begin in brain tissue or the spinal cord are known as central nervous system cancers. Primary brain tumors develop in the brain. If the tumor began in another part of the body but spread to the brain, it is called a secondary brain tumor or brain metastases. The most common type of brain tumour develops from glial cells and is called glioma.

[III] Classification by Grade

Cancers can also be classified according to grade. The abnormality of the cells with respect to surrounding normal tissues determines the grade of the cancer. Increasing abnormality increases the grade, from 1–4.

Cells that are well differentiated closely resemble normal specialized cells and belong to low grade tumors. Cells that are undifferentiated are highly abnormal with respect to surrounding tissues. These are high grade tumors.

- Grade 1: Well differentiated cells with slight abnormality.
- Grade 2: Cells are moderately differentiated and slightly more abnormal.
- Grade 3: Cells are poorly differentiated and very abnormal.
- Grade 4: Cells are immature and primitive and undifferentiated.

Types of Staging

Staging is done when a person is first diagnosed, before any treatment is given. The main types of staging are:

Clinical staging: This is an estimate of the extent of the cancer based on results of physical exams, imaging tests (x-rays, CT scans etc.), and tumor biopsies. For some cancers, the results of other tests, such as blood tests, are also used in staging.

The clinical stage is a key part of deciding the best treatment to use. It is also the baseline used for comparison when looking at how the cancer responds to treatment.

Pathologic staging: If surgery is being done, surgeon can also determine the pathologic stage (also called the surgical stage) of the cancer. The pathologic stage relies on the results of the exams and tests mentioned before, as well as what is learned about the cancer during surgery. Often this is surgery to remove the cancer and nearby lymph nodes, but sometimes surgery may be done to just look at how much cancer is in the body and take out tissue samples.

Classification by Stage

Cancer staging consists of determining the level of severity of the disease by means of clinical and complementary diagnostic tests. The aim is to detect the presence of visible metastases.

The most commonly used method uses classification in terms of tumor size (T), the degree of regional spread or node involvement (N), and distant metastasis (M). This is called the TNM staging.

The TNM staging system for solid tumors was developed by the Union for International Cancer Control (UICC) most commonly used in oncology.

- T stands for the original (primary) tumor.
- N stands for nodes. It tells whether the cancer has spread to the nearby lymph nodes.
- M stands for metastasis. It tells whether the cancer has spread to distant parts of the body.

The following chart illustrates the different types of cancer according to the tissue in which they originated.

Table 13.2 : Different types of cancer according to the tissue origin

Main types of cancer	Tissue of origin of tumour	Frequency (estimate)	Locations
Adenocarcinoma	Epithelium (gland surface tissue)	85% of all cancers	Breast, liver, kidneys, prostate, ovaries, thyroid, colon, stomach, salivary gland, lungs etc.
Squamous cell carcinoma	Squamous epithelial cell (skin, mucous membranes, skin)	85% of all cancers	Skin, gastrointestinal tract, lungs, head and neck (larynx, pharynx, oral cavity), cervix etc.
Sarcoma	Supporting or musculoskeletal tissue (bone, muscle, connective and fatty tissue etc.)	2% of all cancers	Bone, cartilage, fatty tissue, vessels etc.

Contd...

Hodgkin lymphoma	B or T lymphocytes, cancer characterized by the presence of large, atypical cells	5-7% of all cancers	Lymph nodes, spleen
Non-Hodgkin lymphoma	B or T lymphocytes	5-7% of all cancers	Lymph nodes, gastrointestinal tract, skin, brain, bones, genitals, lungs etc.
Leukemia	Bone marrow cells (blasts)	4% of all cancers	Blood
Myeloma	Bone marrow cells (plasma cells)	4% of all cancers	Bone marrow

When a malignant tumour has the same name as a benign tumour, the word carcinoma or sarcoma is added to the end of the name to specify that it is cancerous. There are exceptions: lymphoma and melanoma are always cancerous; the word "malignant" is often added to them.

Table 13.3 : Typical characteristics of benign Vs malignant tumors

Benign tumor	Malignant tumor
Mobile mass.	Fixed or ulcerating mass.
Smooth and round with a surrounding fibrous capsule.	Irregular shaped with no capsule.
Cells multiply slowly.	Cells multiply rapidly.
Histopathologically similar to tissue of origin.	Different histopathology.
Tumor grows by expanding and pushing away and against surrounding tissue.	Tumor grows by invading and destroying surrounding tissue.
Mass is mobile.	Mass is fixed.
Not attached to surrounding tissue.	Attached to surrounding tissue and deeply fixed in surrounding tissue.
Never spread to other sites.	Almost always spreads to other sites if not removed or destroyed.
Normal nuclei.	Abnormally large, numerous and intensely staining nuclei.
Easier to remove and does not recur after excision.	Difficult to remove and recurs after excision.

Neoplastic Cell Characteristics

- Uncontrolled proliferation
- Dedifferentiation and loss of function
- Invasiveness
- Metastasis.

Uncontrolled proliferation: Normal cell division and tissue growth occurs by regulatory processes but proliferation of cancer cell is not controlled by these processes and leads to uncontrolled proliferation which varies from type to type. Some cells slowly multiply and few fast multiply.

Dedifferentiation and loss of function: The multiplication of normal cells in a tissue begins with division of the undifferentiated stem cells giving rise to daughter cells. These daughter cells eventually differentiate to become the mature cells of the relevant tissue by achieving specific and characteristic physical forms, physiologic functions and chemical properties and ready to perform their programmed functions. One of the main characteristics of cancer cells is that they dedifferentiate to varying degrees. In general, poorly differentiated cancers multiply faster and carry a worse prognosis than well differentiated cancers.

Invasiveness: Change in factor that regulate cell adhesion and motility (process of invading responsible for rapid spread of cancer to secondary site, marked by a tendency to spread especially into healthy tissue; "invasive cancer cells").

Metastasis: Migration of primary tumors to another site through blood vessels or lymphatics results in formation of secondary tumor.

The Genesis of A Cancer Cell

A normal cell turns into a cancer cell because of one or more mutations in its DNA, which can be inherited or acquired, usually through exposure to viruses or carcinogens (e.g. tobacco products, asbestos).

However, carcinogenesis is a complex multistage process, usually involving more than one genetic change as well as other epigenetic factors (hormonal, co-carcinogen and tumour promoter effects, etc.) that do not themselves produce cancer but which increase the likelihood that the genetic mutation(s) will eventually result in cancer.

There are two main categories of genetic change that are important:

1. Activation of proto-oncogenes to oncogenes: Proto-oncogenes are genes that normally control cell division, apoptosis and differentiation, but it can be converted to oncogenes that induce malignant change by viral or carcinogen action.

2. Inactivation of tumor suppressor genes: Normal cells contain genes that have the ability to suppress malignant change termed as tumor suppressor genes (antioncogenes) and mutations of these genes are involved in many different cancers. The loss of function of tumor suppressor genes can be the critical event in carcinogenesis.

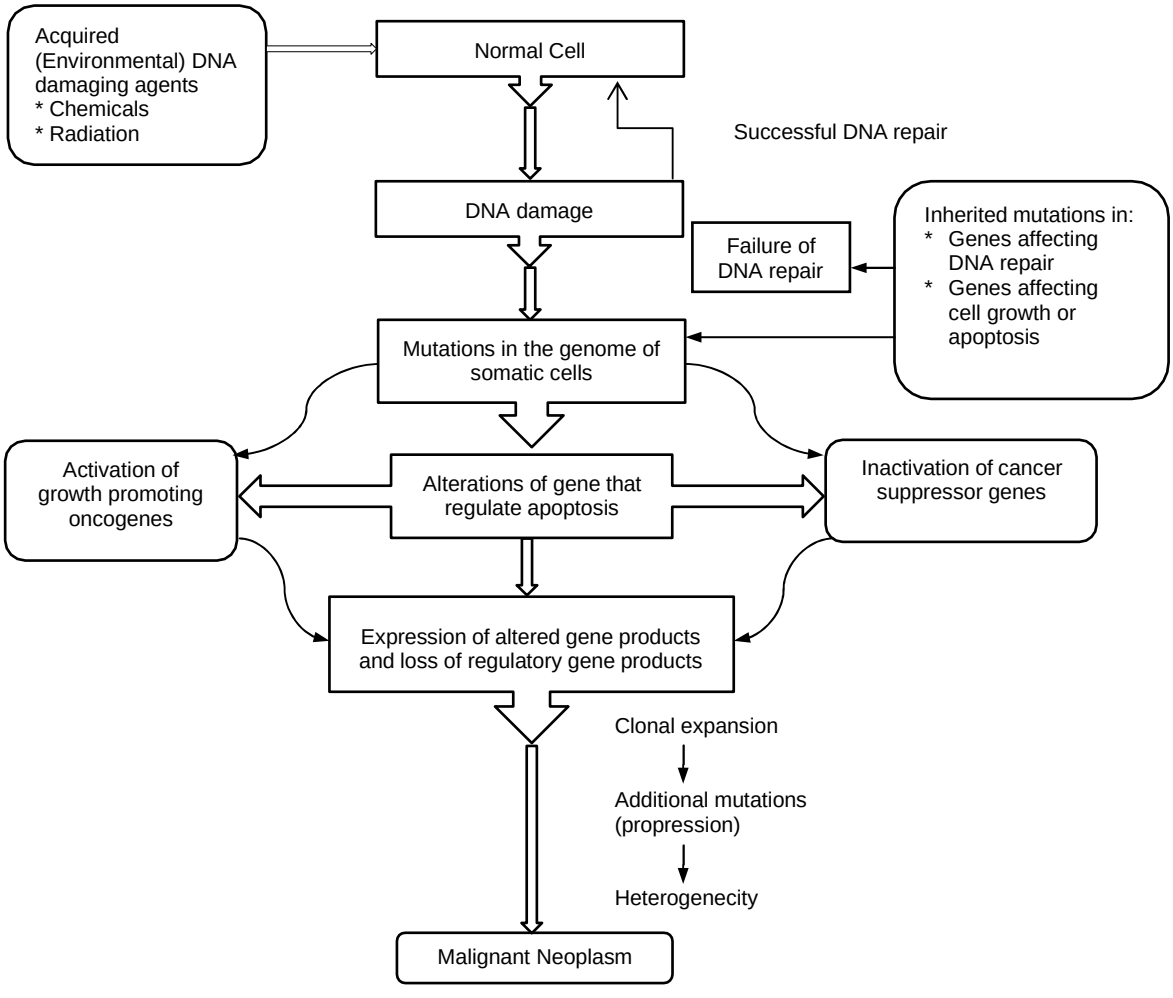

Fig. 13.1 : Mechanism of carcinogenesis

Phases of Carcinogenesis

Cancer cells develop from normal cells in a complex process consisting of four phases of transformation. These four phases convert normal cell to highly malignant cell.

13.3 ETIOLOGY

Cancer is caused by changes (mutations) to the DNA within cells. While the underlying causes for tumor growth can vary, the process by which they grow is the same. Normally, cells in body will naturally refresh themselves by dividing. This allows for dead cells to be disposed off naturally. In the case of tumors, dead cells may remain behind and form a growth known as a tumor. Cancer cells grow in this way as well; however, unlike the cells in benign tumors, they also invade nearby tissue. Out of control growth of abnormal cells causes damage to these adjacent tissues and organs, and can lead to cancerous tumors in other parts of the body.

Some cancer causes remain unknown while other cancers may develop from more than one known cause. Some may be developmentally influenced by a person's

genetic makeup. Many patients develop cancer due to a combination of these factors.

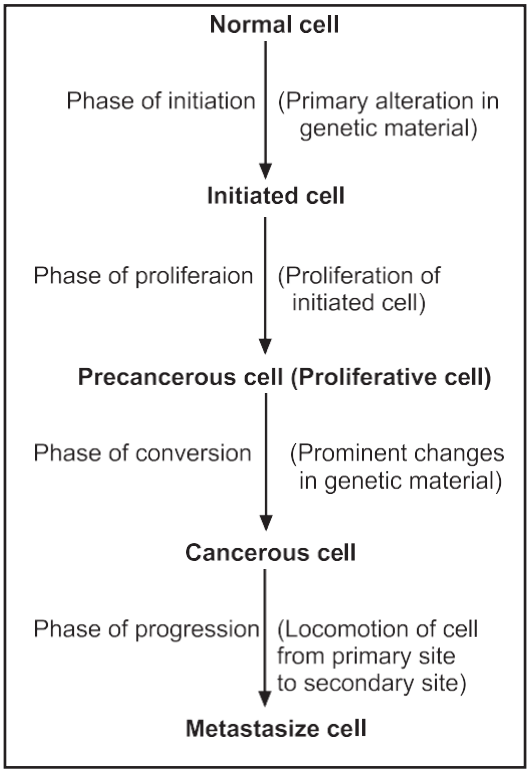

Fig. 13.2 : Phases of carcinogenesis

Host factor: Host factors are intrinsic to individual patient and include age, sex, genetic factor, psychological factor, immune suppression and chronic tissue trauma. Few cancers found in children commonly originate from embryonic tissues. In general, overall incidences increases with increase in age and are higher in man than women, may be due to lifestyle factors rather than biological differences is susceptibility. Some cancers, such as breast, endometrial and prostate cancers are hormonally influenced. The exact mechanism is unknown but certain psychological factors such as stress or depression increases the risk of cancer development. An increased risk of cancer has been demonstrated in patients with AIDS and those on immunosuppressive drugs, strongly suggesting a role for immunosupression in the process of cancer development.

Environmental and life style factor: Environmental and life style factors include geographic location, cigarette smoking, nutrition and occupation. Certain cancers are more prevalent in some geographic locations. The risk of developing certain cancers is increased by obesity, lack of regular exercise, drinking too much alcohol, smoking and eating a lot of red meat. Cigarette smoking greatly increases risk of lung cancer. About 9 out of 10 people who develop lung cancer are smokers.

A carcinogen is something (chemical, radiation etc.) which can damage a cell and make it more likely to turn into a cancerous cell. The more the exposure to a carcinogen, the greater the risk of cancer development.

Infection: Some germs (viruses and bacteria) are associated to certain cancers. hepatitis B and hepatitis C virus is usually related to hepatocellular carcinoma and have an increased risk of developing cancer of liver. Another example is the link between human papillomavirus (HPV) and cervical cancer. Most women who develop cervical cancer have been infected with a strain of HPV at some point in their life. The relative risk of Kaposi's sarcoma occurs in patient with HIV infection. The Epstein Barr virus (EBV) is associated with Burkitt's lymphoma and nasopharangeal carcinoma. Hodgkin's disease is also believed to be a viral origin. Another example is, *Helicobactor pylori* is linked to stomach cancer.

Radiation: Exposure to radioactive materials and nuclear fallout can increase the risk of leukemia and other cancers. Too

much sun exposure and sunburn (radiation from UVA and UVB) increase risk of developing skin cancer.

Genetic factors: Genetic mutation is inherited from parents. This type of mutation accounts for a small percentage of cancers. Most gene mutations occur after birth and are not inherited. A number of forces can cause gene mutations, such as smoking, radiation, viruses, cancer causing chemicals (carcinogens), obesity, hormones, chronic inflammation and a lack of exercise.

Obscure defects: Racial predilections (American women have breast cancer more often than Japanese women; Japanese men have stomach cancer far more often than American men). However, genetic factors are less conspicuous and more difficult to identify. There is probably a complex inter-relationship between heredity, susceptibility and environmental carcinogenic stimuli in the causation of a number of cancers.

Age: Older persons have a greater tendency to develop neoplasm from lack of effective control mechanisms. This is due to an accumulation of damage to cells over time. Also, body's defenses and resistance against abnormal cells may become less good as become older. For example, the ability to repair damaged cells and immune systems which may destroy abnormal cell may become less efficient with age.

13.4 PATHOPHYSIOLOGY

Local Growth and Loss of Differentiation:

The rate of local tumor growth is dependent on cell cycle time and rate of angiogenesis or development of blood vessels within the tumor. Epithelial cell origin tumors have shorter cell cycle and grow rapidly than connective tissue origin. Tumor cannot enlarge beyond 1 or 2 mm in diameter, however, unless it develops its own blood supply. Angiogenic cytokines that promote vessel growth are apparently secreted by tumor cells as well as by inflammatory cells, such as macrophages, which infiltrate the area.

Initially the cells within the malignant tumor are monoclonal or identical daughter cells of the originally mutated cells. By the time such tumors are clinically detectable, however, they have accumulated additional genetic damage. This finding is attributed to the increased risk of random mutation in cells that are dividing rapidly. Each generation of tumor cells thus becomes more poorly differentiated, bearing less resemblance in structure and function to the cell of origin.

Invasion and Metastasis:

Cancers typically invade tissues adjacent to the site of origin (primary site) and may metastasize to distant (secondary or metastatic) sites by mechanical or lymphatic or haematogenous (blood-born) spread.

Tumor cells within a body cavity may fall, by gravity, to lower points, establishing metastatic tumors. During surgery, manipulation of tumors may free some cells within cavities and facilitate its spread. More commonly, however, tumor cells travel in the blood stream or lymphatic system after invasion into these channels. Cancer cells cannot metastasize unless they first separate from cells at the site of origin, invade a lymphatic or blood vessel and attach to tissues at secondary sites.

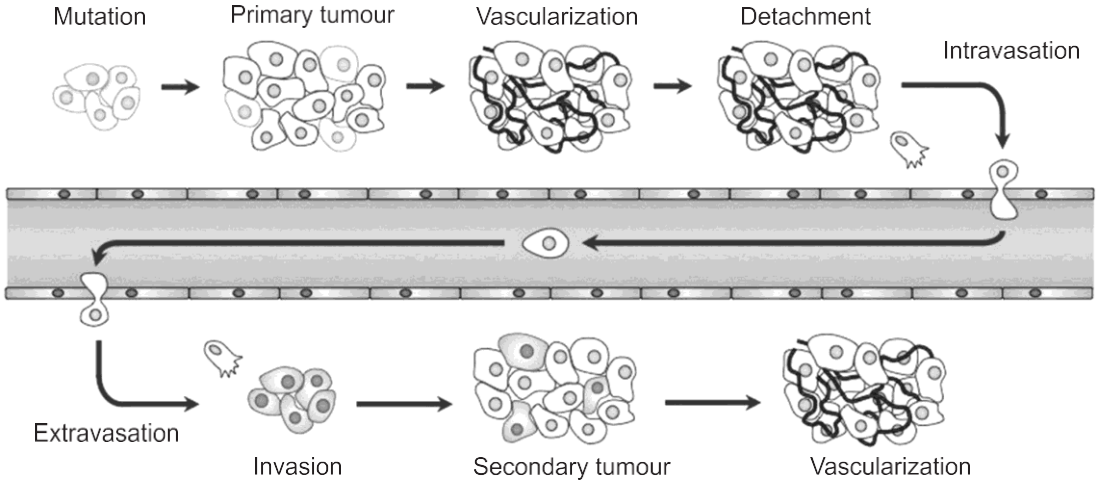

Fig. 13.3 : Pathogenesis of cancer

Generally cells are held together in tissues by adhesion molecules (cadherins) is an important means of intercellular signaling. Cells that become detached are normally destroyed by apoptosis. During the process of neoplastic transformation, cancer cells may lose the ability to express these molecules, promoting detachment; other genetic alteration permits survival in the detached state.

Once detached, cancer cells must breach natural barriers before entering blood or lymphatic vessels. These barriers are the basement membranes of the tissue of origin and the vessel and the extracellular matrix between. Cancer cells, like white blood vessel accomplish this invasion by releasing proteolytic enzymes that break down the tissue barriers. Although normal cells contain enzyme-inhibitor system, these may be overcome, permitting local extension of the tumor and asses into the blood and lymph.

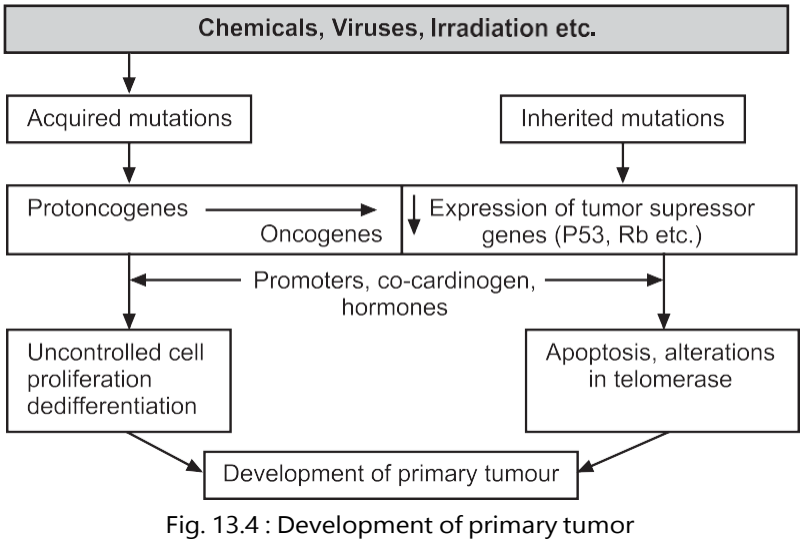

Fig. 13.4 : Development of primary tumor

Metastasis is not inevitable once the cancer cells are in the blood or lymph. In some cases, the cells undergo apoptosis once entering these fluids. Tumor cells may be filtered out of lymph at lymph nodes, or out of blood in the spleen. Immune cells may then destroy the tumor cells at these locations. Metastatic tumors may also form at these sites or within downstream capillaries, where tumor cells become trapped because of the small vessel size.

Attachment and proliferation of cancer cells at metastatic sites depend on several factors. Usually, cancer cells in blood become trapped within the first capillary bed downstream of their point of entry into the circulation. Blood leaving most organs first enters the capillary beds of the lungs, the most common site of metastasis. Blood from the intestine first encounter the capillary beds of the liver, and this is the second most common metastatic site. Cancer metastasis cannot always be predicted on this basis. However, some cancers appear to prefer metastatic site other than those immediately downstream in the blood or lymphatics. Prostate cancer can spread to any part of the body, but most commonly to the bones. The reason for this selectivity apparently resides with adhesion molecules (integrins) on the cancer cells, which bind preferentially two adhesion molecules (selectins) lining vessels within certain tissues. Secretion of hormones or growth factors by these tissues may also facilitate metastatic growth.

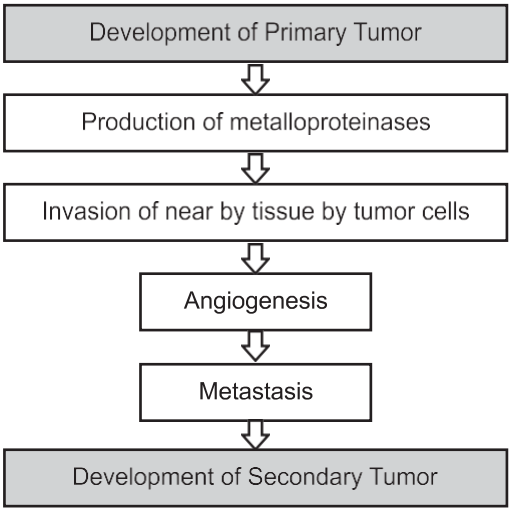

Fig. 13.5 : Development of secondary tumor

Symptoms

Symptoms depend on the type and location of the tumor. For example, lung tumors may cause coughing, shortness of breath, or chest pain. Tumors of the colon can cause weight loss, diarrhoea, constipation, iron deficiency anemia, and blood in the stool. Some tumors may not cause any symptoms. In certain tumors, such as pancreatic cancer, symptoms often do not start until the disease has reached an advanced stage.

Symptoms occur with most tumors includes fatigue, weight changes including unintended loss or gain, Skin changes such as yellowing, darkening or redness of the skin, changes in bowel or bladder habits, persistent cough, difficulty in swallowing, hoarseness, persistent indigestion or discomfort after eating, persistent,

unexplained muscle or joint pain, persistent, unexplained fevers or night sweats.

Depending on cell type, origin, location of trauma, condition of host includes:

- Malnutrition due to cytokines produced by tumor, obstruction of GIT, anorexia, depression.
- Pain due to nerve injury related to radiation or chemotherapy.
- Infection due to immunosuppressant (barrier break down by cancer).
- Fatigue due to malnutrition, anemia and depression.
- Bleeding due to platelet deficiency tumor production interfere normal clotting.
- Hormonal imbalances due to inappropriate secretion of hormone by tumor cells.
- Obstruction of hollow organs.

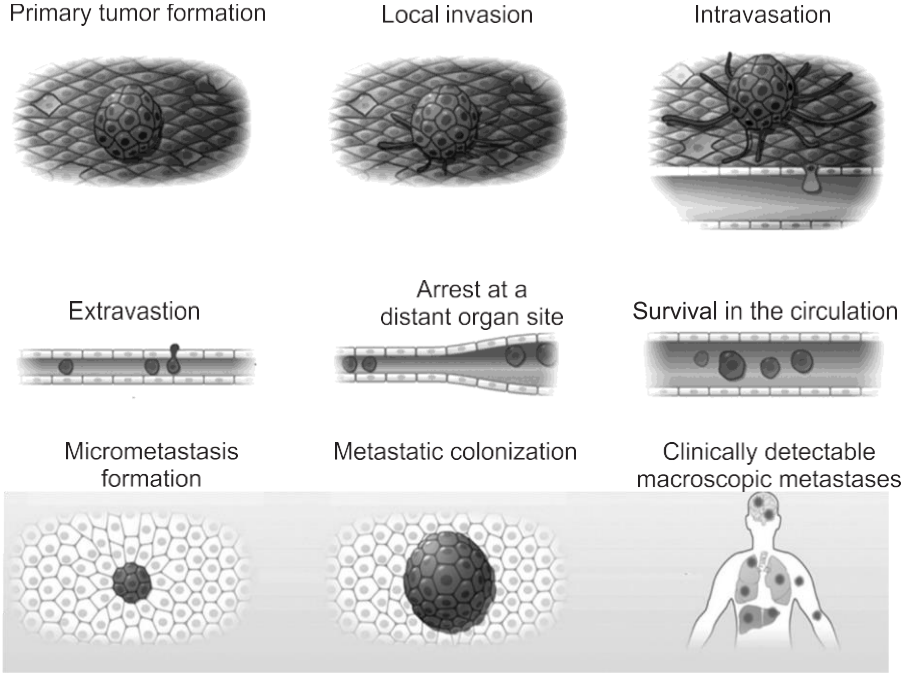

Fig. 13.6 : Pathway of cancer development

Cancer Diagnosis

Like the symptoms, the signs of tumors vary based on their site and type. Some tumors are obvious, such as skin cancer. However, most cancers cannot be seen during an exam because they are deep inside the body. When a tumor is found, a biopsy is performed to determine if the tumor is noncancerous (benign) or cancerous (malignant). Depending on the location of the tumor, the biopsy may be a simple procedure or a serious operation.

Physical exam: Areas of body for lumps that may indicate a tumor. Physical exam include looking for abnormalities, such as changes in skin colour or enlargement of an

organ that may indicate the presence of cancer. A mass may be palpable or visible.

Radiographic techniques: The use of plain films (x-rays), computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) scans, mammography, and ultrasonography (US) may be very helpful to detect the tumor type, presence and location of mass lesions which also aid in staging and determination of therapy.

Laboratory analyses: Laboratory tests, such as urine and blood tests, may help to identify abnormalities that can be caused by cancer. For instance, in people with leukemia, a common blood test called complete blood count (CBC) may reveal an unusual number of white blood cells. Tumor markers in serum such as carcinoembryonic antigen (CEA), α-fetoprotein (AFP), or human chorionic gonadotropin (HCG) can be performed.

Genetic Testing: Genetic markers include chromosomal alterations (translocations, deletions, duplication etc.); specific gene defects; single nucleotide polymorphisms, and gene rearrangements. Detection of specific genes (such as BRCA-1 for breast cancer) may suggest an increased risk for some malignancies.

Tissue Biopsy and Surgery: Methods that sample small pieces of tissue (biopsy) from a particular site, often via endoscopic techniques (such as colonoscopy, upper endoscopy, or bronchoscopy) can often yield a specific diagnosis of malignancy. It is also helpful to determine the stage and grade of the neoplasm.

Autopsy: The autopsy serves as a means of quality assurance for clinical diagnostic methods, as a way of confirming diagnoses helpful in establishing risks for family members, as a means for gathering statistics for decision making about how to approach diagnosis and treatment of neoplasm and to provide material for future research.

Treatment

Surgery: The goal of surgery is to remove the cancer or as much of the cancer as possible. The outcome of surgery also must be acceptable to the patient in terms of quality of life issues such as disfigurement or dysfunction.

Chemotherapy: Chemotherapy uses drugs to kill cancer cells. The ideal chemotherapeutic agent would preferentially target cancer cells, by virtue of their genetic makeup, increased blood flow, or high oxygen consumption, while sparing normal cells.

Radiation therapy: Radiation therapy uses high-powered energy beams, such as X-rays to kill cancer cells.

Stem cell transplant: Stem cell transplant is also known as bone marrow transplant. A stem cell transplant can use own stem cells or stem cells from a donor.

Biological therapy: Biological therapy uses body's immune system to fight cancer. Cancer can survive unchecked in body because immune system does not recognize it as an intruder. Biological therapy can help immune system "see" the cancer and attack it. Biologic response modifiers are agents that boost immune system activity or antagonize tumor growth through the

biologic effects. These agents may be isolated from human blood, or they may be produced by recombinant DNA technology. It includes antibodies and cytokines such as interferons, interleukins, tumor necrosis factor and colony stimulating factors.

Hormone therapy: Some types of cancer are fuelled by body's hormones. Examples include breast cancer and prostate cancer. Removing those hormones from the body or blocking their effects may cause the cancer cells to stop growing.

Gene therapy: Modes of gene therapy under investigation include the use of synthetic nucleotide strands to bind defective segments of cellular DNA or mRNA. Such binding prevents production of proteins involved in the molecular mechanism of neoplastic transformation.

Targeted drug therapy: Targeted drug treatment focuses on specific abnormalities within cancer cells that allow them to survive.

Prevention

Many cancers can either be prevented or the risk of developing cancers can be markedly reduced by avoiding its potential causes, public information campaign through media and warning labels (cigarette, tobacco, alcohol and drug abuse). Risk of cancerous (malignant) tumors may be reduced by:

- Eating a healthy diet.
- Exercising regularly.
- Limiting alcohol.
- Maintaining a healthy weight.
- Minimizing exposure to radiation and toxic chemicals.
- Not smoking or chewing tobacco.
- Reducing sun exposure, especially if burn easily.

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UNIT V

Chapter...14

INFECTIOUS DISEASES

14.1 MENINGITIS

Meningitis is an Inflammation of brain and spinal cord membranes (meninges). The meninges are the three membranes that cover the brain and spinal cord. Meningitis can occur when fluid surrounding the meninges becomes infected. The most common causes of meningitis are viral and bacterial infections, but can also be cancer, chemical irritation, fungi and drug allergies. Viral and bacterial meningitis are contagious. They can be transmitted by coughing, sneezing or close contact.

Types of Meningitis

Viral and bacterial infections are the most common causes of meningitis. There are several other forms of meningitis. Examples include cryptococcal, which is caused by a fungal infection, and carcinomatous, which is cancer-related. These types are rare.

Viral Meningitis: Viral meningitis is the most common type of meningitis. Viruses in the Enterovirus category cause 85 % of cases. Viruses in the Enterovirus category cause about 10 to 15 million infections per year, but only a small percentage of people who get infected will develop meningitis. These are more common during the summer and fall, and they include:

- Coxsackievirus A
- Coxsackievirus B
- Echoviruses

Other viruses can cause meningitis. These include:

- West Nile virus
- Influenza
- Mumps
- HIV
- Measles
- Herpes viruses
- Coltivirus, which causes Colorado tick fever.

Bacterial Meningitis: Bacterial meningitis is contagious and caused by infection from certain bacteria. It is fatal if left untreated. Between 5 to 40 % of children and 20 to 50 % of adults with this condition die. This is true even with proper treatment. The most common types of bacteria that cause bacterial meningitis are:

- Streptococcus pneumoniae: It is typically found in the respiratory tract, sinuses and nasal cavity, and can cause meningitis called "pneumococcal meningitis".
- Neisseria meningitides: It is spread through saliva and other respiratory fluids and causes meningitis called "meningococcal meningitis".
- Haemophilus influenza: This can cause not only meningitis but infection of the blood, inflammation of the windpipe, cellulitis, and infectious arthritis.
- Listeria monocytogenes: It is a foodborne bacteria.

Table 14.1

Neonates (<3 month)	Children	Adults	Elderly (>65)
Group B Streptococcus Escherichia coli Listeria monocytogenes	Streptococcus pneumoniae Neisseria meningitidis Haemophilus influenzae type B	Streptococcus pneumoniae Neisseria meningitidis	Streptococcus pneumoniae Neisseria meningitidis Listeria monocytogenes

Table 14.2 : CSF findings in meningitis by etiologic agent

Agent	Opening pressure (mm H_2O)	WBC count (cells/μL)	Glucose (mg/dL)	Protein (mg/dL)	Microbiology
Bacterial meningitis	200-300	100-5000; >80% PMNs	< 40	>100	Specific pathogen demonstrated in 60% of gram stains and 80% of cultures.
Viral meningitis	90-200	10-300; lymphocytes	Normal, reduced in LCM and mumps	Normal but may be slightly elevated	Viral isolation, PCR assays
Tuberculous meningitis	180-300	100-500; lymphocytes	Reduced, < 40	Elevated, >100	Acid-fast bacillus stain, culture, PCR
Cryptococcal meningitis	180-300	10-200; lymphocytes	Reduced	50-200	India ink, cryptococcal antigen, culture
Aseptic meningitis	90-200	10-300; lymphocytes	Normal	Normal but may be slightly elevated	Negative findings on workup
Normal values	80-200	0-5; lymphocytes	50-75	15-40	Negative findings on workup

Note:

LCM = lymphocytic choriomeningitis; PCR = polymerase chain reaction;
PMN = polymorphonuclear leukocyte; WBC = white blood cell.

Clinical Features and Pathophysiology

Chills, Rigors or Fever (T>38°):

- Endogenous cytokines (released during the immune response to the invading pathogens) affect the thermoregulatory neurons of the hypothalamus, changing the central regulation of body temperature.
- Invading viruses or bacteria produce exogenous substances (pyrogens) that can also re-set the hypothalamic thermal set point.

Nuchal rigidity (neck stiffness):

- Flexion of the spine leads to stretching of the meninges.
- In meningitis, traction on the inflamed meninges is painful, resulting in limited range of motion through the spine (especially in the cervical spine).

Altered mental status: ↑ ICP → brain herniation → damage to the reticular formation (structure in the brainstem that governs consciousness).

Focal neurological deficits:

- Cytotoxic edema and ↑ ICP lead to neuronal damage.
- Signs or symptoms depend on the affected area (cerebrum, cerebellum, brainstem etc.)

Examples: Cranial nerve palsies, hemiparesis, hypertonia, nystagmus.

Seizures: Inflammation in the brain alters membrane permeability, lowering the seizure threshold. Exact seizure pathophysiology is unknown.

Headache: Bacterial exotoxins, cytokines, and ↑ ICP stimulate nociceptors in the meninges (cerebral tissue itself lacks nerve endings that generate pain sensation).

Photophobia: Due to meningeal irritation. Mechanisms unclear; pathways are thought to involve the trigeminal nerve.

Nausea and vomiting: ↑ ICP stimulates the area postrema (vomiting centre), causing nausea and vomiting.

Petechial rash: Meningococcemia (due to N. meningitidis)

In the pediatric population, all of the above signs and symptoms are applicable. Additional signs and symptoms in children include:

- Bulging fontanelles,
- Bones of the skull do not join fully (form sutures) until age 2,
- ↑ ICP → meninges protrude through gaps in skull bones,
- Jaundice,
- Impaired bilirubin excretion,
- Exact mechanism unclear, associated with sepsis,
- Reduced feeds, irritability, lethargy, and toxic appearance,
- Fever, shock and cerebral edema can lead to such manifestations in children.

Complications

Longer the cause of the disease without treatment, the greater the risk of seizures and permanent neurological damage. These following complications are typically associated with meningitis:

- Seizures
- Hearing loss
- Gait problems
- Memory difficulty
- Learning disabilities
- Brain damage
- Hydrocephalus
- A subdural effusion, or a buildup of fluid between the brain and the skull
- Kidney failure
- Shock
- Death

Symptoms

Table 14.3: Symptoms

Viral meningitis	Bacterial meningitis
In infants • Decreased appetite • Irritability • Sleepiness • Lethargy • A fever In adults • Headaches • A fever • Stiff neck • Seizures • Sensitivity to bright light • Sleepiness • Lethargy • Nausea • Decreased appetite	• Altered mental status • Nausea • Vomiting • A sensitivity to light • Irritability • A headache • A fever • A stiff neck

Risk Factors

The following are some of the risk factors for meningitis:

Compromised Immunity: An immune deficiency is more vulnerable to cause meningitis infections. Certain disorders and treatments can weaken immune system. These include:

- HIV
- AIDS
- Autoimmune disorders
- Chemotherapy
- Organ or bone marrow transplants

Cryptococcal meningitis, which is caused by a fungus, is the most common form of meningitis in people with HIV or AIDS.

Community Living: Meningitis is easily spread when people live in close quarters. Being in small spaces increase the chance of exposure. Examples of these locations include:

- College dormitories
- Barracks
- Boarding schools
- Day care centers

Pregnancy: Pregnant women have an increased risk of listeriosis, which is an infection caused by the Listeria bacteria. Infection can spread to the unborn child.

Age: All ages are at risk for meningitis. Children under the age of 5 are at increased risk of viral meningitis. Infants are at higher risk of bacterial meningitis.

Working with Animals: Farm workers and others who work with animals have an increased risk of infection with Listeria.

Diagnosis

- Physical exam: Physical exams like monitoring of fever, an increased heart rate, neck stiffness and reduced consciousness can be important clues for diagnosis of meningitis in early stage.
- Lumbar puncture: This test is also called a spinal tap. It allows looking for increased pressure in the central nervous system. It can also find inflammation or bacteria in the spinal fluid. This test can also help to determine the best antibiotic for treatment.
- Blood cultures: Identification of bacteria in the blood. Bacteria can travel from the blood to the brain. N. meningitidis and S. pneumoniae can cause both sepsis and meningitis.
- Complete blood count: A complete blood count with differential is a general

index of health. It checks the number of red and white blood cells in blood. White blood cells fight infection. The count is usually elevated in meningitis.

- Chest X-rays: Chest X-rays can reveal the presence of pneumonia, tuber-culosis, or fungal infections. Meningitis can occur after pneumonia.
- CT scan: A CT scan of the head may show problems like a brain abscess or sinusitis. Bacteria can spread from the sinuses to the meninges.

Treatment

Bacterial or severe viral meningitis may require treatment in a hospital, including:

- Medicines such as antibiotics, corticosteroids, and medicines to reduce fever.
- Oxygen therapy, for patients have trouble breathing.
- Supportive care. In the hospital, watch the person closely and provide care if needed. For example, if patient may need to drink extra liquids or get fluids in a vein (IV).

Prevention

- Maintaining a healthy lifestyle,
- Getting adequate amounts of rest,
- Not smoking,
- Avoiding contact with sick people,
- Vaccinations can also protect against certain types of meningitis.

Vaccines that can prevent meningitis include the following:

- Haemophilus influenzae type B (Hib) vaccine
- Pneumococcal conjugate vaccine
- Meningococcal vaccine

14.2 TYPHOID FEVER

Typhoid fever is also called enteric fever. It is an acute infectious illness associated with fever that is most often caused by the Salmonella typhi bacteria. It can also be caused by Salmonella paratyphi, a related bacterium that usually leads to a less severe illness. The bacteria are deposited through fecal contamination in water or food by a human carrier and are then spread to other people in the area. Typhoid fever is rare in industrial countries but continues to be a significant public health issue in developing countries.

Pathophysiology

All the pathogenic Salmonella species, when present in the gut are engulfed by phagocytic cells, which then pass them through the mucosa and present them to the macrophages in the lamina proprietor. Nontyphoidal salmonellae are phagocytized throughout the distal ileum and colon. With toll-like receptor (TLR)–5 and TLR-4/MD2/CD-14 complex, macrophages recognize pathogen-associated molecular patterns (PAMPs) such as flagella and lipopolysaccharides. Macrophages and intestinal epithelial cells then attract T cells and neutrophils with interleukin 8 (IL-8), causing inflammation and suppressing the infection.

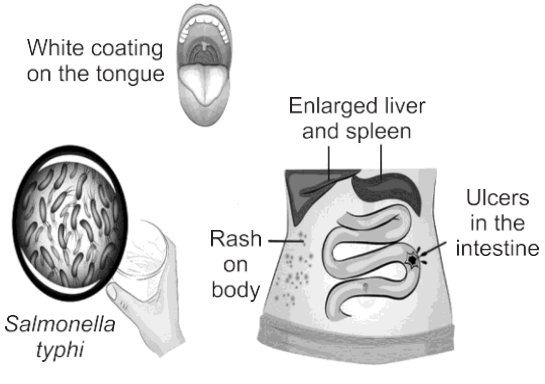


Fig. 14.1 : Typhoid fever

In contrast to the nontyphoidal salmonellae, S typhi and paratyphi enter the host's system primarily through the distal ileum. They have specialized fimbriae that adhere to the epithelium over clusters of lymphoid tissue in the ileum (Peyer patches), the main relay point for macrophages traveling from the gut into the lymphatic system. The bacteria then induce their host macrophages to attract more macrophages. S typhi has a VI capsular antigen that masks PAMPs, avoiding neutrophil-based inflammation, while the most common paratyphi serova, paratyphi A, does not. This may explain the greater infectivity of typhi compared with most of its cousins.

Typhoidal salmonella co-opt the macrophages' cellular machinery for their own reproduction as they are carried through the mesenteric lymph nodes to the thoracic duct and the lymphatics and then through to the reticuloendothelial tissues of the liver, spleen, bone marrow, and lymph nodes. Once there, they pause and continue to multiply until some critical density is reached. Afterward, the bacteria induce macrophage apoptosis, breaking out into the bloodstream to invade the rest of the body.

The bacteria then infect the gallbladder via either bacteremia or direct extension of infected bile. The result is that, the organism re-enters the gastrointestinal tract in the bile and reinfects Peyer patches. Bacteria that do not reinfect the host are typically shed in the stool and are then available to infect other hosts.

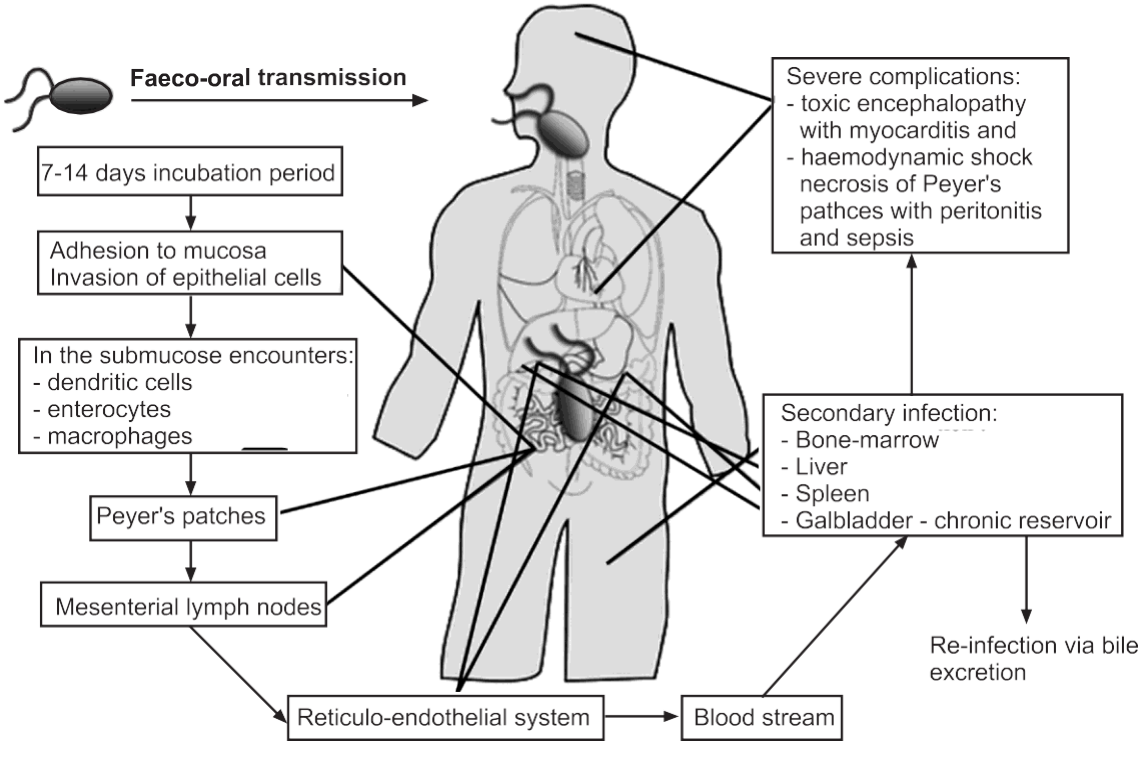


Fig. 14.2 : Life cycle of Salmonella typhi

Epidemiology

Typhoid fever occurs worldwide, primarily in developing nations whose sanitary conditions are poor. Typhoid fever is endemic in Asia, Africa, Latin America, the Caribbean, and Oceania, but 80% of cases come from Bangladesh, China, India, Indonesia, Laos, Nepal, Pakistan, or Vietnam. Within those countries, typhoid fever is most common in underdeveloped areas. Typhoid fever infects roughly 21.6 million people (incidence of 3.6 per 1,000 population) and kills an estimated 200,000 people every year. In the United States, most cases of typhoid fever arise in international travelers. The average yearly incidence of typhoid fever per million travelers from 1999-2006 by country or region of departure was as follows:

- Canada - 0
- Western hemisphere outside Canada / United States - 1.3
- Africa - 7.6
- Asia - 10.5
- India - 89 (122 in 2006)
- Total (for all countries except Canada/United States) - 2.2

Symptoms and Complications

Symptoms usually appear 1 or 2 weeks after infection but may take as long as 3 weeks to appear. Typhoid usually causes a high, sustained fever, often as high as 40°C (104°F), and extreme exhaustion.

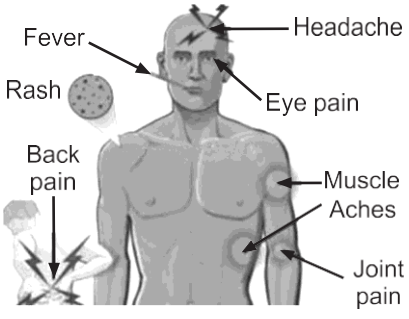
Other common symptoms include:

- Constipation,
- Cough,
- Headache,
- Loss of appetite,
- Stomach pains,
- Sore throat.

Rarer symptoms include:

- Bleeding from the rectum,
- Delirium,
- Diarrhoea.

Temporary pink spots on the chest and abdomen



14.3 : Symptoms of typhoid

Diagnosis

Infection with typhoid or paratyphoid fever results in a low-grade septicemia. It is diagnosed as follows:

Differential Diagnosis:

The group of symptoms which most clearly suggests the diagnosis of typhoid fever is:

- Gradually increasing fever with evening exacerbation and morning remission.
- General malaise with headache.
- Furred tongue with red edges and tip.
- Epistaxis.
- Relatively slow pulse (possibly dicrotic).
- Abdominal distension with increased bowel sounds.
- Tenderness in the right iliac fossa on firm pressure.
- A roseolar eruption confined principally to the abdomen and chest.
- Splenomegaly.
- Bronchial catarrh.

The differential diagnosis of this group of symptoms will depend on travel history and may include a wide variety of tropical

and non-tropical causes of fever and rash. Always consider co-existent malaria or schistosomiasis and others.

Organism Culture:

- Diagnosis is made by culturing the organism. This may be obtained from stool or other sources.
- Blood cultures are only positive in 40-60% of cases. However, this may be enhanced to above 80% using two sets of blood cultures and modern methods.
- The most sensitive source (90% isolation rate) is bone marrow aspiration.
- Isolation of S. typhi is highest in the first week and becomes more difficult as time passes.

Serology:

- The traditional serological test is Widal's test. It measures agglutinating antibodies against flagellar (H) and somatic (O) antigens of S. typhi.
- High or rising O antibody titres generally indicate acute infection, whereas H antibody is used to identify the type of infection.
- The test is positive on admission in between 40-60% of patients but the test has enormous variation between laboratories in terms of sensitivity, specificity and predictive value.
- The validity of rapid diagnostic tests for typhoid and paratyphoid was submitted for Cochrane review in 2010.

Treatment

Typhoid fever is treated with antibiotics that kill the Salmonella bacteria. Prior to the use of antibiotics, the fatality rate was 20%. Death occurred from overwhelming infection, pneumonia, intestinal bleeding, or intestinal perforation. With antibiotics and supportive care, mortality has been reduced to 1%-2%. With appropriate antibiotic therapy, there is usually improvement within one to two days and recovery within seven to 10 days. Several antibiotics are effective for the treatment of typhoid fever.

1. Chloramphenicol was the original drug of choice for many years. Because of rare serious side effects, chloramphenicol has been replaced by other effective antibiotics.
2. Fluoroquinolones like Ciprofloxacin, Gatifloxacin, and Ofloxacin are the most frequently used drugs for nonpregnant patients.
3. Ceftriaxone an intramuscular injection medication is an alternative for pregnant patients.
4. Ampicillin and trimethoprim-sulfamethoxazole is frequently prescribed antibiotics although resistance has been reported in recent years.
5. Antipyretic therapy is used if required.
6. Steroids have occasionally been used in severe cases. However, they may induce relapse, so are not generally recommended.
7. Surgical - if perforation of the bowel occurs, it will require closure. Treatment with antibiotics alone was once favoured but simple closure and drainage are required.

Complications

- The two most common complications are haemorrhage (including disseminated intravascular coagulation) and perforation of the bowel. Before antibiotics, perforation had a mortality of around 75%.
- Jaundice may be due to hepatitis, cholangitis, cholecystitis or haemolysis.

- Pancreatitis with acute kidney injury and hepatitis with hepatomegaly are rare.
- Toxic myocarditis occurs in 1-5% of patients (ECG changes may be present). It is a significant cause of death in endemic areas.
- Toxic confusional states and other neurological and psychiatric disturbances have been reported.

Prevention

- Wash hands thoroughly with soap and water after going to the toilet and before eating.
- Boil or disinfect all water before drinking it – use disinfectant tablets or liquid available in pharmacies or drink commercially bottled (preferably carbonated) beverages.
- Peel all fruit and vegetable skins before eating.
- Keep flies away from food.
- Watch out for ice cubes, ice cream, and unpasteurized milk, which can easily be contaminated.
- Cook all food thoroughly and eat it while it is hot.
- Be aware of the "danger foods" shellfish, salads, and raw fruit and vegetables.
- Do not eat food or drink beverages from street vendors.

14.3 LEPROSY

Leprosy (also known as Hansen's disease) is an infection caused by slow-growing bacteria called Mycobacterium leprae or M. lepromatosis bacteria. It is a slowly developing (from six months to 40 years), progressive disease that damages the skin and nervous system. It results in skin lesions and deformities, most often affecting the cooler places on the body (for example, eyes, nose, earlobes, hands, feet and testicles). The skin lesions and deformities can be very disfiguring and are the reason that infected individuals historically were considered outcasts in many cultures. Although human-to-human transmission is the primary source of infection, three other species can carry and (rarely) transfer M. leprae to humans: chimpanzees, mangabey monkeys, and nine-banded armadillos. The disease is termed a chronic granulomatous disease, similar to tuberculosis, because it produces inflammatory nodules (granulomas) in the skin and nerves over time.

The disease has been known to man since time immemorial. DNA taken from the shrouded remains of a man discovered in a tomb next to the old city of Jerusalem shows him to be the earliest human proven to have suffered from leprosy. The remains were dated by radiocarbon methods to 1–50 A.D. The disease probably originated in Egypt and other Middle Eastern countries as early as 2400 BCE. An apparent lack of knowledge about its treatment facilitated its spread throughout the world. Mycobacterium leprae, the causative agent of leprosy, was discovered by G. H. Armauer Hansen in Norway in 1873, making it the first bacterium to be identified as causing disease in humans. Over the past 20 years, the WHO implementation of MDT has rendered leprosy a less prevalent infection in 90% of its endemic countries with less than one case per 10,000 populations. Though, it continues to be a public health problem in countries like Brazil, Congo, Madagascar, Mozambique, Nepal, and Tanzania.

Leprotic patients can be classified into three groups, each with slightly different signs and symptoms:

Paucibacillary (PB), or tuberculoid, Hansen's disease: It is characterized by one or a few hypopigmented or hyperpigmented skin macules that exhibit loss of sensation (anesthesia) due to infection of the peripheral nerves supplying the region. The body's immune response may also result in swelling of the peripheral nerves; these enlarged nerves may be palpated under the skin, and may or may not be tender to the touch. The nerves most often found to have swelling are:

- Great auricular nerve,
- Ulnar nerve above the elbow and dorsal cutaneous branches at the wrist,
- Median nerve at the wrist (in the carpal tunnel),
- Radial nerve (superficial at wrist),
- Common peroneal nerve (also femoral cutaneous and lateral popliteal nerves where they wind around the neck of the fibula),
- Posterior tibial nerve, posterior to the medial malleolus,
- Sural nerve.

Multibacillary (MB), or lepromatous, Hansen's disease: It is characterized by generalized or diffuse involvement of the skin, a thickening of the peripheral nerves under microscopic examination, and has the potential to involve other organs, the eyes, nose, testes and bone. The nodular form of this condition is the most advanced form of the disease. Ulcerated nodules contain large numbers of M. leprae acid-fast bacilli packed in macrophages that appear as large foamy cells. MB form of Hansen's disease is associated with:

- Multiple, symmetrically-distributed skin lesions that might not exhibit loss of sensation,
- Nodules and Plaques,
- Thickened dermis,
- Frequent involvement of the nasal mucosa resulting in nasal congestion and epistaxis.

Borderline, or dimorphous, Hansen's disease: It is the most common form. When compared to tuberculoid or lepromatous forms, it is of intermediate severity. The skin lesions seem to be of the tuberculoid type, but are more numerous, and may be found anywhere on the body. Peripheral nerves are affected as well, with ensuing weakness and anesthesia.

Pathogenesis of Leprosy

Onset of leprosy is insidious. It affects nerves, skin and eyes. It may also affect mucosa (mouth, nose and pharynx), testes, kidney, voluntary/smooth muscles, reticulo-endothelial system, and vascular endothelium.

Bacilli enter the body usually through respiratory system. It has low pathogencity, only a small proportion of infected people develop signs of the disease. Though infected, majority of the population do not develop the disease. After entering the body, bacilli migrate towards the neural tissue and enter the Schwann cells. Bacteria can also be found in, macrophages, muscle cells and endothelial cells of blood vessels.

After entering the Schwann cells or macrophage; fate of the bacterium depends on the resistance of the infected individual towards the infecting organism. Bacilli start multiplying slowly (about 12-14 days for one bacterium to divide into two) within the cells, get liberated from the destroyed cells

and enter other unaffected cells. Till this stage, person remains free from signs and symptoms of leprosy.

As the bacilli multiply, bacterial load increases in the body and infection is recognized by the immunological system. Lymphocytes and histiocytes (macrophages) invade the infected tissue. At this stage, clinical manifestation may appear as involvement of nerves with impairment of sensation and/or skin patch. If it is not diagnosed and treated in the early stages, further progress of the diseases is determined by the strength of the patient's immune response. Specific and effective cell mediated immunity (CMI) provides protection to a person against leprosy. When specific CMI is effective in eliminating/ controlling the infection in the body, lesions heal spontaneously or it produces pauci-bacillary (PB) type of leprosy. If CMI is deficient; the disease spreads uncontrolled and produces multi bacillary (MB) leprosy with multiple system involvement. Sometimes, the immune response is abruptly altered, either following treatment (MDT) or due to improvement of immunological status, which results in the inflammation of skin or/and nerves and even others tissue, called as leprosy reaction (types 1 and 2).

Epidemiology

M. leprae is a fastidious, acid-fast, intracellular pathogen. In 2008, there were approximately 250,000 new cases reported, predominantly in India, Brazil and Indonesia. Humans were previously thought to be the only important reservoirs of the bacteria, but it is now appreciated that leprosy, or Hansen's disease, may also be acquired from environmental sources. Leprosy is likely transmitted by aerosol droplets taken up through nasal or other upper airway mucosa, where it has been detected by PCR techniques. Large number of organisms have been found in the nasal secretions of lepromatous leprosy patients.

Signs And Symptoms

Symptoms mainly affect the skin, nerves, and mucous membranes (the soft, moist areas just inside the body's openings). The disease can cause skin symptoms such as:

- Discoloured patches of skin, usually flat, that may be numb and look faded (lighter than the skin around).
- Growths (nodules) on the skin.
- Thick, stiff or dry skin.
- Painless ulcers on the soles of feet.
- Painless swelling or lumps on the face or earlobes.
- Loss of eyebrows or eyelashes.

Symptoms caused by damage to the nerves are:

- Numbness of affected areas of the skin.
- Muscle weakness or paralysis (especially in the hands and feet).
- Enlarged nerves (especially those around the elbow and knee and in the sides of the neck).
- Eye problems that may lead to blindness (when facial nerves are affected).

Symptoms caused by the disease in the mucous membranes are:

- A stuffy nose and nose bleeds.

Since Hansen's disease affects the nerves, loss of feeling or sensation can occur. When loss of sensation occurs, injuries such as burns may go unnoticed. Because you may not feel the pain that can warn you of harm to your body. Take extra caution to ensure the affected parts of your

body are not injured. If left untreated, the signs of advanced leprosy can include:

- Paralysis and crippling of hands and feet,
- Shortening of toes and fingers due to reabsorption,
- Chronic non-healing ulcers on the bottoms of the feet,
- Blindness,
- Loss of eyebrows,
- Nose disfigurement,
- Painful or tender nerves,
- Redness and pain around the affected area,
- Burning sensation in the skin.

Diagnosis

The majority of cases of leprosy are diagnosed by clinical findings, especially since most current cases are diagnosed in areas that have limited or no laboratory equipment available. Hypopigmented patches of skin or reddish skin patches with loss of sensation, thickened peripheral nerves, or both clinical findings together often comprise the clinical diagnosis. Skin smears or biopsy material that show acid-fast bacilli with the Ziehl-Neelsen stain or the Fite stain (biopsy) can diagnose multibacillary leprosy, or if bacteria are absent, diagnose Paucibacillary leprosy. Other tests can be done, but most of these are done by specialized labs and may help a clinician to place the patient in the more detailed Ridley-Jopling classification and are not routinely done (lepromin test, phenolic glycolipid-1 test, PCR, lymphocyte migration inhibition test or LMIT). Other tests such as CBC test, liver function tests, creatinine test, or a nerve biopsy may be done to help determine if other organ systems have been affected.

Treatment

- Paucibacillary leprosy is treated with two antibiotics, dapsone and rifampicin, while multibacillary leprosy is treated with the same drugs, in addition with another antibiotic, clofazimine. Usually, the antibiotics are given for at least six to 12 months or more to cure the disease.
- Multibacillary leprosy can be kept from advancing, and living. M. leprae can be essentially eliminated from the person by antibiotics, but the damage occured before administration of antibiotics is usually not reversible. Recently, the WHO suggested that single-dose treatment of patients with only one skin lesion with rifampicin, minocycline (Minocin), or ofloxacin (Floxin) is effective.
- Steroid medications have been used to minimize pain and acute inflammation with leprosy.

Complications

Without treatment, leprosy can permanently damage your skin, nerves, arms, legs, feet and eyes.

Complications of leprosy can include:

- Blindness or glaucoma.
- Disfiguration of the face (including permanent swelling, bumps and lumps).
- Erectile dysfunction and infertility in men.
- Kidney failure.
- Muscle weakness that leads to claw-like hands or an inability to flex the feet.
- Permanent damage to the inside of the nose, which can lead to nose bleeds and a chronic, stuffy nose.
- Permanent damage to the nerves outside the brain and spinal cord, including those in the arms, legs and feet.

Prevention

The prevention of leprosy ultimately lies in the early diagnosis and treatment of those individuals suspected or diagnosed as having leprosy, thereby preventing further transmission of the disease to others.

- Public education and community awareness are crucial to encourage individuals with leprosy and their families to undergo evaluation and treatment with MDT.
- Household contacts of patients with leprosy should be monitored closely for the development of leprosy signs and symptoms.
- A study demonstrated that prophylaxis with a single dose of rifampicin was 57% effective in preventing leprosy for the first two years in individuals who have close contact with newly diagnosed patients with leprosy.
- There is currently no widely used standard for using medications for the prevention of leprosy.
- Currently, there is no single commercial vaccine that confers complete immunity against leprosy in all individuals.
- Several vaccines, including the BCG vaccine, provide variable levels of protection against leprosy in certain populations.

14.4 TUBERCULOSIS

There are many subgroups in the genus mycobacterium such as M aviumintracellulare, M kansasii, M bovis, but M tuberculosis alone is pathogenic in human. Mycobacterium tuberculosis, most commonly affects the lungs. It is transmitted from person to person via droplets from the throat and lungs of people with the active respiratory disease. Most commonly, tuberculosis is caused by air-borne infection.

In healthy people, infection with Mycobacterium tuberculosis often causes no symptoms, since the person's immune system acts to "wall off" the bacteria. Most people who are exposed to TB never develop symptoms because the bacteria can live in an inactive form in the body. But if the immune system weakens, such as immunocompromised (HIV) or elderly adults, TB bacteria can become active and their active state causes death of tissue in the organs they infect. Active TB disease can be fatal if left untreated.

Tuberculosis is communicable infection of lung tissue (Pulmonary TB), and potentially other tissues (extrapulmonary or miliary TB).

Epidemiology

Tuberculosis is most prevalent infectious disease in the world.

Tuberculosis is one of India's major public health problems. According to WHO estimates, India has the world's largest tuberculosis epidemic and approximately two to three million people are infected with tuberculosis out of a global incidence of 8.7 million cases. This is a public health problem. India bears a disproportionately large burden of the world's tuberculosis rates, as it resides to be the biggest health problem in India.

Etiology

Tuberculosis is caused by Mycobacterium tuberculosis, which spread from person to person through microscopic droplets released into the air. This can happen when someone with the untreated, active form of tuberculosis, coughs, speaks, sneezes, spits, laughs or sings.

Risk Factor

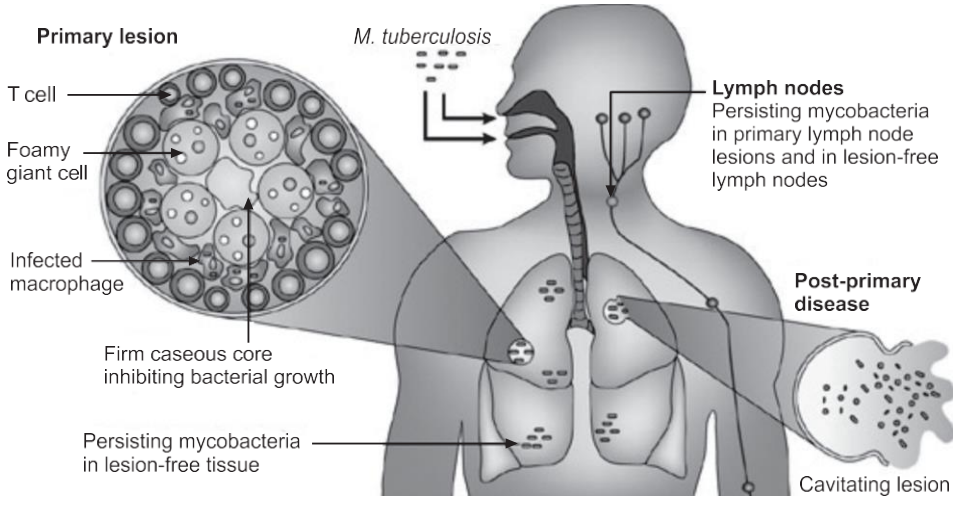
The person more prone to the infection includes:

- Immigration and infection with HIV
- Frequent and prolonged contact
- Host debilitation due to malnutrition enhance risk of transmission (condition exist in refugee and living in poverty).
- Opportunistic infection (immunocompromised)
- Other risk factors include old age, alcoholism, diabetes and environmental lungs disease.

Pathophysiology

Infection with TB requires inhalation of droplet nuclei. Following deposition in the alveoli, Mycobacterium tuberculosis is engulfed by alveolar macrophages, but survives and multiplies within the macrophages. Proliferating bacilli kill macrophages and are released; this event produces a response from the immune system. Exposure may lead to clearance of Mycobacterium tuberculosis, persistent latent infection, or progression to primary disease. Successful containment of TB is dependent on the cellular immune system, mediated primarily through T-helper cells (TH1 response). T cells and macrophages form a granuloma with a centre that contains necrotic material (caseous centre, Fig. 12.2). Mycobacterium tuberculosis, and peripheral granulation tissue consisting primarily of macrophages and lymphocytes; the granuloma serves to prevent further growth and spread of M.tuberculosis. These individuals are non-infectious and have latent TB infection; the majority of these patients will have a normal chest X-ray (CXR) and be tuberculin skin test (TST) positive. Active TB typically occurs through a process of re-activation (Fig 12.3).

Approximately 10% of individuals with latent infection will progress to active disease over their lifetime. The risk is greatest within the two years following initial acquisition of M. tuberculosis. A number of conditions can alter this risk, particularly HIV infection, in which the annual risk of developing active TB is 8% to 10%. Immunocompromised conditions and treatment with immunosuppressing medicines, including systemic corticosteroids and TNF-α antagonists, also contribute to re-activation.



Clinical Manifestations

During initial infection and granulomas, there are no symptoms of mild bronchial pneumonia but sputum test is positive.

In active TB, sign of chronic inflammation include:

- Anorexia,
- Overall sensation of feeling unwell,
- Weight loss,
- Fatigue,
- Low grade fever,
- Night sweating,
- Coughing that lasts longer than 2 weeks with green, yellow, or bloody sputum,
- Shortness of breath,
- Chest pain,
- Hemoptysis.

The occurrence of additional symptoms depends on where the disease has spread beyond the chest and lungs. For example, if TB spreads to the lymph nodes, it can cause swollen glands at the sides of the neck or under the arms.

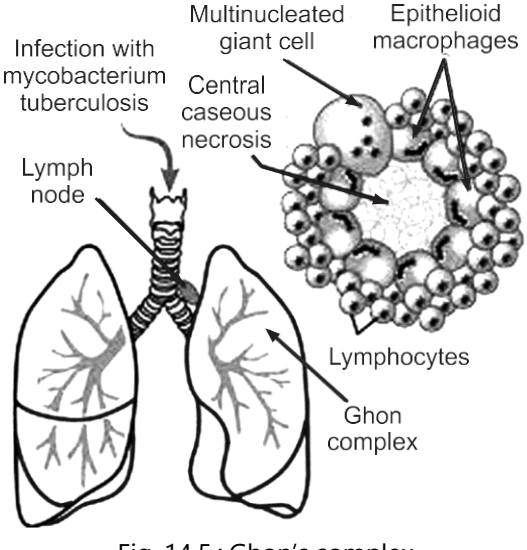


Fig. 14.5 : Ghon's complex

When TB spreads to the bones and joints, it can cause pain and swelling of the knee or hip.

Genitourinary TB can cause pain in the flank with frequent urination, pain or discomfort during urination, and blood in the urine.

Diagnosis

Medical history and physical exam include checking the symptoms such as an ongoing cough, fatigue, fever, loss of weight, anorexia and night sweats.

Lab Tests include:

Sputum culture: Testing mucus from the lungs is used to diagnose active TB. But a sputum culture can take 1 to 8 weeks to provide results.

Sputum cytology: Examination of sample of sputum (mucus) under a microscope to determine whether abnormal cells are present. It may be done to help detect certain non-cancerous lung conditions, such as pneumonia or inflammatory diseases, or the buildup of asbestos fibers in the lungs.

Test for TB Infection: The Mantoux tuberculin skin test (TST) or the TB blood test can be used to test for M. tuberculosis infection.

Additional tests are required to confirm TB disease. The Mantoux tuberculin skin test is performed by injecting a small amount of fluid called tuberculin into the skin in the lower part of the arm. The test is read within 48 to 72 hours by a trained health care worker, who looks for a reaction on the arm.

The TB blood test measures the patient's immune system reaction to M. tuberculosis.

An uncertain reaction to the tuberculin skin test because of a weakened immune system, or to a previous Bacillus Calmette-Guerin (BCG) vaccination.

Chest X-ray: A posterior-anterior chest radiograph is used to detect chest abnormalities. Lesions may appear anywhere in the lungs and may differ in size, shape, density, and cavitation. These abnormalities may suggest TB, but cannot be used to definitively diagnose TB. However, a chest radiograph may be used to rule out the possibility of pulmonary TB in a person who has had a positive reaction to a TST or TB blood test and no symptoms of disease.

Rapid sputum test: This test can provide results within 24 hours. This test is done only when a person is strongly suspected of having TB.

Diagnosing TB outside the lungs: Diagnosing TB in other parts of the body (extrapulmonary TB) requires more testing. It includes:

Biopsy: A sample of the affected area is taken out to look for TB causing bacteria.

Urine culture: This test looks for TB infection in the kidneys (renal TB).

Lumbar puncture: A sample of fluid around the spine is taken to look for a TB infection in the brain (TB meningitis).

CT scan: This test is used to diagnose TB that has spread throughout the body (miliary TB) and to detect lung cavities caused by TB.

MRI scan: This test looks for TB in the brain or the spine.

Testing for HIV infection, blood test for hepatitis is often done at the time of TB diagnosis.

Tests during TB Treatment:

Drug Resistance: For all patients, the initial M. tuberculosis isolate should be tested for drug resistance. It is crucial to identify drug resistance as early as possible to ensure effective treatment. Drug susceptibility patterns should be repeated for patients who do not respond adequately to treatment or who have positive culture results despite 3 months of therapy.

Treatment

Treatment for TB depends on whether it is active or latent. Patient may be hospitalized or suggested to avoid contact with other people until tests show that the patient is not contagious.

Antibiotics: For TB lung infections, antituberculosis drugs eg. isoniazid, rifampicin, ethambutol, Pyrazinamide and streptomycin (I^{st} line) drugs are more effective. While para-amino salicylic acid, thiacetazone, ethionamide, cycloserine, kanamycin and rifabutin are II^{nd} line drugs. A number of new drugs are available to overcome the current drug resistant combination treatment including: bedaquiline, delamanid, linezolid and sutezolid.

If a particular type of TB infection is resistant to regular antibiotic treatment (a condition known as multidrug resistant TB or MDRTB), a combination of different medications must be taken for 18 to 24 months.

Vaccination: A vaccine is available to limit the spread of bacteria after TB infection: The vaccine is generally used in countries or communities where the risk of TB infection is greater than 1% each year. It is used in new borns in these communities to prevent TB and its complications in the first few years of life.

Table 14.4 : Tuberculosis treatment

Short term treatment (06 month course of treatment)	Long term treatment (12 month course of treatment)
Initiation phase: Four drugs in combination for first two months: Isoniazide Rifampicin Pyrazinamide Ethambutol Continuation phase: Initiation phase followed by 4 months of two drug combination: Rifampicin Isoniazid	Initiation phase: For first 2 months out of 12 months, use following drugs plus glucocorticoid for first 2-3 weeks Isoniazide Rifampicin Pyrazinamide Ethambutol Continuation phase: Initiation phase followed by 10/12 months of two combination: Isoniazid Rifampicin

DOT:

DOTS (directly observed treatment, short-course), is the name given to the World Health Organization recommended tuberculosis control strategy that combines five components:

- Government commitment (including both political will at all levels, and establishing a centralized and prioritized system of TB monitoring, recording and training).
- Case detection by sputum smears microscopy.
- Standardized treatment regimen directly observed by a healthcare worker or community health worker for at least the first two months.
- A regular drug supply.
- A standardized recording and reporting system that allows assessment of treatment results.

Clinical Features

1. MTB has remarkable tendency to develop resistance against antitubercular drugs. The drug treatment must be continued for many months, often an year or more. In the long period, the tubercule bacteria can become resistant to the drug even though the person is receiving antitubercular drugs. To prevent the development of resistance, one must use two or more drugs concurrently.
2. Drug treatment consist of Ist line and IInd line drugs.
3. Compliance: One major trouble is non-compliance of the patient. This is global phenomenon but more common in poor countries. If compliance is good and the patient is immunocompetent, the cure rate is excellent, nearly 100%. Where compliance is defective recurrence rate is high.
4. Host defense is also an important factor.

Prevention

1. Education and screening: To reduce risk of infection and transmission, peoples with close contact with patient may undergo prophylactic therapy. To

minimize air born infection use protective measures such as covering mouth and nose when coughing. Do not spend long periods of time in stuffy, enclosed rooms with anyone who has active TB until that person has been treated for at least 2 weeks. Someone who has active TB, help and encourage the person to follow treatment instructions.

2. Early diagnosis and treatment: TB should be treated early in order to prevent deterioration of the disease and spread of the infection.
3. Leading a healthy life style: The germs attack the lungs when a person's body resistance is reduced. Try to guard by leading a healthy lifestyle in order to minimize the chance of contracting the illness. This includes: adequate exercise, enough rest and sleep, balanced diet, avoidance of smoking and alcohol, breathing fresh air and maintaining good indoor ventilation.
4. BCG (Bacillus Calmette-Guerin) vaccination: The TB and Chest Service provides BCG vaccination to all new born babies to protect them against tuberculosis.

TB germs are spread by:

- TB germs are spread through the air when a person, who is sick with TB disease coughs, sings, sneezes, or laughs.
- To become infected with TB germs, a person usually needs to share air space with someone sick with TB disease (e.g., live, work, or play together).
- The amount of time, the environment, and how sick the person is all contribute to whether or not get infected.
- In most cases, body is able to fight off the germs.

TB germs are not spread by:

- Through quick, casual contact, like passing someone on the street.
- By sharing utensils or food.
- By sharing cigarettes or drinking containers.
- By exchanging saliva or other body fluids.
- By shaking hands.
- Using public telephones.

14.5 URINARY TRACT INFECTION

Urinary tract infection (UTI) is second to respiratory infection as the most common type of infection in the body. It is a bacterial infection involving the kidneys, ureters, bladder, or urethra. These are the structures that urine passes through before being eliminated from the body.

The upper urinary tract is composed of the kidneys and ureters and lower urinary tract consists of the bladder and the urethra.

Types

An infection affects the lower urinary tract (urethra or bladder), it may be called Urethritis, or Cystitis, if it only affects the bladder. If it migrates to and affects the upper urinary tract (ureters or kidneys) it is called Ureteritis and if it affects just the kidneys, it is called Pyelonephritis.

Urinary tract infections are much more common in adults than in children, but about 1%-2% of children do get urinary tract infections. Urinary tract infections in

children (besides bedwetting) are more likely to be serious than those in adults and should not be ignored (especially in younger children).

These infections are common in girls and women than in boys and men younger than 50 years of age. The lifetime risk of a woman having a UTI is over 50%. They are especially prone due to anatomical reasons; a woman's urethra is shorter than a man's, and is situated closer to the anus, making it quicker for bacteria to enter the bladder. About 40% of women and 12% of men have a urinary tract infection at some time in their life. When the kidneys are involved, UTIs can be life threatening.

Causes of UTIs

More than 90% of UTI cases are a type of bacteria called Escherichia coli, (E. coli). These bacteria normally live in the bowel and around the anus. E. coli bacteria are fairly sedate in its natural environment of the bowel. However, the bacteria will thrive when introduced to urine's acidic state.

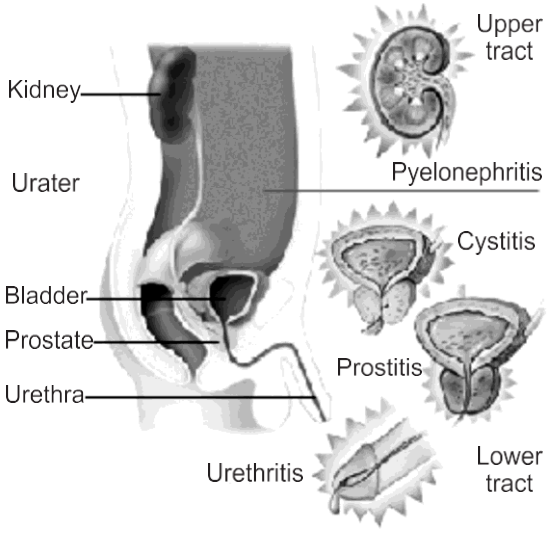


Fig. 14.6 : Urinary tract infections

Urinary tract infections normally occur when E.coli bacteria get into the urine and begin to grow. The infection usually starts at the opening of the urethra where the urine leaves the body and moves upward into the urinary tract to the bladder. If the infection is not treated at this point, it will continue on and quickly infect the kidneys.

E. coli bacteria can move quite easily from the area around the anus and the perineum, to the opening of the urethra. The two most common causes of this are improper wiping and sexual intercourse. Women are more prone to UTIs because they have shorter urethras, which provide the bacteria a quicker pathway to the bladder.

The normal process of urination flushes the bacteria out through the urethra. However, if the infection has already taken hold and there are too many bacteria, urinating may not stop their spread.

The danger here is the infection spreading further. If it reaches the kidneys, it can cause a kidney infection (pyelonephritis), which can become a very serious and even life-threatening condition if not treated immediately.

Risk Factors for UTIs

Anything that reduces bladder emptying or irritates the urinary tract can cause UTIs.

Obstructions: Blockages that make it difficult to empty the bladder can cause a UTI. Obstructions can be caused by an enlarged prostate, kidney stones and certain forms of cancer.

Sexual Activity: Pressure on the urinary tract during sex can move bacteria from the colon into the bladder. Most women have bacteria in their urine after intercourse. However, the body usually can get rid of

these pathogens within 24 hours. Bowel bacteria may have properties that allow them to stick to the bladder.

Bathroom Hygiene: Wiping from back to front after going to the bathroom can lead to a UTI. This motion drags bacteria from the rectal area towards the urethra.

Spermicides: Spermicides can increase UTI risk. They may cause skin irritation in some women. This increases the risk of bacteria entering into the bladder.

Condoms: Latex condoms can cause increased friction during intercourse. They may also irritate the skin. This may increase the risk of UTI in some individuals. However, condoms are important for reducing the spread of sexually transmitted infections.

Diaphragms: Diaphragms may put pressure on the urethra. This can decrease bladder emptying. Some studies have seen a higher UTI risk in women who use diaphragms.

Diabetes: Changes to the immune system make a person with diabetes more vulnerable to infection. Also, a higher sugar level in the urine makes it easier for bacteria to grow.

Loss of Estrogen: After menopause, a loss of estrogen changes the normal bacteria in the vagina. This can increase the risk of UTI.

Prolonged Use of Bladder Catheters: Catheters are used when someone cannot urinate normally. These thin, flexible tubes are inserted into the bladder. They allow urine to drain into a container. Long-term catheter use can increase the risk of UTI. They may make it easier for bacteria to get into the bladder.

Weakened immune system: Medical conditions that impair immune system, such as diabetes and HIV, increase risk of kidney infection. Certain medications, such as drugs taken to prevent rejection of transplanted organs, have a similar effect.

Symptoms

Urinary tract infections do not always cause signs and symptoms, but when they do they may include:

- A strong, persistent urge to urinate.
- A burning sensation when urinating.
- Passing frequent, small amounts of urine
- Urine that appears cloudy.
- Urine that appears red, bright pink or cola coloured a sign of blood in the urine.
- Strong smelling urine.
- Pelvic pain, in women.
- Rectal pain, in men.
- UTIs may be overlooked or mistaken for other conditions in older adults.

Table 14.5 : Symptoms of urinary tract infection

Part of urinary tract affected	Signs and symptoms
Kidneys (acute pyelonephritis)	Upper back and side (flank) pain High fever Shaking and chills Nausea Vomiting
Bladder (cystitis)	Pelvic pressure Lower abdomen discomfort Frequent, painful urination Blood in urine
Urethra (urethritis)	Burning with urination

Tests and Diagnosis

Tests and procedures used to diagnose urinary tract infections include:

- Analyzing a urine sample: A urinary tract infection is diagnosis by detection of white blood cells, red blood cells or bacteria in patient's urine.
- Growing urinary tract bacteria in a lab: Lab analysis of the urine is sometimes followed by urine culture, a test that uses urine sample to grow bacteria in a lab. This test tells which bacteria are causing infection and helpful for selection of most effective medications.
- Creating images of your urinary tract: An ultrasound, a computerized tomography (CT) scan, intravenous pyelogram (IVP), use of X-rays with contrast dye to create images. These images are helpful to know abnormality in urinary tract which causes frequent infections.
- Using a scope to see inside bladder: The cystoscopy, using a long, thin tube with a lens (cystoscope) to see inside urethra and bladder.

Treatments and Drugs

Antibiotics are generally used for the treatment of urinary tract infections. Specific antibiotics and the duration of treatment depend on health condition and the type of bacterium found in urine.

Simple infection:

Drugs commonly recommended for simple UTIs include:

- Sulfamethoxazole-trimethoprim
- Amoxicillin
- Nitrofurantoin
- Ampicillin
- Ciprofloxacin
- Levofloxacin

Usually, symptoms clear up within a few days of treatment. But may need to continue antibiotics for a week or more. To ensure that the infection is completely eradicate.

For an uncomplicated UTI that occurs when patient is otherwise healthy, may require a shorter course of treatment, such as taking an antibiotic for one to three days. And depends on particular symptoms and medical history.

Pain medication (analgesic) may recommended, that numbs bladder and urethra to relieve burning while urinating. One common side effect of urinary tract analgesics is discolored urine changes into orange or red.

Frequent infections:

If person experience frequent UTIs, often require certain treatment recommendations, such as:

Longer course of antibiotic treatment or a program with short courses of antibiotics at the start of urinary symptoms.

A single dose of antibiotic after sexual intercourse if infections are related to sexual activity.

Vaginal estrogen therapy if postmenopausal, to minimize chance of recurrent UTIs.

Severe infection:

For a severe UTI, may need treatment with intravenous antibiotics in a hospital.

Prevention

Not all UTIs can be prevented, but there are some simple steps which can be taken to reduce risk of developing and to help prevent UTIs.

- Drinking water after having sex.
- Cleaning vaginal and rectal areas daily.
- Taking showers instead of baths
- Drink lots of fluids (six to eight glasses of water) to flush the urinary system.
- Urinate as soon as, feel the need rather than holding on.
- For women and girls, wipe bottom from front to back to prevent bacteria from around the anus entering the urethra.
- Urinate shortly after sex to flush away bacteria that might have entered in the urethra during sex.
- Wear cotton underwear and loose fitting clothes so that air can keep the area dry. Avoid tight-fitting clothes and nylon underwear, which trap moisture and can help bacteria grow.
- Using a diaphragm or spermicide for birth control can lead to UTIs (in women) by increasing bacteria growth. Unlubricated condoms or spermicidal condoms increase irritation, which may help bacteria to grow.
- Take vitamin C or cranberry juice, because these are said to be urinary antiseptics.

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Chapter...15

SEXUALLY TRANSMITTED DISEASES

15.1 ACQUIRED IMMUNODEFICIENCY SYNDROME

AIDS (Acquired Immunodeficiency Syndrome) is a chronic, potentially life-threatening condition caused by the human immunodeficiency virus (HIV). By damaging immune system, HIV interferes with body's ability to fight against the organisms that cause disease.

Acquired immunodeficiency syndrome (AIDS) is defined in terms of either a CD4+ T cell count below 200 cells per µL (CD4 lymphocyte percentage below 14% are considered to have AIDS) or the occurrence of specific diseases in association with an HIV infection. AIDS is the most advanced stage of infection with HIV.

HIV stands for human immunodeficiency virus:

H – Human: This particular virus can only infect human beings.

I – Immunodeficiency: HIV weaken immune system by destroying important cells that fight disease and infection.

V – Virus: A virus can only reproduce itself by taking over a cell in the body of its host.

Virus can be isolated from body fluids, blood, semen, vaginal secretion, saliva, breast milk, tears, urine, cerebrospinal fluid, peritoneal fluid. Important cause of infection is unsafe sexual intercourse, sharing unsterilized needles, blood and blood products.

The presence of HIV in saliva, urine and tears is not significant to transmit infection. The casual, non-sexual contact does not transmit infection. Mosquito bite is also not responsible for transmission of HIV.

HIV Structure

It is around 100 to 120 nm in diameter (around 60 times smaller than a red blood cell) and roughly spherical. It is 20 sided enveloped virus of the lentivirus subfamily of retroviruses.

HIV is different in structure from other retroviruses. Two viral strands of RNA are found in core surrounded by protein outer coat. Outer envelope contains a lipid matrix within which specific viral glycoproteins are embedded and these knob like structures are responsible for binding to target cell.

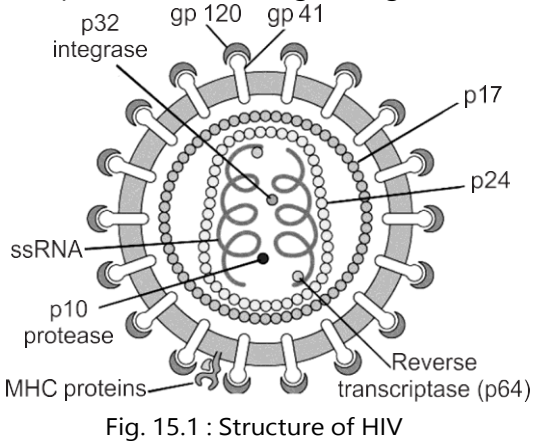

Fig. 15.1 : Structure of HIV

The outer shell of the virus is known as the viral enevlope. Embedded in the viral envelope is a complex protein known as envelope (env) which consists of an outer protruding cap glycoprotein (gp) 120, and a stem gp41. Within the viral envelope is an HIV protein called p17 (matrix), and within this is the viral core or capsid, which is made up of another viral protein p24 (core antigen).

Three main structural genes are: Group Specific Antigen (Gag), Envelope (Env) and Polymerase (Pol).

Group Specific Antigen (Gag): Gag proteins are encoded by the gag gene, and provide structural elements of the virus.

Envelope (Env) gene codes for envelope proteins gp160, gp120 and gp41. These polyproteins will eventually be cleaved by proteases to become HIV envelope glycoproteins gp120 and gp41.

gp41 is a transmembrane glycoprotein antigen that spans the inner and outer membranes and attaches to gp120 and both involved with fusion and attachment of HIV to CD4 antigen on host cells.

Polymerase (Pol) codes for p66 and p51 subunits of reverse transcriptase and p31 an endonuclease. They are located in the core, close to nucleic acids and responsible for conversion of viral RNA into DNA, integration of DNA into host cell DNA and cleavage of protein precursors.

During first step, HIV attaches to susceptible host cell. Site of attachment is the CD4 antigen found on a variety of cells, helper T cells, macrophages, monocytes, B cells, microglial brain cells and intestinal cells. T cells infected later on.

Pathophysiology

After the virus enters the body there is a period of rapid viral replication, leading to an abundance of virus in the peripheral blood. During primary infection, the level of HIV may reach several million virus particles per milliliter of blood. This response is accompanied by a marked drop in the number of circulating CD4+ T cells. The acute viremia is almost invariably associated with activation of CD8+ T cells, which kill HIV-infected cells, and subsequently with antibody production, or seroconversion. The CD8+ T cell response is thought to be important in controlling virus levels, which peak and then decline, as the CD4+ T cell counts recover. A good CD8+ T cell response has been linked to slower disease progression and a better prognosis, though it does not eliminate the virus.

Ultimately, HIV causes AIDS by depleting CD4+ T cells. This weakens the immune system and allows opportunistic infections. T cells are essential to the immune response and without them, the body cannot fight infections or kill cancerous cells. The mechanism of CD4+ T cell depletion differs in the acute and chronic phases. During the acute phase, HIV-induced cell lysis and killing of infected cells by cytotoxic T cells accounts for CD4+ T cell depletion, although apoptosis may also be a factor.

During the chronic phase, the consequences of generalized immune activation coupled with the gradual loss of the ability of the immune system to generate new T cells appear to account for the slow decline in CD4+ T cell numbers.

Although the symptoms of immune deficiency characteristic of AIDS do not appear for years after a person is infected, the bulk of CD4+ T cell loss occurs during the first weeks of infection, especially in the intestinal mucosa, which harbors the majority of the lymphocytes found in the

body. The reason for the preferential loss of mucosal CD4+ T cells is that the majority of mucosal CD4+ T cells express the CCR5 protein which HIV uses as a co-receptor to gain access to the cells, whereas only a small fraction of CD4+ T cells in the bloodstream do so.

A specific genetic change that alters the CCR5 protein when present in both chromosomes very effectively prevents HIV infection.

HIV seeks out and destroys CCR5 expressing CD4+ T cells during acute infection. A vigorous immune response eventually controls the infection and initiates the clinically latent phase. CD4+ T cells in mucosal tissues remain particularly affected. Continuous HIV replication causes a state of generalized immune activation persisting throughout the chronic phase. Immune activation, which is reflected by the increased activation state of immune cells and release of pro-inflammatory cytokines, results from the activity of several HIV gene products and the immune response to ongoing HIV replication. It is also linked to the breakdown of the immune surveillance system of the gastrointestinal mucosal barrier caused by the depletion of mucosal CD4+ T cells during the acute phase of disease.

Modes of Transmission

Sexual transmission: The most frequent mode of transmission of HIV is through sexual contact with an infected person occurs through unprotected heterosexual contacts. Risk of transmission increases in the presence of many sexually transmitted infections like syphilis, gonorrhea and genital ulcers.

Exposure to infected blood or blood products: The secondmost frequent mode of HIV transmission is via blood and blood products through needle-sharing during intravenous drug use, needle stick injury, transfusion of contaminated blood or blood product, or medical injections with unsterilized equipment.

Mother to fetus: HIV can be transmitted from mother to child during pregnancy, during delivery, or through breast milk. This is the thirdmost common way in which HIV is transmitted globally. In the absence of treatment, the risk of transmission before or during birth is around 20% and in those who also breastfeed 35%. Perinatal transmission is variable and dependent on viral load and mother's CD 4 count.

Use of contaminated clotting factors by hemophiliacs: People living with hemophilia require regular transfusions of clotting factors in order to maintain a normal blood clotting system. Therefore, those hemophilia patients receiving untested and unscreened clotting factors are at an extreme risk for contracting HIV via the blood products.

Transplantation of infected tissues or organs: The risks of transplant related HIV infection are low. All organ and tissue donors are screened for risk factors, and tested for HIV and other infectious agents that potentially could be transmitted through transplantation.

Primary HIV Syndrome:

Most people who are infected with HIV experience a short, flu-like illness (also known as seroconversion illness) that occurs two to six weeks after infection. It is estimated that upto 80% of people who are

infected with HIV experience this illness. After this, HIV often causes no symptoms for several years. The most common symptoms are fever, sore throat, body rash, headache, diarrhoea, tiredness, joint pain, muscle pain and lymphodenopathy.

Primary HIV syndrome resolves itself and HIV infected person remains asymptomatic for a prolonged period of time, often years, HIV continues to reproduce, CD4 count gradually declines from its normal value of 500-1200 cells per µL. Once CD4 count drops below 500 cells per µL, HIV infected person is at risk for opportunistic infections.

Signs and Symptoms of Common Opportunistic Infections include:

- Dry cough or shortness of breath,
- Difficult or painful swallowing,
- Diarrhoea lasting for more than a week,
- White spots or unusual blemishes in and around the mouth,
- Pneumonia-like symptoms,
- Shaking chills or fever higher than 100 F (38°C) for several weeks,
- Vision loss,
- Nausea, abdominal cramps, and vomiting,
- Red, brown, pink, or purplish blotches on or under the skin or inside the mouth, nose, or eyelids,
- Seizures or lack of co-ordination,
- Neurological disorders such as depression, memory loss, and confusion,
- Severe headaches and neck stiffness,
- Coma.

CD4 count drops below 200 cells per µL, person is considered to have advanced HIV disease:

During late stage HIV infection, the risk of developing a life-threatening illness is much greater. Examples include:

- Esophagitis (an inflammation of the lining of the lower end of the esophagus).
- Infections to the nervous system (acute aseptic meningitis, subacute encephalitis, peripheral neuropathy).
- Pneumonia.
- Some cancers, such as Kaposi's sarcoma, invasive cervical cancer, lung cancer, rectal carcinomas, hepatocellular carcinomas, head and neck cancers, lymphomas etc.
- Toxoplasmosis (a disease caused by a parasite that infects the brain. It can also cause disease in the eyes and lungs).
- Tuberculosis.

Life-threatening illnesses may be controlled and treated with proper HIV treatment.

If CD4 count drops below 50 cells per µL –

- Persistent herpes-zoster infection (shingles),
- Oral candidiasis (thrush),
- Oral hairy leukoplakia,
- Kaposi's sarcoma (KS),
- Mycobacterium avium,
- Cytomegalovirus infections,
- Lymphoma,
- Dementia.

Most deaths occur with CD4 counts below 50 cells per µL.

Infants with HIV

- Failure to thrive,
- Persistent oral candidiasis,
- Hepatosplenomegaly,
- Lymphadenopathy,
- Recurrent diarrhoea,
- Recurrent bacterial infections,
- Abnormal neurologic findings.

Diagnosis

There are several types of tests that screen blood (and sometimes saliva) for HIV infection.

Newer tests can detect the presence of HIV antigen, a protein, upto 20 days earlier than standard tests. It is confirmed by demonstrating certain serological tests.

Performance of medical tests is often described in terms of:

- Sensitivity: The percentage of the results that will be positive when HIV is present.
- Specificity: The percentage of the results that will be negative when HIV is not present. All diagnostic tests have limitations, and sometimes their use may produce erroneous or questionable results.
- False positive: The test incorrectly indicates that HIV is present in a non-infected person.
- False negative: The test incorrectly indicates that HIV is absent in an infected person. Tests used for the diagnosis of HIV infection in a particular person require a high degree of both sensitivity and specificity.

Antibody Tests:

The most common HIV tests look for HIV antibodies in body, rather than looking for HIV itself.

ELISA: The enzyme-linked immuno-sorbent assay (ELISA) was the first screening test commonly employed for HIV. ELISA tests use blood, oral fluid, or urine to detect HIV antibodies. If result from either of these tests is positive, will need to take another test, called a Western blot test, to confirm that result. It can take upto two weeks to confirm a positive result.

Western blot test: Like the ELISA procedure, the western blot is an antibody detection test. However, unlike the ELISA method, the viral proteins are separated first and immobilized. In subsequent steps, the binding of serum antibodies to specific HIV proteins is visualized.

Antigen tests: These tests are not as common as antibody tests, but they can be used to diagnose HIV infection earlier from 1-3 weeks after first infected with HIV. Antigen tests require a blood sample.

PCR test (Polymerase chain reaction test): This test detects the genetic material of HIV itself, and can identify HIV in the blood within 2-3 weeks of infection.

Babies born to HIV-positive mothers are tested with a special PCR test, because their blood contains their mother's HIV antibodies for several months. This means, they would test HIV-positive on a standard antibody test but a PCR test can determine whether the babies have HIV themselves.

Therapeutic Approach to HIV Infection:

There is currently no cure for AIDS or HIV infection. Although antiretroviral treatment can suppress HIV and can delay AIDS related illness for many years to live a long and healthy life, it cannot clear the virus completely.

A combination of antiretroviral drugs, called antiretroviral therapy (ART), also known as highly active antiretroviral therapy (HAART), is very effective in reducing the amount of HIV in the bloodstream. This

is measured by the viral load (how much free virus is found in the blood). Preventing the virus from reproducing (replicating) can improve T-cell counts and help the immune system recover from HIV infection.

In 1987, a drug called Azidothimidine (AZT) became the first approved treatment for HIV disease. Since then, approximately 30 drugs have been approved to treat people living with HIV/AIDS, and more are under development.

e.g. Didinosine, Stavudine, Zalcitabine etc.

The classes of anti-HIV drugs include:

Non-nucleoside reverse transcriptase inhibitors (NNRTIs): NNRTIs disable a protein needed by HIV to make copies of itself. Examples include Efavirenz, Etravirine and Nevirapine.

Nucleoside reverse transcriptase inhibitors (NRTIs): NRTIs are faulty versions of building blocks that HIV needs to make copies of itself. Examples include Abacavir and the combination drugs Emtricitabine and Tenofovir and Lamivudine and Zidovudine.

Protease inhibitors (PIs): PIs disable protease, another protein that HIV needs to make copies of itself. Examples include Atazanavir, Darunavir, Fosamprenavir and Ritonavir.

Entry or fusion inhibitors: These drugs block HIV's entry into CD4 cells. Examples include Enfuvirtide and Maraviroc.

Integrase inhibitors: It is a disable integrase, a protein that HIV uses to infect CD4+ T cells. The most common integrase inhibitor is Raltegravir.

Prevention

Certain educational and motivational programmes can effectively reduce the spread of HIV and AIDS.

Safe sex practice: Such as using latex condoms, are effective in preventing HIV transmission. But there is a risk of getting the infection, even with the use of condoms.

Abstain: (Abstain from sex) Not having vaginal, anal, or oral sex is the surest way to avoid HIV. Abstinence or delay of sexual onset can reduce transmission rate especially in young population who have not started sexual activity.

Drug abuse and needle sharing: Intravenous drug use is an important factor in HIV transmission in developed countries. Sharing needles can expose users to HIV and other viruses. Strategies such as needle exchange programs are used to reduce the infections caused by drug abuse.

Body fluid exposure: Exposure to HIV can be controlled by employing precautions to reduce the risk of exposure to contaminated blood. At all times, health care workers should use barriers (gloves, masks, protective eyewear, shields and gowns). Frequent and thorough washing of the skin immediately after being contaminated with blood or other bodily fluids can reduce the chance of infection.

Pregnancy: Anti-HIV medicines can harm the unborn child. But an effective treatment plan can prevent HIV transmission from mother to baby. Precautions have to be taken to protect the baby's health. Breast feeding may have to give way to bottle feeding if the mother is infected.

15.2 SYPHILIS

Syphilis is sexually transmitted infection (STI) caused by the spirochete bacterium Treponema pallidum. This disease can be passed to another person through kissing or close physical contact. The infected person is often unaware of the disease and unknowingly passes it on to his or her sexual partner.

Stages of Disease

The symptoms of syphilis developed in three stages, are described below.

- Stage 1 (Primary syphilis): Symptoms of syphilis begin with a painless but highly infectious sore on the genitals or sometimes around the mouth. If somebody else comes into close contact with the sore, typically during sexual contact, they can also become infected. The sore lasts two to six weeks before disappearing.
- Stage 2 (Secondary syphilis): Secondary symptoms, such as a skin rash and sore throat develop. These symptoms may disappear within a few weeks, after which person may experience a latent (hidden) phase with no symptoms, which can last for years. After this, syphilis can progress to its third, most dangerous stage.
- Stage 3 (Tertiary syphilis): Around a one third of people who are not treated for syphilis will develop tertiary syphilis. At this stage, it can cause serious damage to the body.

The symptoms of syphilis are the same for men and women. Also symptoms are mild and thus can be difficult to recognize. The symptoms develop in three stages:

- Primary syphilis
- Secondary syphilis
- Tertiary syphilis

Primary Syphilis:

The initial symptoms of syphilis can appear any time from 10 days to three months after one have been exposed to the infection.

The most common symptom is the appearance of a small, painless sore or ulcer (called chancre). The sore will appear on the part of body where the infection was transmitted, typically the penis, vagina, anus, rectum, tongue or lips. Most people only have one sore, but some people can have more.

The sores are painless and may be overlooked, so the condition can be spread without realizing that have an infection.

The sore will then disappear within two to six weeks and, if the condition is not treated, syphilis will move into its second stage.

Secondary Syphilis:

The symptoms of secondary syphilis will begin a few weeks after the disappearance of the sore. Common symptoms include:

- A non-itchy skin rash appearing anywhere on the body, but commonly on the palms of the hands or soles of the feet,
- Tiredness,
- Headaches,
- Swollen lymph glands,

Less common symptoms include:

- Fever,
- Weight loss,

- Patchy hair loss,
- Joint pains.

These symptoms may disappear within a few weeks, or come and go over a period of months.

Latent Phase:

Syphilis will then move into its latent (hidden) phase, where one will experience no symptoms, even though person remains infected. Latent syphilis can still be passed on during the first year of this stage of the condition, usually through sexual or close physical contact. However, after a couple of years, one cannot pass the infection to others, even though he/she remain infected. The latent stage can continue for many years (even decades) after person have first become infected.

Without treatment, there is a risk that latent syphilis will move on to the most dangerous stage – tertiary syphilis.

Tertiary Syphilis:

The symptoms of tertiary syphilis can begin years or even decades after initial infection. Around a one third of people who are not treated for syphilis develop serious symptoms at this stage.

Pathophysiology

The understanding of T. pallidum pathophysiology is impeded by the inability to grow the organism in culture. Thus, knowledge of the growth characteristics and metabolism of this bacterium are quite limited.

Early local infection: Treponema pallidum initiates infection when it gains access to subcutaneous tissues via microscopic abrasions that occur during sexual intercourse. Despite a slow estimated dividing time of 30 hours, the spirochete evades early host immune responses and establishes the initial ulcerative lesion, the chancre (picture 1). During the period of early local replication, some organisms establish infection in regional draining lymph nodes, with subsequent dissemination.

Immune response: Treponema pallidum elicits innate and adaptive cellular immune responses in skin and blood. The host immune response begins with lesional infiltration of polymorphonuclear leukocytes, which are soon replaced by T lymphocytes. In some respects, the immune response to T. pallidum is paradoxical. On one hand, the various immune responses during early infection appear to be efficacious, since they coincide with resolution of the primary chancre, even in the absence of therapy. Despite this apparent immune control, however, widespread dissemination of spirochetes occurs at the same time, leading to subsequent clinical manifestations of secondary or tertiary syphilis in untreated patients.

After acquisition on T. pallidum, humoral immune responses are generated, leading to the development of a variety of antibodies that can be detected relatively early in the course of syphilis.

Causes

- Syphilis is caused by the bacteria Treponema pallidum.
- The bacteria can enter one's body if he/she have close contact with an infected sore, normally during vaginal, anal or oral sex or by sharing sex toys.

Diagnosis

Physical examination: Syphilis is diagnosed by examine the genitals. For men,

it involves examining the penis, foreskin and urethra (the hole at the end of the penis where urine comes out). For women, it involves an internal examination of the vagina. Both men and women may also have their anus examined.

Blood tests: If one is infected with syphilis, then his/ her body produces antibodies (proteins released as part of immune response) against the syphilis bacteria. Therefore, one way to determine whether one have syphilis is to have a sample of blood tested for the presence of these antibodies. A positive result (antibodies present) indicates that one can either have the infection or used to have it (because the antibodies can remain in the body for years, even after a previous infection was successfully treated).

A negative result does not necessarily mean that one does not have syphilis as the antibodies may not be detectable for three months after infection. Person may be advised to repeat the test in three months' time.

Every pregnant woman should have a blood test for syphilis as the infection can kill unborn or new born babies. The blood test is usually done during an antenatal appointment at weeks 11–20 of pregnancy. If the test is positive, treatment for both the mother and baby can begin.

Venereal Disease Research Laboratory test (VDRL): The VDRL test is a screening test for syphilis. It measures substances, called antibodies that body may produce if a person comes in contact with the bacteria that causes syphilis. This bacteria is called Treponema pallidum.

Swab test: If sores are present, a swab (like a cotton bud) will be used to take a small sample of fluid from the sore. This is then either looked at under a microscope in the clinic or sent to a laboratory for examination.

Treatment

Effective antibiotic treatment is available. Treatment needs to be supervised carefully and long-term follow-up is required, particularly for patients with late stage syphilis infection. Treatment of the mother during pregnancy may be sufficient to prevent fetal infection. Sometimes babies require an additional course of antibiotics after birth.

Primary Option: Penicillin G Benzathine 2.4 million units intramuscularly as a single dose.

Secondary Option: Doxycycline 100 mg orally twice daily and Prednisone 40-60 mg orally once daily for 3 days; start 24 hours before penicillin.

Prevention

- Protected physical contact through the use of condoms reduces the risk of infection.
- Promoting sex-education among teen-agers.
- Providing awareness among the population about their sexual health especially in high risks population (high risks population involves sex workers and their partners, Intravenous drug users, truck drivers, labour migrants, refugees and prisoners).
- People with syphilis should refrain from any sexual contact for at least 1 week after completing treatment or until the lesions of early syphilis (if they were present) are fully healed.
- People with syphilis should also refrain from any sexual contact until sexual

partners have been contacted, tested and if indicated treated.
- Follow-up blood tests must be done to make sure that treatment has cleared the infection.
- Pregnant women are screened for syphilis in early pregnancy and again in late pregnancy if they are at increased risk of acquiring syphilis.
- Testing to exclude other sexually transmitted infections is advisable.

15.3 GONORRHOEA

Gonorrhoea is a sexually transmissible infection (STI) caused by bacteria known as Neisseria gonorrhoeae (gonococcus). It usually affects the genital area, although the throat or anus may also be affected. Gonorrhoea affects both men and women and is easily transmitted during vaginal intercourse. It can also be transmitted during anal or oral sex. Gonorrhoea is transmitted from any kind of sexual contact, including:

- Vaginal intercourse
- Anal intercourse
- Oral intercourse (both giving and receiving)

Pathophysilogy

Gonococci are readily seen in smears (urethral, endcervical, or conjunctival exudates) and cultures, and appear as bean-shaped pairs, with the flat sides apposed. The organisms are cultured from tampons, urethral swabs, urine, specimens from endocervix, vagina, anus, and pharynx.

Gonorrhoea begins as a surface infection of the mucous membranes, that is, a catarrh. The bacteria attach to and spread along the cells of the surface mucous membranes, after which they invade superficially and provoke acute inflammation. The mucous membranes of the urethra, endocervix, and salpinx are characteristic sites.

The cell wall of Neisseria gonorrhoeae contains lipopolysaccharide, protein and phospholipid. It lacks a true polysaccharide capsule, but projecting from the cell wall are hairlike extensions called pili. Within these pili is a protease that digest IgA on the surface of the mucus membrane, thus facilitating the attachment of gonococci to the columnar and transitional epithelium of the urogenital tract. "Smooth" strains with few pili are less virulent and less prone to cause urethritis or cervicitis. After an incubation period of 3 to 5 days, men usually have purulent urethral discharge and dysuria.

With prompt antibiotic treatment, the infection is arrested and gonococci are confined to the mucosa of the anterior urethra. However, if treatment is not instituted promptly, the organisms extend to the prostate, epididymis, accessory glands, where they cause urethral stricture, epididymitis, orchitis, and sometimes male infertility. Urethral stricture may be associated with fistulas between the urethra and perineum (“watering can” perineum). Male homosexuals develop pharyngitis and proctitis.

The first manifestation of infection in women is usually endocervicitis, with vaginal discharge or bleeding. There may be urethritis, manifestated by dysuria rather than by urethral discharge. In some women (usually during the first menses after exposure), the infection extends to the

fallopian tubes, where it produces acute and chronic salpingitis and pelvic inflammatory disease. The fallopian tubes swell with pus, causing acute abdominal pain. Infertility occurs when inflammatory adhesions close the tubes at both ends, blocking the ascent of sperm and the descent of ova. Infected fallopian tubes ('pus tubes') have the shape of a retort flask. From the fallopian tubes the infection may spread to the peritoneum, healing as fine adhesions ("violin string" adhesions) between the capsule of the liver and the parietal peritoneum. The vaginal discharge may infect the anal crypts, leading to mucopurulent anal discharge, rectal pruritus and tenesmus.

Chronic endometritis is a persistent complication of gonococcal infection and is usually a consequence of chronic gonococcal salpingitis. In such cases the endometrium contains many lymphocytes and plasma cells.

Women (and to a lesser extent men) may also develop bacteremia, producing disseminated gonococcal infection, which in turn leads to monoarthritis or polyarthritis. Neonatal infections from infected amniotic fluid or an infected birth canal result in symptoms within a few days after birth. These infections involve the conjunctiva and constitute a major cause of blindness. Other sites of neonatal infection are the pharynx, respiratory tract, vagina, anus, leptomeninges, joints and blood.

Uncomplicated gonococcal infections of the urethra and endocervix are treated with penicillin and other antibiotics. Neisseria gonorrhoea is displaying increasing resistance to penicillin. Penicillinase-producing strains are especially common in Africa and Asia.

Signs And Symptoms

Both men and women may have gonorrhoea without having any symptoms and so can be infected, or spread infection, without knowing anything is wrong. Some men never develop symptoms, but most do. Symptoms that may occur include:

- Throat and anal infections can occur following receptive oral and anal intercourse and infections at these sites are often without symptoms.
- Joint pain and infection (arthritis).
- Conjunctivitis (inflammation of the lining of the eyelids and eye) in both adults and children. Babies born to infected mothers can become infected as they pass through the infected cervix and may develop gonococcal conjunctivitis soon after birth.
- Having any sexually transmitted infection (STI) increases the risk of HIV infection if exposed to HIV virus while the other infection is present.

Men

In addition to the above, gonorrhoea in men causes' urethritis (infection of the urethra, the urinary canal leading from the bladder to exit at the tip of the penis) causing:

- A burning sensation in the penis when urinating.
- A white or yellow pus-like discharge from the penis (may be observed in underwear).
- Swelling and pain in the testicles, which can occur if the gonorrhoea infection goes untreated.

Women

In addition to the above, gonorrhoea in women usually affects the cervix (opening of the uterus at the top of the vagina) causing:

- An unusual vaginal discharge.
- Discomfort on urination.
- Bleeding between periods, often after having sex.
- Pain while urinating or passing water.

The infection may spread from the cervix to the fallopian tubes, causing pelvic inflammatory disease (PID). Pelvic inflammatory disease due to gonorrhoea is often without symptoms, but there may be:

- Fever,
- Low abdominal pain,
- Pain on intercourse.

If untreated, pelvic inflammatory disease may lead to scarring of the fallopian tubes and ectopic (tubal) pregnancy or infertility.

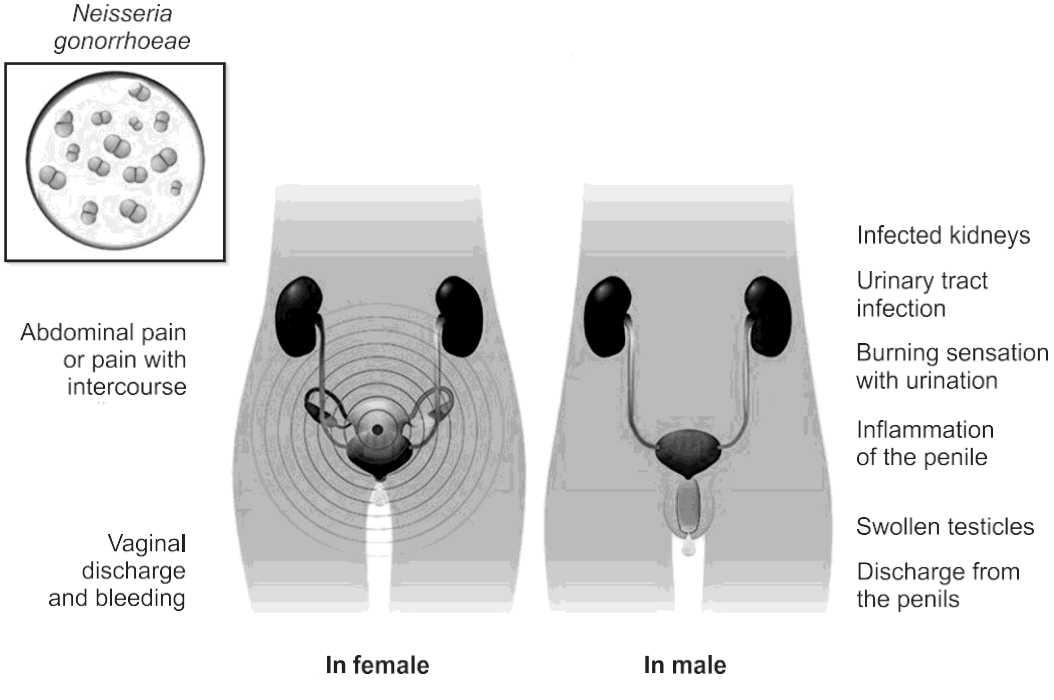

Fig. 15.2 : Signs and symptoms of gonorrhoea

Risk Factors

Risk factors for gonorrhea include the following:

- Sexual exposure to an infected partner without barrier protection (e.g., failure to use a condom or condom failure),
- Multiple sex partners,
- Male homosexuality,
- History of concurrent or past STDs,
- IV drug users,
- Use of crack cocaine,
- Early age of onset of sexual activity,
- Pelvic inflammatory disease (PID) - Use of an intrauterine device (IUD).

Diagnosis

To determine whether the gonorrhoea bacterium is present in body, analyze a sample of cells. Samples can be collected by:

- Urine test: This may help to identify bacteria in urethra.
- Swab of affected area: A swab of throat, urethra, vagina or rectum may collect bacteria that can be identified in a laboratory.

- Traditionally, gonorrhoea was diagnosed with gram stain and culture; PCR-based testing methods are common. All people testing positive for gonorrhoea should be tested for other sexually transmitted diseases such as chlamydia, syphilis, and human immunodeficiency virus.

Treatment

Antibiotic resistance has developed to a number of agents, including macrolides, clindamycin and rifampin. Ceftriaxone, a third-generation cephalosporin antibiotic, may be as effective as penicillin-based treatment.

CDC recommendation for uncomplicated gonorrhoea: Ceftriaxone 125 mg single IM dose or Ciprofloxacin 500 mg single oral dose plus doxycycline 100 mg twice daily for 7 days or Erythromycin 1 g single oral dose.

Prevention

- Practice safer sex.
- No sex until antibiotic treatment is completed and usual sexual partner has completed treatment.
- A follow-up test must be done to make sure that treatment has cleared the infection.
- All sexual partners need to be contacted, tested and treated, if indicated. Even if partners have no symptoms, they may be able to transmit infection to other sexual partners.
- Testing to exclude other sexually transmitted infections is advisable.

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GLOSSARY

- Abdominal hernia: A hernia is the protrusion of an organ or piece of tissue from its normally contained space.
- Achalasia: It is a rare disease of the muscle of the esophagus (swallowing tube). The term achalasia means "failure to relax" and refers to the inability of the lower esophageal sphincter (a ring of muscle situated between the lower esophagus and the stomach) to open and let food pass into the stomach. As a result, patients with achalasia have difficulty in swallowing food.
- Achondroplasia: Achondroplasia is a genetic (inherited) condition that results in abnormally short stature and is the most common cause of short stature with disproportionately short limbs. The average height of an adult with achondroplasia is 131 cm (52 inches, or 4 foot 4 inches) in males and 124 cm (49 inches, or 4 foot 1 inch) in females.
- Acidosis: A condition marked by a high concentration of hydrogen ions.
- Acquired: A disease, condition, or trait that developed because of being exposed to something during life.
- Actin filaments (Microfilaments): These are the bundles of globular structural proteins or actin fibrils that aid in cell movement and structure and are necessary for regulating cell growth.
- Active transport: A carrier mediated process that can move substances against a concentration gradient.
- Acute Lymphoblastic Leukemia (ALL): An excessive production and continuous multiplication of malignant and immature white blood cells (lymphoblasts) in the bone marrow that progresses rapidly if left untreated.
- Acute Myelogenous Leukemia (AML): An excessive number of immature myeloid cells (myeloblasts) in the blood and bone marrow crowding out the marrow and decreasing other cell line functions.
- Acute stage: The time during an infection when clinical signs and symptoms begin to develop.
- Acute: A disease that develops and resolve rapidly.
- Adhesions: The binding together of two surfaces by scar tissue.
- Aerobic: Pertaining to the presence of air or oxygen.
- After load: The total resistance against which blood must be pumped.
- Alkalosis: A condition marked by a low concentration.
- Allergens: Substances that can produce hypersensitivity reaction in the body.
- Allergy: Allergy involves an exaggerated response of the immune system, often to common substances such as foods or pollen.
- Alzheimer's disease: The most common form of dementia.
- Amebiasis: It is a disease caused by the parasite Entamoeba histolytica. It can affect anyone, although it is more common in people who live in tropical areas with poor sanitary conditions. Diagnosis can be difficult because other parasites can look very similar to E. histolytica when seen under a microscope. Infected people do not always

become sick. If your doctor determines that you are infected and need treatment, medication is available.

- Amenorrhea: Amenorrhea refers to the absence of menstrual periods; it may be either primary (meaning a woman never developed menstrual periods) or secondary (absence of menstrual periods in a woman who was previously menstruating).
- Amyloidosis: It is a group of diseases that result from abnormal protein deposits in various tissues of the body. These abnormal proteins are called amyloid.
- Anaerobic: Pertaining to the absence of oxygen.
- Anaphylaxis: A severe, systemic allergic response that is characterized by vasodilation (which causes a severe drop in blood pressure) and bronchoconstriction (resulting in severe difficulty in breathing).
- Anemia: Anemia is a medical condition in which the red blood cell count or hemoglobin is less than normal. For men, anemia is typically defined as hemoglobin level of less than 13.5 gram/100 ml and in women as hemoglobin of less than 12.0 gram/100 ml.
- Aneurysm: An aneurysm is a bulge or "ballooning" in the wall of an artery.
- Angina: Angina pectoris describes the pain, discomfort, or other symptoms that occur when blood flow to heart muscle cells is not enough to meet its energy needs.
- Angiogenesis: The development of new blood vessels, especially capillaries.
- Angioplasty: Coronary angioplasty is accomplished using a balloon-tipped catheter inserted through an artery in the groin or arm to enlarge a narrowing in a coronary artery.
- Anion: An ion with a negative charge.
- Anorexia nervosa: It is a psychiatric condition, which is part of a group of eating disorders.
- Antigens: Substances (usually proteins) that cause formation of an antibody and that react specifically with that antibody.
- Aortic aneurysm: An aortic aneurysm is dilation or bulging of the aorta.
- Aphthous ulcer: A small sensitive painful ulcer crater in the lining of the mouth, commonly called a canker sore.
- Arthritis: Arthritis is inflammation of one or more joints.
- Ascites: Accumulation of fluid in the peritoneal cavity, causing abdominal swelling.
- Asthma: Asthma is a disease that affects lungs. It causes repeated episodes of wheezing, breathlessness, chest tightness, and night time or early morning coughing. Asthma can be controlled by taking medicine and avoiding the triggers that can cause an attack.
- Atrial fibrillation: Atrial fibrillation is an abnormal rhythm of the heart.
- Atrophy: A wasting or decrease in size of body organ, tissue or part owing to disease, injury or lack of use.
- Autopsy: An autopsy is the examination of the body of a dead person.
- Barium enema: A barium enema (lower GI series) is an X-ray procedure used to define the anatomy of the large intestine (colon) and the rectum.
- Bedwetting: It is also called nocturnal enuresis, an involuntary passage of urine (urinary incontinence) while asleep. Inherent in the definition of bedwetting is satisfactory bladder control while the person is awake. Therefore, urination while awake is a different condition and has a variety of different causes than bedwetting.
- Benign: A non-malignant neoplasm.

- Bone marrow: The soft material in the center of bones is the bone marrow. The bone marrow contains the different types of cells that give rise to red cells, white cells and platelets found in our blood.
- Bronchitis: Bronchitis is a term that describes inflammation of the bronchial tubes (bronchi and the smaller branches termed bronchioles) that results in excessive secretions of mucus into the tubes with tissue swelling that may narrow or close off bronchial tubes.
- Cancer: Cancer is the uncontrolled growth of abnormal cells anywhere in a body.
- Carcinogenesis: The process of developing a malignant neoplasm.
- Carcinoma: A malignancy that originates in epithelial tissues.
- Cellulitis: It is a spreading bacterial infection of the skin and tissues beneath the skin.
- Cervical dysplasia: Cervical dysplasia is precancerous change in the lining cells of the cervix of the uterus.
- Chemotherapy: The use of chemicals to kill cells within the body. Two main types of chemotherapy are used to kill cancer cells or microorganisms.
- Chronic cough is a cough that persists: Chronic cough is not a disease in itself, but rather a symptom of an underlying condition. Chronic cough is a common problem and the reason for many doctor visits.
- Chronic obstructive pulmonary disease: Chronic obstructive pulmonary disease (COPD) is a slowly progressive obstruction of airflow into or out of the lungs.
- Chronic: A disease that develops gradually and last for six months or longer.
- Cirrhosis: Cirrhosis is a complication of liver disease which involves loss of liver cells and irreversible scarring of the liver.
- Cleft lip and cleft palate: Cleft lip and palate are developmental defects of the upper lip and roof of the mouth that are present at birth (congenital malformations).
- Colitis: Colitis is inflammation of the inner lining of the colon. It may cause abdominal pain and diarrhoea with or without blood. Fever may be present.
- Colposcopy: Colposcopy is a gynecological procedure that illuminates and magnifies the vulva, vaginal walls, and uterine cervix in order to detect and examine abnormalities of these structures.
- Complications: A morbid process or event ocurring during a disease that is not an essential part of the disease, although it may result from it. (Example: Blindness is a complicaiton often associated with diabetes).
- Congenital: A disease, condition, or trait that is present at birth.
- Constipation: Constipation is defined medically as fewer than three stools per week and severe constipation as less than one stool per week.
- Contracture: The shortening of scar tissue over time or the shortening of muscle tissue as a result of fibrotic changes.
- Contrast X-rays: X-rays that utilize a contrast media to increase the radio density of selected fluids within the body, producing an image of the structures containing the fluid.
- C-reactive protein (CRP): It is a blood test marker for inflammation in the body. CRP is produced in the liver and its level is measured by testing the blood.
- Crohn's disease: Crohn’s disease is a chronic inflammatory disease of the intestines.
- Cushing's syndrome: Cushing’s syndrome or “hypercortisolism”, is a relatively rare hormonal disorder caused by prolonged exposure of the body’s tissues to high levels of the hormone cortisol.

- Cyst facts: Cysts are closed sac-like or capsule structures that may be filled with semisolid material, gaseous material or liquid.
- Deafness: Hearing loss, or deafness, can be present at birth (congenital), or become evident later in life (acquired).
- Deficiency: Lacking in something that is essential. (Vitamin glucose, protein, oxygen, water.)
- Dehydration: Dehydration occurs when water intake is less than water loss.
- Dementia: Dementia is a term that describes a collection of symptoms that include decreased intellectual functioning that interferes with normal life functions and is usually used to describe people who have two or more major life functions impaired or lost such as memory, language, perception, judgment or reasoning; they may lose emotional and behavioural control.
- Dengue fever: Dengue fever is a disease caused by a family of viruses that are transmitted by mosquitoes.
- Depression: A depressive disorder is a syndrome (group of symptoms) that reflects a sad, blue mood exceeding normal sadness or grief.
- Diabetes insipidus: It is caused by problems related to the hormone antidiuretic hormone (ADH) or its receptor and causes frequent urination.
- Diabetes Mellitus: Diabetes is a chronic condition associated with abnormally high levels of sugar (glucose) in the blood.
- Diabetic neuropathy: Diabetic neuropathy is damage to nerves that occurs as a result of diabetes.
- Dialysis : The kidneys are responsible for filtering waste products from the blood. Dialysis is a procedure that is a substitute for many of the normal duties of the kidneys.
- Diarrhoea: Diarrhea is an increase in the frequency of bowel movements, an increase in the looseness of stool or both.
- Dilated Cardiomyopathy: Dilated cardiomyopathy (DCM) is a condition in which the heart's ability to pump blood is decreased because the heart's main pumping chamber, the left ventricle, is enlarged and weakened.
- Disease: Being unable to maintain homeostasis when exposed to normal conditions.
- Down syndrome: Down syndrome is a genetic disorder and the most common autosomal chromosome abnormality in humans, where extra genetic material from chromosome 21 is transferred to a newly formed embryo. These extra genes and DNA cause changes in development of the embryo and fetus resulting in physical and mental abnormalities. Each patient is unique and there can be great variability in the severity of symptoms.
- Dyspepsia (indigestion): Dyspepsia is a functional disease in which the gastrointestinal organs, primarily the stomach and first part of the small intestine, function abnormally.
- Dysphagia: Dysphagia means difficulty in swallowing.
- Dysplasia: Irregular cell or tissue structure. Often condsidered a potentially cancerous change.
- Dysthymia: Dysthymia, now referred to as persistent depressive disorder, is a form of depression that lasts for more than two years at a time in adults and more than one year at a time in children and adolescents.

- Dystonia: Dystonia is a disorder characterized by involuntary muscle contractions that cause slow repetitive movements or abnormal postures. The movements may be painful, and some individuals with dystonia may have a tremor or other neurologic features.
- Ectopic pregnancy: An ectopic pregnancy is a pregnancy located outside the inner lining of the uterus.
- Edema: Edema is a swelling, usually of the legs, due to the accumulation of excessive fluid in the tissues.
- EEG: An EEG, or electroencephalogram, is a test that can help to diagnose epilepsy. During an EEG, the electrical signals of the brain are recorded. This electrical activity is detected by electrodes, or sensors, placed on the patient's scalp and transmitted to a polygraph that records the activity.
- Electrocardiograms: A recording of the electrical activity of the cardiac conduction system.
- Electroencephalogram: A recording of the electrical activity of the brain, most often recording the cerebral cortex.
- Electromyogram: An electromyogram (EMG) is a test that is used to record the electrical activity of muscles. When muscles are active, they produce an electrical current. This current is usually proportional to the level of the muscle activity. An EMG is also referred to as a myogram.
- ELISA test (Enzyme Linked Immunosorbant Assay): An ELISA test uses components of the immune system and chemicals to detect immune responses in the body (for example, to infectious microbes). The ELISA test involves an enzyme (a protein that catalyzes a biochemical reaction). It also involves an antibody or antigen (immunologic molecules).
- Emphysema: Emphysema is a destructive disease of the lung in which the alveoli (small sacs) that promote oxygen exchange between the air and the bloodstream are destroyed.
- Encephalopathy: Encephalopathy is a term that means brain disease, damage, or malfunction. Encephalopathy can present a very broad spectrum of symptoms that range from mild, such as some memory loss or subtle personality changes, to severe, such as dementia, seizures, coma, or death.
- Endoscopy (Upper): Upper endoscopy is a procedure that enables the examiner (usually a gastroenterologist) to examine the esophagus (swallowing tube), stomach, and duodenum (first portion of small bowel) using a thin, flexible tube called the upper endoscope through which the lining of the esophagus, stomach, and duodenum can be viewed using a TV monitor.
- Endoscopy: A procedure that utilizes a fiber optic camera to view structures inside of the body.
- Epilepsy: Epilepsy is a brain disorder in which clusters of nerve cells, or neurons, in the brain sometimes signal abnormally causing strange sensations, emotions and behaviour, or sometimes convulsions, muscle spasms and loss of consciousness.
- Episiotomy: An episiotomy is an incision performed between the vagina and the rectum that is used to increase the size of the opening of the vagina to assist in delivery of a baby.
- Erectile dysfunction (impotence): Erectile dysfunction (ED), also known as impotence, is the inability to achieve or sustain an erection for satisfactory sexual activity.

- Erythropoietin (EPO): Erythropoietin (EPO) is a hormone produced by the kidney that promotes the formation of red blood cells by the bone marrow.
- Esophagitis: Esophagitis is a term used to describe inflammation of the esophagus.
- Etiology: The study of the cause of a disease.
- Exacerbation: An increase in the severity of a disease or any of its signs or symptoms.
- Exudate: The excess fluid that accumulates at the site of inflammation. Contains a high level of proteins and neutrophils when compared to normal tissue fluid.
- Fatigue: Fatigue (either physical, mental or both) is a symptom that may be difficult for the patient to describe and words like lethargic, exhausted and tired may be used.
- Felty's syndrome: Felty's syndrome is a complication of long-standing rheumatoid arthritis.
- Ferritin blood test facts: The ferritin test measures the level of ferritin, the major iron storage protein in the body.
- Fragile X syndrome: Fragile X syndrome (also called Fragile X) is the most common inherited form of mental problems (mental retardation).
- Gallstones: Gallstones are "stones" that form in the gallbladder or bile ducts. The common types of gallstones are cholesterol, black pigment and brown pigment.
- Gangrene: Gangrene refers to dead or dying body tissue(s) that occur because of inadequate blood supply.
- Gastritis: Gastritis is inflammation of the lining of the stomach.
- Gastroenteritis: Gastroenteritis (often referred to as the "stomach flu", however, it is not related to the influenza virus) is a nonspecific term for various problems in the gastrointestinal tract with the most common symptoms and signs of diarrhoea, nausea, vomiting and abdominal pains.
- Gaucher disease: Gaucher disease is an inherited disorder of metabolism that interferes with many body functions.
- Genetic: A disease, condition, or trait that is inherited as a result of a single gene.
- Genital herpes: Genital herpes is a sexually transmitted disease caused by herpes simplex virus (HSV).
- GERD: GERD (acid reflux) is a condition in which the acidified liquid content of the stomach backs up into the esophagus.
- Giardiasis: Giardiasis (gee-ar-die-a-sis with a soft "G") is an infection of the small intestine that is caused by the parasite, Giardia intestinalis, also known as Giardia lamblia.
- Gilbert syndrome: Gilbert syndrome is a common, harmless genetic condition in which a liver enzyme essential to the disposal of bilirubin (the chemical that results from the normal breakdown of hemoglobin from red blood cells) is abnormal.
- Gingivitis: Gum disease, or gingivitis, is inflammation of the tissues surrounding and supporting the teeth and is most commonly a result of poor dental hygiene.
- Glaucoma: Glaucoma is a disease that is often associated with elevated intraocular pressure, in which damage to the eye (optic) nerve can lead to loss of vision and even blindness.
- Glioma: A malignancy that originates within the tissue of the central nervous system.
- Glucose-6-phosphate dehydrogenase deficiency: Glucose-6-phosphate dehydrogenase deficiency (also called G6PD deficiency) is a genetic disorder that mainly

affects red blood cells, which carry oxygen from the lungs to tissues throughout the body. A defect in an enzyme called glucose-6-phosphate dehydrogenase causes red blood cells to break down prematurely (hemolysis).

- Goodpasture Syndrome: Goodpasture syndrome is a rare but serious autoimmune disease that attacks the lungs and kidneys.
- Gonorrhea: Gonorrhea is a bacterial infection that is transmitted during sexual activity.
- Gout: Gout is a type of arthritis that causes inflammation, usually in one joint, that begins suddenly.
- Graves' disease: Graves' disease is a thyroid condition that results from abnormal stimulation of the thyroid gland by a material in the blood referred to as thyroid stimulating immunoglobins (TSIs) that bind to and activate thyrotropin receptors.
- Guillain-Barré syndrome: Guillain-Barré syndrome occurs when the immune system attacks the peripheral nervous system, leading to weakness or tingling in the legs. Symptoms sometimes affect the arms and upper body. Severe cases of Guillain-Barré can lead to paralysis and are life-threatening.
- Gynecomastia: Gynecomastia is enlargement of the glandular tissue of the male breast.
- Health: Having the ability to maintain homeostasis when exposed to normal conditions.
- Heart attack: A heart attack (also known as a myocardial infarction or MI) is the death of heart muscle from the sudden blockage by a blood clot in a coronary artery that supplies blood to the heart.
- Heart murmur facts: Turbulent blood flow within the heart causes abnormal sounds called murmurs.
- Heartburn definition: Heartburn is a sensation of burning in the chest caused by stomach acid backing up into the esophagus (food pipe).
- Hematospermia: The presence of blood in the semen (ejaculate).
- Hemophilia: Hemophilia is one of a group of inherited bleeding disorders that cause abnormal or exaggerated bleeding and poor blood clotting.
- Hemophilia: Hemophilia is one of a group of inherited bleeding disorders that cause abnormal or exaggerated bleeding and poor blood clotting.
- Hiccup: A hiccup is a sudden, involuntary contraction (spasm) of the diaphragm muscle. When the muscle spasms, the vocal cords snap shut, producing the hiccup sound.
- High blood pressure: High blood pressure (hypertension) is defined as high pressure (tension) in the arteries, which are the vessels that carry blood from the heart to the rest of the body.
- Huntington's disease: Huntington's disease (HD) is a complex disorder that affect's a person's ability to feel, think and move.
- Hyperplasia: An increase in the rate of mitosis and therefore cell number.
- Hypersomnia: Hypersomnia, or excessive sleepiness, is a condition in which a person has trouble staying awake during the day.
- Hyperthyroidism: Hyperthyroidism is a condition in which there is an excessive amount of thyroid hormones.
- Hypoglycemia: Hypoglycemia is the clinical syndrome that results from low blood sugar.
- Hyponatremia: Hyponatremia refers to a low level of sodium in the blood.

- Hypothyroidism: Hypothyroidism refers to any state in which thyroid hormone production is below normal.
- Idiopathic: Without a clearly identified cause.
- Immunosurveillance: The immune system's constant search for an antigen.
- Immunotolerance: The immune system's ability to recognize and not attack normally occurring tissues with the body.
- Impetigo: Impetigo is a bacterial infection of the surface of the skin.
- Implantable cardiac defibrillators (ICDs): An implantable cardioverter defibrillator (ICD) is a small electronic device installed inside the chest to prevent sudden death from cardiac arrest due to life threatening abnormally fast heart rhythms (tachycardias). The ICD is capable of monitoring the heart rhythm. When the heart is beating normally, the device remains inactive. If the heart develops a life-threatening tachycardia, the ICD can attempt pacing to bring the heart rhythm back to normal, or it can deliver an electrical "shock(s)" to the heart to terminate the abnormal rhythm and return the heart rhythm to normal.
- Incubation: The development of an infection from the time the infectious organism enters the body unil the appearance of the first clinical signs and symptoms.
- Infertility: Infertility means not being able to become pregnant, within certain parameters.
- Inflammation: A protective response of tissue to injury or infection. Causes an increase in blood flow and pain in the affected region, as well as leukocytosis.
- Influenza: Influenza, commonly called "the flu", is caused by viruses that infect the respiratory tract.
- Initiators: Carcinogens that increase the rate of cancer cell production by activating oncogenes.
- Insomnia: Insomnia is a condition characterized by poor quality and/or quantity of sleep, despite adequate opportunity to sleep, which leads to daytime functional impairment.
- Intoxication: Being exposed to a toxic level of something.
- Jaundice: Jaundice is a yellowish discolouration of the skin, mucous membranes and white of the eyes caused by elevated levels of bilirubin in the blood (hyperbilirubinemia).
- Kawasaki's: Kawasaki's disease is a syndrome of unknown cause that mainly strikes young children. Signs of the disease include fever and redness of the eyes, hands, feet, mouth and tongue.
- Keloid scarring: The overproduction of scar tissue that sometimes occurs in the dermis and subcutaneous layer and results in a mass of scar tissue that is often tender or painful.
- Kelley-Seegmiller syndrome: A rare genetic disorder characterized by the formation of stones in the urinary tract, early-onset gout and mild neurological symptoms. It is caused by a partial deficiency of hypoxanyhine-guanine phosphoribosyl transferase.
- Keratitis: Keratitis is the medical term for inflammation of the cornea.
- Kidney stone: A kidney stone is a hard, crystalline mineral material formed within the kidney or urinary tract.
- Lactose intolerance: Lactose intolerance is an inability to digest lactose.
- Laryngitis facts: Laryngitis is an inflammation of the voice box (larynx).
- Leukemia: Leukemia is a cancer of the blood cells.

- Leukocytosis: An increase in the number of white blood cells to more than 10,000 per mm^3. A WBC count of 15,000 - 25,000 commonly occurs as a result of infection, inflammation or hemorrhage.
- Lesch-Nyhan syndrome (LNS): also known as Nyhan's syndrome, Kelley-Seegmiller syndrome, and juvenile gout, is a rare inherited disorder caused by a deficiency of the enzyme hypoxanthine-guanine phosphoribosyl transferase (HGPRT), produced by mutations in the HPRT gene located on the X chromosome.
- Local: A condition that is confined to one area.
- Malaria: Malaria is a serious, sometimes fatal, disease spread by mosquitoes and caused by a parasite.
- Malignant: A cancerous neoplasm.
- Menstrual cramps: Menstrual cramps are pains in the belly and pelvic areas that are experienced by a woman as a result of her menstrual period.
- Menstruation: Menstruation is a monthly shedding of a female's uteral lining; it lasts about 3 to 5 days (average) and contains blood and tissue that exits her body through the cervix and vagina.
- Metaplasia: A change in cell or tissue structure.
- Narcolepsy: Narcolepsy is a chronic disease of the central nervous system. The symptoms include excessive daytime sleepiness (EDS), loss of muscle tone (cataplexy), distorted perceptions (hypnagogic hallucinations), inability to move or talk (sleep paralysis), disturbed nocturnal sleep, and automatic behaviour.
- Necrosis: The death of most or all of the cells in an organ or tissue due to disease, injury or failure of blood supply.
- Neoplasia: Growth of cells and tissue into new areas, resulting in a tumor. May be benign or maligment.
- Neutropenia: It is a condition in which the number of neutrophils in the bloodstream is decreased. Neutrophils are a type of white blood cell also known as polymorphonuclear leukocytes or PMNs. Neutropenia reduces the body's ability to fight off bacterial infections.
- Nightmares: Nightmares are dreams that are threatening and scary.
- Noonan syndrome: Noonan syndrome is a genetic disorder that may cause short stature, distinctive facial features and heart abnormalities.
- Obesity: Obesity means having excess body fat. For adults 35 and older, having a BMI greater than 30 is considered obese.
- Osteoarthritis: Osteoarthritis is a joint inflammation that results from cartilage degeneration.
- Osteopenia: Osteopenia is decreased bone density but not to the extent of osteoporosis. This decreased bone density leads to bone fragility and an increased chance of breaking a bone (fracture).
- Osteoporosis: Osteoporosis is a condition of fragile bone with an increased susceptibility to fracture.

- Pacemaker: A pacemaker is a small device that is placed in the chest or abdomen to help control abnormal heart rhythms. This device uses low-energy electrical pulses to prompt the heart to beat at a normal rate.
- Palliative: Any form of treatment that relieves signs and symptoms without curing a disease. May include the use of medication (such as decongestant or pain reliever), therapeutic massage, counseling, physical therapy, othotic devices.
- Pancreatitis: Pancreatitis is inflammation of the pancreas, the organ that secretes digestive enzymes into the gastrointestinal tract; it also synthesizes and secretes insulin and glucagon.
- Parkinson's disease: Parkinson's disease is a neurodegenerative disorder which leads to progressive deterioration of motor function due to loss of dopamine-producing brain cells.
- Patechial lesion: A small purpilish spot on a body surface, such as the skin or mucous membrane, caused by a minute hemorrhage.
- Pathogenesis: The events that lead to the development of a disease and the signs and symptoms that occur as the disease progresses.
- Pathognomonic: A sign or symptom that is so characteristic of a disease that it can be used to make a diagnosis. For example, Koplik spots in the mouth opposite the first and second upper molars are pathognomonic of measles.
- Pathology: The study of changes in cell/tissue structure related to disease or death.
- Pathophysiology: The study of how disease affects body function.
- Pericarditis: Pericarditis is an inflammation of the lining surrounding the heart (the pericardial sac).
- Pernicious anemia: Pernicious anemia is a condition caused by too little vitamin B_{12} in the body. It is a form of vitamin B_{12} deficiency anemia.
- Pharmacological: The use of drugs to treat disease.
- Pheochromocytoma: Pheochromocytomas are a type of tumor of the adrenal glands that can release high levels of epinephrine and norepinephrine.
- Phobia: The definition of a phobia is the unrelenting fear of a situation, activity, or thing that causes one to want to avoid it.
- Pleurisy: Pleurisy involves inflammation of the tissue layers (pleura) lining the lungs and inner chest wall.
- Polymyalgia Rheumatica: Polymyalgia rheumatica is a disorder of the muscles and joints characterized by muscle pain and stiffness, affecting both sides of the body, and involving the shoulders, arms, neck and buttock areas.
- Prodromal stage: An early stage in the development of a disease or infection that is characterized by a lack of appetite and lack of energy. The time when a person feels as if they are "Coming down with something".
- Prognosis: A prediction of the likely outcome or consequences of having a disease.
- Promoters: Carcinogens that decrease the body's ability to find and fight cancer cells by damaging tumor suppressing genes.
- Psoriasis: Psoriasis is a chronic inflammatory skin disease.

- Pulmonary fibrosis: "Fibrosis" is a term used to refer to scarring, so pulmonary fibrosis means scarring throughout the lungs.
- Purulent exudates: A thick, creamy white or yellow fluid that accumulates at the site of inflammation. Also called pus.
- Pyrogens: Chemicals that cause a fever.
- Radiodensity: The ability of an object to stop or slow radiation.
- Regeneration: Replacing damaged tissue through the process of mitosis, restoring the tissue to its original condition.
- Remission: The lessening in severity of the symptoms of disease.
- Renal artery stenosis: Renal artery stenosis (narrowing) is a decrease in the diameter of the renal arteries.
- Repair: Replacing damaged tissue with scar tissue.
- Rhabdomyolysis: Rhabdomyolysis is the breakdown of muscle tissue that leads to the release of muscle fiber contents into the blood. These substances are harmful to the kidney and often cause kidney damage.
- Rheumatic fever: Rheumatic fever (acute rheumatic fever or ARF) is an autoimmune disease that may occur after a group. A streptococcal throat infection that causes inflammatory lesions in connective tissue, especially that of the heart, joints, blood vessels, and subcutaneous tissue.
- Rheumatoid arthritis (RA): Rheumatoid arthritis is an autoimmune disease that can cause chronic inflammation of the joints and other areas of the body.
- Rheumatoid factor: Rheumatoid factor is an antibody that is detectable in the blood of 80% of adults with rheumatoid arthritis.
- Sarcoma: A malignancy that originates in connective tissues.
- Sclerosis: The process of hardening can occur as the result of scar formation or the accumulation of deposits known as plaques.
- Sequela: A consequence of a previous disease. (Example: Rheumatic heart disease sometimes occurs following a strep infection.)
- Serous exudates: A thin, clear, watery fluid that accumulates at the site of inflammation.
- Signs: Evidence of a disease that is objective and can be seen, measured and recorded.
- Sleep apnea: Sleep apnea is defined as 'a reduction or cessation of breathing during sleep'.
- Spirometry: Any procedure used to measure a persons ability to move air or the capacities of the respiratory system. Often referred to as PFT (Pulmonary function tests)
- Spondylolisthesis: Spondylolisthesis is a forward or backward slippage of one vertebra on an adjacent vertebra.
- Stenosis: The narrowing of any canal or opening, such as the intestine, a blood vessel of a heart valve.
- Suppurative inflammation: A response to injury or infection that leads to the production of pus.
- Swimmer's ear: Swimmer's ear, or external otitis, is typically a bacterial infection of the skin of the outer ear canal.

- Swine flu: It is a respiratory disease caused by influenza viruses that infect the respiratory tract of pigs and result in a barking cough, decreased appetite, nasal secretions.
- Symptoms: Evidence of a disease that is subjective and cannot be seen, measured, or recorded.
- Syndrome: A group of symptoms that collectively indicate or characterize a disease, psychological disorder, or other abnormal condition.
- Systemic: A condition that affects the entire body.
- Testicular cancer: Testicular cancer is a disease when testicular cells become abnormal (malignant) in one or both testicles.
- Thalassemias: The thalassemias are a group of genetic (inherited) blood disorders that share in common one feature, the defective production of hemoglobin, the protein that enables red blood cells to carry and deliver oxygen. There are many different mechanisms of defective hemoglobin synthesis and, hence, many types of thalassemia.
- Tumor markers: Proteins produced by tumor cells that can be detected in screening tests of the person's blood.
- Turner syndrome: Turner syndrome is a chromosomal condition related to the X chromosome that alters development in females, though it is not usually inherited in families.
- Typhoid fever: Typhoid fever is an acute illness associated with fever that is most often caused by the Salmonella typhi bacteria.
- Ulcerative colitis: Ulcerative colitis is an inflammation of the large intestine (colon).
- Ultrasound: A visual recording of differences in the rate of return and intensity of sound waves reflected off of objects within the body.
- Urinary retention: Urinary retention is the inability to empty the bladder. Urinary retention can be acute or chronic.
- Urinary tract infection: A urinary tract infection (UTI) is an infection involving the kidneys, ureters, bladder or urethra.
- Uterine fibroids facts: Uterine fibroids are benign tumors that originate in the uterus (womb).
- Vertigo: Vertigo is a sense of rotation, rocking, or the world spinning, experienced even when someone is perfectly still.
- Wart: Warts are local growths in the skin that are caused by human papillomavirus (HPV) infection. They should be distinguished from sexually transmitted (genital) warts, which are caused by other HPV types.
- Whooping cough (pertussis): Whooping cough (pertussis) is an acute, highly contagious respiratory infection that is caused by the bacterium Bordetella pertussis.
- X-rays: A visual recording of differences in radio density of anatomical structures.

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23. **A Practical Book of Computer Applications In Pharmacy**

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