INSIGHTS IN PHYSIOLOGY

SUDHA VINAYAK KHANORKAR

JAYPEE

Insights in Physiology

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Dedicated to

My son Shantanu
who was killed
in an air crash in 2000,
while the writing of the book
was going on

Preface

On popular demand from students, the effort was made to consolidate my lecture notes in the form of a book.

The book is useful for students as well as teachers. The teachers may find some lectures lengthy and some short. This is to keep information regarding one subject compact. The two short lectures may be combined together and lengthy lectures may be split into two.

Utmost effort has been made to avoid mistakes; if some have crept in inadvertently the author will be glad to correct them.

The author can be contacted at khanorkarsudha@yahoo.co.in

Sudha Vinayak Khanorkar

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SECTION I: GENERAL PHYSIOLOGY

CHAPTER 1

Introduction to Physiology

The term physiology refers to the functioning of a living organism or its parts.

PHYSIOLOGICAL PROCESSES

In the more complex animals such as birds and mammals the first characteristics of life that come to mind are: (i) warmth, and (ii) movement.

By taking food and oxidizing it, the animal obtains energy, which is used to produce heat and movement. The breakdown processes in the body known as *catabolism*, obtain energy. The energy obtained by these catabolic processes may also be used for *anabolic* or synthetic processes such as those necessary for growth. Since, both processes occur side by side—it is convenient to use the word *metabolism,* when referring to the total chemical changes occurring in the cell or in the body. So long as metabolic processes continue, however, slowly, the cell is alive. Their arrest is *death*.

Chemical processes are under control of *enzymes*. If the temperature is too high, the cell is destroyed and at low temperature, the *enzymic* reactions are retarded and finally cease.

Living material is *organized*. That is, it has a definite structure and a particular function. The cells and organs, whose structure is peculiarly fitted to the functions, carry out the functions.

For a cell to survive, there must be *integration* of functions within it. In multicellular organisms, there must be coordination of activities of various cells. This is done by chemical messengers (hormones) or by a system of nerves.

Growth is a characteristic feature of living organism. Growth of a single cell cannot go on indefinitely, because as the cell increases in volume, its surface through which oxygen and nutrients are absorbed, becomes so far away from the center that its supply cannot be maintained. Before, this stage is reached the cell divides into two daughter cells. A process known as *Reproduction*.

Because a cell cannot live in isolation, it must be capable of reacting to changes in its environment. Such changes are called *stimuli*. If the stimulus increases the rate of chemical changes in the cell it is said to *excite*, if it decreases the metabolic rate it is said to depress or *inhibit*.

Homeostasis

All cells of the body except those on the surface are provided with a fluid environment of relatively constant: (i) temperature, (ii) hydrogen ion concentration, (iii) electrolyte composition, and (iv) osmotic pressure. This permits many bodily activities to be carried out under *optimum conditions*. Small changes in the composition of the extracellular fluid, produces reactions, which quickly restore the internal environment to its original state. The maintenance of *constant environment* for the cells is known as Homeostasis.

The first requirement for homeostasis is a *detector* of deviation from the standard conditions. The appropriate *regulator* must then be instructed to reduce the deviation. The new state of affairs is continuously assessed by the detector and the regulator is given fresh instructions. In other words, the activity of the regulating device is constantly modified, on the basis of information fed to it from the detector. Such systems are termed *feedback* or control mechanisms, for example:

1. Sensory receptors in muscles and joints send information to central nervous system (CNS) about length of muscles and angle of joints, and movement and postures are regulated.
2. Cells sensitive to osmotic changes in the blood regulate the loss of water from the body.
3. Receptors in blood vessels detect changes in blood pressure and allow appropriate adjustments in the output of heart and caliber of blood vessels.

Thus, the study of physiology may be of great practical importance in leading to methods of diagnosis and treatment of disease.

Diseases are regarded as disordered biochemical or physiological processes, which the homeostatic mechanisms have been unable to correct.

The bodily activities depend so closely on one another so we need to consider briefly the subject as a whole before beginning a more detailed description of its various parts.

OUTLINE OF HUMAN PHYSIOLOGY

Nutrition

The source of all the energy required by the body is *food*. This consists mainly of:

1. *Proteins*, *fats* and *carbohydrates* which are oxidized in the body.
2. In addition, food must contain inorganic substances which are necessary for example, to provide material for formation of blood and bone. *Ca* is required for formation of bone and *Fe* is required for blood. So, calcium and iron must be provided in food.
3. Food must supply certain substances which the body cannot synthesize such as *vitamins* and *essential amino acids*.
4. Since fluid is lost continuously from the body, by way of the kidneys, lungs and skin, *water* must be drunk to make good this loss.

Digestive System

When food is swallowed, it reaches the stomach and small intestine, where it is broken down by enzymes into substances of simpler chemical composition, which are absorbed through the lining of the small intestine into the blood and distributed throughout the body.

Respiration

Oxygen required for combustion of foodstuff reaches blood through lungs. During breathing the chest expands and air flows into the lungs, which are richly supplied with capillary blood

vessels. Oxygen diffuses readily through very thin walls of blood vessels and becomes attached to hemoglobin (Hb) contained in the red cells, in which it is distributed throughout the body by circulation. CO_2 produced in combustion in the tissues is taken up by the blood and carried to the lungs where it escapes from the blood and is breathed out.

Blood

Blood is circulating in the blood vessels and acting as a transport system of the body, providing nutrients, oxygen and other substances (like hormones, immunological substances), to the cells and carrying away the waste products of their metabolism and CO_2 is also carried away.

Excretion

Byproducts of oxidation not needed by the body reach the kidneys via the blood and are excreted into the urine.

Circulation

The heart is a two sided muscular pump which drives the blood along the blood vessels. The *left side* pumps blood to: (i) the heart muscle itself, (ii) to the skeletal muscles, (iii) to the brain, and (iv) other organs.

The blood from these parts return to the *right heart,* which sends blood to the lungs, where oxygen is taken up and CO_2 is eliminated.

Arteries

The blood is conveyed away from the heart at a fairly high pressure in thick walled tubes—*the arteries,* which branch repeatedly and become smaller in diameter, with thinner and thinner walls. In the tissues, the smallest blood vessel—the *capillaries* are bound by a single layer of cells, through which the gases, water and chemical substances of small molecule move easily.

Veins

The blood is drained away from the tissues, at low pressure in the veins—which are wide vessels with relatively thin walls.

William Harvey's great discovery of circulation of the blood is the basis of modern physiology.

Nervous System

The skeletal muscles are the main effector tissues. By their contractions the position of bones is altered during: (i) movement, (ii) respiration, and (iii) speech.

The highly complex movements of the limbs in walking and of the tongue in speech are coordinated by central nervous system (CNS) consisting of *Brain* and *Spinal cord*.

Nerves called *efferent* or *motor* leave this system and pass to all the structures of the body and control: (i) muscular movement as well as, (ii) secretion of some glands, (iii) the heartbeat, and the (iv) caliber of blood vessels.

Central control is of no use unless the CNS has full information about events in the body and around it. This information is conveyed to the central nervous system by *sensory* or *afferent* nerves, which convey impulses from: (i) eye, (ii) ear, (iii) skin, (iv) muscles, (v) joints, (vi) heart, (vii) lungs, and (viii) intestines.

The sensory nerves are much more numerous than motor nerves.

Although many of the activities occurring in the CNS are exceedingly *complex* relatively few rise to consciousness. We are quite unaware for example of the: (i) muscular adjustments needed to maintain balance or (ii) to move our eyes so that images of the external world are kept fixed on the retinae. These adjustments are called *reflexes* and the

pathways involved are called *reflex arc,* which include: (i) sensory nerve, (ii) CNS, and (iii) motor nerve.

Endocrines

In addition to the rapidly acting coordinating mechanism of nervous system, the body possesses a chemical (humoral) system which operates more slowly. For example, during the digestion of food a chemical substance (hormone) called secretin is produced in the mucous membrane of duodenum, is absorbed into the blood and carried to the pancreas which responds by pouring out its digestive juices.

Reproduction

Reproduction are the processes necessary for the maintenance of the species. The male cells—the spermatozoa are produced by testis and when deposited in female genital tract, one of them may fertilize an *ovum* produced in the ovary. This sets off a series of complicated changes, mainly under hormonal control, to provide for the nutrition of the fertilized cell in the uterus.

At the end of the pregnancy, the muscular walls of the uterus contract, the fetus is delivered and then acquires oxygen directly by breathing air into its lungs instead of indirectly through placenta.

CHAPTER 2

Internal Environment Homeostasis and Feedback Mechanisms

INTERNAL ENVIRONMENT HOMEOSTASIS

The cell is a structural and functional unit of life.

1. It ingests nutrients from environment—(a) by diffusion, (b) by phagocytosis (= cell eating), and (c) by pinocytosis (= cell drinking).
2. It gets rid of waste products (Fig. 2.1)— (a) by diffusion, and (b) by exocytosis.
3. It can synthesize all the enzymes required for optimal utilization of the ingested nutrients.
4. It can reproduce by simple dividing into identical daughter cells.

But it functions—only within the limited range of—(a) temperature, (b) pH, (c) osmolarity, and (d) electrolyte composition.

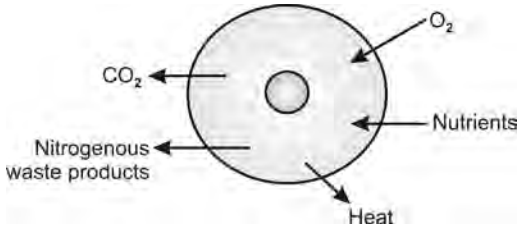


Fig. 2.1: Single cell

Therefore, survival of the cell requires immediate environment of the cell be relatively constant and uniform in these characters.

1. For unicellular organisms this poses no problem, because they exist surrounded by large body of sea water.
2. The process of evolution led to the development of multicellular organism (Fig. 2.2). Cells in the interior no longer remained in direct contact with external environment.
3. In the course of evolution, this problem was initially solved by having sea water run through the organism to bring sea water in direct contact with every cell. But this simple solution could not work if the number of cells in organism increased beyond a certain limit.

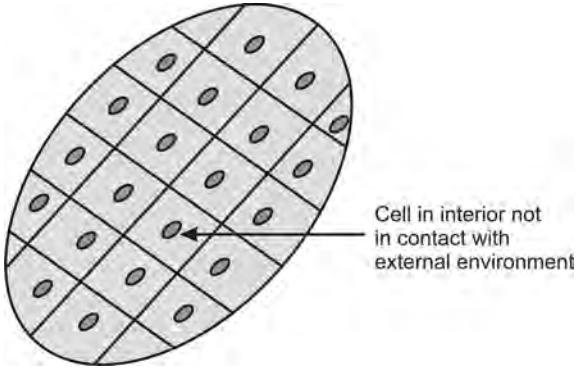


Fig. 2.2: Multicellular organism

4. When the organisms became more complex a thin layer of fluid resembling sea water around each cell was developed. Thus, if sea water could not be carried to each cell, each cell was furnished with a small private sea of its own. This private sea or intercellular fluid or interstitial fluid persists in highly evolved organism such as man. Its composition is reminder of origin in the sea. This environment surrounding each cell is called *internal environment*. It is part of extracellular fluid (= fluid outside the cells). It is from this fluid the cells receive oxygen and nutrients and cells excrete their waste into it. But the interstitial fluid is small quantity so that:
   i. Nutrients in it must be replenished.
   ii. Waste products should be removed continuously and promptly otherwise its pH will change, and its composition does not remain suitable for optimal functioning of the cell.

Therefore, a set of tubes called capillaries are developed:

1. Fluid in the capillaries is in constant exchange with interstitial fluid.
2. Interstitial fluid is doing same thing with the cells.

The fluid in capillaries must be in constant motion, so that:

1. Continuous replenishment of nutrients is there.
2. Prompt removal of waste products take place.

This motion was possible by evolution of pump to provide the force for motion—the heart.

The capillaries at least at few points in circulatory system must come in close contact with external environment for fresh supply of nutrients and disposal of waste and such structures were evolved. They are:

1. *Lungs:* Where oxygen is taken up and CO_2 is disposed off.
2. *Kidneys:* Nitrogenous waste products are disposed off.
3. *Gut:* Where nutrients are picked up.

Thus, digestive system, excretory system and respiratory systems establish link between internal and external environment (Fig. 2.3).

Blood supplies nutrients and oxygen to all tissues and removes waste. While passing through lungs, gut and kidney it does some-

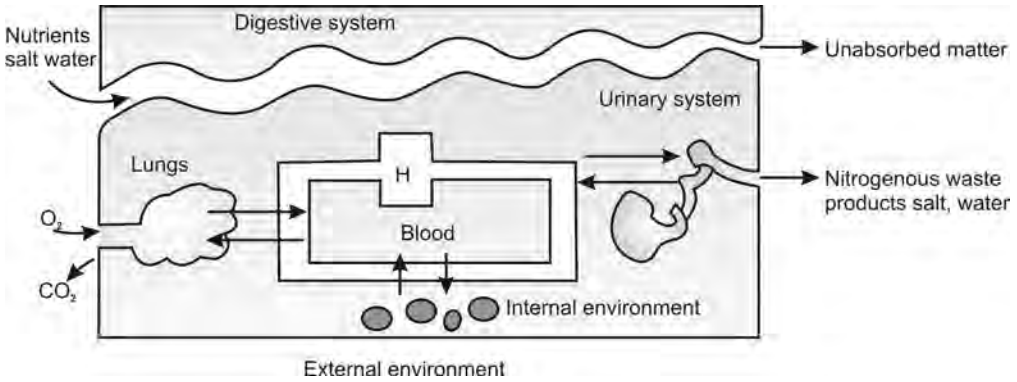


Fig. 2.3: Elaborates link between internal and external environment

thing in addition. For example: (i) in lungs, it absorbs large quantity of oxygen and gives out large quantity of CO_2, (ii) in gut, it absorbs nutrients and water, and (iii) in kidney, it excretes nitrogenous waste products and absorbs water, glucose, etc.

Ultimate aim of the work of all the systems is to maintain constancy in the characteristics of thin layer of fluid surrounding every cell of the body or internal environment or in other words all the systems work for homeostasis.

Importance of constancy of the internal environment was first stressed by Claude Bernard in 1857. It is also called Milieu Interieur (= French word for internal environment).

His concepts were further supported by extensive experimental work of Walter Cannon in early 20th century. Cannon coined the word Homeostasis to describe constancy of internal environment (homios = similar; stasis = position).

All systems contribute to homeostasis:

1. Systems such as digestive, respiratory and excretory contribute directly.
2. Role of blood and cardiovascular system is obvious.
3. Endocrines and NS work for coordination of activities of other systems.

Like this every part of the body makes some contribution to the survival of whole organism by doing something to maintain: (i) temperature, (ii) pH, (iii) osmolarity, and (iv) electrolyte composition of internal environment at optimal level. Optimal level is that at which the enzymes function best.

FEEDBACK MECHANISMS

Control systems: Principles on which they work to maintain homeostasis.

They work on the basis of feedback. Therefore, they are called feedback systems or feedback mechanism (Fig. 2.4).

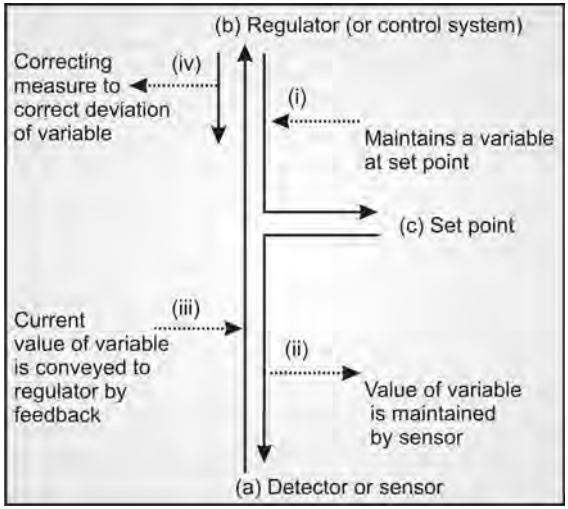


Fig. 2.4: Scheme of control system feedback mechanism

For feedback systems to work there must be: (a) a detector (or sensor), (b) a regulator (or control systems) and for most variables there is, (c) a set point. For example, for body temperature or blood glucose there is a fixed set point at which level is maintained.

Current value of the variable minus set point = deviation or error. This error is corrected by correcting measures which work in opposite direction. Therefore, these mechanisms are called as negative feedback mechanism, as the effector response is negative to initiating stimulus. For example, for body temperature set point is 37°C. When temperature increases, the correcting processes decrease the body temperature.

Positive feedback would be disastrous. Therefore, most of the control systems in the body are of negative feedback type.

However, there are some situations in the body in which control system operates on the basis of positive feedback.

For example:

1. Sex hormones normally inhibit gonadotropins by negative feedback. But one to two days before ovulation, estrogen level

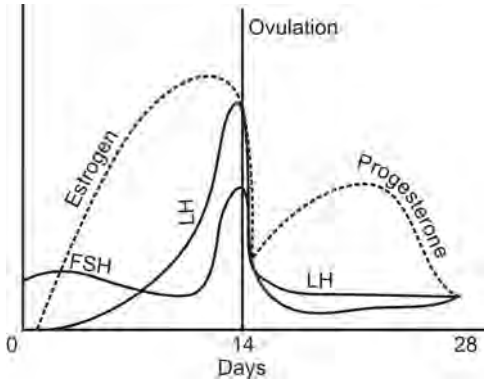


Fig. 2.5: FSH and LH surge positive feedback

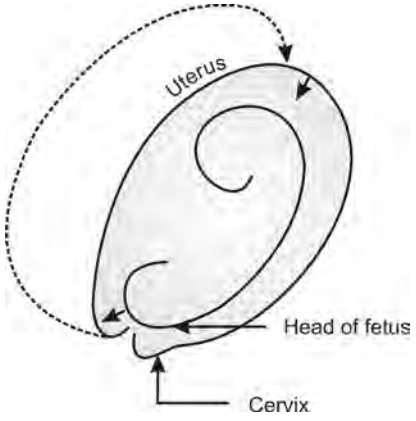
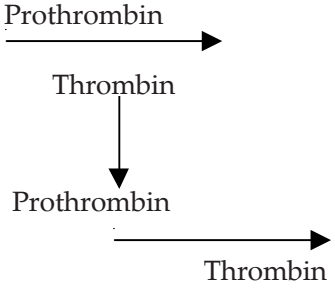


Fig. 2.6: Strong uterine contraction in labor positive feedback

increases the level of LH, and FSH. This LH, and FSH, surge is essential for ovulation (Fig. 2.5).

2. During labor—uterine contractions push the fetus down towards the cervix. It causes stretching of cervix. This stimulates uterine contraction by positive feedback—stretching the cervix still more resulting in more strong uterine contraction (Fig. 2.6). Like this stronger contractions continue till baby is delivered.
3. Some blood coagulation reactions are auto catalytic in nature. Once a small amount of thrombin is formed it acts on prothrombin to form still more thrombin.



CHAPTER 3

Body Fluid Compartments, Extracellular Fluid and Intracellular Fluid

Maintenance of a relatively: (a) constant volume, and (b) stable composition of body fluid is essential for homeostasis.

Fluid intake and output must be balanced during steady state conditions inspite of variable intake that must be matched carefully by equal output from the body to prevent body fluid volumes from increasing or decreasing.

DAILY INTAKE OF WATER

1. Ingested in the form of liquids or water will add about 2100 ml/day to body fluids, and
2. It is synthesized in body as a result of oxidation of carbohydrates will add 200 ml/day.

Thus, total water intake is 2300 ml/day water intake varies in different persons, also in same person on different days depending on: (a) climate, (b) habits, and (c) levels of physical activity.

DAILY LOSS OF BODY WATER

1. Insensible fluid loss includes:
   i. Evaporation from respiratory tract (300-400 ml/day): Water is lost by evaporation from respiratory tract because vapor pressure of inspired air is less, in cold it becomes zero. Expired air is saturated with moisture.
   ii. Diffusion through skin (300-400 ml/day) more loss is prevented by cholesterol filled cornified layer of skin. In burns, skin is denuded which leads to more loss of water and more fluids should be given intravenously.

   Insensible fluid loss cannot be controlled. Total amount lost is 700 ml/day. It is also called invisible water loss.
2. *Fluid loss in sweat:* The amount of fluid lost by sweating is highly variable depending on physical activity and environmental temperature.
   For example: Normal loss—100 ml/day—hot temperature or heavy exercise—1 to 2 L/hour.
3. *Water loss in faeces:* Small amount is lost normally—100 ml/day.

   It is increased to several liters per day in severe diarrhea.
4. *Water loss by the kidneys:* Remaining water loss is by urine, excreted by the kidneys. Various mechanisms control this loss of water.
   For example: Normal urine output is 1.5 L/day.

It can be as low as 0.5 L/day in dehydrated person or 20 L/day, in person who is drinking tremendous amount of fluid.

BODY FLUID COMPARTMENTS

Compartments are because of the presence of barriers and properties of barriers determine the movement of substances and fluid between contiguous compartments.

In normal 70 kg adult human (Physiological man) the total body water averages about 60% of the body weight (= 42 liters). Percentage can change depending on— (a) age (b) sex, and (c) degree of obesity, because total body water depends on fat content.

Total body fluid is distributed among two major compartments:

1. *Extracellular fluid (ECF):* Fluid outside the cell (1/3 of total body water).
2. *Intracellular fluid (ICF):* Fluid inside the cell (2/3 of total body water).

Extracellular Fluid

Extracellular fluid is present in two compartments:

1. *Intravascular*: Fluid inside blood vessels = Plasma (20% of total ECF).
2. *Extravascular*: Fluid outside blood vessels. (80% of total ECF).

Extracellular fluid includes:

1. Interstitial fluid
2. Blood plasma
3. Transcellular fluid
   This includes:
   i. Synovial fluid
   ii. Peritoneal fluid
   iii. Pericardial fluid
   iv. Intraocular fluid
   v. Cerebrospinal fluid (CSF).
4. Lymph

Extracellular fluid is 20% of body weight in 70 kg man or 14 L in 70 kg man.

Its two largest compartments are:

1. Interstitial fluid
2. Plasma: It is noncellular part of blood.

Interstitial fluid and plasma are in communication through large pores in capillary membrane which is freely permeable to almost all solutes of plasma except protein (Fig. 3.1).

Constituents of ECF

Ionic composition of plasma and interstitial fluid are similar because they are separated by highly permeable capillary membrane. Important differences between the two is:

1. Higher concentration of protein in the plasma because capillaries have low permeability to plasma proteins, therefore only small amount of protein leaks in interstitial spaces.
2. Concentration of positively charged ions is slightly greater (2%) in plasma than in interstitial fluid because proteins are negatively charged therefore attract positively charged ions.

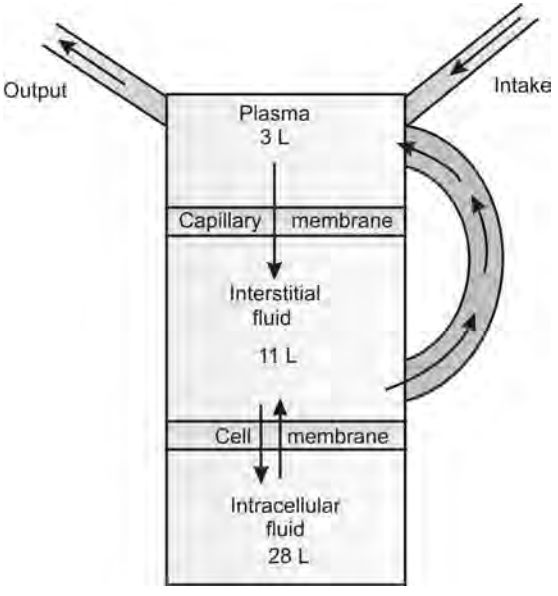


Fig. 3.1: Body fluid compartments
(values for average 70 kg man)

But for all practical purposes concentration of ions in interstitial fluid and plasma are considered to be equal.

ECF Contains (Fig. 3.2)

1. Large amounts of sodium and chloride ions.
2. Reasonably large quantity of bicarbonate ions.
3. Small quantity of potassium, calcium, magnesium, phosphate and organic ions.

Composition of ECF is carefully regulated by various mechanisms, but especially by kidneys.

Intracellular Fluid

Intracellular fluid is 40% of body weight in 70 kg man or 28 L in 70 kg man.

Composition is reasonably similar in all cells of our body. Therefore, considered as one large fluid compartment.

ICF is separated from ECF by selectively permeable cell membrane which is highly permeable to water but not to most of the electrolytes of the body. Cell membrane maintains a fluid composition inside the cells that is similar among different cells of the body.

ICF Contain (Fig. 3.2)

1. Small quantities of sodium and chloride ions.
2. Almost no calcium.

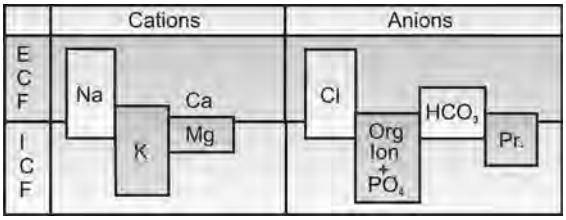


Fig. 3.2: Composition of ECF and ICF

3. Large amount of potassium and phosphate ions.
4. Moderate amount of magnesium and sulfate ions, and
5. Reasonably large amount of protein ions.

Blood Volume

Blood is plasma with cells suspended in it. They are: (i) RBC, (ii) WBC, (iii) platelets.

Blood is present in separate fluid compartments of its own. Therefore, considered as separate fluid compartment. It contains ECF and ICF both. Average blood volume of normal adult is 5 L. Out of which 55-60% is plasma and 40-45% is blood cells. Volume occupied by blood cells is known as packed cell volume or hematocrit. It is determined by centrifuging blood in a hematocrit tube until the blood cells become tightly packed in the bottom.

Measurement of the Volume of the Body Fluid Compartment

Volume of a compartment is measured by using dilution principle. If a known quantity of substance is added to a compartment and if it is evenly distributed throughout the compartment the extent to which the added substance is diluted can be determined and the volume of the compartment can be found out.

If Q = Quantity of substance added
C = Concentration of the substance when evenly distributed.
and V = Volume of the compartment.

then $V = \frac{Q}{C}$

Requirements

1. Marker must be freely diffusible and must be confined to the compartment to be measured.

2. If it is excreted it should be at a constant measurable rate.
3. The marker must be nontoxic, neither synthesized nor metabolized.
4. Accurate measurement of the concentration of the marker must be possible.
5. A representative sample must be easily obtained from the compartment.

TOTAL BODY WATER

To measure total body water the marker should diffuse freely in the water outside the cells, but also cross the cell membranes.

Three substances are used:

i. *Tritiated water ($3H_2O$):* Radioactive water where tritium is use.
ii. *Heavy water (D_2O):* Radioactive water where deuterium is use.
iii. *Antipyrine:* A lipid soluble substance, therefore crosses the cell membrane.

1. A known quantity of labeled water is injected intravenously as an isotonic solution of NaCl.
2. It mixes freely with the water of the body in a few hours.
3. At the end of this period the blood sample is taken and concentration of labeled water is measured.
4. Some marker is lost in the urine, so this loss is allowed for.

For example: 100 ml of D_2O was infused into a 70 kg man. *After 2 hours* when equilibrium has occurred a sample of blood was taken and concentration of D_2O was found to be 0.0025 ml/ml of plasma.

At the same time of plasma sample, urine was voided and was found to contain 0.5 ml D_2O.

$$\text{TBW} = \frac{100 \text{ ml} - 0.5 \text{ ml}}{0.0025 \text{ ml/ml}}$$

$$= 39.81 \text{ L or } 57\% \text{ of body weight}$$

ECF Volume

The marker for ECF must be a substance that diffuses readily through ECF space but does not enter the cells.

Number of substances are used but all cross the cell membrane to some extent. It is usual to use: (a) radioactive isotopes of—sodium, chloride, bromide, thiosulfate, thiocyanate. (b) sucrose and inulin.

Sucrose and inulin penetrate the cell membrane to a smaller extent than others therefore, give a more accurate estimate of ECF. Since all the markers give slightly different values, because of their varying ability to penetrate cell membrane, the results are often quoted as 'sodium space', the thiocyanate space, the inulin space, etc.

For inulin space—a known quantity of inulin (Polysaccharide) inulin is injected intravenously.

1. Plasma inulin concentration is determined at 30 min interval.
2. Plasma concentration falls with time. Graph is plotted of plasma concentration of inulin against time (Fig. 3.3). A curved line is obtained. It is converted to straight line when plasma concentration is plotted against log of time. After a period of mixing the concentration of inulin falls off in a predictable manner because of loss of inulin in urine. If a straight part of the curve is extrapolated back to cut concentration axis, the value of the intercept is the concentration of inulin that would have been achieved had it been distributed instantaneously. This method allows for the losses in urine. For example, 4 gm inulin is injected intravenously, extrapolation of concentration time graph cuts the concentration axis at 0 time (that is the time of injection) at 0.275 g/L.

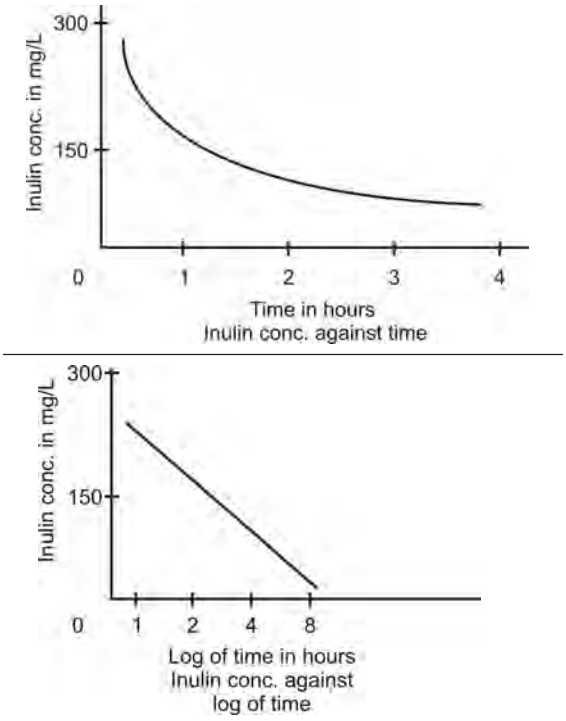


Fig. 3.3: Graph of inulin concentration against time

$$\text{Volume of ECF} = \frac{4\,\text{g}}{0.275\,\text{g/L}}$$

$$= 14.5\,\text{L for a 70 kg man}$$

Plasma Volume

Markers used to measure plasma volume are:

1. Vital dye Evans blue (T 1824) or
2. Iodinated albumin.

Normal value—3 L in 70 kg man, 2.4 L in woman.

Interstitial Fluid Volume

There is no method to measure interstitial fluid volume, which has to be calculated by subtracting the plasma volume from ECF volume.

ECF volume – Plasma volume = Interstitial fluid volume

Intracellular Volume

Cannot be measured directly, therefore determined by subtracting the ECF volume from total body water.

TBW – ECF = Intracellular volume

Measurement of Blood Volume

1. If you know plasma volume and hematocrit value, one can determine blood volume.
2. Another way to measure blood volume is to inject into circulation red cells that have been labeled with radioactive material.

After these mix in the circulation the radioactivity of mixed sample can be measured and the total blood volume can be calculated.

CHAPTER 4

Formation of Interstitial Fluid and Lymph

FORMATION OF INTERSTITIAL FLUID

Exchange of water and dissolved substances through capillary wall depends upon the type of capillary.

In general, three types of capillaries have been described.

Type 1

These capillaries have uninterrupted membranes with pores of 4-5 nm in diameter. They occur in muscle, pulmonary circulation and adipose tissue.

Type 2

These capillaries have fenestrated membranes. Fenestration being of the order of 0.1 micrometer.

Typical sites are glomeruli of the kidneys and intestinal epithelium.

Type 3

Capillaries have discontinuous membranes. They are interrupted by large intercellular spaces through which not only fluids but cells can pass. These capillaries are found in the bone marrow, spleen and liver.

Two processes are involved in the transfer of fluid, nutrients and waste products across the capillary membrane:

1. Diffusion
2. Filtration/reabsorption.

Diffusion

1. The capillary membrane is very leaky. Its permeability is high but its selectivity is low. Substances of molecular weight less than about 70,000 cross freely down their concentration gradient to reach equal concentration on both sides of capillary, therefore, do not contribute to an osmotic pressure difference across the wall.
2. Plasma proteins are largely retained and create osmotic pressure or oncotic pressure which is 25 mm Hg (3.3 kpa).
3. Diffusion is fast process and most cells are within 5-10 micrometer of capillary and diffusion distance between adjacent cells may be less than 0.1 micrometer.
4. Diffusion is more effective, the greater the capillary density in a tissue, because the surface area is greater.
5. An increase in capillary density and surface area occurs when a tissue becomes active during vasodilatation because more capillaries open up.

Filtration/Reabsorption Across Capillary Membrane

Starling proposed that fluid exchange across the capillary wall between plasma and interstitial fluid was achieved by a balance between two forces (Fig. 4.1).

1. Hydrostatic pressure in the capillary - (caused by action of heart)—directs the fluid movement outwards (filtration).
2. This effect is opposed by the colloid osmotic pressure of the plasma protein—a force that is directed inwards (reabsorption).

   Thus, at the arterial end of a capillary, the hydrostatic pressure exceeds colloid osmotic pressure and net filtration takes place.

   At the venous end hydrostatic pressure falls below the colloid osmotic pressure and reabsorption occurs.

   Two other factors affect the trans-capillary movement of fluid.
3. There is a small negative hydrostatic pressure in tissues outside the capillary. This increases the outward force.
4. Also the capillaries are not entirely impermeable to proteins and some escape into the interstitial fluid where it opposes the inwardly directed force of the colloid osmotic pressure.

   Hydrostatic pressure—at the arterial end of the capillary depends on:
   1. The type of tissue.
   2. Activity of the tissue, and
   3. Vasomotor supply.

For example:

a. In resting state - the pressure in glomerular capillary is 70 mm Hg and ultrafiltration only occurs.
b. In lungs and liver it is 8 mm Hg and absorption only occurs. Important, that filtration does not occur in lungs otherwise respiratory exchange would be impeded.
c. In human finger, the pressure at the arterial end of the capillary is about 32 mm Hg and both filtration and re-absorption occur.

FORMATION OF LYMPH

Distal lymphatics form a closed system of tubes consisting of endothelial lining supported by fibrous tissue and out of the filtered fluid from the capillary 10% enters in these lymphatics whereas 90% is reabsorbed at the venous end (Fig. 4.2).

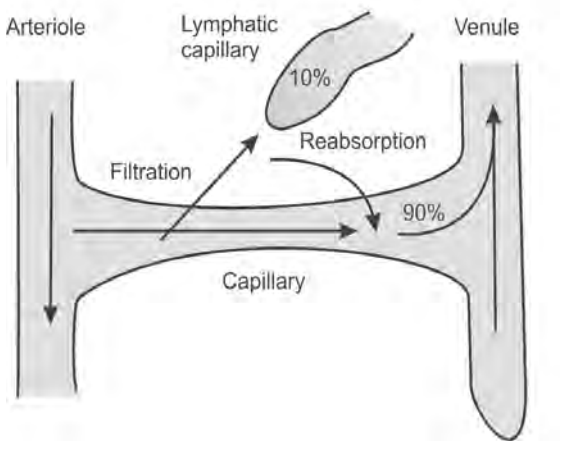


Fig. 4.1: Filtration/reabsorption

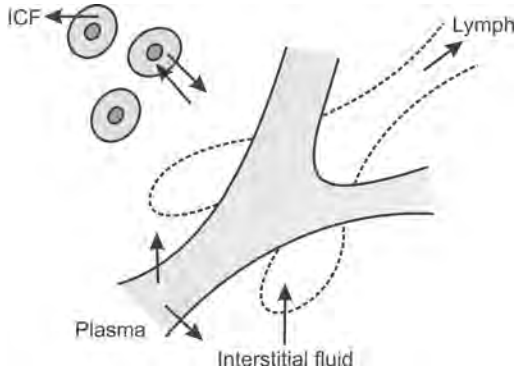


Fig. 4.2: Formation of lymph

Lymphatics are much more permeable to proteins than capillaries. The proteins leaked from plasma into interstitial space cannot return to capillary because of adverse concentration gradient. Their accumulation in interstitial space will upset starling equilibrium and proteins diffuse into the very permeable lymphatic capillaries together with large molecules produced by cells such as: (a) hormones, (b) enzymes, (c) lipoproteins, (d) chylomicrons.

Large lymphatics have muscle fibers in their walls, lymphatic vessels posses numerous valves and the flow of lymph from periphery to thoracic duct and right lymphatic duct is brought about by muscular and respiratory movement in the same way as blood flows in the veins.

Right lymphatic duct opens in right subclavian vein and thoracic duct opens in left subclavian vein.

The lymphatics of intestine (lacteals) show rhythmic contraction which, because of the many valves propel lymph into the thoracic duct. This contractile activity is an intrinsic property of the lymphatics and is not coordinated by NS.

Lymph

1. Has same concentration of salts as interstitial fluid and plasma.
2. Has lower concentration of proteins than plasma.
3. Has slightly higher concentration of proteins than interstitial fluid.

Before reaching the blood lymph passes through at least one or more, usually 8-10 lymph nodes. Lymph nodes are placed at strategic points along the route—axilla, elbow, groin, abdomen, thorax and neck where several lymphatic vessels join. During its passage through a lymph node the lymph is altered in composition.

i. Small molecules pass into the blood.
ii. Large molecules are retained.
iii. Newly formed antibodies (immunoglobulins) are added.
iv. Lymphocytes enter.

Functions of Lymph

1. Return of proteins to blood from tissue spaces.
2. Role in fluid distribution in body.

   It is estimated that in an adult man some 20 L of water are ultrafiltered from capillary. Of this some 16-18 L return to the capillary at venular end by reabsorption and 2-4 L return to circulation through lymph.
3. Lymph acts as middle man between blood and tissue fluid.
4. Fat from intestine are mainly absorbed through lymph.

Lymphedema

Complete obstruction of lymphatic vessel draining a part of the body leads to edema of the area known as lymphedema.

Edema

Edema can be explained by starling hypothesis. It means accumulation of excessive amounts of salt and water in interstitial space.

In this condition the tissues—usually in dependent parts become swollen with fluid that resembles plasma but has a low protein content.

Edema accumulates when:

1. The hydrostatic pressure in the veins is increased, e.g. congestive heart failure.
2. Colloid osmotic pressure of plasma is reduced (because albumin level is low).

Edema from hypoalbuminemia arises in (a) malnutrition (famine edema) (b) chronic liver disease (cirrhosis) when albumin synthesis is low and (c) in nephrotic syndrome in which excessive amounts of albumin are lost in urine.

CHAPTER 5

Cell Membrane and Principles of Biological Transport—Across Cell Membrane

The structural and functional unit of life is a cell. Initially only cell had a membrane around it, its contents floated freely within. Bacterial cells are still like that and are called Prokaryotic cells.

In the next step of evolution the nucleic acids were packed in membrane bound structure—the nucleus and various organelles, which are also membrane bound, appeared.

Thus, a cell is bound with: (a) cell membrane and contains, (b) protoplasm, (c) nucleus, and (d) organelles.

CELL MEMBRANE

Cell membrane is a vital and dynamic structure. It is also called as plasma membrane to distinguish it from other membrane surrounding organelles. Structure of both the membranes is similar. Hence, the term unit membrane includes both.

Under electron microscope the cell membrane is a three layered structure 8-10 nm in thickness.

Structure

I. Simplest interpretation of the structure is provided by Danielli-Davson model (Fig. 5.1).

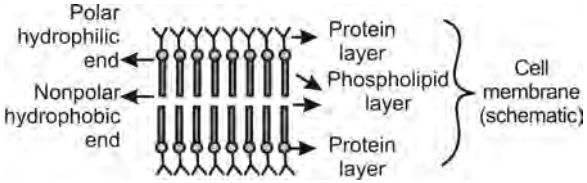


Fig. 5.1: Danielli-Davson model

It consists of:

i. Outer most layer of protein molecules.
ii. Layer of lipid molecule.
iii. Further layer of lipid molecules, and
iv. Innermost layer—the fourth layer is again made up of protein molecules.

Thus, there are two layers of lipid molecules sandwiched in between two layers protein molecules.

The lipids of the cell membrane are mostly phospholipids. These individual phospholipid molecules are elongated structures looking like bamboos.

Individual lipid molecule has two ends:

1. Hydrophilic end which is polar end. They are facing the protein layer.
2. Hydrophobic end which is nonpolar end. They meet the hydrophobic ends of their fellows. These molecules are placed side by

side in a row due to: (a) their polarity, and (b) electrical charges.

II. Currently accepted interpretation of the structure is the fluid mosaic model of Singer and Nicolson, first proposed in 1972 (Fig. 5.2). Similarity with previous model is—the lipid bilayer is intact in this model as well.

Distinguishing features are:

1. Dynamic nature of membrane.
2. Presence of transmembrane proteins or integral proteins, which span entire width of the membrane, instead of being confined to the surface.
3. Presence of peripheral proteins confined to surface also known as extrinsic proteins.
4. Surface carbohydrates: (a) phospholipids (b) cholesterol, and (c) glycolipids form the major lipids of the cell membrane. Composition is affected to some extent by nature of dietary lipids.
   - Transmembrane proteins form hydrophobic linkage with fatty acyl chain.
   - Peripheral proteins are attached to polar end of lipids through electrical linkage.

Functions and Characteristics of Cell Membrane

1. It is responsible for guarding the contents of the cell, which are unique as compared to outside.
2. It is the first point of contact with any agent which is capable of influencing the cell.
3. It is selectively permeable barrier.
4. It acts as receiver and transducer of information.
5. It incorporates:
   i. Several enzymes.
   ii. Transport proteins.
   iii. Receptors for hormones and neurotransmitter.
   iv. Antigens.
   v. Several channels for passage of Na, K, etc.

Since all these functions differ from cell-to-cell, time-to-time and on the inside as compared to outside the surface membrane, the cell membrane is: (i) heterogeneous, (ii) dynamic, and (iii) asymmetrical structure.

Cell Junctions

In multicellular organisms the adjacent cells are joined to each other (Fig. 5.3). Their points of contact show varying degrees of: (a) fusion (Fig. 5.4), and (b) specialization depending on the requirements of the tissue.

Junctions found in various tissues are classified into three types:

1. Tight junctions.
2. Gap junctions.
3. Desmosomes.

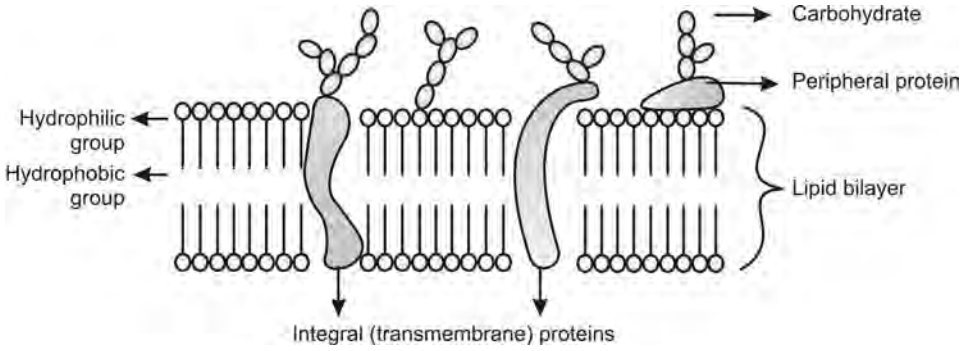


Fig. 5.2: Diagrammatic fluid mosaic model

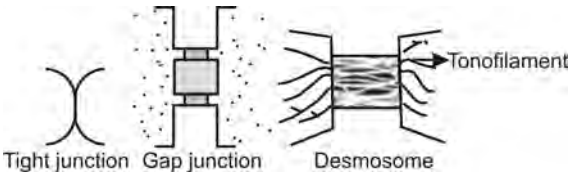


Fig. 5.3: Cell junctions

1. *Tight junctions*: The cell membranes between the adjacent cells are fused together. No molecules can pass through. They are found in gastrointestinal tract and prevent passage of substances from the lumen to the interior of the gut by the intercellular route.
2. *Gap junctions:* The cells are very close to each other but there is a small gap of 2 nm between adjacent cells and cytoplasm of the two cells are connected with each other by sort of channels. So, molecules can pass from cytoplasm of one cell to cytoplasm of other cell without coming in contact with ECF.

   It is widespread in distribution. Even cells with tight junctions show gap junction below. It is important where rapid communication between adjacent cells is required. For example:
   i. Smooth muscle—gap junction is called nexus.
   ii. Cardiac muscle—gap junction forms a part of intercalated disk.
3. *Desmosomes*
   i. Gap of 25-30 nm between the cells is filled with carbohydrate rich material.
   ii. On cytoplasmic side of the membrane there are electron-dense plaques.
   iii. In the electron dense plaques are fine fibrillar structure called tonofilaments.
   iv. Function of desmosomes is to provide structural support.
   v. Most abundant where firm support is essential, as in epidermis.

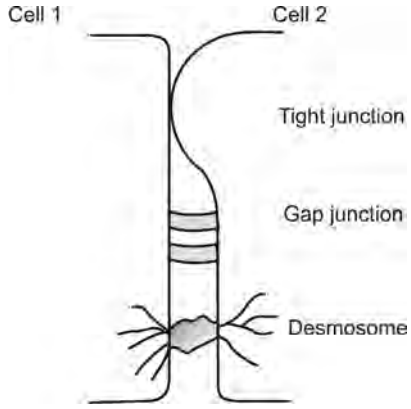


Fig. 5.4: Cell junctions (Fusion)

The same tissue may have tight junctions near the surface in order to provide an impermeable surface, gap junction at an intermediate depth to allow intracellular transport and communication and desmosomes at a still greater depth to keep the cells together.

PRINCIPLES OF BIOLOGICAL TRANSPORT

Cells utilize nutrients and produce waste products continuously, rate may vary from time-to-time. Nutrients are picked up from immediate surroundings and waste products are dumped into the surroundings. Both are transported across the cell membrane.

Transport may be governed only by physical processes, membrane acting as semipermeable membrane. Such transport is known as passive transport or transport may involve expenditure of biologically produced energy. Such transport is known as active transport.

Passive Transport

Passive transport—across the cell membrane depends on (a) physical factors such as:
1. Concentration gradient
2. Electrical gradient

3. Pressure gradient, and (b) permeability of membrane—permeability of a substance depends on:
   i. Its molecular size.
   ii. Lipid solubility, and
   iii. Whether a carrier is available to shuttle the substance across the membrane.
      a. Lipid soluble substance is transported faster because such substance can dissolve in the lipid bilayer of cell membrane and cross it.
      b. For some special important substances—a carrier protein is available in cell membrane which carries it across cell membrane.

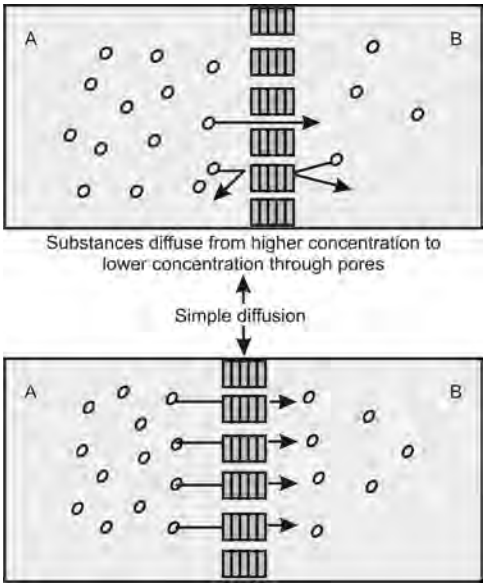


Fig. 5.5: Lipid soluble substances diffuse fast

Major Processes

Major processes by which passive transport is accomplished are:
1. Simple diffusion.
2. Facilitated diffusion.
3. Osmosis, and
4. Ultrafiltration.

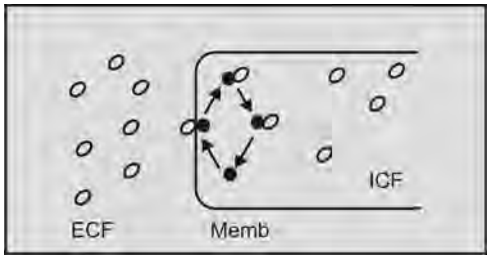
Simple Diffusion

1. Dissolved substances are in a state of random molecular motion. Molecules therefore, strike the membrane. Frequency is more on the side on which concentration is more. Therefore, there is greater possibility of striking a pore through which they can go to the other side of the membrane.
2. Or if lipid soluble—higher the concentration greater is the possibility of particles striking the membrane and dissolving in it. Therefore, substances diffuse from the side on which they are present in a larger concentration to the side of lower concentration (Fig. 5.5).
3. If there is electrical charge across the membrane—a charged particle will have a tendency to diffuse towards oppositely charged side.
4. Pressure gradient = sum total of collisions on a given side of the membrane. Pressure has nonspecific effect of driving substances out. Hence, diffusion is increased from the side with higher pressure to that of lower pressure.
5. Molecular size also affect simple diffusion. Respiratory gases are transported across the alveolar membrane in the lungs by simple diffusion.

Facilitated Diffusion

Transport by diffusion may be made faster even if molecular size is large, if a suitable carrier is available in cell membrane.

Since, the carrier merely facilitates diffusion the process is called facilitated diffusion



o Transported substance
• Carrier molecule
Memb = cell membrane

Fig. 5.6: Facilitated diffusion

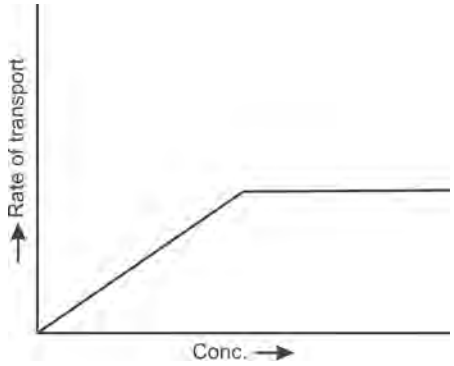


Fig. 5.7: Graph showing relationship of increased conc. and rate of transport

(Fig. 5.6), because it occurs in such a way that molecule moves from a region of higher concentration to a region of lower concentration. For example, in small intestine fructose is absorbed by facilitated diffusion.

Note

1. Molecule must fit in the receptor on the carrier.
2. Substances with similar molecular structure compete with one another for transport.
3. Transport can be blocked by specific agents, if the blocking agent binds to the carrier but does not get transported, it blocks the carrier irreversibly.
4. Concentration of a substance and rate at which it is transported bear linear relationship only up to a limit. After which even if concentration increase, rate does not increase.

Reason is when all the available carrier molecules are in use, further increase in concentration of transported substance cannot increase the rate of transport (Fig. 5.7).

Osmosis

If selectively permeable membrane (semipermeable membrane) separates two compartments, the membrane allows water to pass through but not a solute.

On side A is water. On side B is solute dissolved in water. Membrane is permeable only to water. Concentration of water is higher on side A. Hence, water diffuses from side A to B, but in this type of situation water is said to be transported by osmosis.

Osmosis of water increases the hydrostatic pressure on side B—when excess hydrostatic pressure on side B equals osmotic pressure exerted by the solute, osmosis stops which means—when excess hydrostatic pressure (pushing force) becomes equal to pulling force (osmotic pressure exerted by the solute) there is no further net movement of water (Fig. 5.8).

Ultrafiltration

You are familiar with filtration. If we try to pass a solution through a filter, the solvent and other small molecules pass through the filter. Whether a given substance will pass through a filter depends on: (a) the relative size of its molecules, and (b) that of pores of the filter.

The rate of filtration can be increased by applying pressure. Filtration under pressure is called ultrafiltration. For example, the hydrostatic pressure in renal glomeruli is higher than hydrostatic pressure in any other

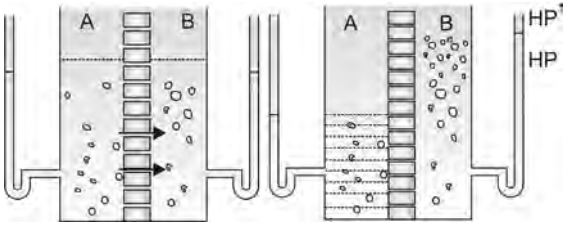


Fig. 5.8: Osmosis. Note increase in hydrostatic pressure from HP to HP^1; due to diffusion of water to side B. When hydrostatic pressure HP^1-HP = osmotic pressure exerted by the solute osmosis stops

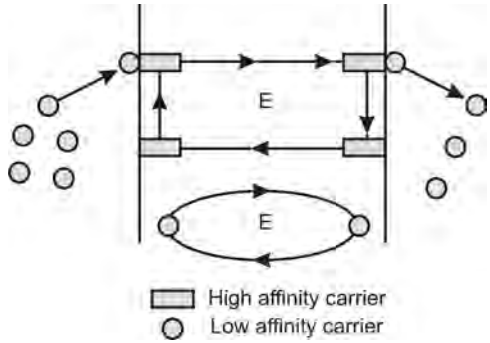


Fig. 5.9: Active transport

capillaries of the body. As a result, water and small molecules filter through glomeruli rapidly while proteins and blood cells do not.

Active Transport

Active transport utilizes biologically produced energy. This makes it possible to transport a substance: (a) at faster rate or (b) even against the gradient.

Active transport may also be carrier mediated. The carrier may be high affinity career or low affinity carrier (Fig. 5.9).

1. Active transport is required for maintaining the difference in electrolyte composition between intracellular and extracellular fluids.
   For example: Inside the cell: (i) sodium ion concentration is much lower than outside, (ii) potassium ion concentration is much higher than outside.
2. Actively transporting cell membranes often contain ATPase, which will breakdown ATP and liberate energy.
3. Active transport may be inhibited by:
   i. Inhibitors of ATPase—specifically or
   ii. Nonspecifically by attacking various processes which are involved in formation of ATP.

Secondary Active Transport

Ingenious device used by cells to utilize the active transport of one substance to drive the uphill transport of one or more other substances as well.

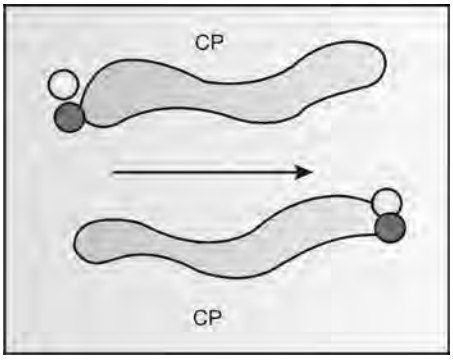
Few varieties:

1. Coupled transport—which includes: (i) cotransport or symport, (ii) counter transport or antiport.
2. Osmosis—entry of solute into the cell by active transport increases the osmotic pressure within the cell, hence water also enters the cell by osmosis, e.g. reabsorption of water from gut.
3. Solvent drag—along with water some substances dissolved in water may move in the same direction by bulk flow. This is known as solvent drag.

Coupled Transport

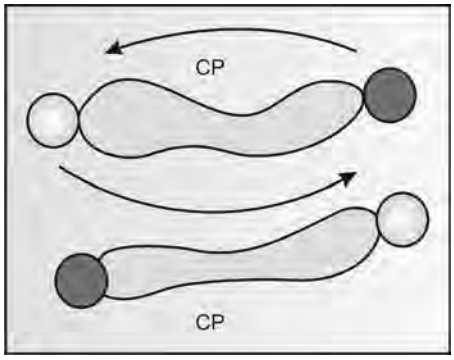
Transport of two substances may be coupled to each other because they bind to the same carrier in the cell membrane.

1. *Cotransport or symport*: If the substances whose transport is coupled move in the same direction the phenomenon is called cotransport or symport (Fig. 5.10). For



CP = Carrier protein

Fig. 5.10: Cotransport or symport



CP = Carrier protein

Fig. 5.11: Counter transport or antiport

example, in small intestine absorption of sodium ion is coupled with that of glucose because they bind to the same carrier in cell.

2. *Counter transport or antiport*: If two substances whose transport is coupled move in opposite direction the phenomenon is called counter transport or antiport (Fig. 5.11). For example, in proximal convoluted tubule of kidneys sodium is reabsorbed actively. Simultaneously for each sodium ion reabsorbed one hydrogen ion is transported by the same carrier into the lumen of the tubule.

CHAPTER

6

Bioelectricity

MEMBRANE POTENTIAL AT REST AND DURING ACTIVITY

Concentrations of Biological Substances

Traditionally, the concentrations were expressed in mg/100 ml. It is still used, but molecular weight of different substances are different. Therefore, although concentrations of substance A and B in blood may be M mg/100 ml each, the number of molecules of each in 100 ml of blood will be different.

Since, substances interact in terms of molecules expressing the concentration in terms of mass/volume (e.g. mg /100 ml) is no longer considered to be best mode of expression.

Currently popular modes of expressing concentrations are:

1. Moles/L
2. Equivalents/L
3. Osmols/L.

For small concentrations suitable units are:

i. millimoles/L
ii. milliequivalents/L
iii. milliosmols/L

Abbreviations

- m Mol/L
- mEq/L
- mOsm/L.

1. One mole of substance is = to its molecular weight in grams, e.g. 1 mole of NaCl = 58.5 g of NaCl.
2. Equivalent weight of a substance is in relation to its participation in chemical reactions, e.g. 1 molecule of HCl will completely neutralize one molecule of NaOH but ½ a molecule of H_2SO_4 is enough to neutralize 1 molecule of NaOH. Equivalent weight of HCl will be equal to its molecular weight but that of H_2SO_4 will be half its molecular weight.

   In case of acids and alkalis, when the concentration is 1 gram equivalent weight/ 1L it is called a 'Normal' or 1 N solution.
3. Osmolarity of a substance is in relation to the osmotically active entities that its molecule provides. One molecule of NaCl provides two osmotically active entities— Na^+ and Cl^-.

   Thus, 180 g/L of glucose (an unionized compound) is equal to 1 mole/L and also 1 osmols/L.

   But 58.5 g/L of NaCl is equal to 1 mole/ L, but is= 2 osmoles/L.

If instead of volume of the solvent, concentration is expressed in terms of mass of the solvent, the concentration is called molal or osmolal concentration.

Thus, molality of a solution is its concentration in moles/kg and osmolality is concentration in osmols/kg.

Since volume is affected by temperature but the mass is not, molality and osmolality are independent of temperature.

Membrane Potential at Rest

Most living cells show some difference in electrical potential across the cell membrane. This difference is called membrane potential.

Excitable cells, i.e. muscle and nerve cells - show: (a) membrane potential while at rest, but also show (b) a dramatic change in the potential during activity.

GENESIS OF RESTING MEMBRANE POTENTIAL (RMP)

RMP—may be measured by means of fine intracellular glass electrode filled with solution of KCl, with a tip diameter less than 1 micron, which can penetrate the excitable tissue without causing too much injury (Fig. 6.1).

As compared to the ECF the interior of the cell is electrically negative.

- In smooth muscle cells
- Thin nerve fibers and neurons of CNS

RMP = – 40 to – 60 mv.

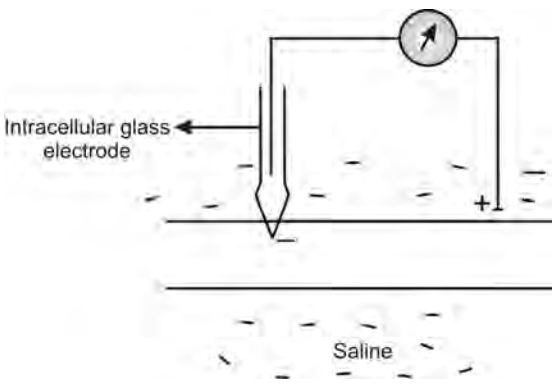


Fig. 6.1: Measurement of RMP

- In skeletal muscle cells and large diameter peripheral nerve fibers

RMP = – 90 mv.

RMP is mainly the result of following factors:

1. Difference between intracellular and extracellular potassium concentration.
2. Impermeability to protein ions.
3. Poor permeability of the membrane to sodium ions.
4. Sodium pump.

Let Us Explain

In living cells the major intracellular negative ions are protein ions at physiological pH. These protein ions cannot diffuse out of the cell, because the membrane is not permeable to them.

Inside the cell the positively charged potassium ions will try to diffuse outward due to concentration gradient, through the leak channels in the cell membrane. But the negatively charged protein ions cause them to diffuse inwards. A point will be reached when outward movement of potassium ions will be exactly balanced by their inward movement. From this point onward there will be no net diffusion of the potassium ions. The potential difference at this point will be called equilibrium potential. At equilibrium potential potassium ion concentration in a mammalian muscle cell is:

- 155 m Eq/L in ICF.
- 4 m Eq/L in ECF.

Difference in potassium concentration between the intracellular and extracellular fluid is due to presence of impermeable negatively charged protein ions inside the cell.

Chloride

Chloride in a mammalian muscle cell, chloride ion concentration is:

- 4 m Eq/L in ICF, and
- 120 m Eq/L in ECF.

Chloride is the only major anion to which the cell membrane is freely permeable. Its concentration adjusts itself passively to the potassium equilibrium potential.

Sodium

Sodium in a mammalian muscle cell, the sodium ion concentration is:

- 12 m Eq/L in ICF, and
- 145 m Eq/L in ECF.

The concentration gradient as well as electrical gradient favor the diffusion of sodium ion in the cell. This extremely strong tendency is neutralized by the sodium pump, which is present in the cell membrane. Na pump is a carrier mediated active transport mechanism located in the cell membrane.

Carrier for the pump is Na – K ATPase which means that the carrier protein binds with both sodium and potassium ions and also acts as an enzyme for hydrolysis of ATP.

Hydrolysis of ATP—generates energy which drives the pump. The mechanism pumps 3 sodium ions out of the cell in exchange for 2 potassium ions which are pumped into the cell.

Since the number of positive ions pumped out exceeds, those pumped in, the pump generates an electrical potential across the cell membrane. That is why the pump is also referred to as electrogenic sodium pump.

This pump neutralizes the passive leakage of sodium ions into the cell through pores in the membrane, referred to as leak channels, which occurs due to electrical as well as concentration gradient. As it is cell membrane is poorly permeable to sodium ions.

At RMP the Na influx through leak channels is exactly equal to sodium efflux due to sodium pump.

Action Potential (Fig. 6.2)

A resting nerve or muscle cell becomes active as a result of stimulus. Irrespective of the nature of stimulus the response is—change in the membrane potential. Membrane becomes less polarized (for example, from –90 mv to –70 mv) which is known as depolarization. If the magnitude of depolarization exceeds the threshold value, it leads to a well defined electrical change known as action potential (If magnitude of depolarization is below a certain threshold value, it gradually fades away).

1. Thus, action potential is a brief depolarization of large magnitude followed by repolarization.
2. There is a change in the membrane potential from about –90 mv to +30mv during action potential.
3. Repolarization means return of membrane potential to the RMP (–90 mv).
4. Because action potential is a brief depolarization of large magnitude it is known as spike.

Towards the end of action potential there may be long lasting phases of deviation from RMP before the membrane potential finally

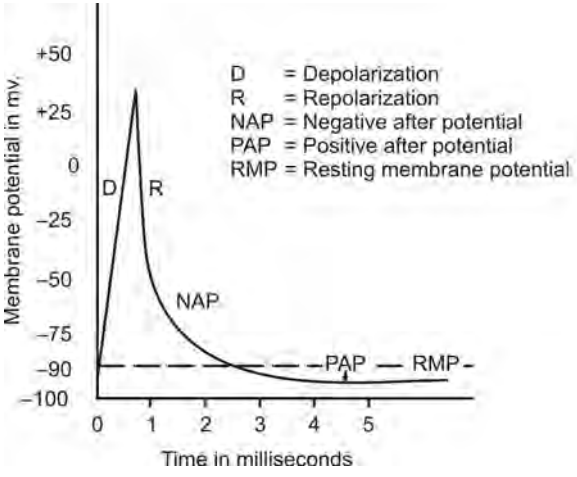


Fig. 6.2: Action potential

settles down at RMP. These deviations are known as after potentials, which are of two types:

1. Negative after potential, and
2. Positive after potential.

Action potential is generated by sequential changes in membrane permeability to sodium and potassium ions, due to opening up of voltage gated channels for sodium and potassium sequentially (Fig. 6.3).

The sequence of events are (Fig. 6.4):

1. Stimulus of excitable tissue leads to immediate increase in the permeability to sodium due to opening of voltage gated channels of sodium to about 5000 times. Therefore, large influx of sodium ions takes place as: (a) concentration gradient of sodium, and (b) negativity of the inside of the resting cell, both factors favor inflow of sodium.
2. Increased permeability of sodium lasts only for a short while then it declines.
3. When sodium permeability starts declining the membrane permeability to potassium ions start increasing as the voltage gated channels of potassium now open up.
   i. Since the concentration of potassium is higher inside the cell, and
   ii. Outside of the cell is negative at the peak of action potential.

   Hence, potassium ions diffuse out and bring the membrane potential back to normal. RMP is restored.

   In short depolarization is due to entry (influx) of sodium ions and repolarization is due to exit (efflux) of potassium ions.
4. At the end of the action potential the excitable cell has more sodium ions and less potassium ions than at the beginning. Bringing the concentrations back towards the original is the job of the sodium pump, which it does slowly.

Voltage Gated Channels

By now, we know that action potential is triggered by membrane depolarization above a threshold value.

This is due to existence of voltage gated sodium and potassium channels in the membrane.

Voltage gated means that, whether the channel is open or closed depends on the

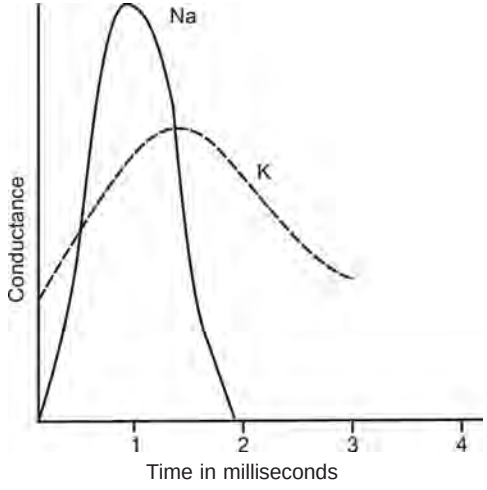


Fig. 6.3: Graph showing conductance of membrane to Na and K ions during action potential

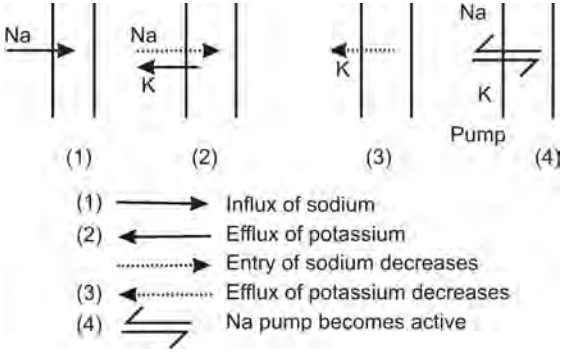


Fig. 6.4: Schematic diagram of sequential events leading to action potential

voltage. At the resting membrane potential the channels are closed. When the membrane depolarization is beyond a certain threshold value the channels open: (a) temporarily, and (b) with fixed time course which is different for sodium and potassium. These voltage gated channels are different than leak channels.

Sodium Channel

Voltage gated sodium channel opens promptly at super threshold depolarization (Fig. 6.5). This increases the permeability to sodium 5000 times and massive influx of sodium ions takes place—in accordance with electrical and concentration gradient (=electrochemical gradient). Large influx of sodium ions renders the Na pump ineffective and there is explosive change of membrane potential from –90 mv to +30 mv. Then, there is inactivation of sodium channels. Therefore, there is decrease in sodium permeability.

Voltage gated sodium channel has two components: (a) the activation gate, and (b) inactivation gate.

At RMP—activation gate is closed and inactivation gate is open.

At suprathreshold depolarization—opening of activation gate and closure of inactivation gate takes place.

But opening of activation gate is quick, while the closure of inactivation gate is delayed. That is why there is a short interval during which both components of the gate are open—this leads to action potential.

Potassium Channels

They are simple channels:

1. In response to a suprathreshold depolarization the voltage gated potassium channels open with slow time course.
2. Opening of potassium channels coincides with closure of the inactivation gate of sodium channel. Both these processes contribute to repolarization and restore the RMP.
3. At RMP the potassium channel close automatically.

In summary—action potential consists of:

1. Depolarization of large magnitude followed by
2. Repolarization, and (i) depolarization is due to influx of Na ions whereas (ii) repolarization is due to efflux of K ions aided by the fact Na influx is declined.

Characteristics of Action Potential

1. It is all or none change.
2. It has a fixed value.

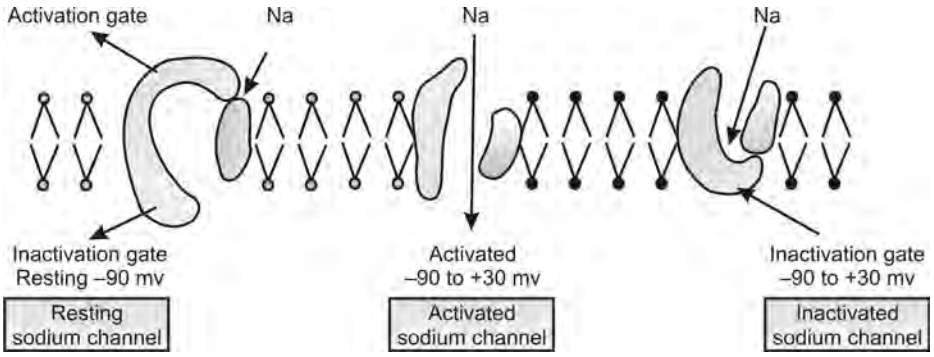


Fig. 6.5: Voltage gated sodium channel

3. It is propagated without decrease in its value.
4. It is uniquely biological phenomenon and it is seen only in living excitable cells.
5. One action potential must be complete before second one is induced. Therefore, excitable tissues have refractory period.
6. Action potential cannot be fused together or superimposed on each other.

After potentials (See Fig. 6.2) towards the end of action potential there are phases of small deviation from RMP, before the membrane potentials finally settles down at RMP. These deviations are known as after potentials:

1. *Negative after potential*: Towards the end of action potential, membrane potential remains less negative than RMP for a short while. This is known as negative after potential. Cause for it is excess potassium accumulate outside the cell membrane. Hence, diffusion of potassium ions out of the cell becomes slow.
2. *Positive after potential:* After a phase of negative after potential the membrane potential becomes more negative than RMP for sometime. This is known as positive after potential.
   Cause for it:
   i. Excess potassium permeability continues leading to negativity inside the cell.
   ii. Sodium pump becomes active again—pumping sodium out.

Propagation of Action Potential

Action potential is propagated without decrement along the membrane of the excitable cell.

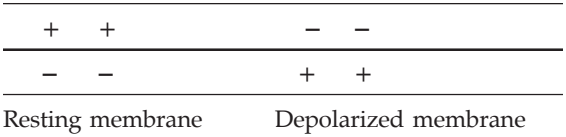


Fig. 6.6: Resting and depolarized membrane

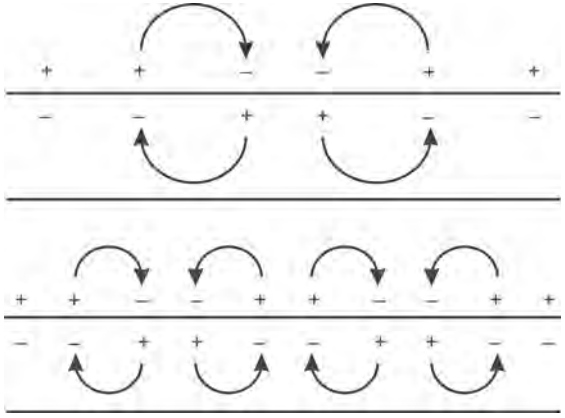


Fig. 6.7: Propagation of action potential

Resting membrane is positive outside and negative inside.

During action potential the membrane becomes negative outside and positive inside (Fig. 6.6).

Hence in neighboring membrane on the outside the ions are attracted towards the site of action potential. On the inside reverse happens. So depolarization of neighboring membrane takes place. When this depolarization of neighboring membrane reaches the suprathreshold value the action potential develops at the neighboring new site and the process goes on (Fig. 6.7).

Thus, stimulation of excitable tissue leads to an electrochemical change—action potential, and propagated action potential is impulse.

CHAPTER 7

Intercellular Communications and Genetics

Mostly cells communicate with each other via chemical messengers. Different ways of communication via chemical messengers are:

1. Within a given tissue, some messenger move from cell-to-cell via gap junctions without entering the ECF.
2. Cells are affected by chemical messengers —secreted into the ECF.

These chemical messengers bind to protein receptors: (i) on the surface of the cell, (ii) in the cytoplasm or (iii) the nucleus.

Binding of chemical messengers with appropriate receptors triggers sequences of intracellular changes that produce their physiological effects.

There are three types of intracellular communication mediated by messenger in the ECF (Fig. 7.1):

1. Neural communication.
2. Endocrine communication.
3. Paracrine communication.

Neural communication: In which neurotransmitters are released at synaptic junctions from nerve cells. They travel a narrow synaptic cleft, and act on a postsynaptic membrane.

Endocrine communication: In which hormones reach the cell via the circulating blood.

Paracrine communication: In which the products of the cell diffuse in the ECF to affect neighboring cells that may be some distance away.

1. Some cells secrete chemical messengers that bind the receptors on same cell. This is known as autocrine communication.
2. Recently an additional form of intercellular communication called juxtacrine communication has been described.

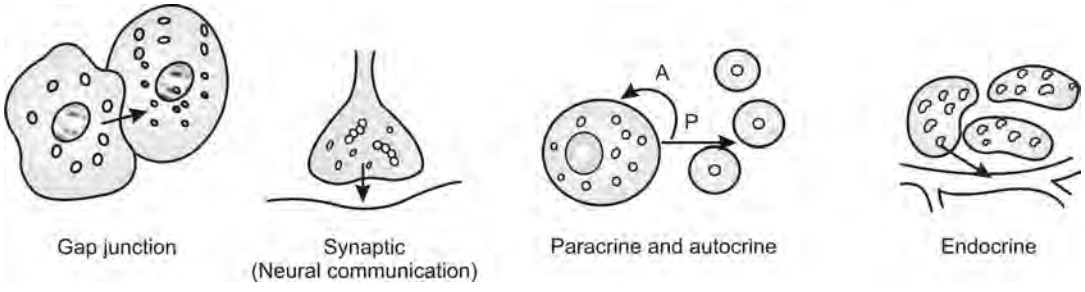


Fig. 7.1: Intercellular communications

Some cells express growth factors such as transforming growth factor alpha (TGFα) extracellularly on transmembrane protein. Other cells have TGFα receptors. Therefore, TGFα anchored to the cell bind to TGFα receptor on another cell, linking the two.

CHEMICAL MESSENGERS

Chemical messengers include:

i. Amines.
ii. Amino acids.
iii. Polypeptides.
iv. Steroids and in few instances.
v. Other substances like small proteins.

In various parts of the body the same chemical messenger can function as: (i) a neurotransmitter, (ii) a paracrine messenger, (iii) neurohormone, and (iv) hormone secreted by gland into the blood.

Receptors for hormones, neurotransmitters and other ligands (ligand = a substance which binds) are found.

Many receptors for chemical messenger have now been isolated and characterized. They are protein in nature.

These proteins are not static component of the cell, but their—(a) number increase and decrease in response to various stimuli, and (b) their properties change with changes in physiological conditions.

When a hormone or neurotransmitter is present in excess the number of active receptors decrease (downregulation).

Whereas in the presence of a deficiency of the chemical messenger, there is an increase in the number of active receptors (upregulation).

MECHANISMS BY WHICH CHEMICAL MESSENGERS ACT

1. Open or close ion channels in the cell membrane—for example, ligands such as acetylcholine bind directly to ion channels in the cell membrane changing their conductance.
2. Act via cytoplasmic or nuclear receptors. The activated receptors bind to DNA and increase transcription of selected mRNA. For example, thyroid hormones, steroid hormones.
3. Almost all other ligands in the ECF bind to receptors on the surface of cells—which trigger release of cyclic AMP or alike substances which initiate changes in cell function.

The extracellular ligands are called first messenger and the intracellular mediators are called second messengers, e.g. cyclic AMP is the second messenger.

The second messengers generally activate protein kinases—they are the enzymes that catalyze the phosphorylation of amino acids or proteins. More than 100 protein kinases have been described.

SECOND MESSENGERS AND MECHANISM OF ACTIONS OF SECOND MESSENGERS

1. *Cyclic AMP*: It is important second messenger. Cyclic AMP is 3′-5′ adenosine monophosphate. It is formed from ATP by the actions of enzyme adenyl cyclase, cyclic AMP activates protein kinase A which catalyzes the phosphorylation of protein.
2. *G proteins:* A common way to translate a signal to biologic effect inside cells is by way of nucleotide regulatory protein (G protein) that binds GTP or Guanosine triphosphate. GTP—protein complex brings about the effect.
3. Some second messengers act by increasing cytoplasmic Ca concentration. IP3 or Inositol triphosphate is the major second

messenger that causes Ca release from internal stores.
4. At some places Ca^{++} is necessary for action of a second messenger.
5. *DAG (diacylglycerol):* It is also a second messenger—it stays in the cell membrane where it activates protein kinase C.
6. *Growth factors*: Are important. They are polypeptides and proteins divided in three groups:
   i. Agents that cause multiplication and development of various types of cells, e.g. insulin like growth factors.
   ii. Cytokines are produced by macrophages and lymphocytes, and are important regulator in immune system.
   iii. Colony stimulating factors—that stimulate proliferation and maturation of red and white blood cells.

RECEPTOR DISEASES

Many diseases are due to mutation of genes: (a) for receptors or (b) for G protein subunits. Receptor mutation that cause disease have been reported for:

i. 1,25-dihydroxycholecalciferol receptor
ii. Insulin receptor
iii. Thyroid hormone receptor
iv. Vasopressin receptor.

Transmission of Characters of Individual Genetics

We know, children resemble parents, and some twins are remarkably similar and some diseases are familial. How parental characters are transmitted? and what determines characteristics of individual? Now we know because of the work of a Monk Gregor Mendel in 1850s. He summarized the essential features of genetics in terms of few laws.

Broadly

1. Parents have capacity of passing on a character to the progeny through two genes.
2. In sexual reproduction the individual receives two genes for each character, one from mother and one from father.
3. The expression of a character in the progeny depends on whether both parents transmit same type of gene or two different types of genes.
   i. If both parents transmit same type of gene to the progeny, it is homozygous and the character is expressed.
   ii. If both parents transmit different type of genes, the progeny is heterozygous for the character and only dominant trait is expressed in the progeny, the recessive trait remains hidden.
   iii. Heterozygous individual passes on the dominant or recessive character to the progeny with equal probability - This is explained in Mendelian theory.

MOLECULAR BASIS OF THE GENES

1. Progeny acquires a pair of each chromosome—one member from the mother and one member from the father.
2. Chromosomes are composed of: (i) nucleic acids, and (ii) proteins.
3. Hereditary material is Deoxyribonucleic acid (DNA) which carries genetic code.

First gene was synthesized under laboratory conditions by Hergobind Khorana in 1970.

How DNA is Eventually Decoded?

For that structure of DNA must be known (Fig. 7.2):

1. DNA has double helical structure.

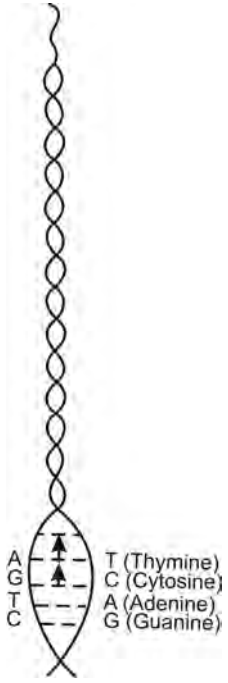


Fig. 7.2: Structure of DNA

2. Each strand of helix has repeated units of
   i. Nitrogenous base—Adenine (A)
      – Guanine (G)
      – Thymine (T)
      – Cytosine (C)
      A is paired with (T), and
      G is paired with (C)
   ii. Sugar (deoxyribose), and
   iii. Phosphate group.
3. Sequence of nitrogenous base in a given chromosome in a given individual is fixed.

Two Processes affect DNA

Replication

During mitosis DNA replicates itself exactly. Therefore, constancy is possible.

Transcription

DNA is carrying a code. Decoding of DNA is known as transcription.

1. Code is in terms of sequence of nitrogenous bases.
2. A set of 3 bases (triplets) codes for an amino acid. Triplet, coding for an amino acid is known as codon.
3. A long chain of codons thus, codes for a protein.

Note: In transcription, one of the two strands of DNA are involved. DNA strand serves as a template for its transcription.

How does the Nuclear Code Express Itself in the Cytoplasm?

1. The message is carried from the nucleus to the cytoplasm by the messenger ribonucleic acid (mRNA).
2. A portion of mRNA, mirrors the portion of DNA strand which has served as template for its transcription.
3. mRNA goes to cytoplasm and arranges itself on the ribosome.
4. Then another variety of RNA (transfer RNA) = tRNA, brings amino acids one by one to mRNA—which are complementary.
5. Amino acid is transferred from tRNA to a ribosome. The ribosome then moves to the next codon on mRNA and stays there till the appropriate amino acid has been brought there.
6. The process continues till all the amino acids required for the protein have been linked to each other.
7. There are codes on mRNA for start signal and termination signal.
8. When chain terminant codon is reached the polypeptide gets detached from the ribosome and enters the rough endoplasmic reticulum. Here the modification of protein takes place. Then it is passed on to Golgi complex.

Proteins to Characters

What a cell does? and what it looks like? or characteristics of cells depend primarily on proteins which it synthesize.

For example:

1. All enzymes are proteins. Therefore, alteration in protein may alter enzymic activities.
2. Several hormones are proteins.
3. Vital substances like hemoglobin are proteins. Alteration in few single proteins of hemoglobin are linked with sickle cell anemia. And you can imagine that the shape of nose depends on protein molecules in it.

Modes of Inheritance—Two Modes

1. A trait may be transmitted by a gene (or genes) located on one (or more) of the 22 pairs of autosomes-autosomal transmission.
2. Some traits are transmitted by sex chromosomes such traits are called sex linked characters.

Autosomal Transmission

A given autosomal trait may be dominant or recessive and the inheritance will be of: (a) autosomal dominant or (b) autosomal recessive (Fig. 7.3).

1. Character coded by A is dominant. Therefore, B does not express itself.
2. Out of two DNA strands only one shown as continuous line is transcribed into mRNA.

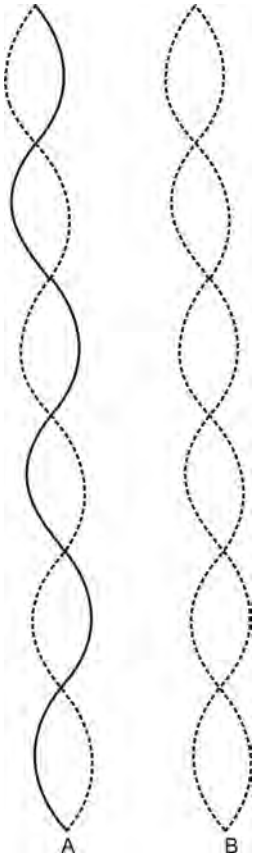


Fig. 7.3: Pair of chromosomes (character coded by 'A' is dominant, therefore, 'B' does not express itself)

ALLELES

Alternative forms of a gene are called alleles. Sometimes neither of the alleles present in an individual is clearly dominant or recessive. Such inheritance is called *codominar.* For example, inheritance of blood group substance A and B. If the gene for group A is present on one chromosome and that for group B on the other, the person will have blood group AB.

Some traits are transmitted by sex chromosomes. Such traits are called sex linked characters.

Examples:

1. Y-linked dominant character—testes determining factor (TDF), which is responsible for forming testes.
2. X-linked dominant inheritance are few – example is vitamin D resistant rickets.
3. X-linked recessive inheritance are many – example:
   i. Red-green color blindness.
   ii. Hemophilia.

These diseases usually affect only the males, because females are protected by the dominant normal gene on the other X-chromosome.

What are Genotype and Phenotype?

Genetic make up of individual is genotype. Actual characteristic manifested by individual is phenotype.

Environment has profound effect on genetic expression. *For example:*

1. Height of an individual is the product of genetic make up and environmental factors such as nutrition and exercise.
2. IQ is product of inherited intelligence and environmental factors such as nutrition and environmental stimuli.

CHAPTER 8

Composition and Function of Blood and Plasma Proteins

BLOOD

Blood may be described as specialized connective tissue whokse matrix is liquid, known as plasma in which formed elements such as:

1. Red blood cells (RBCs)
2. White blood cells (WBCs)
3. Platelets (Thrombocytes) remain suspended.

Composition of Blood

Blood is scarlet (red) in color when taken from artery and darkish (red) when taken from vein. It has a tendency to solidify when shed—known as clotting (Fig. 8.1). Clotting can be prevented by adding, anticoagulants like heparin, oxalate, etc.

It consist of two parts:

1. Liquid part—55% known as plasma (clear, yellowish fluid).
2. Solid portion—45% consists of cells (formed elements).

Normal Values

1. Plasma proteins—6.4 to 8.3 gm% (average 7%).
   - i. Albumin— 4.8 gm%
   - ii. Globulin— 2.3 gm%
     - α globulin (α_1, α_2)— 0.79-0.84 gm%
     - β globulin (β_1, β_2)— 0.78-0.81 gm%
     - ϒ globulin (Υ_1, Υ_2)— 0.66-0.70 gm%
   - iii. Fibrinogen— 0.3 gm%
   - iv. Prothrombin— 0.02 to 0.04 gm%

   Albumin, globulin ratio = 1.7 : 1
2. Nonprotein nitrogenous substances:
   - i. Urea — 20-40 mg%
   - ii. Uric acid — 2-4 mg%
   - iii. Creatinine — 1 mg%
   - iv. Creatine — 1-2 mg%
   - v. Xanthine — Traces
   - vi. Hypoxanthine — Traces
3. Other substances:
   - i. Neutral fats (triglycerides) — 30-150 mg%
   - ii. Phospholipids e.g. lecithin, cephalin, and

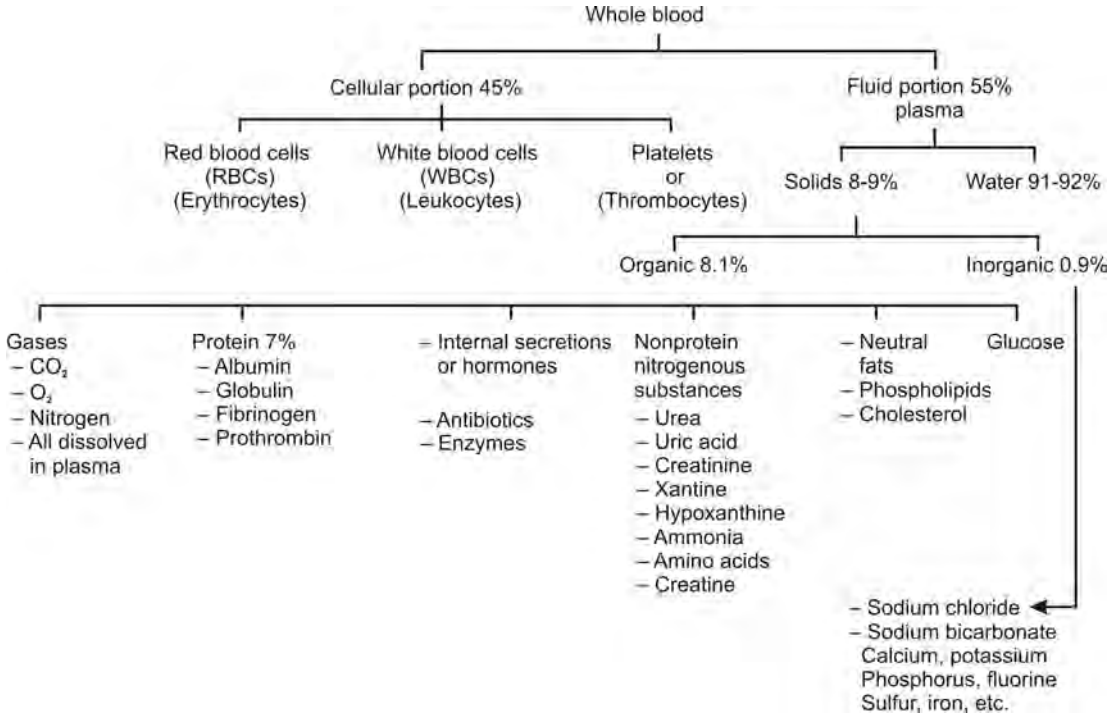


Fig. 8.1: Composition of whole blood

sphignomyelin — 150-300 mg%
iii. Cholesterol — 150-240 mg%
iv. Glucose (fasting) — 80-100 mg%

Functions of Whole Blood

Blood serves as a connecting link between the individual cells of distant organs and tissues, along with lymph and tissue fluid.

The various functions are:

1. *Nutritive:* (a) Nutrients derived from the digestive food material, e.g. glucose, amino acids, lipids, vitamins are absorbed from the alimentary canal and carried by blood to tissue cells for growth and supplying energy, (b) It also carries nutritive material from storage depots to the tissue cells.
2. *Transport of respiratory gases:* It carries oxygen from air (through lungs) to the tissues and remove carbon dioxide from tissues, carries it to lungs from where it is exhaled to air.
3. *Excretory*: It removes waste products derived from metabolism to outside of the body, through excretory channels of kidney, skin and lungs.
4. *Maintenance of water content of tissue and its homogeneity:* Liquid portion of blood is freely interchangeable with interstitial

fluids. Thus, it helps to maintain water content of tissues.

5. *Regulation of body temperature:* The water content of the blood helps in regulation of body temperature:
   i. Due to its high specific heat it can absorb large amount of heat and prevent sudden change of body temperature.
   ii. Due to its high conductivity it helps in dissipation of heat.
   iii. Due to high latent heat of vaporization it helps in heat loss.
   iv. Due to quick flow it helps in even distribution of heat.
6. *Protective function:*
   i. It carries antibodies to protect body against infection.
   ii. White blood cells are present in blood which engulf (or phagocytose) bacteria, foreign particles, etc.
7. *Storage - Blood serves as ready source for*: (i) water, (ii) electrolytes like Na^+, K and, (iii) glucose.
8. Acts as vehicle for transport of hormones. It carries internal secretions of ductless glands or endocrine glands called hormones to their target organs.
9. By property of coagulation it guards against hemorrhage.
10. Maintenance of acid base balance by its buffering power it helps to maintain acid base balance.
11. Colloid osmotic pressure of plasma is maintained by plasma proteins present in blood.

PLASMA PROTEINS

The total plasma protein concentration is 6.4 to 8.3 gm% (average 7 gm%).

That means on an average 7 gm plasma proteins are present in 100 ml of blood.

There are mainly four plasma proteins:

1. Albumin — 4.8 gm%
2. Globulin — 2.3 gm%
   Globulins are divided in α, β, γ globulin. Each of them are further subdivided into: α_1, α_2 and β_1, β_2 and Υ_1, Υ_2, etc.
   Albumin, globulin ration = 1.7 :1
3. Fibrinogen — 0.3 gm%
4. Prothrombin — 0.02 to 0.04 gm%

Rate of Regeneration of Plasma Proteins

In depletion of plasma proteins such as by hemorrhage or after blood donation the plasma proteins come to normal in about 14 days. Fibrinogen is regenerated first then globulin and last to regenerate is albumin.

Origin of Plasma Proteins

In Adult

1. Albumin and plasma proteins concerned with coagulation, e.g. prothrombin, fibrinogen are exclusively formed by liver. In liver disease, concentration of these plasma proteins may fall considerably.
2. Plasma globulins are formed widely in the body by:
   i. *Reticuloendothelial system:* Phagocytic cells found in bone marrow, lymphoid nodule, liver, spleen.
   ii. *Lymphoid nodule:* Lymphocytes (gamma globulins) (gamma globulins are also known as immunoglobulins or immune bodies or antibodies, are concerned with resistance to infection).
   iii. *Plasma cells:* These are large, oval cells found in medullary cords of lymphoid follicles.
3. Different food proteins have varying ability to contribute to the formation of plasma proteins depending on their amino acid composition and the amino acid pattern of the plasma protein to be formed.

This may be studied in the standard plasma depleted dog, as described by Whipple. In this experiment whole blood is withdrawn and corpuscles are reinjected suspended in Ringer Locks solution which is a protein free fluid. This procedure is known as plasmapheresis. If this process is repeated daily, it leads to progressive diminution of concentration of plasma proteins, as the rate of protein withdrawal exceeds rate of regeneration. The process is continued till the plasma protein concentration has fallen to 4%. Then the plasma protein formation is studied by giving different food. The results show that plasma proteins are formed from food, but in starvation they may be formed from body proteins.

If the food protein is having an amino acid pattern which resembles a particular plasma protein it is most efficient in forming that particular plasma protein.

1. So, naturally plasma proteins themselves are most efficient raw material for formation of plasma proteins. That means, if animal is fed on plasma proteins, then plasma protein formation is at maximum rate.
2. Plasma proteins can also be synthesized from different essential amino acid like valine, isoleucine, tyrosine, tryptophan, histidine, alanine, leucine, lysine, methionine and phenylalanine.
3. Proteins of muscles and viscera (Non-vegetarian diet) favors albumin formation.
4. Plant and grain proteins favor globulin formation.
5. Presence of infection depresses protein regeneration.
6. Apart from food source plasma proteins may be formed from disintegrated Red and White blood corpuscles and tissue cells.
7. In starvation tissue proteins are the chief source of plasma protein formation.

Various Methods of Separation of Plasma Proteins

1. Precipitation by salts like $(NH_4)\ 2SO_4$, NaCl, Na_2SO_4, and $MgSO_4$.
2. Cohn fractional precipitation—various proteins can be differentiated by differences in their solubility. Therefore, individual plasma proteins can be isolated by fractionation with low salt concentrations, at low temperatures, varying the pH and modifying condition by addition of alcohol. Many plasma proteins can be isolated in a high degree of purity. For example, albumin, immune globulins active against measles, mumps.
3. Sedimentation in ultracentrifuge.
   Principle—the different proteins sediment at different rates when their solution is centrifuged at very high speeds because of differences in their density.
4. If specific gravity of plasma is known , then total plasma protein, concentration can be found out:
   P = K (S–A)
   P = Plasma proteins total concentration
   S = Specific gravity of plasma
   K and A are constants (K = 63, A = 1.006)
5. *Electrophoresis:* Principle—proteins can ionize as acids or bases because side chain of their amino acids contain amino (NH_2^+) group and carboxyl group $(COOH^-)$.

Method: Filter paper is first dipped in the serum and then in sodium bicarbonate buffer, is finally put in the electric field with electrical poles at the end. Since each protein has different surface charges they therefore, migrate at different rates (electrophoresis).

- Pre-albumin and albumin move fastest,
- Gammaglobulin move slowest,
- Other plasma proteins move at intermediate rates.

After sometime, the filter paper is taken out and stained with Sudan blue to denmark the different zones of plasma proteins.

6. *Immunoelectrophoresis* same as electrophoresis but here the pattern is formed by precipitation of local antigen—antibody reaction.

Forms of Plasma Protein

1. **Albumin is of two types:**
   i. Prealbumin
   ii. Albumin.
2. **Globulin (A) is of three types:**
   i. α globulin — α_1 and α_2
   ii. β globulin — β_1 and β_2
   iii. γ globulin — γ_1 and γ_2.

   (B) Forms of globulin:
   i. Lipoprotein (α_2 globulin + lipid)
   ii. Glycoprotein (carbohydrate + protein).

   Subtypes of Lipoprotein
   i. High density lipoprotein (HDL) or a lipoprotein contain 50% protein.
   ii. Low density lipoprotein (LDL).
   iii. Very low density lipoprotein (VLDL). (b) and (c) are also called β lipoprotein.
   iv. Chylomicrons - contain 2% protein and 98% triglycerides.
3. Transferrin
   i. Mainly β globulin, α_2 globulin
   ii. Binds iron (ferric iron).
4. Haptoglobulin
   i. α_2 globulin.
   ii. forms stable complex with free hemoglobin.
5. Ceruloplasmin—mainly α_2 globulin, β globulin. Binds with copper and help its transport and storage.
6. Coagulation factors—α, β globulin.
7. Angiotensinogen—α_2 globulin.
8. Hemagglutinins—antibodies against red cells.
9. Immunoglobulin (Ig)—gammaglobulin.

Main Functions of Plasma Proteins

1. *Albumin*: Maintain colloid osmotic pressure in plasma, which is responsible for retaining water in blood vessel. Albumin having smaller molecular weight contributes to approximately 80% of colloid osmotic pressure, whereas globulin and fibrinogen contribute 20%. Total colloid osmotic pressure maintained by plasma proteins is 25 mm Hg.
2. *Globulin:* (a) Antibodies which are γ globulins are produced in the body against variety of antigens, for example, diphtheria, typhoid, cholera, measles, infective hepatitis.

   Purified γ globulins are utilized for immunizing against these infections.

   (b) Carriage of other substances (by α_1 , α_2, β_1 , β_2 globulins)

   For example – Mucopolysaccharides
   – Lipids
   – Lipid soluble substances
   – Phospholipids
   – Cholesterol
   – Steroids
   – Hormones (e.g. thyroxine, cortisol)
   – Bilirubin
   – Metals - Iron (α_2, β_1 globulin = transferrin)
   – Zinc
   – Copper (α_2 , β_1 globulin = ceruloplasmin) and drugs.
3. Fibrinogen and prothrombin are main factors in blood coagulation, when blood

is shed, the damaged tissue and platelets liberate thromboplastin. This thromboplastin alongwith Ca^{++} ions acts on prothrombin and converts it into thrombin. The thrombin acts on fibrinogen and converts it into fibrin. Fibrin is laid down in the form of network which entangles the red blood cells and white blood cells and form a clot.

$$\frac{\text{Prothrombin + Thromboplastin}}{\text{ca}} \rightarrow \text{Thrombin}$$

$$\text{Fibrinogen} + \xrightarrow{\text{Thrombin}} \text{Fibrin}$$

4. *Other functions of plasma proteins:*
   i. Maintenance of acid-base balance of blood. Proteins are good buffers as they have power to accept H^+ ions.
   ii. Carriage of CO_2 as carbamino compounds.
   iii. Protective function—proteins being colloid particles protect the various suspended corpuscles from collision and mutual damage.
   iv. Regulation of fluid interchange between blood and tissues.

Serum

If blood is allowed to clot in a test tube and kept for sometime the clot retracts and gives out serum. Therefore, serum is plasma minus fibrinogen and clotting factors, because these factors get consumed in clotting.

Serum is rich in serotonin (5 HT = 5 hydroxytryptamine), because of the breakdown of the platelets during clotting.

CHAPTER 9

Erythrocytes, Erythropoiesis, Fate and Functions of RBC

ERYTHROCYTES

Human red blood cells (RBCs) or erythrocytes are:

1. Discoid
2. Nonmotile
3. Highly differentiated cells which have lost their nuclei and other organelle during maturation.

Size (Fig. 9.1)

i. Average diameter 7.3 μm
   Range is 6.5-8.8 μm
ii. Thickness at the end—2-2.4 μm
iii. Thickness at the center—1.2-1.5 μm
iv. Average surface area—140 μm^2
v. Volume – 78 to 94 μm^3 (86 $\pm$ 3 μm^3).

The cell is larger in venous blood due to inbibation of water when pH changes to acid side.

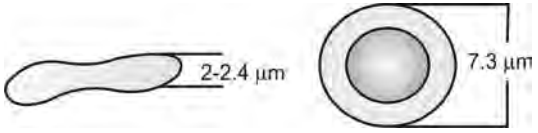


Fig. 9.1: Human red blood cell and its dimensions

Shape

It is biconcave disk, from side view they look like elongated body with rounded ends and constricted middle part.

Their *biconcave shape:* (a) make them extremely flexible so that they can pass through smaller blood vessels, (b) allows considerable alteration in volume, therefore can withstand considerable changes in osmotic pressure and resist hemolysis.

Composition

It mainly contains hemoglobin, which carries oxygen from lungs to tissues.

Hemoglobin concentration in adult male 14-18 gm% (average 15.5 gm%).

1. In adult female 12-15.5 gm% (average 14 gm%).
2. At birth hemoglobin concentration is high —23 gm%.
   i. 1 gm hemoglobin can combine with 1.34 ml of oxygen. It carries oxygen by forming loose compound with oxygen – (oxyhemoglobin) which gives up oxygen at tissue level and becomes reduced hemoglobin.

Normal RBC indices

Help in diagnosis of anemia

1. Mean corpuscular volume (MCV) = Volume of a single RBC in cubic microns (μm^3)

$$MCV = \frac{\text{PCV per 100 ml of blood}}{\text{RBC count in million/cumm}}$$

$$= \frac{450}{5} = 90\ \mu m^3$$

(Range 78 – 94 μm^3)

MCV normal – Normocyte
MCV > normal – Macrocyte
MCV < normal – Microcyte

2. Mean corpuscular Hb (MCH) = Hb in a single RBC in picograms

$$MCH = \frac{\text{Hb in grams per 100 ml}}{\text{RBC count in million/cumm}}$$

$$= \frac{150}{5} = 30\ pg$$

(Range 28 – 32 pg)
(not in use to type anemia)

3. Mean corpuscular Hb concentration (MCHC) = amount of Hb as percentage of volume of RBC or Hb in single RBC.

$$MCHC = \frac{\text{Hb in gm\%}}{\text{PCV per 100 ml of blood}} \times 100$$

$$= \frac{15}{45} \times 100 = 33\%$$

(Range 35 ± 3%)

MCH = within normal range RBC is normochromic

MCHC = < than normal range RBC is hypochromic

MCHC—can never be more than 38%.

Therefore, anemia can never be hyperchromic.

4. Color index (CI)

It is ratio of hemoglobin to RBC

$$CI = \frac{Hb\%}{RBC\%}$$

$$= \frac{100}{100} = 1$$

Range—0.85 to 1.15

Note: 14.8 gm%
Hb = 100%
and 5 millions/cumm
RBC count = 100%

Normal values

Adult males—5-6 millions/cumm of blood (average 5.5 millions/cumm) Adult females—4.5 - 5.5 millions/cumm (average 4.8 millions/cumm) Clinically – 5 millions/cumm is taken as 100% RBC count. At birth—6-7 millions/cumm

i. When red cell count falls below 4 millions/cumm and Hb% also falls below normal, the condition is known as *anemia*.
ii. When red cell count rises above 6.5 millions/cumm the condition is known as polycythemia.
iii. Muscular exercise, high altitude and emotions (excitatory) increase the red cell count.

Lifespan of RBC—120 days

RBC has no mitochondria and no ribosomes and no nucleus. Still it can live up to 120 days because RBC uses glucose, which can be transported in RBC by facilitated diffusion (carrier mediated passive process) and it has cytoplasmic enzymes for metabolizing glucose and other substances, and for utilization of oxygen.

These metabolic systems become progressively less active with time, thus limit the lifespan of RBC.

Packed cell volume = When blood mixed with anticoagulant is centrifuged at 3000 revolutions/per minute for half an hour—corpuscles settles at the bottom and occupy 45% of the blood volume. This is known as packed cell volume or hematocrit value of blood.

Variations in size and shape

1. Anisocytosis—variation in size of RBCs.
2. Poikilocytosis—variation in the shape of RBCs.
3. Spherocytosis—spherical RBCs, more fragile.
4. *At birth*
   - RBCs are larger in size and RBC count is 6-7 million/cumm.
   - PCV – 54% because RBC count is more and RBC is are large.

Reticulocytes are 2-6% of RBCs in circulation. They decrease to < 1% during 1st week of life. At this level it remains throughout life.

ii. 1 ml of red cells contain 1 mg of iron in the form of hemoglobin. Therefore, hemoglobin is iron containing red pigment of blood known as chromoprotein. It consist of globin and hem (iron containing part).

c. Apart from hemoglobin–RBC contains:
   i. Water – 62.5%
   ii. Other substances like—glucose, lipids (cephalin, cholesterol lecithin) protein, glutathiones, (albumin like insoluble protein, acts as a reducing agent, thus prevents damage of hemoglobin)
      - Enzymes of glycolytic system; carbonic anhydrase, and catalase
      - Vitamin derivatives
      - Ions – Na^+, K^+, Ca^{++}, PO_4^{3-} and SO_4^{2-}.

FUNCTIONS OF RBC

1. Transports oxygen in combination with hemoglobin from lungs to tissues.
2. Transports carbon dioxide from tissues to the lungs in combination with hemoglobin.
3. Hemoglobin in RBC acts as an excellent acid base buffer.
4. RBCs contain blood group specific substance, i.e. antigen, on its surface. Thus, helps in identifying blood groups.

ERYTHROPOIESIS

Process of Formation of RBC (Fig. 9.2)

1. *In embryo*: RBC formation takes place in mesoderm of the yolk sac (mesoblastic stage). RBC formation is intravascular.
2. *By third month*: RBC formation takes place in spleen and liver (Hepatic stage).
3. *From middle of fetal life:* Bone marrow is the blood forming organ (Myeloid stage).
4. *At birth*: Erythropoiesis takes place only in red bone marrow.

Note: In intravascular formation of red cells the endothelial cell undergoes transformation into blood cells and detaching from vessel wall to enter the circulation.

There are two theories for formation of RBC:

i. Intravascular, and
ii. Extravascular

Extravascular theory is most accepted. Hemocytoblast which is extravascular parent cell, gains entrance in blood sinuses by amoeboid movements. There it multiplies to give RBCs.

Bone Marrow

Bone marrow is of two types:

1. *Yellow:* It contains fat cells, blood vessels and reticular cells.

Cell stage parent cell	*British hemocytoblast (stem cell)*	*American endothelial cell (in intravascular)*	*Staining of cytoplasm*
I	Proerythroblast	Megaloblast	Basophilic
II	Early normoblast	Early erythroblast	Basophilic
III	Intermediate normoblast	Late erythroblast	Polychromatophilic
IV	Late normoblast	Normoblast	
V	Reticulocyte, erythrocyte	Reticulocyte, erythrocyte	

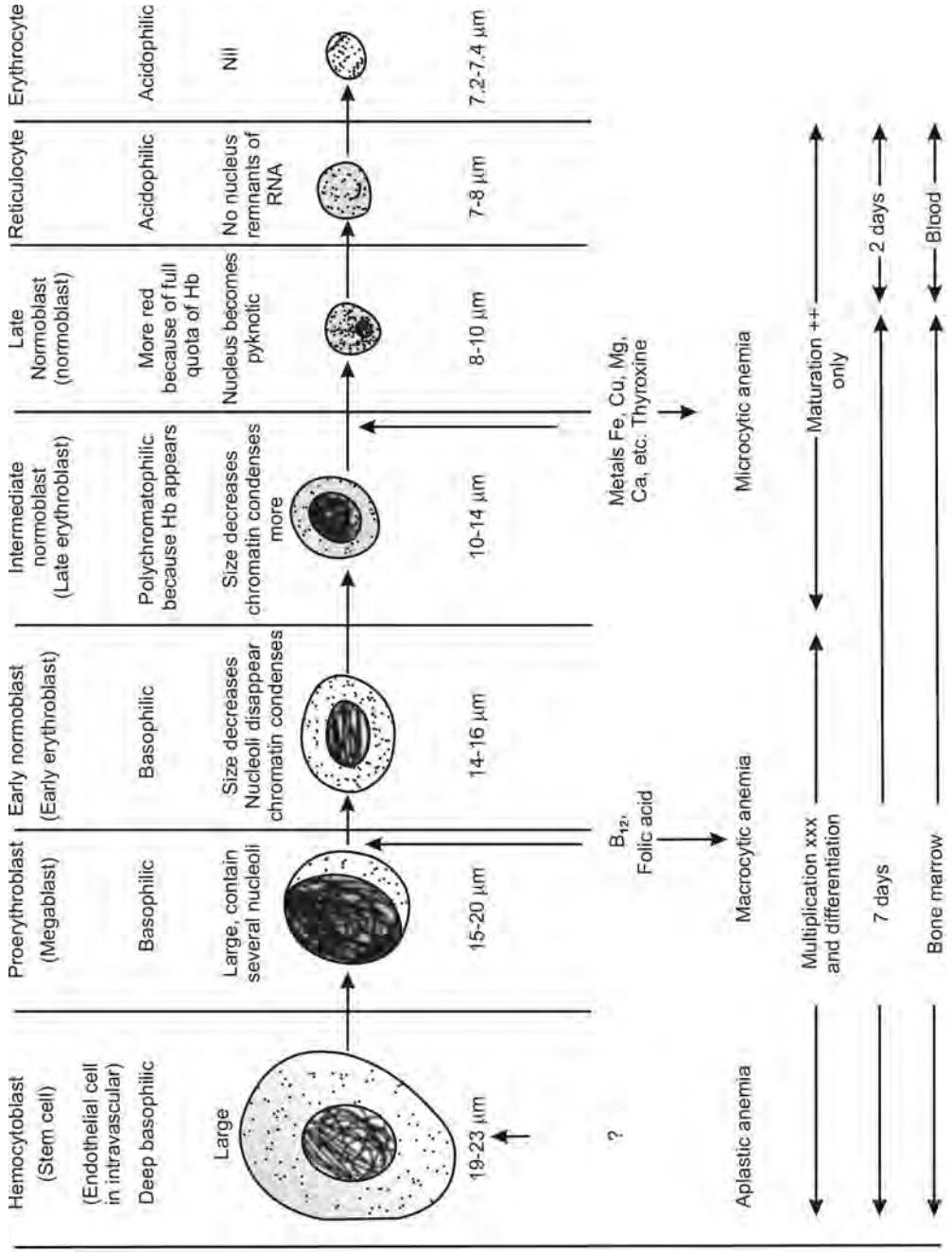


Fig. 9.2: Erythropoiesis

2. *Red:* It contains blood cells at all stages of development.

At Birth

All bones are filled with red bone marrow. As the age advances marrow becomes more fatty. At 20 years all marrow is yellow and red marrow only exists in:

1. Upper ends of femur and humerus
2. Vertebra
3. Sternum
4. Bones of skull
5. Pelvis.

Functions of Bone Marrow

1. Formation of RBC
2. Granulocyte formation
3. Formation of blood platelets
4. Destruction of red cells by macrophages
   - If marrow gets destroyed, then liver and spleen again become important sites of blood formation.

Stages of Erythropoiesis

Two terminologies are used for different stages of erythropoiesis: British and American (Ref chart on page no 45).

In general, the developing cell:

1. Decreases in size.
2. Cytoplasm becomes more extensive.
3. Nucleoli disappear.
4. Chromatin becomes coarser.
5. Cytoplasm becomes less basophilic (when stained with usual stain).
6. Proliferate and differentiate, till mature red cells incapable of proliferation, are formed.

Hemocytoblast

1. 19-23 μm in diameter (stem cell).
2. Cytoplasm rim all round the nucleus and deep basophilic.
3. Nucleus is large.
4. Chromatin fine network.
5. Several nucleoli present (4-5).

Proerythroblast

1. 15-20 μm in diameter.
2. Cytoplasm deep basophilic.
3. Nucleus is large.
4. Contain several nucleoli.

Early Normoblast

1. Size decreases (14-16 μm in diameter).
2. Nucleoli disappears.
3. Chromatin network fine, shows few nodes of condensation.
4. Cytoplasm basophilic.

Intermediate Normoblast

1. Still smaller (10 - 14 μm in diameter).
2. Nucleus shows further condensation of chromatin.
3. Hemoglobin appears and cytoplasm becomes polychromatic.

Late Normoblast

1. Size further decreases (8-10 μm in diameter).
2. Nucleus is small, degenerates, finally becomes pyknotic or ink drop nucleus.
3. Hemoglobin increases (full quota of Hb).
4. Cytoplasm more red.

Reticulocyte

1. Size still further decreases (7-8 μm in diameter).
2. It is so called because on vital staining by cresyl blue reticulum is apparent which is remnant of RNA.

As the red blood cell ages the reticulum disappears. In healthy persons the bone

marrow releases mature erythrocytes and few reticulocytes in circulation. Normally reticulocytes form less than 1% of circulating red cells.

Reticulocyte count increase, when accelerated erythropoiesis takes place, to 25-35%. The condition is known as *reticulocytosis.*

Regulation of Erythropoiesis

Main factors are:
1. General factors
2. Factors affecting hemoglobin formation
3. Maturation factors.

General Factors

Hypoxia means lack of oxygen at tissue level. It stimulates formation of erythropoietin or hemopoietin or erythrocytes stimulating factor (ESF) or erythropoiesis stimulating hormone (ESH).

Formation and Release of Erythropoietin (Fig. 9.3)

1. It is a hormone which is formed by action of REF of the kidney.
2. It reaches via the blood to bone marrow where it stimulates erythropoiesis.
   i. REF is renal erythropoietic factor or erythrogenin.
   ii. Hypoxia of kidney causes release of REF from juxta glomerular cells.
   iii. REF acts on a globulin present in plasma known as erythropoietinogen.
   iv. Hypoxia increases formation of erythropoietinogen in liver.

Mode of Action of Erythropoietin

1. Causes early differentiation of erythropoietin sensitive stem cells to proerythroblasts and its further differentiation.
2. Increases hem synthesis, therefore hemoglobin increases.
3. Increases release of reticulocytes from the bone marrow.

Hormones

i. Throxine
ii. Cortisol
iii. Growth hormone
iv. Androgens

} Stimulate erythropoiesis

- Thyroxine, cortisol and growth hormone increase oxygen consumption at tissue level, so produce tissue hypoxia and erythropoietin formation is increased.
- Androgen stimulates erythropoietin, increases the
- Population of stem cells and stimulate erythropoiesis.

v. Whereas estrogen—suppress erythropoietin production.
- suppress stem cell responses and thus have inhibitory effect.

Therefore, RBC count is less in females as compared to males.

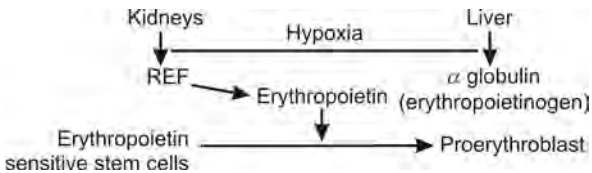


Fig. 9.3: Erythropoietin (formation and action)

Vitamins

Vitamins C, D, vitamin B complex (nicotinamide, riboflavin, thiamine, pyridoxine) are required.

Vitamin C, folic acid, B_{12} help in synthesis of nucleic acid.

Factors Affecting Hemoglobin Formation

1. Iron, manganese, copper help in hem formation.
2. First class proteins help in globin formation.
3. Calcium increases iron absorption from GIT.
4. Bile salts—necessary for absorption of iron, copper, cobalt.
5. Porphyrins.
6. Pyridoxine.

Deficiency of iron results in iron deficiency anemia.

Maturation Factors

1. Arrest of proerythroblast formation results in aplastic anemia. Factors responsible for maturation of hemocytoblast to proerythroblasts are not definitely known.
2. Maturation of erythroblasts (nucleated red cells)—special maturating principles are required for maturation of erythroblasts. They are vitamin B_{12} and folic acid.
   i. *Vitamin B_{12}* is *extrinsic factor*: For its absorption gastric factor known as *intrinsic factor* is necessary.
   ii. One molecule of intrinsic factor binds with one molecule of B_{12} to form *intrinsic factor B_{12} complex* which binds with specific receptor in the ileum mucosa. Intrinsic factor is split off and B_{12} is released in portal blood. This process does not require energy but is calcium dependent. Its optimal pH is 7.0. Intrinsic factor—B_{12} complex is resistant to GIT—proteolytic enzymes.
      a. Deficiency of B_{12} or absence of intrinsic factor results in *megaloblastic anemia* or macrocytic anemia.
      b. Intrinsic factor with extrinsic factor form *hematinic principle* which help in maturation of erythroblasts. This hematinic principle is also known as *Castle s hematinic principle.*

CHAPTER

10

Hemoglobin and Anemias

HEMOGLOBIN

Hemoglobin is the red pigment present in RBC and it gives the characteristic red color to the blood.

Structure (Fig. 10.1)

1. It belongs to the class of conjugal proteins.
2. Its molecular weight is 68,000.
3. Hemoglobin molecule consist of:
   i. Iron containing pigment portion—*Hem.*
   ii. Colorless protein portion—*Globin*.
   Hem—consis of *porphyrin* and *iron*. It is also called iron—*protophyrin* IX
      – The porphyrin nucleus consist of *four pyrrole* rings (tetrapyrrole). Rings are numbered I, II, III and IV. Four pyrrole rings are joined by four methine (=CH) bridges. Carbon atoms in =CH bridges are named α, β, δ and gamma.

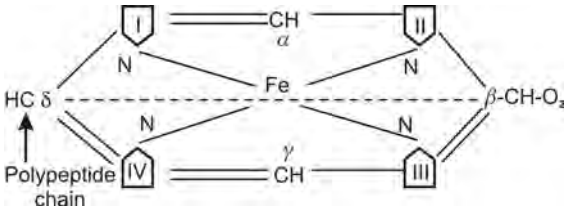


Fig. 10.1: Structure of hemoglobin molecule

      – The iron in hem is in ferrous form (Fe^{2+}). It is attached to N of each pyrrole ring.

Globin is a protein, built from 4 polypeptide chains – two α and two β chains.

Therefore, normal adult hemoglobin is written as HbA ($\alpha_2 \beta_2$). Each polypeptide chain is associated with one hem group.

– *Hemoglobin molecule contains* 4 hem, therefore 4 atoms of iron, each of which can combine with a molecule of oxygen.
– But a true oxide is not formed. Thus, hemoglobin is *oxygenated but not oxidized.*

Functions of Hemoglobin

1. Carriage of oxygen from lungs to tissues. The affinity of hemoglobin for oxygen is remarkable.

When exposed to air it rapidly combines with oxygen to form *oxyhemoglobin*. If oxyhemoglobin is exposed to low oxygen pressure the compound rapidly decomposes and oxygen is liberated and oxyhemoglobin becomes *reduced hemoglobin*. The ease with which hemoglobin unites with oxygen and gives up its oxygen again is of utmost importance in *carriage of oxygen from lungs to tissues*.

Normal values

1. At birth →
   Hemoglobin—23 gm%
2. Adults—Males → 14-18 gm%
   (avg. 15.5 gm%)

   Females → 12-15.5 gm%
   (avg. 14 gm%)

   Clinically—14.8 gm%
   Hb irrespective of sex is regarded as 100%

   Oxygen carrying capacity →
   Males—21 ml%
   Females—18 ml%

1. Oxygenation of 1st hem in hemoglobin, increases affinity of 2nd hem for oxygen and oxygenation of 2nd hem increases the affinity of 3rd hem and so on. Therefore, affinity of hemoglobin for 4th oxygen molecule is many times that of first. This shifting affinity of hemoglobin for oxygen is responsible for *sigmoid shape* of *oxygen hemoglobin dissociation curve.*
2. The affinity of hemoglobin for oxygen is influenced by the presence of 2, 3, Diphosphoglycerate (2,3, DPG) in the RBCs. If concentration of *2, 3, DPG rises*, the affinity of hemoglobin for oxygen *falls* and oxygen hemoglobin dissociation curve is shifted to right and *more oxygen is released* by blood to the tissues.
3. Volumes of oxygen which blood will take up when hemoglobin is fully saturated is the *oxygen carrying capacity* of blood and is proportional to hemoglobin concentration. Each gram of hemoglobin takes up 1.34 ml of oxygen (maximum). Therefore, the oxygen carrying capacity of 100 ml of normal blood which contains 15 gm of hemoglobin is 20 ml.

2. Carriage of carbon dioxide from tissues to lungs carbon dioxide reacts with hemoglobin to form *carbaminohemoglobin.* In this form carbon dioxide is carried from tissues to lungs and liberated.
   $CO_2 + HbNH_2 \rightarrow HbNHCOOH.$
3. It plays important role in regulating the acid base balance of the blood, hemoglobin acting as an efficient buffer.

Carboxyhemoglobin or Carbon Monoxide Hemoglobin

Hemoglobin reacts with carbon monoxide to form carboxyhemoglobin or carbon monoxy hemoglobin (Fig. 10.2).

$$Hb + CO \rightarrow COHb$$

1. COHb is more stable than oxyhemoglobin.

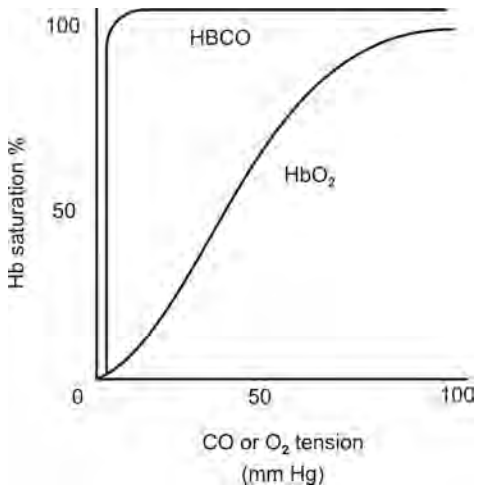


Fig. 10.2: Hb saturation curves for both O_2 (HbO_2) and CO (HbCO)

2. Affinity of hemoglobin to CO is 250 times greater than its affinity for oxygen.

   Therefore, even a small concentration of carbon monoxide in the inspired air is dangerous as it displaces oxygen from hemoglobin, reducing the oxygen carrying capacity of blood.

   Carbon monoxide decreases functional hemoglobin concentration, as the site is occupied by CO, it is unavailable for oxygen transport and CO-poisoning causes acute onset anemia.
3. *Dissociation of CO from hemoglobin:*
   i. CO is slowly displaced from hemoglobin at normal O_2 tensions. This process may require 8-12 hours.
   ii. Administration of 100% oxygen speeds up the dissociation of CO from hemoglobin and secondly increased volume of oxygen gets dissolved in plasma (about 1.5%) at this high oxygen tension, which helps to improve oxygen delivery to the body tissues.

Methemoglobin

When blood is exposed to various drugs and other oxidizing agents *in vitro* or *in vivo*, the ferrous iron (Fe^{2+}) in the molecule is converted to ferric iron (Fe^{3+}), forming methemoglobin.

1. Methemoglobin is dark colored and when it is present in large quantities in the circulation, it causes a dusky discoloration of the skin resembling cyanosis.
2. Some methemoglobin occurs normally but it is converted back to functional hemoglobin by reducing compounds that are produced in the red blood cells by metabolic reactions.

Myoglobin

Hem is also a part of structure of myoglobin, an oxygen binding pigment found in red muscles.

Cytochrome C

Hem is also a part of cytochrome C, a respiratory chain enzyme.

Varieties of Hemoglobin

Several varieties of hemoglobin occur in man, in which hem moiety is same, the physical and chemical differences are due to variations in the composition of the peptides of the globin fraction.

Physiological Hemoglobins

Adult hemoglobin is of two types:

1. Hemoglobin A ($\alpha_2\beta_2$) is the main form with molecular weight 68000.
2. Hemoglobin A_2 ($\alpha_2\delta_2$) is minor component in normal adults. Delta chains have slightly different amino acid composition compared with β chains.
3. Hemoglobin F (α_2,γ_2) occur in fetal red cells and disappears usually in 2-3 months after birth.

It differs from Hb A: (i) having gamma chains in place of β chains, and (ii) in having great affinity for oxygen.

Abnormalities of Hemoglobin Production

Occur as genetic disorder. Hemoglobins have either: (a) abnormal physical characters or (b) abnormal affinities for oxygen.

Sickle Cell Hemoglobin (HbS)

It becomes very insoluble in deoxygenated state causing the molecules to precipitate in the red blood cells and giving the red cells the characteristic shape of sickle, i.e. sickling.

Sickle Shaped Cells

1. Increase greatly the blood viscosity, and
2. Are liable to undergo hemolysis.
3. Sickle cells are rigid. Therefore, they lodge

in capillaries and the reduced blood flow causes damage to different organs in affected individuals.

HbS is produced due to substitution of valine for glutamic acid at position 6 in the β chain of HbA.

Thalassemia (Mediterranean Anemia)

There is a defect in synthesis of the polypeptide chain, α and β of HbA. The red cells are abnormal in having reduced amount of HbA. To compensate for which, there are increased amounts of HbA_2 ($\alpha_2 \delta_2$) and HbF ($\alpha_2 \gamma_2$). Red cells are rapidly hemolyzed *in vivo* and *hypochromic anemia* occurs.

Synthesis of Hemoglobin

1. Synthesis of hemoglobin takes place in developing RBCs. It appears in *intermediate normoblast* stage and continues throughout the *normoblast stage*.
2. Hemoglobin is mainly synthesized from *acetic acid* and *glycine*. α ketoglutaric acid is formed from acetic acid in Kreb's cycle. Then two molecules of α ketoglutaric acid combine with one molecule of glycine to form pyrrole compound. Four pyrrole compounds join to form protoporphyrin. One of them known as protoporphyrin IX combines with iron to form *Hem* molecule.
3. Finally 4 molecules of *Hem* combine with one molecule of *globin* to form *hemoglobin*.
4. Substances needed for formation of hemoglobins are:
   - i. Amino acids } directly needed
   - ii. Iron } directly needed
   - iii. Copper }
   - iv. Cobalt } act as catalyst to
   - v. Nickel, Mn } enzymes in different
   - vi. Pyridoxine } stages of formation of Hb.

Destruction of Hemoglobin (Fate of Hemoglobin) (Fig. 10.3)

1. After a lifespan of about 120 days, the red cells are destroyed in tissue—macrophage system (previously called reticuloendothelial system).
2. *Hemoglobin:* Released is split into *hem* and *globin*.
3. *Hem opens* (the porphyrin ring at one of the methine bridges breaks). As a result a straight chain of four pyrrole nuclei is formed, which is basic structure of bile pigments.
4. *Iron splits off from hem.* This iron can be used again for formation of hemoglobin or is stored in body.

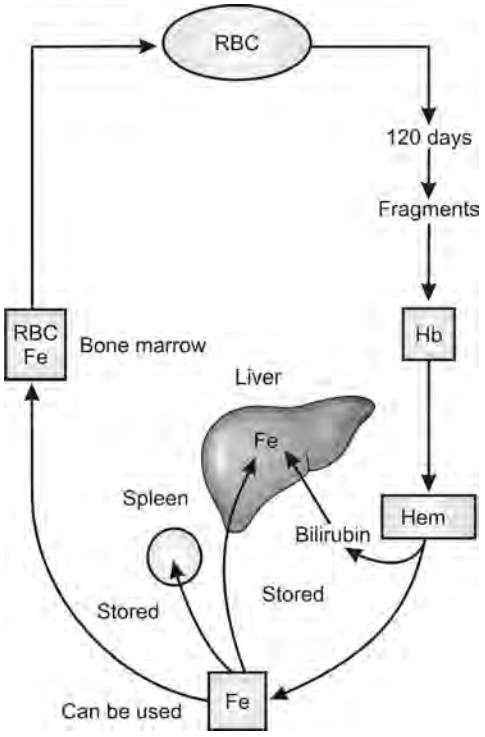


Fig. 10.3: Destruction of Hb

5. From the remaining part of hem, bile *pigments* are formed. At first, *biliverdin* is formed which is reduced to *bilirubin*. Bilirubin is insoluble in water, but it combines with plasma proteins and is transported.
6. In liver, bilirubin is removed from proteins and about 80% is conjugated with glucuronic acid. This is soluble in water and secreted in bile. Bilirubin in bile gives greenish yellow color to the bile.

Any failure of liver to excrete bile causes increased bilirubin in body fluids which gives yellow color to skin and mucus membrane (other tissues also). The condition is known as jaundice.

ANEMIAS

Anemia is a condition in which there is:
1. Reduction in the concentration of hemoglobin (less than 12 gm%).
2. Reduction in the number of RBC (less than 4 millions/cumm).
3. Reduction in packed cell volume.
4. Reduction in oxygen carrying capacity of blood.

Classification

1. Etiological classification—based on underlying cause of anemia.
2. Morphological classification (Wintrobes's classification)—based on size of RBC and its hemoglobin concentration.

Etiological Classification

1. Anemia due to decreased production of RBC.
2. Anemia due to increased destruction of RBC.
3. Anemia due to abnormal blood loss.

Anemia due to Decreased Production of RBC

Decreased production of RBC may be due to:
1. Deficient supply of essential nutrients (dietary deficiency) mostly resulting in nutritional anemias and may be due to:
   i. Iron deficiency—cause iron deficiency anemia.
   ii. Protein deficiency.
   iii. Lack of vitamins – vitamin C or B complex.
   iv. Deficiency of maturation factors – Deficiency of vitamin B_{12} or folic acid cause *Pernicious anemia.*
2. Depression of bone marrow activity-resulting in *Aplastic anemia.* It may occur due to:
   i. Irradiation.
   ii. Anticancer drugs.
   iii. Toxic agents.
   iv. Unknown factors.
3. *Chronic renal disease:* It is often associated with anemia because kidneys are the major source of erythropoietin.
4. *Chronic inflammatory diseases:* Any chronic inflammation may also be associated with anemia due to factors (not well understood) which depress erythropoiesis.
5. *Hypothyroidism:* It is associated with anemia because of reduced metabolic activity in the bone marrow.
6. *Infiltration of bone marrow:* By tumor cells, which might have traveled from any site in body. The process of systemic spread of tumor cells in this fashion is called metastasis.

Anemia Due to Increased Destruction of RBC

This group is called *hemolytic anemia,* may be due to:

1. Abnormal structure of RBC:
   i. Sickle cell anemia or thalassemia
      – Abnormal shape of RBC and abnormal structure of hemoglobin cause damage to cell membrane causing intravascular hemolysis.
   ii. *Spherocytosis:* RBC membrane is excessively permeable to sodium as a result RBC assume biconvex shape and are prone to hemolysis when exposed to hypotonic solution and also are more prone to be destroyed when passing through narrow spaces.
2. Anti Rh-agglutinin causing hemolytic disease in newborn.
3. Hypersplenism—overactive spleen destroys RBCs at faster rate than normal. May be treated by surgical removal of spleen (splenectomy).
4. Glucose 6 phosphate dehydrogenase (G-6PD) deficiency.
5. Specific infections like malaria.
6. Drugs, snake venom, etc.

Anemia due to Abnormal Loss of Blood

Abnormal loss of blood results in hemorrhagic anemia—Blood loss may be:

1. Acute or sudden loss of blood – such as due to injury.
2. Chronic blood loss – slow loss of blood due to piles, worm infestation, peptic ulcer, during menstruation, etc.

Morphological Classification

The etiological factors are not always specific and they cannot be found out easily. In laboratory practice, it is quite easy to *distinguish the morphological characters of the cell* and anemias can be classified on this basis. Treatment can be guided, to some extent, by knowledge of the morphological type of anemia. Therefore, this classification is of importance from clinical angle. There are three groups:

1. i. *Normocytic normochromic anemia* occurs in acute hemorrhages:
      a. There is decrease in number of RBCs.
      b. There is decrease in hemoglobin%.
      c. There is decrease in packed cell volume.
      d. Color index—nearly 1.

   Examples
   – Acute hemorrhage
   – Aplastic anemia

   ii. Normocytic hypochromic anemia: occurs after chronic hemorrhage—RBC size remains normal but the RBC contains less hemoglobin.
2. Macrocytic normochromic anemia: Typical example is pernicious anemia.
   i. Cause is deficiency of vitamin B_{12} , folic acid.
   ii. RBCs are larger than normal.
   iii. Each cell contain more hemoglobin than normal, but proportion of Hb to RBC is normal. Hence, anemia is normochromic.
   iv. But the number of cells is so much reduced that there is anemia.
3. i. *Microcytic hypochromic anemia:*
      a. RBCs are smaller than normal.
      b. Each red blood cell contain less hemoglobin.

      Therefore, anemia is of microcytic hypochromic type.

   Example
   - Iron deficiency anemia
   - Thalassemia.

   ii. *Microcytic normochromic anemia:* RBCs are smaller than normal but the hemoglobin contained is normal.

   Example: Occurs in chronic infections.

Iron Deficiency Anemia

It may be due to:
1. Inadequate dietary intake of iron.
2. Poor intestinal absorption of iron.
3. Abnormal loss of iron from the body (generally due to abnormal blood loss). Or
4. Heavy requirements of iron—for example, during childhood or pregnancy.

Iron is Component of Hemoglobin

Therefore, in iron deficiency:
1. Hemoglobin synthesis is impaired
2. Hence, RBCs are smaller in size, and
3. Contain less hemoglobin. Therefore, anemia is microcytic hypochromic type.

Treatment of Iron Deficiency Anemia

1. The underlying cause should be treated. For example, heavy menstrual loss or hookworm infestation should be adequately treated.
2. In addition, iron may be given in the form of tablets, e.g. ferrous sulfate tablets.
3. Important source of iron in food are *green leafy vegetables*, potatoes, legumes, fruits and *flesh - foods* specially liver. In grains, iron is concentrated in husk. Milk is poor source of iron. In old days, cooking in iron utensils was contributing significant amount. Food iron is divided into: (i) hem iron, and (ii) nonhem iron.
   Intestinal absorption of hem iron is much better and calcium increases absorption of nonhem iron.

Folic Acid and Vitamin B_{12}, Deficiency Anemias

1. Folic acid and vitamin B_{12} belong to vitamin B complex and their metabolic role is interrelated.
2. Therefore, deficiency of any one of them gives rise to similar anemia.
3. In deficiency of both there is maturation arrest during erythropoiesis. Therefore, the precursors of erythrocytes (RBCs), keep growing in size, but they do not divide or differentiate properly.
4. The resulting cells are: (i) large, (ii) immature, and (iii) poorly differentiated and are known as *megaloblasts*. Therefore, resulting anemia is known as *megaloblastic anemia*.
5. Out of the two, *vitamin B_{12} deficiency* anemia is more dangerous and is therefore known as *pernicious anemia*.

Role of Folic Acid and Vitamin B_{12} (Fig. 10.4)

1. Both are required for DNA synthesis, which is specially important for rapidly dividing cells.
2. The vitamin directly required for this is folic and in the form of 5,10 methylene, THFA (tetrahydrofolic acid).

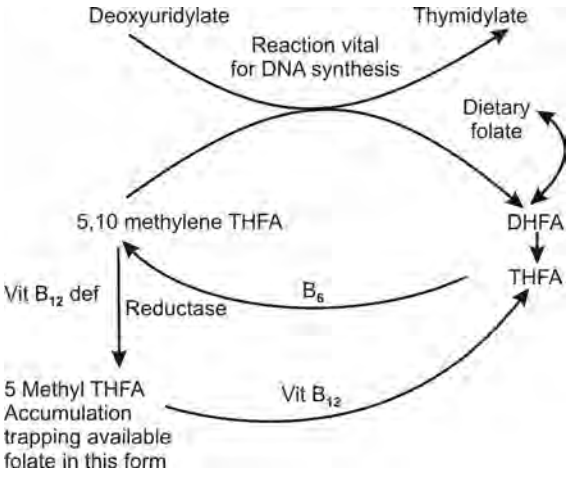


Fig. 10.4: Role of folic acid and vitamin B_{12} in DNA synthesis

3. In order to keep up the supply of 5,10 methylene, THFA an adequate supply of vitamin B_{12} is also important because vitamin B_{12} can regenerate THFA from 5 methyl THFA.
4. Conversion of THFA into 5,10 methylene THFA requires vitamin B_6.
5. In B_{12} deficiency 5 methyl THFA accumulates trapping available folate in this form.

Clinical Features

1. Folic acid deficiency is usually due to deficiency in diet common in pregnant women because of increased demand.
2. B_{12} deficiency usually due to poor absorption of vitamin B_{12} in intestine.
   i. For absorption of B_{12} (extrinsic factor), a glycoprotein manufactured by parietal cells of stomach (intrinsic factor) is required with which it forms a complex.
   ii. Receptors for this complex are present in mucosa of terminal ileum, where vitamin B_{12} gets absorbed.
   iii. If intrinsic factor is not available, vitamin B_{12} absorption is impaired. For example, in gastric atrophy or surgical removal of stomach.
   iv. Parietal cells of stomach also secrete HCl. Therefore, vitamin B_{12} deficiency is also associated with *achlorhydria*.
   v. In vitamin B_{12} deficiency also, the anemia is—*macrocytic, megaloblastic* and *normochromic*.
      a. Bone marrow is overactive because of stimulation of erythropoietin. But it is under productive.
      b. Peripheral blood has *low RBC count* and many of them are large and immature (megaloblasts). They are *not* of uniform *size* (*anisocytosis*) and are not of uniform shape (*poikilocytosis*).

In Vitamin B_{12} Deficiency, Apart from Anemia there is also Neural Involvement

1. Neural lesions mainly involve nerve fibers in—(a) dorsal and (b) lateral columns of the spinal cord.
2. Nerve fibers in cerebral cortex and peripheral nerves may also be affected.
3. As multiple pathways are affected the complex is called *subacute combined degeneration or combined systemic disease.*

Treatment of Folic Acid Deficiency Anemia

1. Prevention can be done by including enough green leafy vegetables in diet.
2. Folic acid tablets can correct the deficiency speedily.

Treatment of Vitamin B_{12} Deficiency Anemia

In deficiency of intrinsic factor, vitamin B_{12} should be given by intramuscular injections. vitamin B_{12} is stored in liver. Therefore, one large does of vitamin B_{12} can be sufficient for several months.

Vitamin B_{12} deficiency is not common in India but folic acid deficiency is quite common in India, especially in pregnant women.

CHAPTER

11

White Blood Corpuscles or Leukocytes

WHITE BLOOD CORPUSCLES

White blood corpuscles (WBCs) are nucleated cells and most are larger than RBC (Fig. 11.1). They are present in blood and are carried to tissues where they perform their main function. Their main function is defence against invading microorganisms.

Normal Counts

1. *Total leukocyte count* (TLC)
   - In adults — 4000-11000/cumm
     At birth 20,000/cumm
2. *Differential leukocyte count* (DLC):
   Granulocytes
   - Neutrophils – 50 to 70%
   - Eosinophils – 1 to 4%
   - Basophils → 1%

   Agranulocytes
   - Lymphocytes – 20-40%
   - Monocytes – 2-8%
3. *Absolute count*
   - Neutrophils— 3000 – 6000/cumm
   - Eosinophils— 150 – 300/cumm
   - Basophils— 10 –100/cumm

   Note: Absolute count means number of that particular leukocyte in total count.

TYPES OF LEUKOCYTES

Granulocytes are characterized by presence of granules in cytoplasm and lobed nucleus.

Size – 10-14 μm diameter.

Using Leishman stain, three types of granulocytes can be recognized by color and character of their granules.

1. *Neutrophils or polymorphonuclear leukocytes*- or polymorphs.

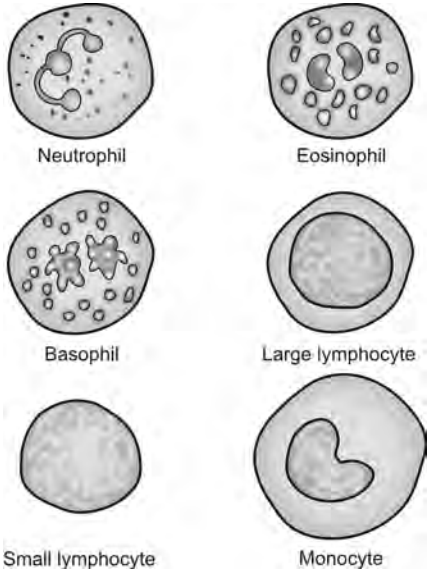


Fig. 11.1: Different WBCs

- Neutrophils constitute 50-70% of total number of leukocytes.
- Size 10-14 µm diameter—Nucleus has 2 to 6 lobes depending on age of the cell. As the cell grows older nucleus becomes multilobed. Youngest cell has horse shoe shaped nucleus.
- Cytoplasm contains fine granules (pinpoint granules). Cytoplasm stains bluish and granules stain red brown. The granules take acid as well as basic stain. Therefore, the cell is called neutrophil. The granules contain various enzymes which can 'lyse' any substance. Therefore, they are 'lysosomes'.
- Neutrophils exhibit marked motility and are most active, capable of phagocytosis.
- Neutrophil count, based on the number of lobes of its nucleus is called *Arneth count (Fig. 11.2).*

i. N_1 means neutrophil having one lobed nucleus.

ii. N_6 means neutrophil having ≥ 6 lobed nucleus.

Normal distribution is as follows:

N_1 – 5% N_4 – 18%

N_2 – 30% $N_{5\,\&\,6}$ – 2%

N_3 – 45%

They are fully mature, maximum in number and functionally most efficient.

- Increase in % of cells $N_1 + N_2 + N_3$ to more than 80% is called 'shift to left'.

This indicates hyperactive bone marrow. It is a regenerative shift.

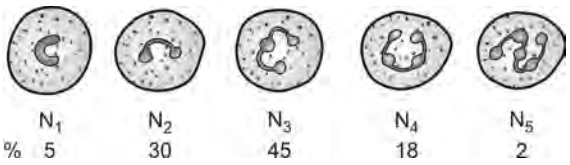


Fig. 11.2: Arneth count

- Increase in % of cells of $N_4 + N_5 + N_6$ to more than 20% is called 'shift to right'. This indicates hypoactive bone marrow. It is a degenerative shift.

2. *Eosinophils*: Size 10-14 µm diameter.
   i. Eosinophils constitute 1-4% of the total leukocyte count.
   ii. Nucleus is usually bilobed.
   iii. Cytoplasm contain coarse granules, stained red with acidic stains (eosin). Granules contain histamine, lysozymes, ECF-A (Eosinophil chemotactic factor of anaphylaxis).
3. *Basophils:* Size 10-14 µm diameter.

Basophils constitute >1% of the total leukocyte count. Nucleus is bilobed.

Cytoplasm contain coarse granules, stained purple or blue with basic dye (methylene blue). Granules are plenty in number and overcrowd the nucleus. Granules contain histamine and heparin.

Agranular Leukocyte

1. *Lymphocytes are of two types:*
   i. Large lymphocytes—10-14 µm diameter.
   ii. Small lymphocytes— 7-10 µm diameter.
   - Lymphocytes constitute 20-40% of the total leukocyte count of which 20 to 25% are the small lymphocytes. Large lymphocytes are precursors of small lymphocytes; which produce antibodies.
   - Both are similar in structure.
   - Nucleus is single, large, stains deeply with basic dyes (blue or purple), round, oval or kidney shaped.
   - Cytoplasm stains pale blue.
   - In small lymphocyte just a narrow rim of cytoplasm is present, so that it appears the whole cell is occupied by nucleus.

- In large lymphocyte rim of cytoplasm is surrounding the large nucleus or at one end of nucleus.
- Large lymphocytes are more plentiful in the blood of young children. They are rare in adults.

Monocyte

1. Largest WBC size— 10-18 μm diameter.
2. Monocytes constitute 2-8% of total leukocyte count.
3. Nucleus is eccentrically situated, has a deep indentation on one side (kidney shaped).
4. Nucleus stains pale blued.
5. Cytoplasm is abundant or relatively large amount. It is clear. Sometimes fine, purple dust like granules are present in cytoplasm – called as "Azure' granules.
6. They are motile and phagocytic.

Functions of Leukocytes

1. *Neutrophils as well as monocytes* and tissue macrophage system constitute the most important mechanism which the body possesses for its defence against invading microorganisms.
   i. Their power to attack depends on: (a) their motility and on, (b) ability of ingestion of solid particles which means *phagocytosis* (literally meaning 'I eat').
   ii. *Neutrophils are first line of defence* of the body whenever the body is invaded by microorganisms like bacteria, neutrophils are the first cells to leak out, to ingest and kill the bacteria, that is they phagocytose the invading organisms.
   iii. The *monocytes* follow neutrophils in the area of attack and constitute *second line of defence*. They enter circulation from bone marrow but after 24 hours, they enter tissues to become tissue macrophages.
   iv. The neutrophils and monocytes get out of the blood by *diapedesis* (= leaping through) through the junction between endothelial cells, enter the tissues and wander from place to place. Large number of neutrophils and monocytes can pass out of vessels in a short time and reach the point of attack by bacteria. Once they come in contact with bacteria or foreign body like suture or thorn, they engulf them and digest them, using the *proteolytic,* enzymes which they contain (phagocytosis). Monocytes also contain large number of lipases which digest the thick membranes of bacilli like tubercle bacilli.
   v. The neutrophils and monocytes are attracted to the site of invasion by bacteria by *chemotaxis,* i.e. chemical agents liberated by interaction of bacterial products and plasma attract the neutrophils and monocytes.
2. *Lymphocytes:* Important function of lymphocytes is:
   i. Manufacture of both β and gamma fractions of serum globulins.
   ii. γ globulins are associated with immune substances or antibodies and thus gamma globulins are concerned with protection against infection.
   iii. Lymphocytes are of two types: (i) T lymphocyte, and (ii) B lymphocyte.
      – B lymphocyte is responsible for humoral immunity by producing gamma globulins.
      – T lymphocyte is responsible for cellular immunity in which invading agent is attacked by sensitized lymphocytes.

iv. Lymphocytes can be transformed into fibroblasts and histiocytes and help in healing.

3. *Eosinophils:* Help in overcoming allergic reactions:
   i. Eosinophils collect at the site of allergic reaction and limit their intensity.
   ii. Eosinophils attack parasites that are too large to be engulfed by phagocytosis. Eosinophil granules release chemicals which are toxic to larvae of parasites.
   iii. Eosinophils enter the tissues and are abundant in mucous membrane of respiratory tract, urinary tract and GI tract. Possibly they provide mucosal immunity.
   iv. ECF-A (eosinophil chemotactic factor of anaphylaxis) contained in granules of eosinophil is chemical substance responsible for hypersensitivity reactions – ranging from mild urticaria to severe anaphylactic shock.
   v. Less phagocytic.
4. *Basophils:* Liberate heparin and histamine.
   Heparin:
   i. Acts as anticoagulant and keeps the blood in fluid state in blood vessels.
   ii. Activates lipoprotein lipase, which facilitates absorption of triglycerides after meals.

   Histamine – leads to allergic reactions.
   Basophils are mild phagocytic.
5. Leukocytes synthesize growth promoting substance from plasma proteins (trephones), which are used by connective tissue and epithelial cells for their growth.

Variations in Number of Leukocytes in Blood Stream

1. *Leukocytosis* means increase in total number of leukocytes in blood above 11,000/cumm.

   Examples:
   i. Muscular exercise and any condition causing oxygen lack and carbon dioxide excess.
   ii. Excitement or injection of adrenaline increases the count.
   iii. In newborn baby and in young children count is high.
   iv. In pregnancy count goes up and it is highest during labor.
   v. Acute infection.
2. *Leukopenia* means decrease in total number of leukocytes in blood below 4000/cumm usually it is due to marked decrease in cells of granulocyte series.

   Examples:
   i. Starvation
   ii. Typhoid fever
   iii. Viral infections
   iv. Depression of bone marrow
   v. Injection of adrenal cortical hormones or ACTH from anterior pituitary.
3. *Leukemia* is a cancerous condition of blood in which there is increase in TLC usually more than 50,000/cumm with immature cells in peripheral blood.

   Whenever there is leukocytosis all varieties of white cells do not show uniform increase. Anyone variety may be increased and depending on this the terminology also differs. Thus, there may be:
   i. Neutrophilia – often responsible for leukocytosis.
   ii. Eosinophilia
   iii. Lymphocytosis.
   iv. Monocytosis is much less frequent.

Neutrophilia means increase in neutrophils.
It occurs in:

A. *Physiological conditions*:
   i. Muscular exercise.
   ii. Excitement or injection of adrenaline.
   iii. Pregnancy, menstruation and lactation.

B. *Pathological conditions:*
   i. Acute infections by pus forming organisms. Therefore, estimation of TLC and DLC of leukocytes furnishes valuable diagnostic sign for detecting hidden inflammatory condition like appendicitis.
   ii. Pneumonia and in some infections fevers.
   iii. Following tissue destruction – burns, myocardial infarction, after surgery.

Eosinophilia means increase in eosinophils.
i. It occurs during allergic conditions – like asthma or during allergic reaction.
ii. Worm infestations like—hookworm, roundworm, filariasis.
iii. Skin diseases.

Lymphocytosis means increase in lymphocytes, occurs in:
i. Blood in infants has high lymphocyte count (60%).
ii. Chronic, infections, e.g. tuberculosis (TB)
iii. Viral infections.
iv. Lymphatic leukemia.

Monocytosis means increase in monocytes, occurs in:
i. Monocytic leukemias
ii. Tuberculosis
iii. Malaria
iv. Syphilis.

Leukopenia means decrease in total circulating leukocyte count below 4000/cumm of blood and whenever there is leukopenia, all varieties of white cells do not show uniform decrease. Thus, there can be:
a. *Neutropenia:* Occur in infancy, typhoid, viral infection and depression of bone marrow.
b. *Lymphopenia:* Occurs in AIDS (acquired Immunodeficiency syndrome) and hypoplastic bone marrow.
c. *Eosinopenia:* Occurs after injection of ACTH or corticosteroids because of increased sequestration of eosinophils in lungs and spleen and by their destruction in the circulating blood.
d. *Monocytopenia:* Occurs in hypoplastic bone marrow.

Lifespan of WBC: 6-10 hours.

Leukopoiesis—Development of Leukocytes (WBCs) (Fig. 11.3)

Site

1. In embryo, WBC develop from mesoderm and migrate into blood vessels.
2. In extrauterine life (i.e. after birth) the granulocytes develop from red bone marrow and lymphocytes and monocytes develop: (a) mainly from lymphoid tissues of the body, and (b) from bone marrow to some extent.

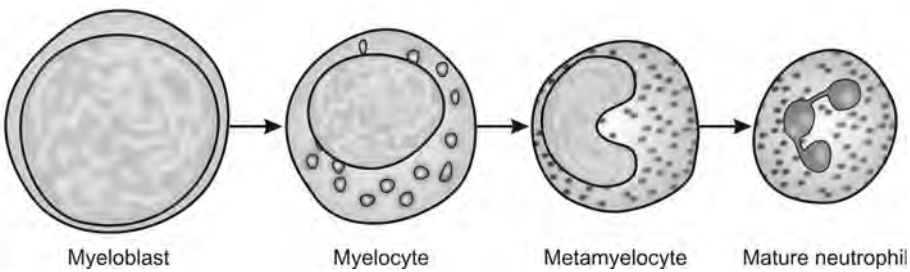


Fig. 11.3: Leukocytes in different stages of development

Granulopoiesis

It is extravascular process.

Stages

Reticulum cell in bone marrow give rise to:

1. Primitive white cells (18-23 µm cell diameter).
2. Myeloblast (16-20 µm).
3. Myelocyte A (Premyelocyte) (14-18 µm).
4. Myelocyte B (Myelocyte proper) (12-16 µm).
5. Myelocyte C (Metamyelocyte) (10-14 µm).
6. Leukocyte (granulocyte) – neutrophil, eosinophil or basophil.

These cells can be identified in a stained marrow smear obtained from sternal puncture in man.

Myeloblast

1. Develops from primitive WBC.
2. Nucleus is pale, purple blue, large and round and several nucleoli are present.
3. Cytoplasm forms narrow rim, contains no granules.

Myelocyte

Characterized by appearance of granules in cytoplasm. Using Leishman's stain they can be classified by color of the granules in:

1. Neutrophil myelocyte
2. Eosinophil myelocyte, and
3. Basophil myelocyte:
   i. *Nucleus is small* and more basophilic (blue).
   ii. Cytoplasm is more extensive.
   iii. *Nucleoli disappear.*

Premyelocyte

1. Intermediate between myeloblast and myelocyte.
2. *Nucleus is round* and no nucleoli are present.
3. Cytoplasm is basophilic and there are few granules at the periphery.

Metamyelocyte

1. Intermediate between myelocyte and mature cell. It is identical with myelocyte but *nucleus is indented.*
2. Each type of metamyelocyte gives rise to corresponding leukocyte:
   i. Neutrophil
   ii. Eosinophil or basophil.

In leukocytes, i.e. neutrophil, eosinophil and basophil:

i. Nucleus becomes lobed.
ii. Cytoplasm becomes more liquid and shows amoeboid movements.
iii. Granules in fresh preparation show dancing movements.

In young neutrophil nucleus is horse shoe shaped.

In old neutrophil nucleus is 4 -5 lobed joined together by faint strand of chromatin.

Entire maturation process from myeloblast to neutrophil takes about 3 days.

Lifespan of granulocyte— 1-2 days.

Regulation of Granulopoiesis

1. Neutrophils are most numerous therefore, this refers to formation of neutrophils. Their number in circulation is kept constant in spite of continued production and destruction.
2. There is involvement of humoral factors in regulation of granulopoiesis.
3. They belong to the category of growth factors:
   i. *Interleukin-1 (IL-1) is produced by macrophages:*
      a. It increases secretion of colony stimulating factor (CSF).
      b. It increases count of all blood cells except lymphocytes.
      c. Also IL-1 directly releases mature neutrophils from bone marrow.

ii. *Granulocyte:* Macrophage colony stimulating factor - (GM - CSF) - is formed by fibroblasts, vascular, endothelial cells and T lymphocytes under influence of IL-1.
   a. It stimulates proliferation of committed cells which are on their way to form granulocytes or macrophages.
   b. GM-CSF also act on mature neutrophils, eosinophils and macrophages to enhance their effector response.

iii. *Interleukin-3 (IL-3) or Multi CSF* - is produced by T-lymphocytes under influence of IL-1.
   a. It stimulates the proliferation of precursors of neutrophils, eosinophils, basophils and mast cells, also T-lymphocytes, macrophages, megakaryocytes and erythrocytes.
   b. It also stimulate the effector responses of mature eosinophil and T-lymphocytes.

iv. Granulocyte colony stimulating factors (G-CSFs) is produced by monocytes, endothelial cells and fibroblast, under influence of IL-1.
   a. It stimulates the proliferation of precursor cells of only granulocytes.
   b. It enhances effector responses of granulocytes, i.e. increases phagocyctic ability.

INHIBITORY FACTORS

Tissue specific, locally produced inhibitors of cell proliferation are known as chalones. A granulocytic chalone is produced by mature as well as immature granulocyte. They inhibit DNA synthesis in granulocyte precursor cells, and so decreased production of granulocytes. Thus, by *negative feedback* the number of granulocytes is kept constant in circulation.

GRANULOPOIESIS

Development of Lymphocytes (Lymphopoiesis)

Site

They are formed chiefly in lymphoid tissues of the body:

1. Lymph nodes
2. Spleen
3. Thymus
4. Payer's patches
5. Tonsil and bone marrow.

Stages of Development

1. In all the above mentioned organs the stem cells proliferate and form.
2. *Lymphoblasts:* It is a large cell with pale nucleus. Lymphoblasts proliferate and differentiate into:
   i. Immature lymphocytes
   ii. Large lymphocytes—condenses to form.
   iii. Small lymphocytes.
      a. Some of the lymphocytes mature in bone marrow, they are called B lymphocytes.
      b. Another group of lymphocytes mature in the thymus and are called T lymphocytes.

      Lymphocytes from bone marrow and thymus travel to secondary lymphoid organs such as lymph nodes and spleen, where lymphopoiesis continues. Lymphocytes leave in lymphatics and enter circulation by thoracic duct and right lymphatic duct.

      They circulate → lymphatics → blood → tissue → blood

      Life of lymphocytes—few hours.

Development of Monocytes

Site

They are formed in bone marrow.

Stages of Development

1. The committed stem cell destined to form monocytes proliferates and differentiates into
2. Promonocytes (or monoblast) and finally into
3. Monocytes

Hemopoiesis (General concept).

It is development of blood cells, i.e. RBC, WBCs and platelets. Therefore, the term hemopoiesis includes:

1. Erythropoiesis, i.e. development of RBC.
2. Leukopoiesis, i.e. development of WBC. and
3. Megakaryocytopoiesis, i.e. development of platelets.

Theories of Hemopoiesis

There are two theories: (i) Monophyletic theory, and (ii) Polyphyletic theory. Out of the two monophyletic theory is most accepted.

i. *Monophyletic theory:* According to this theory different types of blood cells arise from a single progenitor cell called 'pluripotent stem cell' present in the bone marrow.
   Seventy-five percent of the cells in bone marrow are WBCs and their precursors or myeloid tissues, and only 25% cells are RBCs and their precursors or erythroid tissue.
ii. *Polyphyletic theory:* According to this theory there are separate stem cells present in the bone marrow for each main variety of cells, i.e. granulocytes, monocytes, lymphocytes, erythrocytes and platelets.

Monophyletic Theory of Hemopoiesis (Fig. 11.4)

Normally the proliferation and maturation of blood cells that enter the blood from bone marrow is regulated with great precision by:

1. Interleukins (ILs), and
2. Colony stimulating factors (CSFs) = (cytokines) RBC, WBC and platelets all develop from:

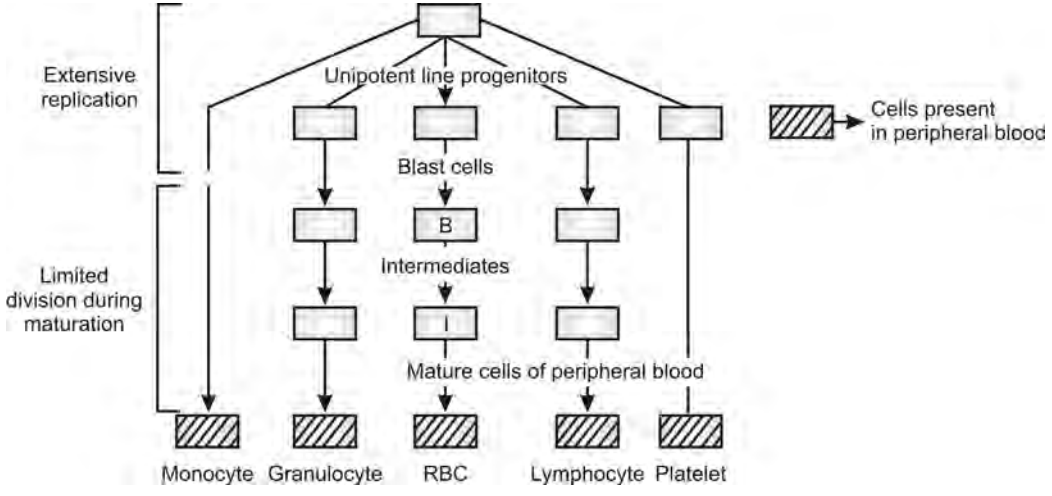


Fig. 11.4: Monophyletic theory of hemopoiesis

Pluripotent stem cell which undergo extensive replication (= multiplication) and can differentiate into unipotent line, that means, progenitor cells which undergo extensive replication but is committed to a particular line of development. These are line progenitor cells also called as stem cells.

Note: pluri = many;
potent = capable of producing

In health the numbers of erythrocytes, leukocytes and platelets in peripheral blood are kept constant within narrow limits, by feedback control mechanisms.

CHAPTER

12

Immunity

Body has mechanisms to keep us free from invading bacteria, viruses and toxins. In other words our body has large immunity which makes it resistant to invading microorganisms.

Immunity is of two types:
1. Innate immunity, and
2. Acquired immunity.

INNATE IMMUNITY

Innate immunity is available since birth.

1. All surfaces of the body, which come in contact with the external environment are provided with: (a) mechanical, and (b) chemical barriers to prevent penetration by microorganisms.
   For example:
   i. Skin – is impermeable covering.
   ii. Bacterial growth is prevented by low pH and fatty acids of sebaceous secretion.
   iii. *Eyes* have tears.
   iv. *Mouth* has saliva.
   v. Stomach has acid.
   vi. Washing action of urine—prevents infection of urinary tract.
      a. They have antibacterial chemicals.
      b. Wash away microorganisms and their toxic products.
2. Some nonpathogenic bacteria are normal residents of skin, gut and genital tract. They inhibit the growth of pathogenic organisms by competing with them for nutrients.
3. Inspite of these barriers if the pathogenic organisms manage to get entry. They are attacked by following systems.

Phagocytosis

A large, variety of pathogenic organisms and inanimate particulate matter is removed from the body by phagocytosis by neutrophils or by macrophages.

Humoral Mechanism—Complement System

Humoral mechanism ˘ complement system is nonspecific defence mechanism found in *plasma* in the form of plasma enzymes. Enzymes are identified by the numbers C_1 to C_9. C_1 is made up of 3 subunits. Like this there are 20 proteins in this system.

Activation of this system begins a sequence of cascade reactions, which activates other components of the system.

The complement system helps to handle microorganism invasion in three ways:

1. Some components of the complement system coat the microorganisms and such

coat makes it easily phagocytosed, because phagocytes have receptors for the same complement (coating = opsonin).
2. Some components of the complement system stimulate the lethal mechanisms of phagocytes such as release of lysosomal enzymes and granule release.
   – They also release histamine and other substances from *mast cells* and basophil granules. Effect is vasodilatation and chemotactic migration of neutrophils and eosinophils to the site of infection.
3. The complement pathway leads to formation of a 'membrane attack complex', which stabs a hole in cell wall of microorganism. This causes entry of sodium and water into the microorganism leading to its lysis.

Other Humoral Mechanisms

1. *Acute phase proteins:* There is rise of several protein concentration following infection. Best known among them is C-reactive protein or CRP.
   i. CRP adheres to surface of number of microorganisms.
   ii. CRP coated organisms activate complement, which will facilitate phagocytosis.
2. *Interferon:* It is released by virally infected cells into the ECF. (1) They diffuse to form a ring of uninfectable cells – so the spread of infection is limited, (2) Interferons also inhibit protein synthesis by interfering with the process of translation and promoting degradation of mRNA. So viral replication is inhibited.
3. *Basic polypeptides:* React with certain types of gram +ve bacteria and inactivate them.

Natural Killer (NK) Cells

Natural killer (NK) cells are large special type of lymphocytes also called as non-T, non-B lymphocytes.

1. They are 10-15% of the circulating agranulocytes.
2. On coming in contact with virally infected cells, N K cells release lethal substances which lead to death of infected cells. Thus, infected cell is killed before virus has had a chance to multiply.
3. They kill cells that have undergone malignant transformation.
4. They are important first time defence against viral infections.

Eosinophils

Eosinophils are specially equipped to deal with large parasites such as helminths.
1. The coating of helminthes with some complement component facilitate adherence of eosinophils.
2. Adherence triggers release of many lethal substances from eosinophil granules, leading to death of the parasite.

ACQUIRED IMMUNITY

Acquired immunity is acquired after birth after exposure to invading agents. It is specific to the agent, which induces it.
1. Human body has ability to develop extremely powerful and specific immunity against invading agents such as:
   i. Lethal bacteria
   ii. Viruses
   iii. Toxins, and
   iv. Foreign tissues from other animals.
2. Acquired specific immunity develops after exposure to such microorganisms or chemical substances or tissues.
3. There are two types of specific acquired immunity:
   i. Mediated by circulating antibodies—globulin molecules attack the invading agent. It is called as humoral immunity or B cell immunity.

ii. Mediated by sensitized or activated lymphocytes which destroy the foreign agents. It is called as cell mediated immunity or T cell immunity because the activated lymphocytes are T lymphocytes.

HUMORAL IMMUNITY

Humoral immunity is mediated by circulating antibodies. Most antibodies are γ globulins.

1. Antibodies are manufactured by B lymphocytes.
2. B lymphocytes are developed during fetal life and neonatal life from lymphocyte precursors which enter liver, spleen or remain in bone marrow and get transformed into B lymphocytes. B lymphocytes migrate to *lymph nodes* and bone marrow (where they are morphologically indistinguishable but can be identified by special technique). B lymphocytes *differentiate* into: (i) plasma cells and (ii) memory B cells.
3. B-lymphocytes remain present throughout life.
4. The molecule, which induces formation of an antibody is called 'antigen'.
5. Each 'antigen' evokes the formation of a different antibody.
6. For a substance to be antigenic:
   i. It must have high molecular weight, 8000 or more.
   ii. There must be regularly recurring molecular groups (called epitopes) on the surface of large molecule.
      a. In case of infectious organisms the antigen is either a part of their body or the toxin they produce.
      b. Most of the *antigens are protein or polysaccharides.*
      c. Substances of molecular weight less than 8000 first combine with plasma protein to become antigenic. The non protein part is called Hapten.
         – *Haptens are* low molecular weight drugs.
         – Chemical constituents of dust.
         – Breakdown products of dandruff from animals.
         – Degenerative products from scaling skin.

Structure of Antibody (Fig. 12.1)

1. Antibodies are gamma globulins called immunoglobulin. They are formed by plasma cells.
2. They have molecular weights between 160000 and 970000.
3. Antibody molecule has two pairs of peptide chain linked by disulfide bonds. Two longer chains in the molecule are called heavy chain and two shorter chains are called light chains. Each heavy chain is paralleled by light chain.
4. Two heavy chains in a given antibody molecule are identical and the light chains are also identical.

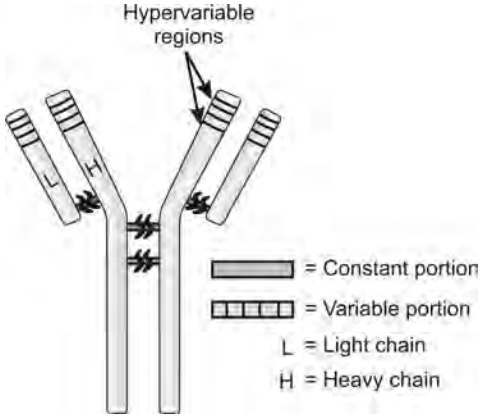


Fig. 12.1: Structure of antibody

5. Antigenic binding site is present at the N terminal end of peptide chain and sites for other biological function are towards terminal, which is *constant* portion. *Specificity of antibodies*: The structure of N terminal varies from one antibody to another and within the *variable region* of the molecule, there are some selected sequences of amino acids which are most variable than the rest these are known as *hypervariable regions*.

Classification of Immunoglobulin (Antibodies)

There are five general classes of antibodies named as:

1. IgM
2. IgG
3. IgA
   Ig = represents immunoglobulin
4. IgD
5. IgE

IgG – It is bivalent antibody
- forms 75% of antibodies of normal person.

IgE – It is involved in allergy.
- forms a small % of the total antibodies.

IgM – It is formed during primary response.
- forms a major share of antibodies formed during primary response.
- It has 10 binding sites, which makes it extremely effective in protecting the body against invaders.

CELL MEDIATED IMMUNITY

Cell mediated immunity is expressed by large lymphocytes of the type known as T cells.

1. During fetal life and neonatal life lymphocyte precursors from the bone marrow enter the thymus gland and become transformed into T lymphocytes (Fig. 12.2).
2. Both types are present throughout life and can be distinguished by special techniques.
3. Most of the processing of lymphocyte precursors in thymus and bone marrow and their migration to lymphoid tissues

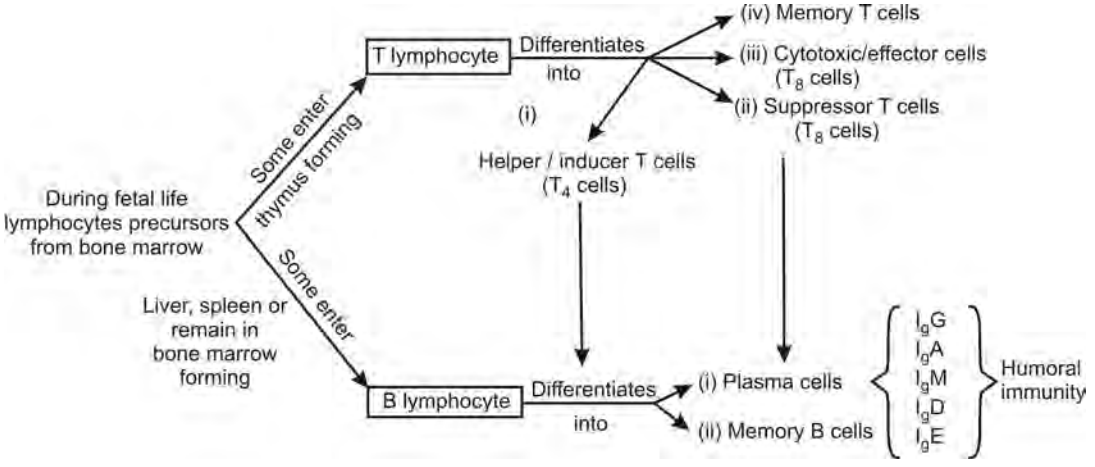


Fig.12.2: Development of immune system

occur during fetal and neonatal life. However, there is a slow continuous production of new lymphocytes from stem cells with processing in the bone marrow in adults.

4. Stem cells differentiate into many millions of different T and B lymphocytes, each with the ability to respond to a particular antigen.
5. Cell mediated immunity acts by two mechanisms: (i) by helping phagocytosis and (ii) by releasing cytotoxic substances—four types of T cells have been identified:
   i. Helper/inducer T cells.
   ii. Suppressor T cells.
   iii. Cytotoxic T cells or effector T or killer cells.
   iv. Memory T cells.
   - Helper/inducer T cells and suppressor T cells are involved in regulation of antibody production by B cell derivatives.
   - Cytotoxic T cells destroy transplanted and other foreign cells.
   - Cytotoxic and suppressor T cells have on their surface the glycoprotein CD8, so they are called T8 cells.
   - Helper/inducer T cells have on their surface the glycoprotein CD4 and so they are called T_4 cells.

For full immune response cooperation of both T and B lymphocytes is needed. Many antigens require cooperation of T cells for activation of B cells.

- CD 8 has coreceptor for major histocompatibility complex (MHC). Class I molecules and CD4 has coreceptors for MHC class II molecules.
- MHC function in antibody processing and distinguishing self from non-self. They are divided in two classes on the basis of tissue distribution and function: (a) Class I—found in all nucleated cells and must be presented with antigen to activate T_8 cells (b) Class II—they are found in: (i) all macrophages (ii) B cells and (iii) activate T cells. They must be presented with antigen to activate T_4 cells.
- Lymphocytes, macrophages and other cells—involved in immune responses communicate partly by hormone like chemical messengers called *interleukins* and *cytokines.*
- When the virus, bacteria and other foreign protein and related substance enter the body:
  i. One of the lymphoid organ traps it and immune response begins.
  ii. If the invading agent reaches the blood stream it is trapped in spleen.
  iii. If it enters the body through mucosal surface it evokes immune response in mucosal associated lymphoid tissue.
- Irrespective of the entry site the response to entry of agent follows a common pattern.
- The invading agents are ingested by macrophages and partially digested. Peptide fragments then combine with MHC and move to cell surface where they are exposed. This helps recognition of the macrophage/phagocyte by immune competent cells
- Recognition is followed by activation of immunocompetent cells finally leading to production of effectors:
  i. Effectors of humoral immunity are specific antibodies.
  ii. In cell mediated immunity effectors are lymphocytes and cytotoxic—lymphocytes.

Details

1. Macrophages contact lymphocytes. T4 cells are activated, when their T receptors bind simultaneously to antigen and a Class II

MHC protein on the surface of the macrophage (Fig. 12.3).

Two models for recognition of cell-surface antigen plus MHC by T cells

2. T_4 cells then contact B cells, activating them and causing them to proliferate and transform into: (a) Memory B cells, and (b) Plasma cells (Fig. 12.4). Plasma cells secrete large quantity of antibodies in general circulation. Memory B cells (lymphocytes) facilitate the antibody response if the same antigen enters the body again. It is because of memory cells the antibody response to subsequent exposure to antigen is faster and better—secondary response than to first response—primary response (Fig. 12.5).

   Thus, when the antigen first enter the body it is processed by antigen binding cells and binds to the appropriate lymphocytes—these are stimulated to divide forming clones of cells, that respond to antigen (clonal selection).

   A clone is the population of cells descended by reproduction from a single cell.

T cells already exist in the body. Exposure of an antigen on the surface of infected cell (macrophage) helps to select appropriate T cells. The clone of selected cells undergoes proliferation and eventually matures in helper T cells, i.e. cytotoxic cells and memory T cells.

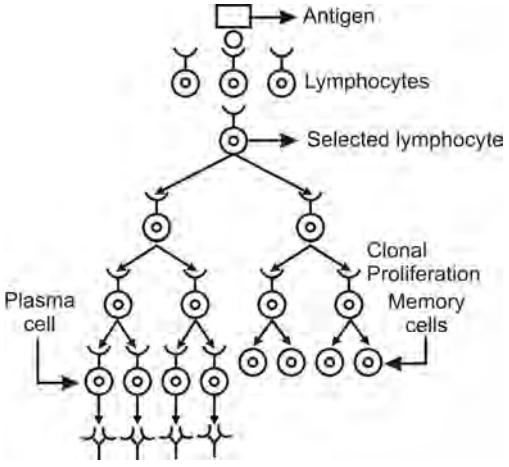


Fig. 12.4: Induction of humoral response

Cell mediated immunity provides protection through two types of effector mechanisms:

1. Through lymphokines
2. Through cytotoxicity.

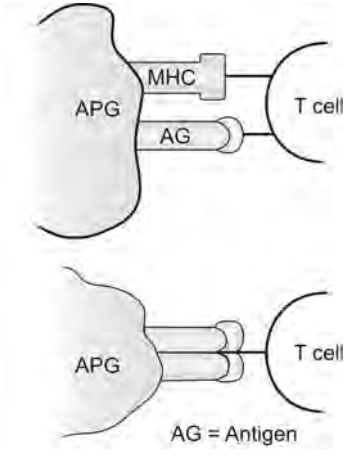


Fig. 12.3: APG = Antigen presenting cell (like macrophage) (Two models for recognizing cell surface antigen plus MHC by T cell)

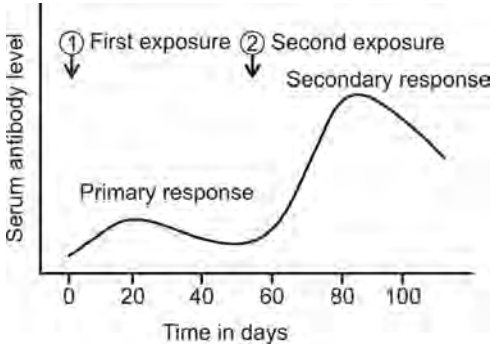


Fig.12.5: Immune responses to antigen

Lymphokines

Lymphokines are soluble chemical mediators released by helper T cells. They have two functions:

1. One group of lymphokines are concerned with growth and differentiation of B and T cells and other types of blood cells.
2. Other group helps phagocytosis:
   i. By attracting phagocytic cells through chemotaxis.
   ii. By activating the phagocytic cell.

Cytotoxicity

Cytotoxicity is a function of killer T cells. They recognize combination of MHC class I molecules and antigen combination on infected macrophages. The killer cells may require help from helper T cells – which produce chemicals which activate macrophages. End result is cytolysis of the macrophage alongwith it the organism invading it also dies.

Helper T Cells

Helper T cells can identify combination of two proteins – MHC Class II and protein belonging to organism trapped within (Fig. 12.6). Helper T cells with specific affinity for the proteins of organism move towards phagocyte. On coming in contact the helper T cells release lymphokine (known as interferon gamma). With the help of this interferon the phagocyte is able to digest the organism.

Cytotoxic T Cells (Fig. 12.7)

These cells kill organisms trapped in cells other than phagocytes. They also recognize the protein specific to organism on the surface of infected cell. In addition, they also recognize the MHC class I molecules on the cell surface. Combination of these two helps to bring the infected cell in contact with specific cytotoxic T cells. Then cytotoxic T cell releases toxic substances which kill the infected cell.

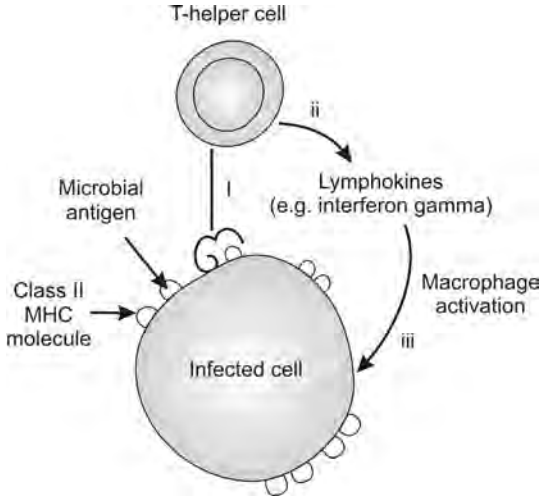


Fig. 12.6: Mechanism of action of helper T cell

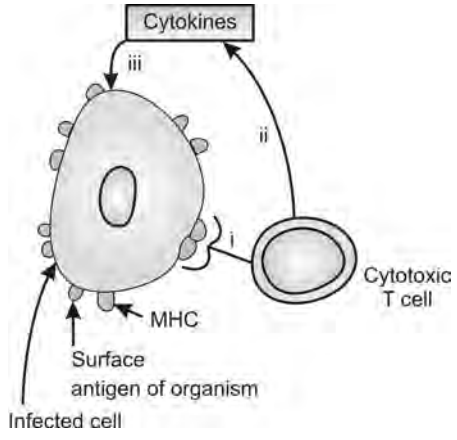


Fig. 12.7: Mechanism of action of cytotoxic T cell

Memory T Cell

Memory T cell helps to improve the speed and efficacy of the response to subsequent exposures to the same infectious agent.

Note:

1. Antigen can also be processed and presented to T_4 cells by various type of cells in the body:
   i. B cells
   ii. Langerhans cells of skin
   iii. Dendritic cells in lymph nodes and spleen.
2. Recognition ability is innate without exposure to antigen.

Mechanism of Action of Antibodies (Fig. 12.8)

The effect of circulating antibodies and cellular immunity are mediated by a system of plasma enzymes called complement system. The enzymes are identified by numbers C_1 to C_9.

Antibodies act as a bridge between microorganisms and phagocytes:

1. Antibodies have specific molecular configuration, which is complementary to antigen of the microorganism.
2. They also have grouping with high affinity for the—C_3b fragment of complement C_3. C_3b coats the microorganism.

   So there are *two points* of attachment of antibody and microorganism.
3. Third portion of antibody attaches with phagocyte.
   - Thus, the antibody helps bring the microorganism and phagocyte in contact with each other.
   - Antibodies binding to antigen initiate and facilitate activation of complement system through *classical pathway.*
   - This pathway is different from *alternate pathway* which is called properdin pathway—initiated by polysaccharides on bacterial cell wall.
   - Antigen—antibody interaction is by close physical intimacy facilitated by their complementary shapes and their binding to each other is strengthened by nonspecific intermolecular forces.

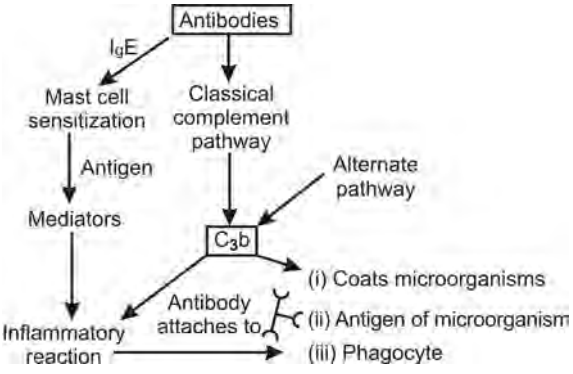


Fig. 12.8: Principle mechanisms of action of antibodies

Regulation of Immune Response

It is regulated by:

1. *Feedback mechanism:* Both humoral and cellular immune systems regulate their own response through feedback mechanisms, e.g. IgM antibodies which appear during humoral immune response help in getting high IgG which exert negative feedback, which prevent antibodies of one type being formed in excess.
2. *Suppressor T cells* which develop more slowly help terminate the immune response by dampening the immune response of T and B cells.
3. But as long as antigen persists the response continues.
4. Effect of hormones on immune response.

   Glucocorticoids and sex hormones inhibit the immune response whereas

growth hormone, thyroxine and insulin stimulate the immune response.

5. *Genetic factors:* Some individuals are more susceptible to infections. This may be due to genetic factor for poor immune response.

Immunological tolerance to one's own proteins or recognition of self:

During development the immune system learns to recognize the bodies own proteins (self). So that antibodies are not formed against them.

Elimination of lymphocytes likely to react to self or bodies own proteins is a lifelong process, but tolerance to self takes place vigorously in: (a) late fetal life, and (b) in perinatal period. During this period B and T lymphocytes (precursors of humoral and cellular immunity) are exposed to potentially antigenic material in tissues and subsequently they are unable to make specific immune response to these materials, as they are recognized as self. Whereas as material with which first contact is made after this period are recognized as not self and evokes immune response.

There are several mechanisms possibly responsible for tolerance to self:

1. Several lymphocytes capable of reacting to self have been eliminated during the course of evolution and lymphocytes that can form antibodies against conserved proteins just do not exist (conserved proteins are proteins whose structure remained unchanged across several species widely separated across evolutionary scale). This is known as *Immunological silence.*
2. Cells capable of reacting to self-antigens are eliminated during differentiation of T and B cells in thymus and bone marrow. This phenomenon is called *clonal deletion.*
3. Suppressor T cells help in tolerance to self as they keep the antiself antibodies in check.
4. Antibody production by B cells needs cooperation of T cells. Tolerance of T cells to an antigen would render B cells helpless and thereby result in failure of antibody synthesis in spite of competent B cells.
5. In a few tissues, e.g. lens of the eye, the self-antigen are almost isolated from the cells of the immune system.

AUTOIMMUNIZATION

Occasionally immunity develops against one's own proteins. This is known an autoimmunization or autosensitization and the antibodies formed are known as autoantibodies.

Cause

1. When new antigenic materials are formed at anytime after perinatal period, e.g. release of abnormal protein products during infection which are similar to body's own proteins.
2. Exposure to certain haptens.
3. Some potentially antigenic substances are anatomically segregated so that normally a barrier exists between them and immunocompetent cells. A breakdown of this barrier after early infancy (perinatal period) leads to formation of autoantibodies.

Examples of Autoimmune Diseases

1. *Insulin dependent diabetes:* Antibodies are formed against pancreatic islet (betacells).
2. *Graves disease (hyperthyroidism*: Antibodies are formed against—TSH receptors.
3. *Rheumatoid arthritis:* Antibodies are formed against collagen tissues.

Vaccination

Specific acquired immunity forms the basis of vaccination. Important points:

1. Introduction of specific antigen, first time in the body will form antibodies in 1 week

to 10 days and its formation continues for 4 to 6 weeks *(primary humoral response).*

2. If exposed to same antigen weeks to year later, antibodies outpour in 2-3 days and quantity is more and there is longer response *(secondary humoral response).*
3. Reason is during primary response large number of sensitized plasma cells are formed which give immediate response after exposure for the second time, to same antigen.
4. Antibodies thus, formed remain in blood and protect the child from the disease against which the child is vaccinated.
5. Various vaccines (e.g. vaccine against measles, typhoid, tuberculosis) are prepared by using attenuated virus/killed bacteria/ or even living bacteria. When introduced in the body they act as antigens.
6. Vaccines given after 3 months of age are more effective than those given before – the reason is: (a) Newborn immune response is quite immature during first 3 months of life and (b) Maternal immunoglobulins of IgG variety are transferred across the placenta to the fetal circulation. These antibodies protect the infant during first 3 months of age, and during this period exogenous vaccines are less effective because maternal antibodies exert negative feedback.

AIDS

Acquired immunodeficiency syndrome (AIDS) is caused by human immunodeficiency virus (HIV). HIV resides within T lymphocytes and ultimately destroys T lymphocytes. As a result, immunity of affected person is severely reduced. *Therefore*:

1. He falls prey to trivial infections.
2. Some virus can rarely produce disease in normal human beings, because of excellent immunity against them. In victims of AIDS even these virus can produce disease (opportunistic infections).
3. Certain forms of malignancies are common in these subjects.

AIDS probably originated in Africa and spread from there to other parts of world. Its mortality rate is very high. It is common in homosexuals, drug addicts and the virus can spread also via infected needles or blood transfusion.

CHAPTER

13

Platelets (Thrombocytes) and Coagulation

PLATELETS

Platelets are the smallest of the blood cells and look like plate. Hence, called platelets. Platelets are also called *Thrombocytes*.

Size: 2-5 μm in diameter.

Average volume: 5.8 μm^3.

Shape: Spherical, oval or rounded.

Normal count: 1.5 to 4 lacs/cumm (average 2.5 lacs/cumm).

Leishman staining: Shows a faint blue cytoplasm with distinct reddish purple granules, nucleus is not present.

Electron Microscopic Study (Fig. 13.1)

Platelet Membrane

1. Has identical structure with cell membrane. It shows invaginations which form complicated canalicular system, which is in contact with ECF.
2. Contains various receptors for combining with collagen, fibrinogen and von Willebrand factor (it plays important role in platelet adhesion and regulates circulating level of factor VIII).
3. Contains precursors of thromboxane A2, prostaglandins and platelet factors 3 and 4.

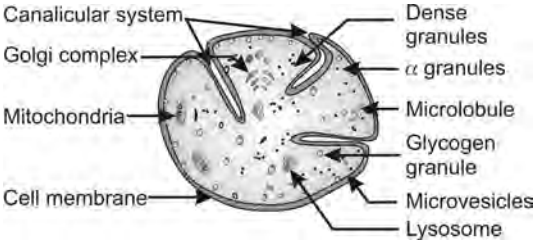


Fig. 13.1: Platelet under electron microscope

Cytoplasm Contains

1. Mitochondria, Golgi apparatus, smooth endoplasmic reticulum, microtubules and microvesicles (arranged in the form of ring at the periphery of the cell).
2. Contractile proteins like actin and myosin (previously called thrombosthenin)
3. Glycogen, lysosomes and granules of two types:
   i. Dense granules, and
   ii. α granules (granules with clear interior).

Dense Granules Contain

- Phospholipid, triglycerides, cholesterol.
- 5 hydroxytryptamine (5HT) or serotonin which is vasoconstrictor.
- ADP—helps platelet aggregation.

- ATP—energy store and other adenine nucleotides.

Alpha Granules Contain

Secreted proteins like:
- Clotting factors
- Platelet derived growth factors (stimulates wound healing and repair of damaged vessel wall).

Lifespan: 9-12 days.

Platelets are destroyed by spleen. Therefore, after splenectomy platelet count increases.

Store house: Spleen stores platelets which can be mobilized by epinephrine during bleeding. Epinephrine is secreted by sympathoadrenal stimulation.

Formation (Thrombopoiesis): Platelet is smallest of blood cells but has largest precursor cells – megakaryocytes, which are present in bone marrow and are formed from committed stem cells.

Megakaryocyte: Diameter is 35-160 μm.
1. It is multinucleated.
2. It sends pseudopodia which enter endothelial lining of bone marrow sinusoids and split. By this process 2000–4000 platelets are formed from one megakaryocyte.

Regulation of Thrombopoiesis

It is regulated by a group of humoral factors. One source of thrombopoietic factor is kidney.

Formation and destruction of platelets is balanced. Hence, normal number varies in a narrow range.

Thrombocytosis—means increase in platelet count.

Causes

1. Splenectomy.
2. Bleeding , injury, surgery which act as acute stress, release epinephrine from stimulation of sympathoadrenal system.

   Epinephrine causes contraction of spleen, which mobilizes platelets.

Thrombocytopenia

Thrombocytopenia—means decrease in platelet count.

Causes

1. Bone marrow depression (impairs production of platelets).
2. Hypersplenism (causes excessive destruction of platelets).
3. Viral infections.
4. Drug hypersensitivity.

Thrombocytopenia leads to purpura—which is a bleeding disorder.

Functions

Platelets contain more than 90 enzymes and other substances. Their chemical composition is controversial because they act as a sponge and absorb many substances.

1. *Platelets aggregate to plug the vascular injury:*
   i. When blood vessel wall is damaged the endothelium is disrupted and underlying layer of collagen is exposed. Platelets adhere to collagen, laminin and von Willebrand factor in vessel wall. Platelet activation begins, which is also produced by high ADP and thrombin.

      The *activated platelet* send pseudopodia and discharge their granule content. ADP and other substances are released. ADP helps in platelet aggregation. They stick to each other, which is called *platelet plug*.

ii. Platelet aggregation activates in vessel wall *phospholipase c*, which in turn activates *phospholipase A2*. This causes release of *arachidonic acid* from membrane phospholipids, which in turn gets converted to *thromboxane A2* and *prostacyclin*.

Thromboxane A2 causes—(a) further increase in platelet aggregation and adhesion and helps to form temporary hemostatic plug. This causes stoppage of bleeding from injured vessel and maintains the integrity of vascular tree. (b) release of platelet contents, i.e. (i) 5 HT and (ii) norepinephrine, both are vasoconstrictor agents and cause *vasoconstriction* immediately after injury.

Prostacyclin – inhibits thromboxane A_2 formation. Thus prevents further aggregation of platelets, keeping platelet plug localized (i.e. prevents intravascular spread of clot).

Thromboxane A_2 formation can be inhibited by: (a) Aspirin and (b) Prostacyclin synthetase (an enzyme normally present in platelet membrane).

(Normally platelets are present in an *inactive state* in circulation. Unless they become active, there can be no hemostasis).

2. Platelets provide platelet factor 3 which accelerates clotting by formation of active factor X in intrinsic pathway of clotting.
3. Platelets have a growth factor which stimulates mitosis in vascular wall. Useful in repair of damaged blood vessels.
4. Contractile proteins of platelets bring about clot retraction. Actin and myosin which are contractile proteins present in platelets.

Summary of Functions of Platelets

1. Platelet aggregation, plugs the vascular injury.
2. Cause vasoconstriction immediately after injury.
3. Help in coagulation.
4. Repair damaged blood vessels.
5. Cause retraction of clot.

COAGULATION

Blood is fluid when inside the living body but when shed it jellified within 5-6 minutes. This process of transformation of fluid blood into jelly like mass is called as coagulation or clotting of blood.

On further standing the clot retracts to a smaller volume squeezing out a clear straw colored fluid called as *serum.*

Fluidity of blood is essential for normal circulation in living body but coagulation of blood is major chemical defence against loss of blood.

Physical and Biochemical Changes Involved in Coagulation

The *essential changes* in coagulation of blood are *two* enzymic reactions in which prothrombin of plasma is converted into thrombin and thrombin reacts with fibrinogen to form fibrin or clot. Fibrinogen is soluble, which is converted into insoluble fibrin. Fibrin is laid down as network in which blood cells entangle and form a clot.

1. Prothrombin

$$\xrightarrow[\text{Thromboplastin}]{Ca^{2+}} \text{Thrombin}$$

2. Fibrinogen

$$\xrightarrow{\text{(Prothrombinase) thrombin}} \text{Fibrin}$$

This is *Morawitz s basic theory*

Conversion of prothrombin to thrombin requires presence of calcium and thromboplastins. Thromboplastins are group of substances present in many tissues and require presence of several additional factors found in blood for their activity (Extrinsic). Platelets come in contact with foreign surface when blood is shed, and they disintegrate to produce thromboplastin (Intrinsic).

Coagulation Factors

International committee suggested the use of Roman numerals for coagulation factors.

Note: Names on left are most commonly used and are easy to remember. Underlined nomenclature on right are also used commonly.

Deficiency of any factor will lead to defective coagulation resulting in prolonged bleeding or bleeding disorder.

Coagulation Process

1. Coagulation begins with contact of plasma with any foreign surface other than vascular endothelium.
2. Activation process begins with activation of the highest factor and ending with the lowest—this theory is known as *Enzyme Cascade Theory* (Macfarlane) or *Waterfall sequence Theory* (Dave and Ratnoff) of blood coagulation.
3. Each step involves enzyme catalyzed reaction in which two reactants are required.
4. Enzyme acts on inactive form of a coagulating factor (which is a proenzyme) converting it into active form (enzyme form). The second enzyme promotes activation of next in series and reactions go on until fibrin is formed.
5. Calcium ions are required in all stages except first and last.

Name	*Number*	*Other nomenclature*
Fibrinogen	I	
Prothrombin	II	
Thromboplastin	III	Tissue factor, prothrombinase
Calcium	IV	
Labile factor	V	Proaccelerin or Accelerator globulin
	VI	Does not exist
Stable factor	VII	Proconvertin, or serum Prothrombin convergen accelerator (SPCA) or Autoprothrombin I
Antihemophilic globulin (AHG)	VIII	Antihemophilic factor (AHF) or Antihemophilic factor –A (AHF-A)
Christmas factor	IX	Plasma thromboplastin component (PTC) or autoprothrombin II or AHF-B
Stuart-Prower factor	X	Autoprothrombin C
Plasma thromboplastin antecedent (PTA)	XI	AHF C
Hageman factor	XII	Contact factor
Fibrin stabilizing factor	XIII	Fibrinase or Laki – Lorand factor

6. But the sequence does not hold good for activation of factors V and X and fibrinogen is not an enzyme.

Thus, factor XII is converted to XIIa (a stands for active).

This in turn catalyzes conversion of XI to XIa, which in turn converts IX-IXa. This sequence continues, each factor helping the activation of another factor, just lower in series. Ultimately, factor I is converted to Ia or fibrin. Fibrin with the help of factor XIII is converted to Ia_s or stable fibrin.

Intrinsic system	*Extrinsic system*
In vivo—is triggered by 1. Exposure of blood to the collagen fibers, underneath the endothelium in blood vessels. 2. Change in blood constituents *In vitro* – brought about by contact of blood to water wettable surface (–vely charged) such as glass	It is triggered by 1. Injury to blood vessel wall or 2. Injury to other tissues.

Platelets also Participate in both Intrinsic and Extrinsic Pathways

Prothrombin

Prothrombin is precursor of thrombin. There is no thrombin in circulating blood. Thrombin is formed by formation of prothrombin activators which is same as active factor X which is formed in both intrinsic and extrinsic pathway.

Prothrombin is α_2 globulin (mol wt 69000). Present in plasma in concentration of approximately 40 mg/100 ml. It is formed in liver in presence of adequate amount of vitamin K. Its concentration decreases in liver diseases.

Vitamin K and its Role in Coagulation of Blood

Vitamin K

1. It is a fat soluble vitamin.
2. Present in green leafy vegetables, also synthesized by bacteria of large intestine.
3. It functions as cofactor for synthesis of prothrombin, factors VII, IX and X in the liver.
4. Drugs like Dicumarol (anticoagulant) antagonize the action of vitamin K and induce deficiency of prothrombin factors VII, IX and X which impairs coagulation.

Thrombin

Thrombin converts fibrinogen to fibrin. It also catalyses conversion of more prothrombin to thrombin.

1. Thus, once some thrombin is formed the reaction becomes autocatalytic.
2. Thrombin also activates factor XIII, the fibrin stabilizing factor. It converts fibrin monomer into fibrin polymer which is stable and insoluble.

Fibrinogen

1. It is soluble plasma protein.
2. Mol weight 3, 30,000.
3. Plasma level 250-400 mg%.

Calcium Ions

Level of calcium ions which is compatible with life is also sufficient for coagulation reactions *in vivo*.

In vitro calcium binding agents are used to prevent. Coagulation and act as anticoagulants.

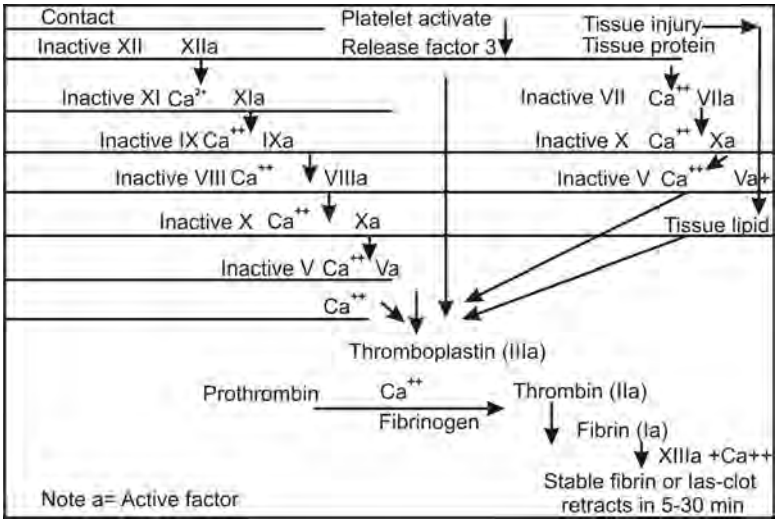


Fig. 13.2: Scheme of clotting mechanism

Dissolution of Clot

Dissolution of clot is necessary for restoration of normal blood flow through blood vessels. This takes place by a process of fibrinolysis, which is much slower than clotting process (Fig. 13.2).

Fibrinolytic enzyme (fibrinolysin or plasmin) is present in plasma as precursor (profibrinolysin or plasminogen).

Plasminogen activators are:

1. Thrombin
2. Tissue plasminogen activator (TPA) (released by tissue damage).

Other stimuli for release of plasminogen activators are:

1. Ischemia of venous walls
2. Adrenaline
3. Exercise, and
4. Stress.

Profibrinolysin (Plasminogen) $\xrightarrow{\text{Activators}}$ Fibrinolysin (Plasmin)

Fibrin $\rightarrow$ Peptides

Inhibitors of plasminogen exist in the body but when clot is formed, a balance is titled in favor of activation of plasminogen.

Note: (i) Human TPA, (ii) Urokinase, and (iii) Streptokinase fibrinolytic enzymes are used in treatment of early myocardial infarction.

1. *Endothelial surface:* Intact vascular endothelium is smooth which prevents platelet adhesion and clotting.
2. *Rate of blood flow:* If the rate of blood flow decreases, it leads to clotting.
3. Presence of natural anticoagulants in the blood, e.g. heparin and protein C and antithrombin.

i. Thrombomodulin is an endothelial cell membrane protein which binds thrombins. Thus, any thrombin which is formed is removed. Secondly thrombomodulin – thrombin combination activate a plasma protein *(protein C)* Activated Protein C in turn inactivates factors V and VIII. Thereby paralyzing both intrinsic and extrinsic systems of coagulation.

Thrombin + Thrombomodulin (act as protein c activator) → Protein C ↓ Activated protein C ↓ Inhibit factors V and VIII

ii. Heparan sulfate—*Antithrombin III system.*
Heparan sulfate is a heparan like substance that coats the vascular endothelium. Heparan sulfate enhances the activity of a plasma protein antithrombin III several fold. Thus, heparan sulfate antithrombin III combination acts as very potent antithrombin.

iii. Heparan—powerful natural anticoagulant, first isolated from mast cells of liver, therefore it is called Heparan. It is also present in lungs. Heparin is secreted by: (i) granules of circulating basophils or (ii) granules of mast cells.

It facilitates the action of antithrombin III, and has powerful antithrombin action.

4. Absence of thromboplastin in circulating blood.

Synthetic Anticoagulants

1. *Calcium binding agents*: For example, sodium citrate, potassium oxalate and ethylenediaminetetraacetate acid (EDTA). Only used *in vitro* when added to blood they form calcium salts and calcium in ionic form is not available for coagulation process. Thus, coagulation is prevented.
2. *Vitamin K antagonists*: They are effective when given orally and can be used *in vivo* only. Their mode of action—is by substrate competitive inhibition of vitamin K in liver. Vitamin K deficiency thus, produced, results in deficiency of prothrombin and factors VII, IX and X and coagulation is prevented.
Example: Cumarine derivatives like Dicumarol and Warfarin.

Other Anticoagulants

1. *Malaysian Pit Viper*: Mode of action destruction of fibrinogen.
2. *Arvin (Ancord)* also a type of snake venom. It also causes destruction of fibrinogen. This process is known as defibrination which produces fibrinogenopenia or lack of fibrinogen and prevents coagulation.
3. Cold-chilling the blood to 5-10°C delays clotting.
4. Preventing contact of blood with water wetable surface, e.g. use of silicon tubes.

BLEEDING DISORDERS

Results due to: (i) deficiency of clotting factors, (ii) defect in platelet or vessel wall.

Common Bleeding Disorders due to Deficiency of Clotting Factors

Common bleeding disorders due to deficiency of clotting factors are:

1. *Hypoprothrombinemia: Spontaneous bleeding occurs due to deficiency of prothrombin ˇ which may be due to:*
   i. Liver diseases, for example, hepatitis, cirrhosis and malignancy cause failure of formation of prothrombin.

ii. *Obstructive jaundice:* Bile is required for absorption of fat soluble vitamin K. In obstructive jaundice absence of bile from GIT depresses fat absorption and consequently vitamin K absorption. Therefore, there is deficiency of prothrombin. Similarly there is deficiency of factors VII, IX and X as vitamin K is required for their formation.

Hemophilia A or Classical Hemophilia (Fig. 13.3): Caused due to deficiency of factor VIII. Abnormality is located on X chromosome and is recessive. This is inherited sex linked disease invariably transmitted by females (who themselves do not show any symptoms) to males—who show signs of the disease like bleeding after trivial injury and bleeding in joints.

In them—(i) Coagulation time is increased to 1-12 hours (normal coagulation time is 6-12 minutes), (ii) Bleeding time is normal (2-6 minutes).

Note: Females do not suffer because they are protected by the second X chromosome and are carrier of the disease.

Treatment

Fresh blood transfusion, because factor VIII is lost rapidly on storage. Or factor VIII concentrate injection or injection of thrombin or thromboplastin.

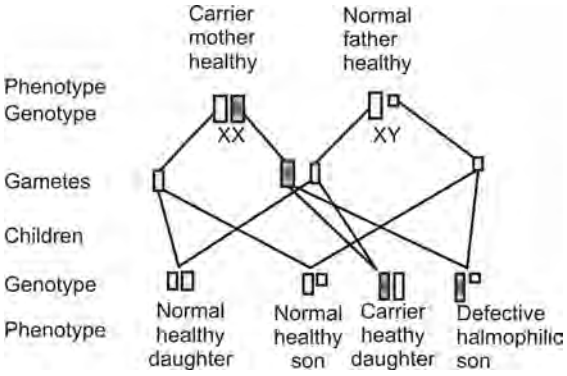


Fig. 13.3: Transmission of hemophilia

Hemophilia B or Christmas Disease

Results due to deficiency of factor IX. First observed in the man of same name. It is clinically indistinguishable from hemophilia. It is also X linked disorder and is rare. One man in 1 lac men suffer from it.

Common Bleeding Disorder due to Defect in Platelets and Vessel Wall

Common bleeding disorder due to defect in platelet or vessel wall is known as:

Purpura: Spontaneous hemorrhages are produced from large number of capillaries. When they occur under the skin, they produce purpuric spots.

Causes

1. Purpura is often caused by *thrombocytopenia* and then the condition is called *thrombocytopenic purpura.* Platelets are reduced in number. Platelets are required to plug the small vents in blood vessels and vasoactive substances required for vasospasm are released from platelets.

   Therefore, deficiency of platelets produces small punctate hemorrhages in many areas of the body.

   Thrombocytopenia may be:

   i. *Due to no cause* then the condition is called *idiopathic purpura.*
   ii. Due to bone marrow depression or reactions to drugs or hypersplenism.
2. *Qualitative defect in platelet:* Commonly induced by deficiency of von Willebrand factor (VWF) in the plasma VWF is a plasma protein which facilitate platelet adhesion to injured vascular endothelium and transports factor VIII is plasma.

Deficiency of VWF impairs platelet adhesion to vessel wall.

3. Purpura may also develop due to diseases of the capillary. In such conditions the capillaries are very fragile and burst frequently. In such condition, the platelet count may be low, as many are utilized for hemostasis.

In Pupura

i. Bleeding time is prolonged.
ii. Clotting time is normal.

Platelet count has to reduce to 50,000/cumm of blood to result in purpura (normal platelet count is 1.5 to 4 lacs per cumm).

Note: Clotting time is normal in purpura because even when the circulating platelets are decreased the circulating platelets are sufficient to liberate platelet factors required for clotting.

Laboratory Tests for Bleeding Disorders

1. *Platelet count* normal 1.5-4 lacs/cumm.
2. *Bleeding time* is determined by observing how long bleeding continues after a sharp pin prick of specified depth (4 mm deep) in the earlobe (Duke's method) or forearm prick (2.5 mm deep) in Ivy method. By Duke's method normal bleeding time is 2-6 min and by Ivy method 3-4 min. (The escaping blood is dried with filter paper every 15 secs).
3. *Clotting time,* i.e. time taken from the puncture of blood vessel to formation of fibrin thread.

   It may be done in: (i) test tube or (ii) fine capillary tube.

   i. Blood in test tube is tilted every minute till it does not flow. Time is noted when the tube can be tilted through an angle greater than 90° without spilling any blood (Lee and White method). Normal clotting time in glass tube 6-12 min; in silicon tube 20-60 min.
   ii. *Capillary tube method:* Blood from finger prick is allowed to flow in thin capillary tube. After one minute the tube is broken every 15 secs, till a fibrin thread appears between the broken ends. The time when thread just appears indicates the clotting time.
4. *Prothrombin time:*
   i. This test evaluates extrinsic clotting system.
   ii. Blood is collected by clean veno-puncture in a test tube and mixed with adequate quantity of sodium citrate (anticoagulant) which will remove calcium.
   iii. Test tube is allowed to stand to collect plasma, which contains all clotting factors except calcium.
   iv. Test tube containing plasma is kept in water bath at 37°C and calcium and tissue thromboplastin (obtained from brain extract) is added, so that activation of prothrombin to thrombin should take place.
   v. Time is noted, when plasma clots. This is prothrombin time.
   vi. Normal prothrombin time is 11-16 secs.
   vii. This test measures the concentrations of prothrombin, factors V, VII and X.
   viii. Prothrombin time increases in vitamin K deficiency.
5. *Clot retraction time:* 2-3 ml of venous blood is kept in a test tube in water bath at 37°C. Clotting takes place and in about 2 hours the clot shrinks to form a firm mass expressing serum.

Clot retraction time is abnormally high in thrombocytopenia.

6. *Thromboplastin generation test* 2 stage test:
   i. This test evaluates intrinsic clotting system.
   ii. Two stage test is performed for obtaining full information about production of thromboplastin by intrinsic pathway.
   iii. Various factors required for the generation of thromboplastin by intrinsic system are factors XII, XI, IX, VIII platelet factors 3, X and V.
   iv. These factors are assembled in this test from 3 different components of the patients blood.
      a. Serum which contain XII, XI, IX and X.
      b. Adsorbed plasma which has factors VIII and V and may also have XII and XI
      c. Platelets which provide platelet factor 3
         – *In stage one:* These three components are mixed with *calcium ions* to generate thromboplastin.
         – *In next stage:* This mixture is made to react with *normal plasma*, which acts as a source of prothrombin and fibrinogen. Thromboplastin, prothrombin and fibrinogen react to produce fibrin clot in 8 to 15 sec after addition of normal plasma, if patients intrinsic system of Coagulation is normal.

   Intrinsic thromboplastin formation is absent in—hemophilia, Christmas disease and thrombocytopenia.
7. *Capillary resistance or fragility test:* Blood pressure cuff is tied and inflated to 60 mm Hg for 2 minutes—crop of minute hemorrhages appear beneath the skin which are known as *petechiae,* distal to compression and also locally. This abnormal response occurs in diminished resistance (i.e. increased fragility) of the capillary endothelium.

SUMMARY

Three major events take place during *hemostasis, which* literally means arrest of hemorrhage.

1. Constriction of injured blood vessel.
2. Formation of a temporary hemostatic plug of platelets.
3. Conversion of a temporary hemostatic plug into 'clot', which brings about permanent arrest of hemorrhage.

CHAPTER

14

Blood Group

Blood group are based on the type of antigens present on the surface of the red blood cells. The membranes of the RBC contain these antigens which are also known as agglutinogens.

More than 30 such antigens are known but very few of them are of practical significance.

They are inherited characteristics and antigens enable the blood group of different individuals to be differentiated. Agglutinogen A and B first appear in 6th week of fetal life. Their concentration is 1/5 th of adult level at birth and progressively rises during puberty.

The chief blood groups are:

1. Classical ABO blood groups.
2. Rhesus (Rh) blood groups.
3. M and N blood groups.

SITES

In addition to being present on the surface of the red blood cells, agglutinogens A and B are also found in many organs like salivary glands and pancreas in significant amount; kidney, urine, liver and lungs in less significant amount and in testes, semen and amniotic fluid.

How are they Detected

Principle

In general, blood group antigen possessed by individual is detected only when a suspension of his red cells is mixed with a serum containing equivalent antibody. Agglutination of the red cells then occurs and individual is classified.

BLOOD GROUP ANTIBODIES OR AGGLUTININS

They are present in plasma. They can be divided into two broad classification:

1. *Immune antibodies:* Are usually gamma globulins and are acquired when red cells containing antigen are introduced in the circulation of a person who lacks it.
2. *Naturally occurring:* Are present in the plasma naturally, are α and β globulins of IgM type and do not cross placenta.

   The agglutinin acting on agglutinogen A is called α (alpha) or anti A and agglutinin acting on agglutinogen B is called β (beta) or anti B.

CLASSICAL ABO BLOOD GROUPS

The ABO blood group of a person depends on whether his red cells contain one, both or neither of the two blood group antigens A and B. There are four main blood groups: (i) AB (ii) A (iii) B, and (iv) O.

1. If the A antigen is not present in the persons red cells (that is he is group B or group O), his plasma contains naturally occurring anti A (or alpha) antibody or agglutinin.
2. Similarly if red cells lack B antigen (that is his blood group is A or O), the plasma contains anti B (or beta) antibody or agglutinin.
3. Plasma of blood group AB person, contains neither of these antibodies.
4. *Landsteiner s law* is based on these facts—it states, if an agglutinogen is present in the RBCs of an individual the corresponding agglutinin must be absent from the plasma and if the agglutinogen is absent in the individual's RBCs the corresponding agglutinin must be present in the plasma.

Exceptions to the Law

Absence of Rh, M and N agglutinogen from the RBCs is not accompanied by presence in the plasma of anti- Rh, anti M or anti-N agglutinins.

Full description of four blood groups is:

Red cells	*Plasma*
1. A	β (anti A)
2. B	α (anti B)
3. AB	–
4. O	αβ (anti A and anti B)

Group A has two subgroups A_1 and A_2. Similarly, AB group is subdivided into A_1B and A_2B and α_1 —agglutinate only A1 and α proper agglutinate A_1 and A_2.

Determination of Classical Blood Groups (Fig. 14.1)

Step 1

Draw a line on a glass slide, take:

i. A drop of isotonic saline
ii. A drop of blood, and
iii A drop of serum anti A on one side.

On the other side take:

i. A drop of isotonic saline
ii. A drop of blood, and
iii. A drop of serum anti B.

Step 2

Mix three drops on each side with separate sticks. Wait for 10 minutes and observe each side of the slide for agglutination (Fig. 14.2).

1. If agglutination (i.e. RBCs are massed together in clumps and lose their outlines) occurs with Anti A serum—person's blood group is (A).
2. If agglutination occurs with Anti B serum – persons blood group is (B).

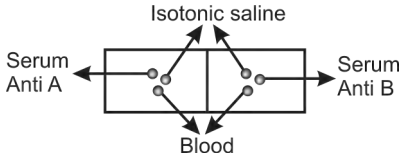


Fig. 14.1: Determination of blood group

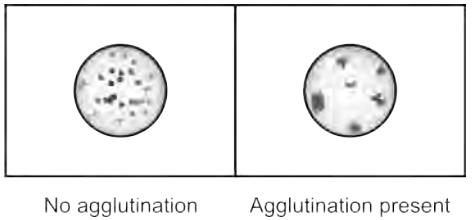


Fig. 14.2: Red blood corpuscles showing agglutination and no agglutination

3. If agglutination – occurs with both anti A and anti B serum person's blood group is (AB).
4. If agglutination does not occur on both sides, person's blood group is (O).

Serum anti A (contains agglutinin α)	*Serum anti B (contains agglutinin β)*	*Blood group*
+	–	A
+	+	AB
–	+	B
–	–	O

+ → agglutination, i.e. RBCs are massed together and lose their outline

– → no agglutination, i.e. RBCs remain separate and evenly distributed

Blood Group O

Red cells of group O lack both A and B antigen but they contain antigens belonging to other systems like Rh, M and N blood groups.

RHESUS (Rh) BLOOD GROUPS

In 1940, Landsteiner and Weiner discovered that an antibody produced in rabbits by injecting them with blood of rhesus monkey, agglutinated not only red cells of monkey but also the cells of 85% of human blood samples.

1. The antibody was called anti Rh antibody and cells agglutinated by it were called Rh +ve cells (Rh positive).
2. No agglutination occurred in 15%. These are called Rh negative.
3. The serum of Rh +ve blood group as well as serum of Rh negative blood group do not contain Rh antibody.
4. Rh blood group substance has not been detected in tissues other than RBCs.
5. Rh antibody is found in serum of certain Rh negative person who had been transfused with Rh +ve blood, or in Rh –ve women who have borne Rh positive child.
6. The Rh antigen is called 'D' antigen and Rh antibody is called anti D.
7. The Rh antibodies are of IgG type and antigen-antibody reaction occurs best at body temperature. Therefore, Rh antibodies are called *warm antibodies. They can cross the placenta.*
8. Inheritance of Rh antigen is controlled by genes present in chromosomes. The gene corresponding to antigen D (Rh antigen) is called D. When D is absent from chromosome its place is occupied by its allele called 'd'.
9. Person inherits these Rh genes, from each of his parents.
10. If the sperm and the ovum both carry 'D' the genotype of offspring is 'DD' and if one gamete carries 'D' and other carries 'd' the genotype of offspring is 'Dd' and if the sperm and the ovum both carry 'd' gene the genotype of offspring is 'dd'.
11. Both 'DD' and 'Dd' are Rh positive and 'dd' is Rh negative.

Rh Incompatibility

1. If Rh negative individual is given Rh positive blood, there is no immediate adverse reaction because Rh negative individuals do not normally have anti-Rh antibodies.
2. But the Rh +ve cells induce an immune response, so anti-Rh antibodies are synthesized. It takes 2-4 months before significantly high titer of anti-Rh antibodies is achieved. By this time the donor red cells have died a natural death and anti Rh antibody cannot agglutinate Rh negative cells. Hence, no untoward reaction occurs after 1st transfusion of Rh positive blood in Rh negative individual.
3. Now, if the same Rh negative individual receives a second Rh positive blood

transfusion anytime later in life anti-Rh antibodies are synthesized promptly. A high titer of anti-Rh antibodies is achieved briskly. The donor cells are damaged and a typical mismatch reaction takes place.

4. Since, anyone may need a second blood transfusion later in life, an Rh negative individual should never be given Rh positive blood.

Rh Incompatibility and Hemolytic Disease in Newborn

If mother is Rh negative and fetus is RH +ve serious complications may occur:

1. Rh +ve fetal cells in number sufficient to induce Rh antibody formation in Rh-ve mother, may cross placenta any time during pregnancy but more commonly when placenta is separating from uterus during delivery or abortion.
2. The anti-Rh antibody (anti D) formed in mothers blood crosses the placenta and enters fetal circulation and destroys fetal RBCs. The degree of damage done to the fetus depends on the magnitude of maternal anti-D response and the ability of maternal Rh antibodies to cross the placenta.
    i. Since, sufficient number of fetal red cells enter mother's circulation at the time of delivery, the *first child is usually normal.* But serious effects may be seen in second or subsequent pregnancies.
    ii. *Effects of anti-D on fetus:* Changes in fetus are termed as 'hemolytic disease' because they are due to destruction of RBCs by maternal anti-D. Various forms of hemolytic disease are:
        a. *Hydrops fetalis* fetus is grossly swollen: (1) it either dies in uterus or (2) if born prematurely or at term dies within few hours.
        b. *Icterus Gravis Neonatorum:*
        Baby born at term is jaundiced or becomes jaundiced within 24 hours.
        Anemia may not be present at birth but develops after birth in few days. Excessive destruction of RBCs is compensated by extensive normoblastic response in the bone marrow. This is associated with increased reticulocyte count and—nucleated cells are present in circulation (erythroblasts).

    Hence, the condition is called erythroblastosis fetalis or erythroblastemia.
    – Free anti-D from mother is present in infants blood for at least 1 week after birth and continues to destroy infants RBCs.
3. Liver is damaged. Death may come due to liver failure.
4. There may be severe neurological lesion involving basal ganglia, which are stained yellow as bile pigments cross bloodbrain barrier (which is poorly developed in fetus and newborn infants). Condition is known as *kernicterus.* It usually develops when serum bilirubin level exceed 18 mgm%.

Treatment

Exchange transfusion is carried out soon after birth. Polythene catheter is introduced in umbilical vein. Small quantities of blood is withdrawn and replaced by compatible Rh negative blood. Rh+ve RBCs which will be destroyed are removed from circulation.

Prevention of Rh Hemolytic Disease

D positive fetal red cells which have entered in mother's circulation, who is Rh negative are destroyed rapidly by administering a single

dose of *anti-Rh antibodies or anti-D* (in the form of Rh-immunoglobulin IgG) soon after birth. It prevents antibody formation in mother.

M AND N BLOOD GROUPS

M and N factors depend on two minor genes. Each person carries two of the genes of M and N group:

- If they are M + M— person has M group
- If they are N + N— person has N group
- If they are M + N— person has MN group.

Whether the blood group is M or N or MN is determined by persons RBCs tested against antiserum M and N.

Significance

M and N blood group is particularly important for investigating cases of paternity dispute (Table 14.1).

In disputed paternity: Offspring's blood group is determined and tested with the father, whether it tallies with his blood group. Mother's blood group is also determined positive, result is not significant but negative result suggests that child is not son of that particular man.

Significance of Blood Groups

For transfusion of blood: Indications are many – whenever there is blood loss or bleeding disorder or anemia or blood dyscrasias.

Table 14.1: Investigation of paternity

Child	*Parents*	*If mother is*	*Father could not be*
M	M + M	M	N
N	N + N	N	M
MN	M + N	N	N
		M	M

Basic Rules to be Observed for Blood Transfusion

1. Blood groups of donor and recipients are determined: (i) same blood group is preferred but, (ii) blood group O is universal donor as it lacks antigen, AB is universal recipient as it lacks agglutinins (Fig. 14.3).
2. Direct crossmatching test is done— between the red cells of the donor and plasma of the recipient *(major reaction).*
   - Agglutinins in donor's plasma do not usually react with agglutinogens in the recipient blood (minor reaction), mainly because they are rapidly diluted in circulation. Sometimes, serious reactions of this type have occurred when blood group O blood containing powerful anti-A, has been given to group A recipient. For this reason:
     a. Same blood group is preferred for transfusion (ABO and Rh).
     b. Directly crossmatch the sample of recipients serum with suspension of donors red cells.

   (Direct crossmatching test should reveal the presence of any agglutinin in recipient, active against blood group antigen in donor cells). In dire emergencies, O negative/(if not available)/O positive blood can be transfused.

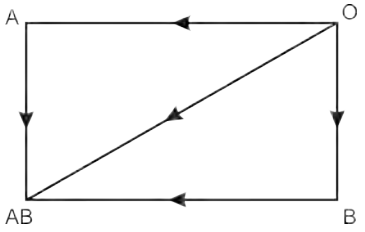


Fig. 14.3: Universal donor O, universal recipient AB, direction of arrow indicates who can give blood to whom

A statistical corelation is found between ABO blood group and certain diseases:

1. Person of O group is more likely to develop peptic ulcer.
2. There is some association between blood group A and cancer of stomach.
3. In pregnancy (Rh incompatibility)—already discussed.
4. Investigating cases of paternity disputes—already discussed.
5. Medicolegal value—analysis of blood at the site of crime and clothes of murderer help in finding him.
6. For establishing identity.

Hazards of Incompatible Blood Transfusion or Effects of Mismatched Blood Transfusion

1. *Agglutination of red cells and hemoly*sis: There is release of hemoglobin which is broken down to bilirubin. When concentration of bilirubin is high—jaundice results. Agglutinated cells form clumps and can block the capillaries so patient complains of pain and tightness of chest.
2. *Hemoglobinuria:* Red cells agglutinate and hemolyze. Released hemoglobin is partly converted into bilirubin and some hemoglobin is excreted in urine as such it blocks renal tubules when precipitated and patient complains of severe pain in back.
3. *Oliguria and renal failure:* Filtered hemoglobin gets precipitated and blocks renal tubules which leads to oliguria. It may lead to anuria.
4. *Fall of blood pressure* (due to circulatory failure and shock) which also leads to reduced glomerular filtrate and oliguria and finally anuria.
5. *Renal failure:* Increase nitrogenous substances in blood (uremia). Potassium accumulation in the body takes place. This finally leads to lethargy, coma and death.
6. *Chemical risks:* Stored blood cells lose K^+ to external plasma. Therefore, after excessive transfusion, e.g. replacement transfusion for erythroblastosis fetalis, death may occur due to hyperkalemia.
   i. In massive transfusion of citrated blood, normal conversion of citrate to bicarbonate may be delayed by tissue cells. As a result, patient may suffer from: (a) lack of ionized calcium causing tetany. (b) alkalosis (specially in patients with defective kidney functions).
7. *Pyrogenic reactions:* Like fever with rigors (chills).
8. *Allergic reactions:* For example, rash, urticaria, anaphylactic shock, etc.
9. *Transmission of diseases:* Like malaria, syphilis, AIDS, hepatitis (viral), etc.

   Note: To prevent AIDS, blood transfusion of HIV tested blood is only permitted.

10. *Circulatory overload:* Additional volume of transfused blood might overload the circulatory system, which tends to produce failure of both right and left ventricles, especially in patients with impaired cardiac and renal functions.
11. Sometimes in mismatched transfusion the hemolysis may be so mild and may lead to only mild jaundice. This is known as inapparent hemolysis.

CHAPTER 15

Structure and Classification of Nerves

Nerves in the body may be likened to the wirings in a machinery. Just as power or electricity from the generator runs in the machine through wirings, similarly, these thread like structures, i.e. nerves carry messages from brain or central nervous system (CNS) to different parts of the body and control their functions. Nerves are widely distributed throughout the body.

Structural units of CNS are called neurons (Fig. 15.1). They are embedded in supporting framework of neuroglia.

Neuron comprises of — a cell body (soma)
and two types of processes:
i. Dendrite, and
ii. Axon

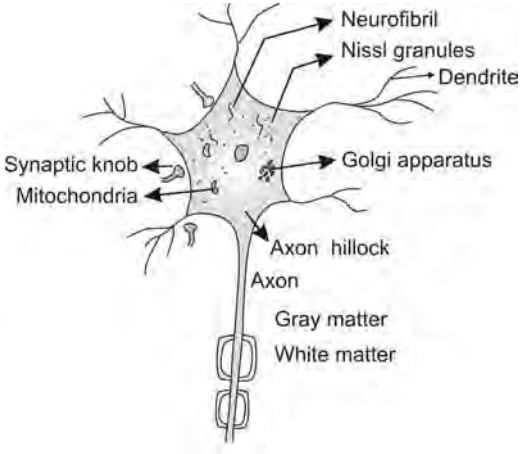


Fig. 15.1: Structure of neuron

DENDRITES

Dendrites many from single neuron—their characters are:

1. Repeated branching
2. Short course
3. Varying caliber
4. Irregular number.

AXON

Single from each neuron.

1. Arise from conical expansion of the cell called axon hillock.
2. Length of axon varies and long axons are called *nerve fibers.*
3. As a general rule, the dendrite convey impulses towards the neuron and axons away from the neuron (messages from CNS are carried in the form of impulses).
4. Many nerve fibers together *form a nerve.*

CELL BODY OR SOMA

Consist of cytoplasm and large spherical nucleus in the center of the cell. It contains mitochondria, endoplasmic reticulum, Golgi apparatus and pigment. In addition it contains:

Nissl Granules

Stain intensely with basic dyes like methylene blue:

1. Contain RNA (ribonucleic acid)
2. They are absent in the region of axon hillock and disappear when axon is cut (process is known as chromatolysis).

Neurofibrils

1. Are delicate thread like structures.
2. Course through the cytoplasm of cell and form complex network in the cell but run parallel to each other in dendrite and axon.

NERVE FIBERS

They are axonal processes of neurons or nerve cell together with their covering sheaths. Their cytoplasm (axoplasm) contain all the intracellular structures found in the neuron except Nissl granules. The supporting cells are called glial cells in CNS and Schwann cells in peripheral nervous system. They are closely applied to axon.

Nerve fibers are of two types:

1. Unmyelinated
2. Myelinated.

Unmyelination

In unmyelinated nerve the axon is enveloped in its whole length by Schwann cell and its membrane.

Myelination (Fig. 15.2)

In the myelinated, the Schwann cell has rotated several times round the axon, wrapping a spiral of lipid protein around it termed as *myelin sheath.* The thicker the nerve, greater are the number of lamellae. However, the myelin lamellae are not continuous along the entire length of nerve fiber. They are interrupted at regular intervals, to leave short segment covered only by Schwann cells. In the peripheral nerves such segments are called the *nodes of Ranvier.*

In peripheral nerve, myelin sheath is enclosed by neurilemma (Fig. 15.3).

Synaptic Knobs

Terminal Buttons or Axons Telodendria

The axon divides into terminal branches each ending in number of synaptic knobs (Fig. 15.4). They are bulbous, round or oval in shape. They contain—(a) vesicles–clustered near the

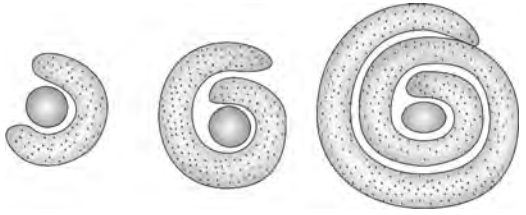


Fig. 15.2: Myelination

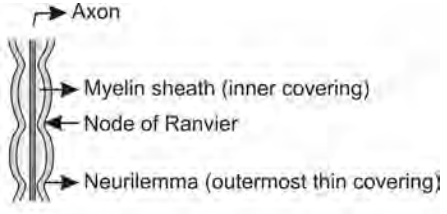


Fig. 15.3: Myelinated nerve fiber

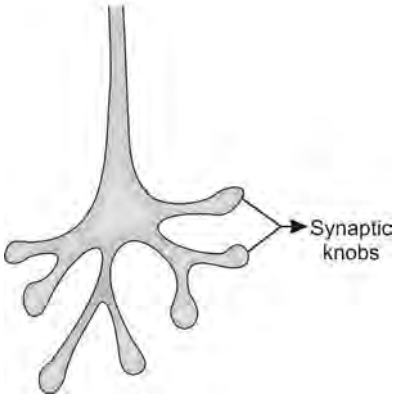


Fig. 15.4: Synaptic knobs

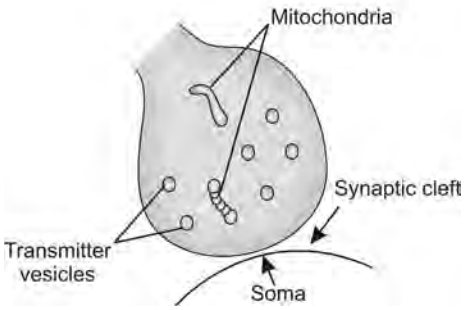


Fig. 15.5: Structure of synaptic knobs

membrane, which contain neurotransmitter (chemical substance), and (b) Mitochondria. They do not contain neurofilaments.

Synaptic knob terminates on the body or dendrite of another neuron. The junction is known as synapse. Synapse is the site of functional continuity between two neurons (there is no anatomical continuity). The name synapse is given by Sherrington after the Greek word synapsein = to clasp. Sherrington was a student of Trinity College Cambridge. The gap between the Synaptic knob and the next neuron is known as synaptic cleft (Fig. 15.5).

Arrival of impulse in synaptic knob releases synaptic transmitter from the vesicles.

Note: Nerve impulse is physicochemical change transmitted by nerves.

Coverings of Nerve Fibers and Nerve

1. *In peripheral nerve trunks*: Neurilemma of medullated nerve fiber is surrounded by thin layer of fine reticular fibers (connective tissue fibers) to form *endoneurium.*
2. Bundles or fascicles of nerve fibers are enclosed in connective tissue capsule called *perineurim,* and
3. Number of such fascicles are bound together by connective tissue fibers called *epineurium.*

Functions

Nerve Cell Body (Soma)

1. It maintains functional and anatomical integrity of axon because if axon is cut the distal part of axon degenerates (Wallerian degeneration).
2. Proteins required for integrity of axons and synaptic transmitters are synthesized in endoplasmic reticulum of the cell body and are transported to the synaptic knob by a process of axoplasmic flow (antegrade transport).

   There is also a retrograde transport of: (a) nerve growth factors and (b) various viruses from nerve endings to cell body.

Dendrites

Receive and transmit impulses towards the cell body.

Axon

1. Initial segment—generates the impulse
2. Axonal process—transmits the impulse away from the cell body to the nerve endings.

Classification of Nerve Fibers

Nerves are classified in various ways:

1. Structurally
   i. Myelinated or medullated
   ii. Unmyelinated or nonmedullated.
2. *Developmentally*
   i. Somatic
   ii. Visceral or autonomic.
3. *Chemically*
   i. Adrenergic which produce noradrenaline
   ii. Cholinergic which produce acethylcholine.
4. According to source of origin:
   i. Cranial
   ii. Spinal.
5. *Functionally*
   i. Depending on thickness and rate of conduction (By Erlanger and Gasser)
      a. A Type fibers—its subgroups are:
         – A alpha
         – A beta
         – A gamma
         – A delta.
      b. B Type fibers
      c. C Type fibers

      This classification covers all fibers.
   ii. Depending on type of impulse conducted
      a. Motor
      b. Sensory nerves.

Lloyd and Hunt classified only sensory fibers into groups:

1. I 2. II 3. III
4. IV.

Classification of mammalian nerve fibers

Group		*Myelination*	*Diameter (microns)*	*Conduction velocity m/s*	*Function*	*Agents to which conduction is most susceptible*
Erlanger and Gasser	*Lloyd and Hunt*					
A Alpha	I	M	13-20	70-120	Proprioception motor supply of skeletal muscles	Pressure
A Beta	II	M	4-13	25-70	Touch, kinesthetic sense, pressure	Pressure
A Gamma	-	M	3-6	15-30	Motor supply to intrafusal fibers	Pressure
A Delta	III	M	1-5	5-30	Pain temperature pressure, touch	Pressure
B -	-	M	1-3	3-14	Preganglionic autonomic fibers	Hypoxia
C	IV	UM	0.2-1.0	0.2-2	Pain, temperature pressure. Postganglionic autonomic fibers	Local anesthetics

Note: 1. The classification is primarily Erlanger & Gasser and roughly equivalent group in Lloyd and Hunt classification is shown.
2. Lloyd and Hunt considers only sensory fibers.
3. M = Myelinated; UM = Unmyelinated

CHAPTER

16

Effect of Injury to Peripheral Nerves—Degeneration and Regeneration

In a nerve the degenerative changes may be initiated by:

1. Transection
2. Crushing of nerve fiber
3. Local injection of toxic substances, or
4. Interference with their blood supply.

The degenerative changes quickly follow in both the segments on either side of injury site.

1. In adverse circumstances the nerve cell dies and both the injured segments disappear.
2. In favorable circumstances the nerve cell survives the effects of initial trauma and after a brief period of degenerative changes, regeneration soon begins:
   i. The degenerative changes that affect the distal segment are called Wallerian degeneration after the name of Augustus Waller, who described these changes in 1862.
   ii. Similar degenerative changes that effect the nerve cell body and the proximal segment are known as *retrograde degeneration.*

   Note: Degenerative changes occur simultaneously in all the segments.

There can be:

1. *Early changes* immediately following the injury, and
2. *Late changes* appearing sometime later.

DEGENERATIVE CHANGES IN THE NERVE CELL BODY

Early Changes

Appear within 24 hours of injury or trauma:

1. *Nissl granules* begin to disintegrate into fine dust. This process is known as *chromatolysis.* So that Nissl substance (RNA) can be mobilized to manufacture proteins for cell survival.
2. Golgi apparatus, neurofibrils and mitochondria are fragmented. Endoplasmic reticulum becomes twisted.
3. Cell body become spherical because it takes up water.
4. Nucleus is pushed to periphery.
5. Cell membrane shows degenerative changes.

In favorable circumstances these changes do not proceed further and regenerative changes begin *(regenerative late changes).*

Repair begins in about 20 days after the nerve section and is complete in 80 days:

1. The Nissl substance and Golgi apparatus gradually reappears.
2. Cell regains its normal size, and
3. Nucleus returns to central position cell repair may occur even if axon does not repair.

   Note: In central nervous system—Most of the affected cells atrophy completely and atrophy is more complete if fibers are cut close to their parent cell.

Late Changes (in Adverse Circumstances)

In adverse circumstances the early degenerative changes proceed further:

1. Nissl granules disappear loosing their staining reaction within 2-3 weeks.
2. Golgi apparatus alongwith endoplasmic reticulum disappears.
3. Nucleus is extruded out of the cell and the cell dies. These changes are complete within 2 to 3 weeks.

DEGENERATIVE CHANGES IN NERVE FIBER

1. Degenerative changes take place along the whole length of distal segment.
2. Degenerative changes also take place in proximal segment. Where fibers are still attached to the body, degeneration is localized to 1 cm or so next to the section. In any case it does not go beyond the proximal node of Ranvier.

Early Changes

Appear within 24 hours

1. Axon becomes swollen then breaks into numerous twisted fragments.
2. Myelin sheath breaks and takes beaded appearance.
3. Schwann cells show proliferative changes and their nuclei show mitosis.

Late Changes

All the changes become intensified.

1. Axon disintegrates and ultimately becomes absorbed by macrophages.
2. *Myelin sheath breaks*: Physical destruction takes place in 8 days and chemical destruction starts on 8th day and goes on till 32 days after the section.

Chemical destruction takes place due to enzymes secreted by Schwann's cells or macrophages lining the endoneural tube. Principal myelin lipids are cholesterol and lipids containing Sphinogomyelin (cerebrosides and sphinosine).

FURTHER DEGENERATIVE CHANGES

Only take place in peripheral nerve and not in CNS.

1. Macrophages remove the debris.
2. Endoneural tube remains filled by cytoplasmic mass produced by proliferation of Schwann's cell. This process takes 3 months.

Functionally

1. Even if the anatomical continuity is maintained, propagation of nerve impulse is impaired. Changes in action potential can be seen within 2 days. After the 3rd day the ability to conduct inpulses is seriously interfered with and after 5 days no conduction is possible.
2. When there is lack of continuity, there will be no propagation of impulse from the beginning.

REGENERATIVE CHANGES

While above processes are going on, in favorable circumstances repair also begins.

1. *At the site of injury,* the first repairative changes take place.

   The proliferated Schwann cells grow out in all directions from both proximal and distal segments. They establish contact with each other and bridge the gap if any. They can bridge gap of up to 3 cm.

   The activity of proliferating Schwann's cells is greater in the distal segment than in proximal segment.

   If the gap is greater than 3 cm, suturing the nerve to establish contact, is helpful to bring about regenerative changes.

   Once the continuity of endoneurial tube is established the subsequent course of events follow smoothly.
2. *Axon from proximal stump* gives rise to 50-100 fibrils (sprouts) which are guided by strands of Schwann's cells into the distal ends of endoneurial tubes.
3. Eventually only one fibril remain in one tube (all others degenerate) which enlarges to fill the tube. Its rate of growth increases to 3-4 mm/day and it establishes contact with nerve ending.
4. In approximately 15 days Schwann cell filling the endoneurial tube starts laying down myelin sheath round the one fibril which is growing. It takes about 1 year.

Note:

1. Regeneration of nerve never occurs in central nervous system.
2. In peripheral nervous system, regenerated nerve never regains its original dimension. Final diameter attained is 80-85% of normal. Therefore, functional recovery is not full.
3. Regeneration is primarily a function of the proximal stump, but it succeeds only if the distal segment provides an endoneurial sheath. So, success of regeneration depends on a viable distal segment, near enough to serve as a guide for the growth of the sprout.
4. For successful regeneration the gap between the proximal and distal cut ends should be less than 3 mm. Therefore, suturing the cut nerve, helps recovery by reducing the gap, between the two ends.
5. If the gap is large or if the distal end is not viable the sprouts form a mass of fibers called neuroma. In case of sensory fibers neuroma can be very painful. It is a dreadful complication of amputations.
6. *Other complications:* (a) If sensory nerve is damaged, an area of anesthesia is produced, (b) Misinterpretation of sensations, because many fibers will establish connections with new kinds of endings in new situations.

CHAPTER

17 Properties of Nerve Fiber

The basic properties are similar to the properties of action potential generating any excitable tissue (for example, muscle). In addition, there are few more properties. The properties are:

1. Excitability or irritability
2. Conductivity
3. Antidromic activity and orthodromic conduction
4. Refractory period
5. Summation
6. Adaptation or accommodation
7. Infatiguability
8. All or none phenomenon.

EXCITABILITY OR IRRITABILITY

Nerve fiber is highly excitable and has ability to respond to various stimulating agents – like:

1. Mechanical
2. Thermal
3. Chemical
4. Electrical, etc.
   (Remember stimulus is nothing but the change in external or internal environment).

Usually in experiments we use electrical stimulus because:

1. Its strength, duration, amplitude and frequency may be accurately adjusted.
2. It rarely damages the living tissue.
3. Its action can be quickly reversed
4. Nerve impulse is electrical in nature and many of its characteristics can be obtained by this type of stimulation.

After application of stimulus a wave of depolarization followed by repolarization travels, which is called impulse.

Explanation (Fig. 17.1)

1. Impulse travels and depolarizes nerve surface (D), a distant point is normal or repolarized (R), the oscilloscope shows deflection in one direction.
2. The depolarization process has traveled to distant point also,—oscilloscope shows no deflection.
3. The distant point is depolarized (D) but earlier point is repolarized (R). The oscilloscope shows deflection in opposite direction.
4. Both the points are repolarized (R) oscilloscope shows no deflection.

Conclusion

Record of excitation process in normal nerve is diphasic. In injured nerve, we get monophasic record as there is potential difference

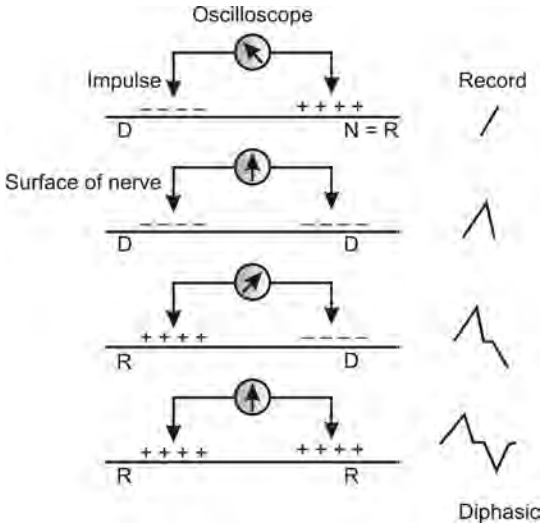


Fig. 17.1: Experiment of stimulation of nerve

in injured and normal part of nerve during resting state.

Excitability is affected by:
1. Injury
2. Drugs
3. Chemicals
4. Bacterial toxins which interfere with normal permeability of ions.

Excitability is also affected by:
1. Strength and duration of the stimulus.
2. Effect of extracellular calcium ions—decrease in calcium ions in ECF increases excitability of nerve and muscle and increase in calcium ions in ECF decreases the excitability.

CONDUCTIVITY

On stimulation action potential is generated which gets propagated. The propagated action potential is called impulse.

In living being, it is always propagated in one direction, i.e. from axon of one neuron to the dendrite or soma of the next neuron and the propagation in opposite direction dies down at first synapse it meets.

Conduction in Unmyelinated Nerve (Fig. 17.2)

Nerve membrane is polarized at rest, which means there is positivity outside and negativity inside. When it is excited at a point the polarity is reversed for a brief period with negativity outside and positivity inside. The positive charges from membrane ahead and behind the excited area flow into the area of negativity (excited area) which forms a *current sink.* Drawing of charges decreases the polarity to a firing level and action potential is generated at next point. Thus, it becomes a vicious circle and action potential moves or is propagated away from the point of stimulation and the nerve impulse is self propagated.

Conduction in Myelinated Nerve (Fig. 17.3) (Saltatory Conduction)

Myelin sheath in myelinated nerves act as a good insulator. Therefore, action potentials are generated only at nodes of Ranvier (which are

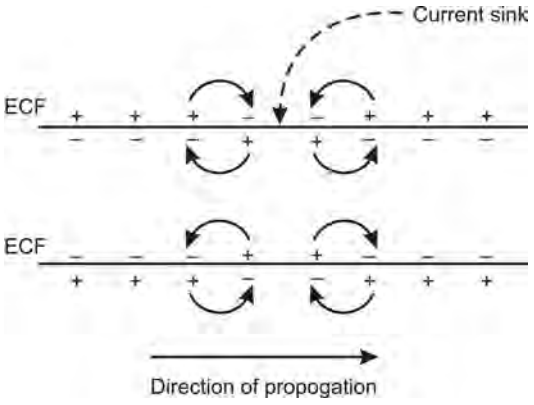


Fig. 17.2: Experiment of stimulation of nerve. Mechanism of conduction in unmyelinated nerve

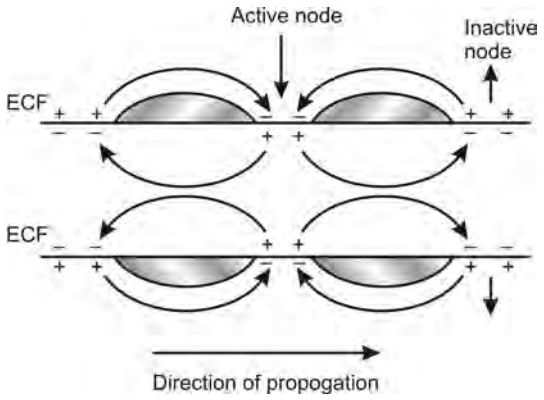


Fig. 17.3: Mechanism of conduction in myelinated nerve

about 1 mm apart), where axon membrane is exposed to ECF. The action potential generated at one-node jumps from this node to next node because current sink is developed at it. Jumping of action potential from node to node is called saltatory conduction. Because action potential is conducted in a leaping fashion, conduction is faster than the unmyelinated nerve.

Note:

1. *Saltatory:* This word comes from Saltaire which means leap.
2. In general as the diameter of nerve fiber increases, the internodal distance increases and the rate of conduction increases.
3. It is advantageous because: (a) conduction is fast, and (b) energy is conserved.

ANTIDROMIC ACTIVITY AND ORTHODROMIC CONDUCTION

In living body, impulse is conducted only in one direction moving distalward from the site of initiation of nerve impulse. This is called *orthodromic* conduction.

Conduction of impulse in opposite direction is called *antidromic conduction* . As the synaptic condition is unidirectional the antidromic impulse is blocked in the first synapse it comes across and fades away.

REFRACTORY PERIOD

Immediately after being excited a nerve fails to be excited by a second stimulus. This means that nerve becomes nonresponsive or refractory to second stimulus. The period for which it remains nonresponsive to second stimulus is called refractory period. Important, because it limits the frequency of impulse generation and conduction in a nerve (maximum is not more than 1000/sec).

SUMMATION

Two consecutive subliminal stimuli, not more than 0.5 milliseconds apart, may give rise to a response due to summation of effects, when each applied individually is incapable of producing a response.

ADAPTATION OR ACCOMMODATION

When nerves are stimulated by continuous slowly rising current, the part which is stimulated becomes less excitable. This fall in excitability is known as accommodation for nerves and adaptation for nerve endings.

Cause

1. Continuous depolarization following continued stimulation leads to increased potassium permeability.
2. Inactivation of sodium pump following continued depolarization.

The phenomenon appears after sometime and once it manifests it continues for sometime after withdrawal of the stimulus.

Note:

1. Sensory nerve fibers have far less power of accommodation than motor nerve fibers.
2. Pain fibers show almost no accommodation.

INFATIGUABILITY

Can be demonstrated experimentally. In a nerve muscle preparation, if nerve is stimulated repeatedly the muscle fails to give any response, but if the nerve is isolated and is connected to another muscle usual response is obtained indicating infatiguability of nerve.

ALL OR NONE PHENOMENON

The nerve fiber under physiological conditions will give maximum response with a spike production, or no response at all. This is known 'as all or none law'.

CHAPTER

18

Neuromuscular Transmission

The motor nerve fiber, when it approaches the muscle fiber, loses its myelin sheath and divides into number of terminal branches. Each one has end feet (flattened) or button (rounded). It lies in a groove or depression on the muscle membrane which is specialized and is known as *motor end plate.* This has special properties. Each branch of motor nerve fiber supplies one muscle fiber.

The junction between the branch of motor nerve fiber and skeletal muscle fiber is known as Neuromuscular or myoneural junction (Fig. 18.1).

ELECTRON MICROSCOPE APPEARANCE (FIG. 18.2)

1. The membrane of the motor end plate is thrown into folds called palisades. They increase the surface area.

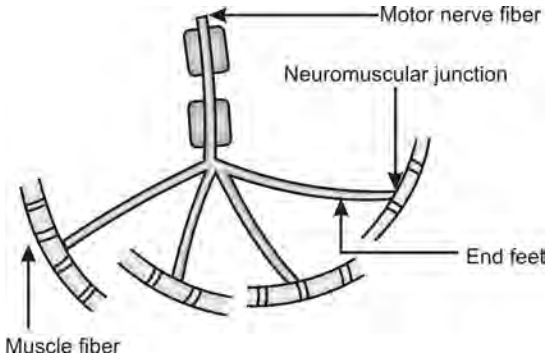


Fig. 18.1: Neuromuscular junction

2. In the end feet or button there are many mitochondria and minute vesicles. These vesicles are membrane bound and contain a chemical transmitter—acetylcholine—for neuromuscular transmission.
3. The nerve membrane forming a part of neuromuscular junction is known as presynaptic membrane and the muscle fiber membrane at the junction is known as postsynaptic membrane.

   The space between the two membranes is called synaptic cleft which is 25 nm wide and it is filled with ECF (In some books cleft is 50-100 nm wide).

CHARACTERISTIC FEATURES OF NEUROMUSCULAR JUNCTION

1. The postsynaptic membrane has specific receptors for acetylcholine in the form of protein channels, which open when acetylcholine binds or attaches itself to receptor (specific character of this receptor is that it is nicotinic acetylcholine receptor. They are so called because they are stimulated by both nicotine and acetylcholine and inhibited by curarae).
2. An enzyme specific cholinesterase or acetylcholinesterase is found in high concentration in postsynaptic membrane

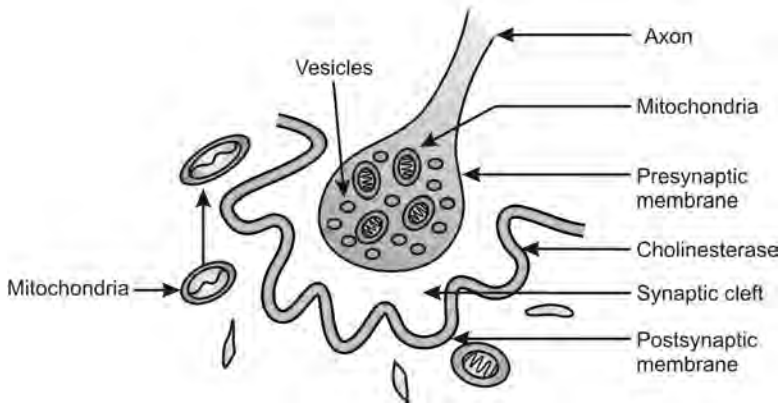


Fig. 18.2: Electron-microscopic structure of neuromuscular junction

which hydrolyzes acetylcholine into acetate and choline.

SYNTHESIS AND STORAGE OF ACETYLCHOLINE

Acetylcholine is synthesized from acetyl CoA and choline using enzyme choline acetyltransferase in the cytosol of motor neurons. It is transported along the axon for being packaged into vesicles in the axon terminal. Fresh synthesis of vesicles take place in the cell body of motor neuron in the Golgi complex. These vesicles are transported along the axon to the axon terminal.

Release of Acetylcholine

1. Even at rest small amounts of acetylcholine are continually released from axon terminal.
2. When action potential arrives at the axon terminal it opens up voltage gated channels in the membrane of the terminal. Calcium enters in axon terminal. Calcium ions bring about movement of acetylcholine vesicles towards the presynaptic membrane. Part of membrane of the vesicles fuse with the presynaptic membrane and acetylcholine is released into synaptic cleft (The mechanism is known as exocytosis).

Events after Release of Acetylcholine

1. Acetylcholine molecules diffuse through the synaptic cleft within few hundred microseconds, to reach postsynaptic membrane.

   Postsynaptic membrane has specific receptors for acetylcholine. These receptors are proteins which traverse entire width of membrane and are shaped like channels.

   When acetylcholine attaches itself to its receptors the receptor proteins undergo a conformational change and the channel becomes wider which becomes permeable to a wide variety of cations, but mainly to sodium ions. Such channels are known as *acetylcholine-gated-channels* (chemically gated channel).
2. Influx of sodium ions into muscle cells leads to depolarization of the postsynaptic membrane. Because this takes place at the

end plate, it is called the *end plate potential (EPP).*

End plate potential is graded phenomenon and its magnitude depends on how many sodium ions enter the motor end plate. Small amounts of acetylcholine are released from axon terminal even at rest which gives rise to small degrees of depolarization of postsynaptic membrane. It is known as *miniature end plate potential (MEPP).*

(When volley of action potential arrive at axon terminal greater degree of depolarization takes place, known as EPP).

If EPP crosses the threshold value the action potential is fired which is propagated along the sarcolemma, which ultimately leads to contraction of muscle.

EPP is graded but action potential is all or none phenomenon.

Explanation (Fig. 18.3)

End plate potential is graded phenomenon. When EPP reaches the threshold of –30 to – 40 mv the action potential is fired which is propagated along the sarcolemma.

Summary of sequence of events at neuromuscular junction during transmission of nerve impulse (Fig. 18.4)

1. Nerve impulse (propagated action potential) reaches the end feet (axon terminal or presynaptic membrane).
2. Opening of voltage gated calcium channels of presynaptic membrane.
3. Calcium enters the axon terminal.
4. Release of acetylcholine into the synaptic cleft and binding with receptors in post synaptic membrane.
5. Opening of acetylcholine gated channels in postsynaptic membrane, which is motor end plate, as a result of binding of acetylcholine to it's receptors on postsynaptic membrane.
6. Large number of Na^+ ions enter the postsynaptic membrane (Na-influx).

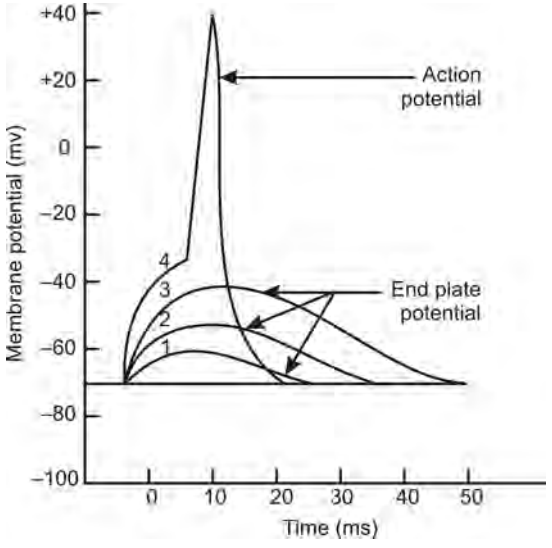


Fig. 18.3: End plate potential and action potential

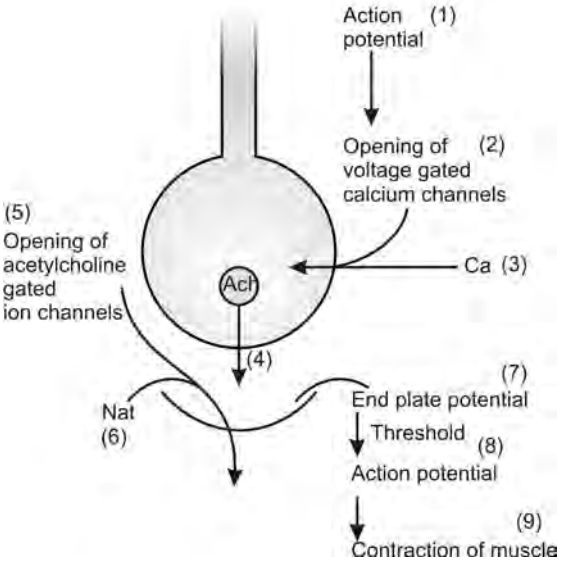


Fig. 18.4: Schematic diagram of sequence of events at neuromuscular junction during transmission of nerve impulse

7. Depolarization of postsynaptic membrane and development of end plate potential (EPP).
8. Membrane potential of end plate reaches the threshold value of –30 to –40 mv and action potential is fired.
9. Action potential thus, generated is propagated in both direction along the muscle membrane. Once it reaches the muscle cells, then muscle contracts.

Fate of Acetylcholine

1. Some acetylcholine get diffused back to presynaptic region from synaptic cleft.
2. A major part of acetylcholine is removed by postsynaptic membrane enzyme—acetylcholinesterase, which hydrolyzes acetylcholine into choline and acetate (Fig. 18.5). Thus, acetylcholine released from vesicles into synaptic cleft has very little time for action. This prevents undue prolonged action of acetylcholine.
    i. Choline is transported back in axon terminal and recycled, which means it is used for synthesis of acetylcholine.
    ii. Similarly vesicle membrane is also recycled.

Once acetylcholine is removed or hydrolyzed the permeability of muscle membrane returns to its initial state. That is depolarized end plate returns to resting potential.

FATIGUE AT NEUROMUSCULAR JUNCTION

If a nerve supplying a skeletal muscle is stimulated repeatedly at a high frequency, after sometime the response becomes progressively weaker and finally the muscle does not contract at all. The muscle is fatigued. The site of fatigue is found to be neuromuscular junction, because synthesis of acetylcholine cannot keep pace with its release and hydrolysis.

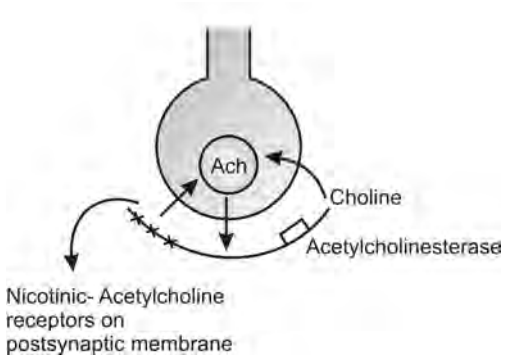


Fig. 18.5: Removal of acetylcholine

In intact organism the site of fatigue is not neuromuscular junction—but is higher up in CNS.

Many Ways

Many ways—in which events at myoneural junction can be modified by disease or drugs, For example:

1. Deadly poison curare applied to arrow head of South American Indians, is bound to acetylcholine receptor sites, but does not change membrane permeability and is not destroyed by acetylcholinesterase. When receptor site is occupied by curare, the acetylcholine released from the axon terminal cannot interact with motor end plate and no neuromuscular transmission of impulse takes place. Muscles responsible for breathing movements depend on neuromuscular transmission to initiate their contraction. Therefore, death of victim occurs from asphyxiation.
2. Neuromuscular transmission can also be altered by inhibition of acetylcholinesterase, e.g. some organophosphates present in many pesticides and nerve gases developed for biological warfare prevent hydrolysis of acetylcholine by inhibiting

acetylcholinesterase. Therefore, there is prolonged depolarization and nerve impulse fails to produce action potential because of previous failure of repolarization of muscle membrane. The result is paralysis and death by asphyxiation.

3. Group of substance affect release of acetylcholine from the nerve terminals, therefore they interfere with its action at neuromuscular junction. Botulinum toxin produced by bacteria—*Clostridium botulinum* blocks the release of acetylcholine in response to action potential and thus prevents the excitation of muscle membrane. Botulinum toxin is produced in food poisoning and is one of the most deadly poison known.

Clinically

Clinically blocking of neuromuscular transmission produces muscle relaxation. This helps in surgery.

Use of neuromuscular blocking agents reduce the dose of anesthetic agent necessary for surgery, which is safe and anesthesia is quickly reversible. The dose of anesthetic agent, just that, which will abolish pain is used. Deep anesthesia which will abolish pain and cause muscle relaxation also is avoided.

Note that patients to whom neuromuscular blockers have been given need artificial respiration because of paralysis of respiratory muscles.

Neuromuscular blocking agents are of two types:

1. *Competitive inhibitors:* These drugs act by competing with acetylcholine for acetylcholine receptors. They block the receptors but do not increase the permeability of muscle membrane. By preventing acetylcholine from binding to its receptors these drugs block neuromuscular transmission.

   Important examples of this group are: (a) curare (plant product) and (b) gallamine (Flaxedil).
2. These drugs act like acetylcholine but are resistant to the action of acetylcholinesterase. Persistent depolarization leads to neuromuscular block.

   Important example of this group is succinylcholine.

   In addition: Acetylcholinesterase inhibitors block the neuromuscular transmission. These drugs are competitive inhibitors of acetylcholinesterase. There takes place accumulation of acetylcholine. Muscle membrane fails to repolarize.

   Important examples of this group are: (a) physostigmine (plant product also called eserine) and (b) its synthetic analog—neostigmine.

Diseases Affecting Neuromuscular Transmission

Myasthenia gravis: It is characterized by profound weakness of muscles (myo = muscle; asthenia = weakness). Disease is characterized by rapid onset of fatigue with marked generalized weakness of muscles.

It is *a rare autoimmune* disease in *which circulating antibodies* are formed to the *nicotinic acetylcholine receptors.* These antibodies destroy acetylcholine receptors.

Patient is better early in the morning, because during the night acetylcholine has accumulated and this can overcome the block produced by antibodies to some degree. But the excess acetylcholine cannot be maintained throughout the day, hence patient gets weaker.

1. Early and prominent sign of this disease is drooping eyelids, weakness of muscles of the upper eyelids leads to drooping eyelids.
2. Facial, swallowing and mastication muscles are affected.

3. In severe cases, patient becomes bed ridden and may die from respiratory paralysis.

Treatment

1. Inhibitors of acetylcholinesterase like *Neostigmine.* It prevents hydrolysis of acetylcholine and excess of acetylcholine accumulates which can displace antibodies from antibody—acetylcholine receptor complex and the neuromuscular block is overcome.
2. *Lambert-Eaton syndrome:* It is characterized by muscle weakness—Cause—antibodies are formed against one of the Ca^{2+} channels in the nerve endings at neuromuscular junction. This decreases the normal Ca^{2+} influx (which causes acetylcholine release) and neuromuscular transmission cannot take place.

CHAPTER 19

Classification of Muscle and Structure of Skeletal Muscle

CLASSIFICATION OF MUSCLE

Muscles in the body are classified into two main groups—depending on presence or absence of striations.

Striated Muscle

1. *Skeletal muscle* is usually attached by tendons to the bony framework *or striated muscle or striped muscle*—because they exhibit light and dark striations or *voluntary muscle*—because they are under control of will.
2. *Cardiac muscle*
   i. Forms musculature of heart
   ii. Contractions are rhythmical and involuntary
   iii. Pumps blood throughout life.

Smooth Muscle or Plain Muscle

1. Absence of striations
2. Therefore, called smooth muscle
3. Contraction is involuntary.

Another way of classifying muscles is:

1. Voluntary
   i. They are under control of will
   ii. All skeletal muscles are voluntary muscles.
2. Involuntary
   i. They are not under control of will
   ii. They are:
      a. Smooth muscle (or plain muscle)
      b. Cardiac muscle.

STRUCTURE OF SKELETAL MUSCLE

1. Skeletal muscle consists of a fat belly with a tendon at either end (at origin and insertion).
2. It stretches across at least two bones to which its tendons are attached.
3. Connective tissue covering of muscle belly is known as *epimysium.*
4. Cross-section of muscle belly show, that it consists of number of muscle bundles or fascicles. In the space between them are the blood vessels.
5. Connective tissue around each muscle bundle or fascicle is known as *perimysium*.
6. Each muscle bundle consists of large number of muscle fibers arranged parallel to each other.
7. A muscle fiber is same as muscle cell.
   Muscle fiber (Fig. 19.1):
   i. It is long and cylindrical.
   ii. Its length vary from 1-40 mm and thickness from 50-100 μm.

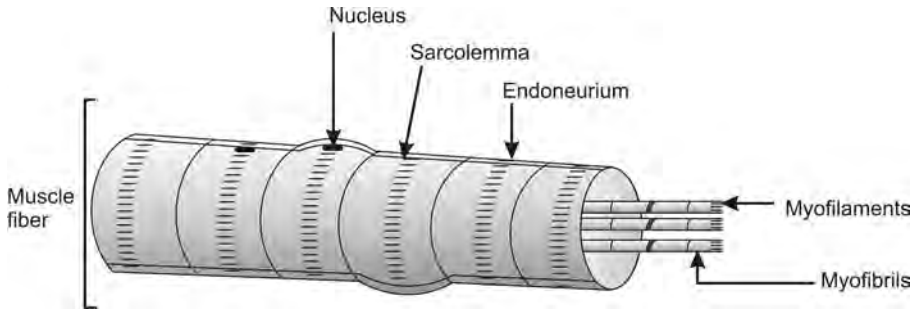


Fig. 19.1: Structure of muscle fiber (muscle cell)

iii. The cell membrane around the muscle cell is known as *sarcolemma.*
iv. Its cytoplasm is called *sarcoplasm.*
v. Muscle cell is multinucleate. Nuclei are pushed to periphery by contractile elements present in it which are densely packed.
vi. Each muscle fiber (or muscle cell) contains many myofibrils (1-2 μm in diameter) which lie parallel to each other in sarcoplasm.
vii. At the end of the muscle cells the myofibrils are in contact with the sarcolemma which at this position shows complex folds into which the collagen fibers of the tendon are fitted.

When examined under ordinary light microscope the myofibrils themselves are striated and are aligned within the sarcolemma such, that the corresponding points of their striation pattern lie at the same level, giving the appearance of disks crossing the whole thickness of the muscle fiber.

TYPES OF MUSCLE FIBERS

There are two types of muscle fibers: 1. Red and 2. White. There are intermediate fibers having both elements. All three are present within a single muscle. But some muscles are predominantly red and some predominantly white.

Difference between Red and White Muscle Fibers

Red Fiber

1. Thin.
2. Red color because of high content of myoglobin (reddish brown).
3. Speed of contraction or velocity of contraction is low.
4 Contract less forcibly.
5 Do not get fatigued easily because myoglobin can provide steady supply of oxygen.
6 Ideal for sustained contractions, e.g. postural muscles.

White Fiber

1. Thick.
2. Less content of myoglobin, therefore white.
3. Speed of contraction or velocity of contraction—high.
4. Contract more forcibly.
5. Fatigue quickly.
6. Useful for brief forceful contractions, e.g. lifting weight.

Contractile Elements

Each muscle fiber, i.e. red, white or intermediate consists of large number of densely packed myofibrils.

1. Myofibrils are composed of both actin and myosin myofilaments and represent contractile portion.
2. Between 500 and 2500 myofilaments are found within a myofibril. Under deep focusing of ordinary light microscope, the myofibrils shows alternate light and dark cross bands (Fig. 19.2).
3. The dark band contains highly refractile material, which is also birefringent. Another term for birefringent is anisotropic. Therefore, the dark band is called A band (1.5 μm in length).
4. The alternate light bands are singly refractive and isotropic. Therefore, light band is called I band.
5. In the center of A band—a less refractile region is called H band (after Hensen, who discovered it, according to some, H is derived from the German word hell = light). Length of H band = 0.5 μm.
6. In the middle of H band is the M line.
7. Lastly in the center of the I band is found a narrow line of highly refractile material, which looks dark. It is called Z line or Dobie's line or Krause's membrane.

- The functional unit of muscle or sarcomere is recognized as the area between two Z lines (Fig. 19.3).

Electron Microscopy

1. Shows that the myofilaments are arranged longitudinally spaced out a few nm apart.
2. *In A band-line the myosin filaments* (10-11 nm thick), called thick filament about 45 nm apart, extending from one end of A band to the other. There are several hundred myosin molecules in each.
3. Actin filaments are thinner (4-5 nm thick) and stretch from the Z line to the edge of the H zone. They are also called as thin filaments.
4. In A band each of the myosin filaments which are themselves arranged hexagonally are surrounded by six actin filaments (Fig. 19.4). These actin filaments are shared with neighboring nearest myosin filaments and each myosin filament has total complement of 6 actins.
5. When muscle contracts:
   i. Two sets of filaments slide past one another—A band remains constant.
   ii. H band changes in width, it becomes narrower and may be obliterated completely.
   iii. I band shortens.

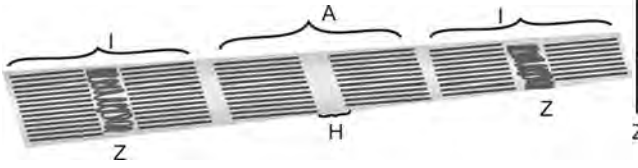


Fig. 19.2: Arrangement of light and dark bands in myofibrils

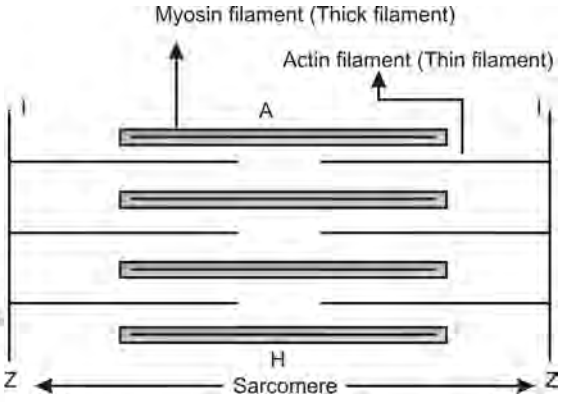


Fig. 19.3: Arrangement of myofilaments in sarcomere

Fig. 19.4: Cross-section through A band
(Each myosin filament is surrounded by six actin filaments)

6. There are cross bridges between the filaments. Each actin filament being connected to the myosin at interval of about 40 nm. These cross bridges are:

   A part of the structure of myosin molecules. These cross bridges are arranged in a spiral round the myosin thick filament. One turn of spiral gives rise to 6 bridges, which are able to interact with actin in six thin actin filament, surrounding each thick myosin filament.

Proteins in muscle are:
1. Contractile proteinss
   i. Myosin
   ii. Actin.
2. Regulator proteins
   i. Tropomyosin } both are present in actin
   ii. Troponin } filament

Contractile Proteins

Myosin

Myosin—myosin (Fig. 19.5) molecule has:
1. Two heavy chains (molecular weight - 200,000 each), and

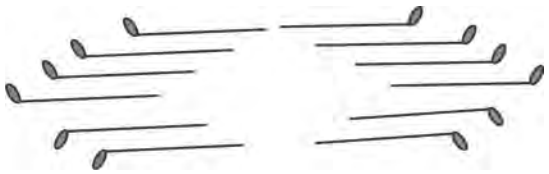


Fig. 19.5: Arrangement of myosin molecules

2. Two light chains (20,000 mol weight each)—heavy chains have helical structure, i.e. amino acids forming it are first coiled into helix (cork screw) which is held by hydrogen bonds and two such helices are twisted and rotated like the strands of ordinary rope. Therefore, the molecules are long thin and mechanically strong.
   i. Two light chains also form part of the head.
   ii. Myosin molecule is formed of a tail and two short arms with a head. Head has two reactive sites: (a) one for actin, (b) ATPase activity.
   iii. The tail is double helical except at one end where the chains are bent away from each other. The bent portion forms two short arms with a head at the tip. The arms and heads together form cross bridges.
   iv. Each cross bridge has two hinges where it can bend: (i) one hinge at the junction of the arm and the tail and (ii) the other is at the junction of the arm and the head (Fig. 19.6).

Function
1. Myosin participates in contraction.
2. Acts as ATPase. As an ATPase, it breaks down ATP to release energy for the process of contraction.

Actin (Fig. 19.7)

1. Actin is globular shaped molecule (G actin), which has a reactive site on its surface

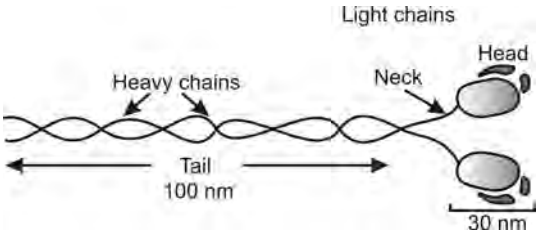


Fig. 19.6: Diagrammatic structure of myosin molecule

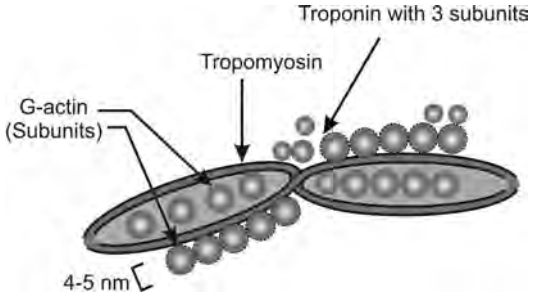


Fig. 19.7: Diagrammatic structure of actin molecule

(probably ADP molecule) which interacts with myosin cross bridge during the process of contraction.

2. Globular actin polymerizes end to end to form fibrillar actin or F actin.
3. Each actin filament has two chains of fibrillar actin which are intertwined helically.
4. Actin is a major portion of the thin filament other proteins which are present in thin filament are: (1) tropomyosin, and (ii) troponin.

Regulator Proteins

Troponin and tropomyosin are called regulator proteins because they prevent actin combining with myosin in resting muscle as they cover active sites of actin. Both also form a part of the filament.

Tropomyosin

1. Tropomyosin (MW 70,000) is a double helical structure, 40 nm long, and it wraps the actin filament. The two strands of tropomyosin lie in two grooves of F actin 180° apart.
2. Several molecules are required to wrap the thin filament, which is about 1000 nm long.

Troponin

This protein is also associated with actin filament.

1. Troponin is a globular protein.
2. It has three subunits:
   i. Troponin I—has strong affinity for actin.
   ii. Troponin T—has a strong affinity for Tropomyosin.
   iii. Troponin C—has a strong affinity for calcium.

Troponin I covers active sites of actin but troponin molecules are few and cannot cover all active sites of actin. But troponin T subunit also combines with tropomyosin and places it in such a position, that it covers maximum actin sites in relaxed state of the muscle.

Sarcoplasmic Reticulum

Sarcoplasmic reticulum is similar to endoplasmic reticulum found in most cells (Fig. 19.8). It surrounds myofibrils. At regular intervals associated with each sarcomere

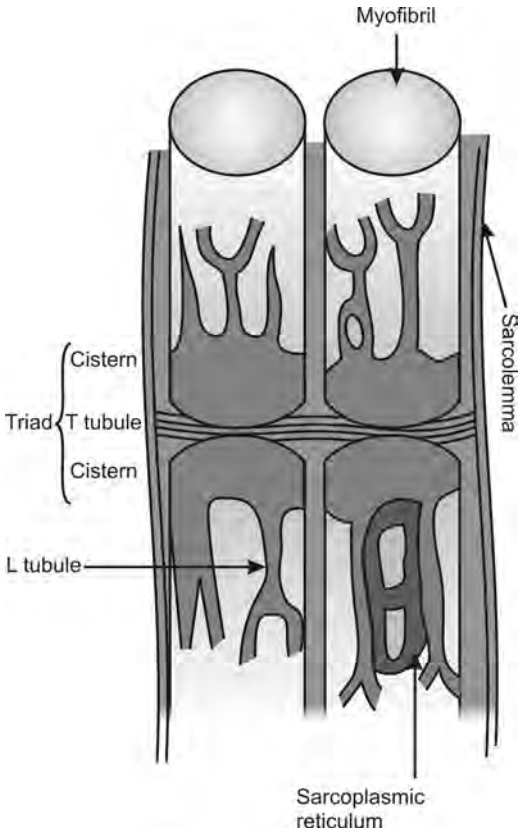


Fig. 19.8: Sarcoplasmic reticulum

where A and I bands meet, there are ring like enlargements known as terminal cisterns or sacs. These contain calcium ions that are released following muscle excitement:

1. In between terminal cisterns or sacs are the tubular invaginations of sarcolemma. They extend transversely into the muscle. Therefore, they are called T tubules.
2. A T tubule and two terminal cisterns or sacs surrounding it form a triad.
3. T tubules are extension of extracellular space into the interior of the muscle fiber. They communicate the changes in the electrical potential of the sarcolemma to the terminal cisterns or sacs and cause release of calcium into the sacroplasm.

CHAPTER

20

Mechanism of Contraction

SLIDING FILAMENT MECHANISM

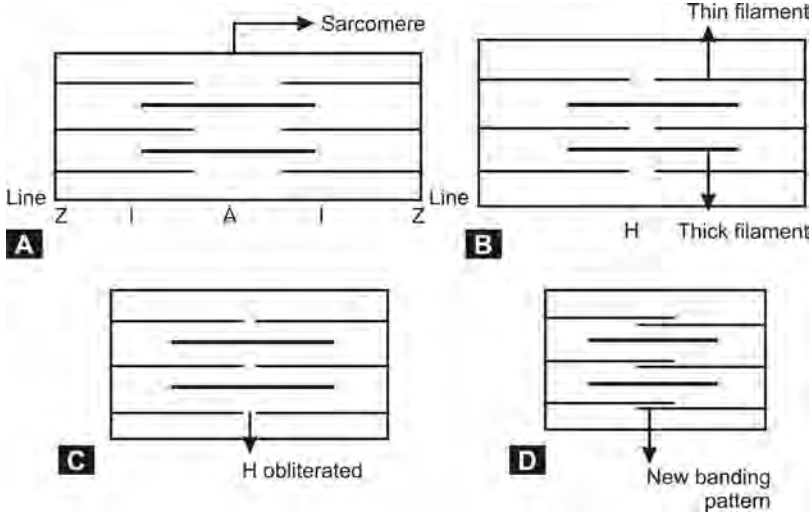
HE Huxley used electron microscope to examine muscle in:

- Resting
- Relaxed, and
- In different degrees of shortening.

His crucial observation was:

1. When muscle becomes shorter and shorter as a result of contraction, thick and thin filaments slide past each other but length of each thick and thin filaments do not change.
2. i. A band remains same:
   ii. I band narrows.
   iii. H band becomes smaller and smaller and may disappear altogether.
   iv. With further contraction new banding pattern appears as thin filaments from opposite ends of sarcomere begin to overlap.

These observations led to sliding filament theory of muscle contraction which states that muscle shortening results from the relative movements of thick and thin filaments past each other (Figs 20.1A to D).



Figs 20.1A to D: Sarcomere in different degrees of shortening during contraction. Sarcomere: (A) in relaxed state, (B) shortening, (C) further shortening, (D) still further shortening

Structures which produce sliding of the filaments are the myosin cross bridges and interaction between actin and myosin resembles *a ratchet* (postulated theory).

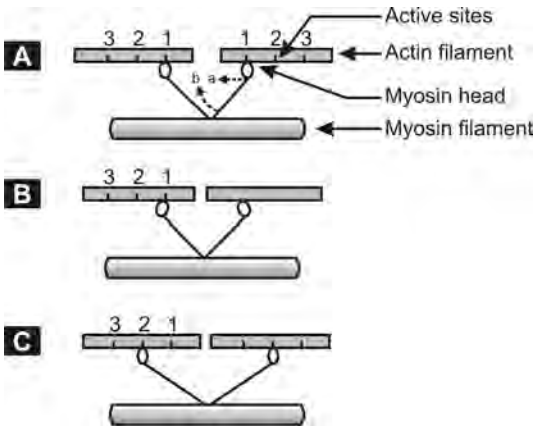
ATP is used as energy for cross bridge movement and Mg^{++} ions are required for this reaction.

Explanation (Fig. 20.2)

1. Relaxed state.
2. Actin filaments slide closer to each other, due to interaction of actin and myosin, and cross bridge movement at hinges a and b.
3. The myosin molecule restores its shape but now is attached to active site 2.

By repetition of the process actin filaments move still closer to each other.

1. In resting muscle, troponin I is lightly bound to actin. Troponin T is bound to tropomyosin. Hence, troponin and tropomyosin together cover the active sites of actin, where myosin heads bind with actin. Therefore, troponin and tropomyosin are called *relaxing proteins* or *regulator proteins*.



Figs 20.2A to C: The ratchet mechanism of contraction: (A) elongated ball is stright at 1, (B) ball in tilted still at 1, (C) ball is straight at 2

2. When Ca^{++} ions are released from terminal cisterns of sarcoplasmic reticulum in response to excitation, calcium binds with troponin C. This produces a change in shape of troponin molecule and it shifts as binding of troponin I is weakened. As troponin is also attached to tropomyosin, this also shifts and it is believed that tropomyosin falls in the groove between actin strands—exposing the binding sites of actin for myosin.
3. Myosin cross bridge combines with actin. This increases the activity of myosin ATPase (allosteric effect). Energy released from the splitting of ATP produces cross-bridge movement (power stroke) at the hinges leading to movement of the actin filament.
4. In the new position myosin cross bridge is under strain. The strain is relieved by the heads getting unhooked from actin and quickly getting attached to new sites. The dissociation of myosin head from active site of actin is achieved by a molecule of ATP, binding to myosin. This reaction (ATP binding) returns cross bridge to its initial state. So that now, it can undergo binding to new active site of actin. The process is repeated to move actin filament further. Since, the process involves sliding of the actin filaments between the myosin filaments, it is called *sliding filament mechanism.*
5. At the molecule level of actin and myosin we can identify the two very specific roles of ATP:
   i. The splitting of ATP by myosin ATPase provides the energy for the movement of the cross bridge, and
   ii. The binding of ATP to myosin dissociates actin from myosin cross bridges.

- Illustrated by phenomenon of rigor mortis (rigor after death) in which the muscles of the body become very stiff and rigid shortly after death. This results directly from the loss of ATP in the dead muscle cell. In the absence of ATP the myosin cross bridges are able to combine with actin, but the bond between them is not broken.

6. Note that muscle contraction is initiated when Ca^{++} ions are made available to troponin, and ceases when calcium is removed. The mechanisms which regulate the available calcium ions to the contractile machinery of muscle are coupled to electrical events that occur in the muscle membrane.

EXCITATION CONTRACTION COUPLING (FIG. 20.3)

For the activity of the muscle, the message is brought through motor nerve supplying the muscle in the form of impulse. It crosses the neuromuscular junction with the help of neuromuscular transmitter—acetylcholine. End plate potential is generated at the motor end plate. When EPP crosses threshold, action potential is generated at the motor end plate which spreads along the sarcolemma.

1. The action potential is an electrical phenomenon which leads to contraction which is a mechanical process.
2. The chain of events that link electrical excitation of the muscle fiber with its contraction is known as *excitation contraction coupling.*

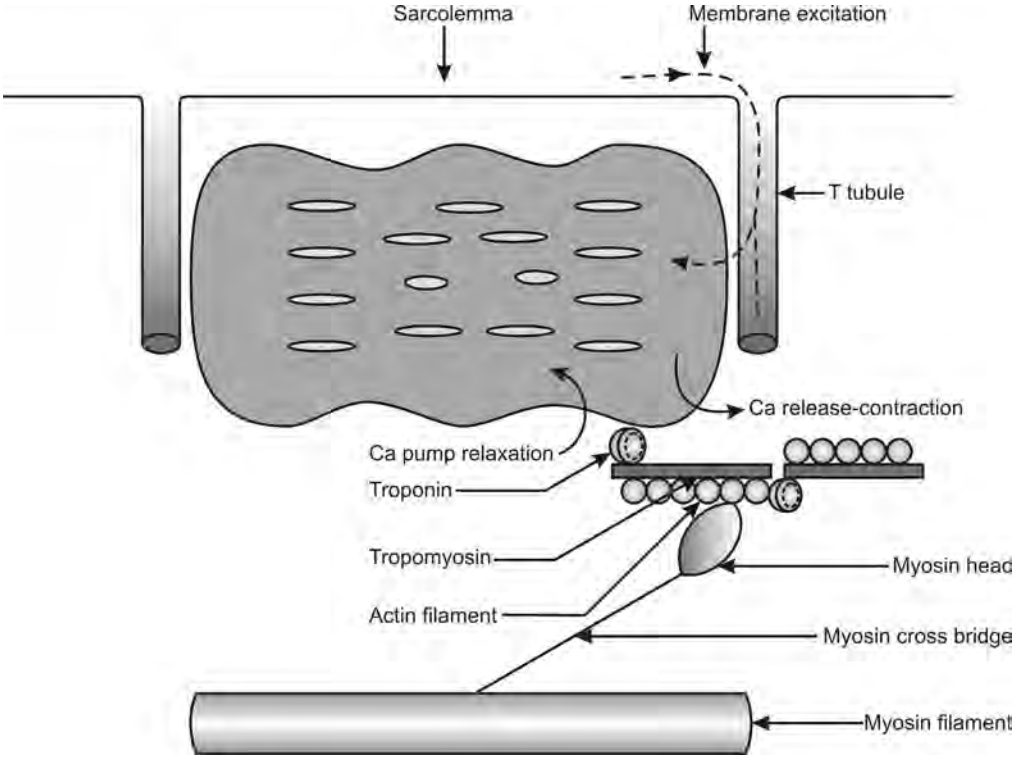


Fig. 20.3: Excitation contraction coupling

3. The excitation of sarcolemma reaches deep inside the muscle by way of *T tubules* which are formed by invagination of the sarcolemma. The T-tubules encircle every myofibril, are present at every A I junction. Thus, they conduct action potential throughout the muscle.
4. The sarcoplasmic reticulum present inside the muscle cell forms an enlargement laterally known as terminal cistern or sac, which is in close association with T tubule. The terminal sac with a T tubule on either side is known as *triad.*

   In human, skeletal muscle triad is present at A-I junction. The terminal sacs contain lots of calcium ions. So, they are storehouse of calcium.

   i. When action potential traveling along the T tubule reach the triad, depolarization spreads to membrane of the cisterns. This releases calcium ions into sarcoplasm and concentration of calcium increases about 1000 fold its resting level.
   ii. Calcium ions combine with troponin C, which result in the change of the shape of troponin, so it shifts. Since troponin is also attached with tropomyosin, tropomyosin shifts laterally and falls in the groove between two actin strands. Now the active sites of actin are exposed so that myosin heads can attach with them. Interaction of myosin and actin increases myosin ATPase activity. ATP splits. With the energy released myosin cross bridges move (power stroke). This causes the actin filaments to slide towards center of the sarcomere. The sarcomere becomes shorter – the muscle contracts.
   iii. The action potential and its release of calcium from terminal sacs lasts only a few milliseconds. Immediately following this electrical activity the calcium pumps in the membrane of the cisterns begin pumping the released calcium back into the terminal sacs. The pump is overpowered only momentarily during excitation by the opening up of a large number of calcium channels. Calcium pumps uses ATP. In muscle contraction this is third role of ATP.
   iv. The process of reaccumulating the released calcium takes much longer than the initial release and contractile activity of the cross bridge proceeds for several milliseconds after the release of calcium, until concentration of free calcium becomes so low that troponin and tropomyosin regain their original position covering the active sites on actin for myosin.
   v. Muscle relaxes.
   vi. Thus, if the contractile activity is to last for more than a few hundred milliseconds, repeated action potentials must occur to maintain the free calcium ion concentration surrounding the myofibril at a high level.

CHAPTER

21

Characteristics of Muscle Contraction

MOTOR UNIT AND ITS PROPERTIES

Skeletal muscle receive their motor nerve supply from anterior horn cells of the spinal cord, or from corresponding cells in the motor cranial nuclei.

Each anterior horn cell supplies to varying number of muscle fibers. Number varies with the individual muscle from 5-2000 muscle fibers (Fig. 21.1).

An anterior horn cell and its efferent fiber is a *motor neuron.* It is called by clinician—*lower motor neuron.*

A motor neuron together with the group of muscles fibers, which it innervates is called *motor unit.*

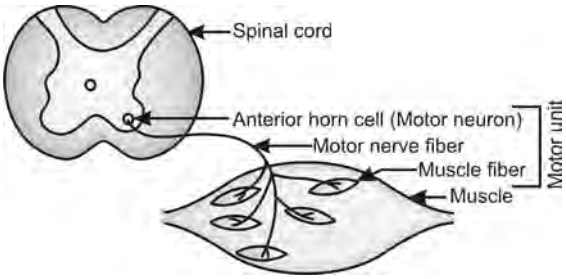
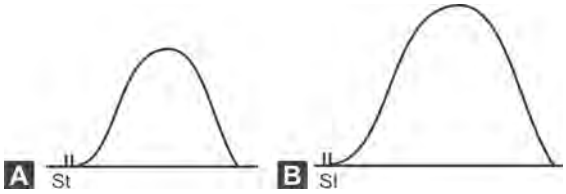


Fig. 21.1: Motor unit with 5 muscle fibers

Properties

1. The smallest group of muscle fibers that can be made to contract naturally in the body, either in a reflex or voluntary activity, is obviously that supplied by single motor neuron.
2. The size of the motor unit varies inversely with the precision of the movement performed by the part. For example, in muscles for more precise action, there are less number of fibers (extrinsic muscle of the eye) and in limb muscles the motor unit may contain up to 2000 muscle fibers.
3. All the efferent fibers passing to the skeletal muscle are excitatory. There are no efferent nerves which on stimulation produce relaxation of the muscle, i.e. there are no inhibitory somatic efferents (In case of smooth and cardiac muscle the efferent supply is both excitatory and inhibitory).
4. Skeletal muscle contraction under natural conditions always results from discharge of the motor neurons. Muscular relaxation is the result of a decrease or cessation of discharge of motor neuron.
5. A single electric shock of adequate strength, applied to a motor nerve gives rise to *simple muscle twitch (Fig. 21.2),* i.e.



Figs 21.2A and B: Record of simple muscle twitch: (A) Single electric shock with adequate strength applied to motor nerve, (B) Maximal strength electric shock applied to motor nerve

it excites a certain number of motor nerve fibers and their related group of muscle fibers (=definite number of motor units).

As the strength of stimulus applied to the nerve is increased more nerve fibers and therefore more group of muscle fibers respond and the strength of resulting contraction is correspondingly greater.

With maximal stimulation all the nerve fibers are excited and consequently all the muscle fibers supplied by the motor nerve contract.

6. In case of repeated stimulation – the rate of discharge from the motor neuron may vary from 5-10 to 100-150/sec. So resulting contraction will vary in nature and strength and in degree of tetanus (partial or complete).
   Note: (Tetanus is explained later in next chapter).
7. The degree of activity of each motor unit can be finely graded from the center:
   - The number of anterior horn cells activated during an act may be varied.
   - Number of motor units in action at any moment is thus regulated.
   - And obviously the larger the number of active motor units the greater is the force of contraction.
8. The central discharge is asynchronous, i.e. the cells in what is called the *motor neuron pool,* which innervate the muscle, do not fire off impulses simultaneously (Fig. 21.3A). Thus, the different muscle units are, at any given moment, in different phases of activity. When one group is contracting the other is relaxing and vice versa. Algebraic summation occurs and individual variations are evened out and muscle gives a steady pull (Fig. 21.3B).

TYPES OF CONTRACTION

When the muscle is excited by adequate stimulus it contracts:

Due to various components in the muscle two types of contractions are possible (Table 21.1):

1. Isometric, and
2. Isotonic.

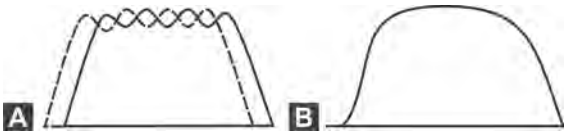
Isometric Contraction

Isometric contraction means contraction in which there is no change in the muscle length but there is increase in tension (Fig. 21.4A). (iso = same, metric = length measure).

Muscle behaves as *two component system* in which the: (1) contractile part of the muscle (i.e. actin, myosin) is in series with an, (2) elastic *component* composed of connective tissue in tendon. This is known as *series elastic element or component*.

The muscle also contains *parallel elastic element or component* in the form of connective tissue in sheath, etc.

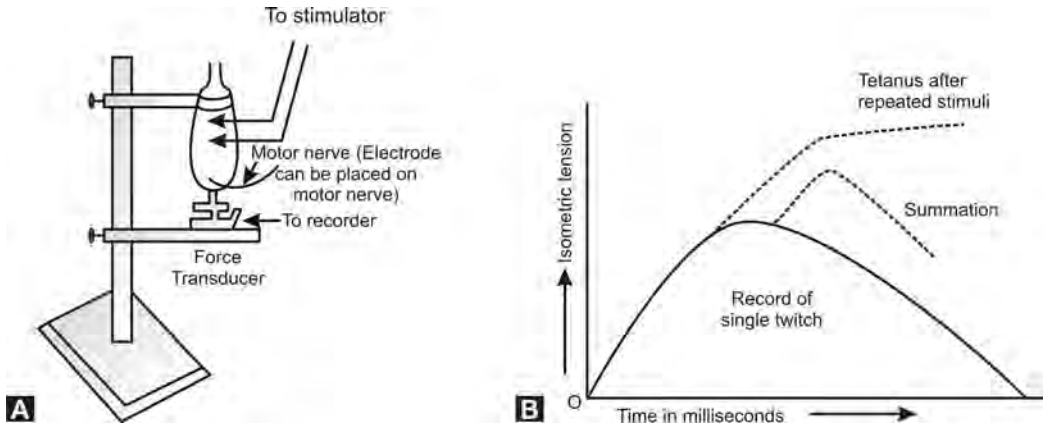
As a result even when muscle is prevented from changing its length as a whole, when excited, the contractile element (sarcomeres)



Figs 21.3A and B: (A) Asynchronous discharge in motor neuron pool, (B) Steady muscle contraction

Table 21.1: Differences between isometric and isotonic contraction

Isometric contraction	*Isotonic contraction*
1. Muscle does not shorten.	1. Muscle shortens.
2. Record of single twitch shows a. Little difference in latent period. b. Contraction period—longer—300 millisec. c. Relaxation period—long—600 millisec.	2. Record of single twitch shows a. Little difference in latent period. b. Contraction period—shorter 40-50 millisec. c. Relaxation period is also shorter 50 millisec.
3. Tension developed is greater	3. Tension developed is always less than developed during isometric contraction.
4. Development of tension depends on the strength of stimulus.	4. Tension is dependent on the load applied to it, not on the strength of stimulus.
5. Muscle does no external work. Example—postural muscles contract (to maintain posture) against gravity.	5. Muscle does external work. Example—muscles of hand Contract to lift weight.
6. Heat produced is less (only activation heat is produced).	6. More heat is produced during contraction and relaxation.



Figs 21.4A and B: (A) Recording arrangement for isometric contraction, (B) record

shorten and thereby stretch the elastic component, resulting in development of tension.

To Record

Isometric contraction—both ends of the muscle is fixed with the help of isometric instrument; tension developed by the muscle during isometric contraction can be recorded with force transducer (Fig. 21.4B).

1. By setting the muscle at various lengths before stimulation, the tension developed at each length can be measured. It is observed that tension development is greatest, when the muscle is at the same length as it was in the body. The length at

which the tension developed is maximal is known as optimal length (Lo) (Fig. 21.5). In this condition the actin and myosin filaments are at such length, as to provide maximum number of reactive sites for interaction.

2. Tension is minimum when length of the muscle cell is much less than the body length (Li) (Fig. 21.5). The tension developed is minimum because the actin filaments overlap in the center (double overlap). So number of reactive sites left to combine with myosin cross bridges is minimum.
3. If muscle is stretched beyond optimal length the overlap of actin and myosin filament is progressively reduced and contractile tension is decreased. It is minimum when there is no overlap. This length is called length maximum (Lm) (Figs 21.5 and 21.6).

Isotonic Contraction

Where contraction is manifested by shortening of the muscle, it is called isotonic contraction. Here the tension remains same but the length decreases.

The muscle is allowed to shorten and move weight so external work is done.

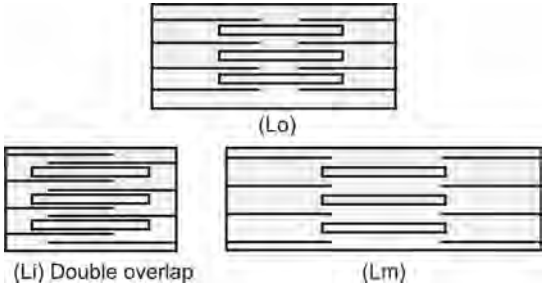


Fig. 21.5: Molecular basis of length—tension relationship (Lo) Optimal length, (Li) much less than optimal length, (Lm) Length maximum

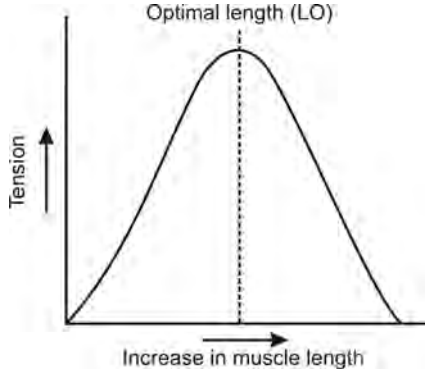


Fig. 21.6: Length tension relationship in skeletal muscle

To Record (Fig. 21.7)

Usually nerve—muscle preparation (gastrocnemius muscle of frog with its nerve—sciatic nerve) is used. The knee joint along with the muscle—nerve is dissected out of the pithed frog's body.

The preparation is fixed by means of a pin inserted through the knee joint on the myograph board. Tendon is fixed to the isotonic lever.

When the isotonic lever is supported by screw, it is after loaded condition or arrangement is known as after loading, where weights do not act on the muscle directly but will act, when the muscle starts contracting.

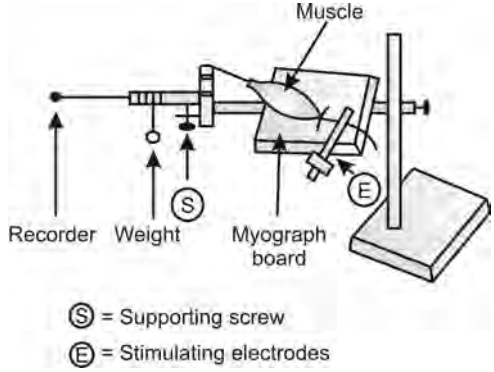


Fig. 21.7: Recording arrangement for isotonic contraction

When the lever is freely hanging without any support from the supporting screw, the arrangement is free loading.

ENERGY FOR MUSCLE CONTRACTION

Immediate source of energy for muscle contraction is ATP, which breaks down by activated myosin ATPase into ADP and energy is liberated. This energy is utilized for cross-bridge movement.

ATP after breakdown is quickly reformed by two processes:

1. By creatine phosphate -
   Creatine phosphate + ADP

$$\xrightarrow[Mg^{++}]{\text{Creatine kinase}} \text{ATP + Creatine}$$

For replenishment of creatine phosphate and ATP:

2. By Glycolysis—breakdown of muscle glycogen or blood glucose
   i. Breakdown of glucose or glycogen up to pyruvic acid does not require oxygen, therefore it is called as anaerobic phase of glycolysis. Only 2 molecules of ATP are produced during this phase.
   ii. If oxygen is not available pyruvic acid is converted to lactic acid and when oxygen is made available, lactic acid is again converted to pyruvic acid.
   iii. In presence of oxygen pyruvic acid enters Kreb's cycle (Tricarboxylic acid cycle or TCA cycle) and is completely oxidized to CO_2 and H_2O. This phase of glycolysis is known as Aerobic phase and it produces 34 more molecules of ATP.

Thus, a total of 36 molecules of ATP are obtained from the oxidative breakdown of each molecule of glucose.

Thus, ultimate energy comes from oxidation process, which require molecular oxygen. The oxygen in muscle is contained in myoglobin, which supplies oxygen.

Body has yet another source of energy—*fat*. The fat stores in muscle and elsewhere can be broken down to yield free fatty acids (FFAs). Free fatty acids are concentrated source of energy.

In starvation *protein* of the body are broken down to amino acids, which provide energy.

Thus, there is a chain of fuels to replenish ATP, which is broken down for muscle contraction. Body shows a slight preference for using carbohydrates as compared to fats. As the duration of exercise increases the proportion of energy provided by fat increases. Carbohydrates with high rate of energy production serve as immediate source, whereas fats with low rate of energy production are consumed later.

OXYGEN DEBT

Oxygen requirement of the exercising muscles increases as soon as the exercise begins (Fig. 21.8). To meet this requirement the cardiac output, pulmonary ventilation and muscle blood flow increases. Even then the oxygen requirement cannot be met with especially in the initial phase of exercise. So there is *oxygen deficit*. Initial processes which yield energy are anaerobic. Therefore, body can perform sudden spurt of activity which require more oxygen than lungs could take in or blood could

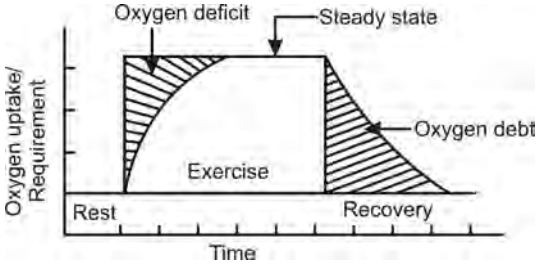


Fig. 21.8: Oxygen debt (during moderate exercise)

carry during the time of exercise. Due to lack of oxygen pyruvic acid is converted to lactic acid, which accumulates in this phase of exercise. So a sort of 'oxygen debt' is incurred which the body has to pay after the end of exercise. After the exercise the body consumes more oxygen, in excess of resting requirement, this is called as *oxygen debt.* The extra volume of oxygen utilized after the end of exercise is for:

1. Replenishing the oxygen stores in muscle, e.g. oxygen bound to myoglobin.
2. To oxidize lactic acid, most of which is first converted to pyruvic acid which is then oxidized to CO_2 and H_2O.
3. Rise of body temperature during exercise stimulates MR or metabolic rate – so oxygen consumption is increased.
4. Adrenaline and noradrenaline released during exercise also stimulate the metabolic rate directly and therefore oxygen consumption is increased.
5. Cardiac output and pulmonary ventilation do not come down to resting level abruptly at the end of exercise. Heart muscle and respiratory muscles continue to consume more oxygen after the exercise.

   All these factors contribute to oxygen debt.

Note:

1. During moderate exercise a steady state is reached, when oxygen uptake is equal to oxygen requirement.
2. In severe exercise in steady state oxygen requirement is more than person's capacity for oxygen uptake.

HEAT PRODUCTION IN MUSCLE

The amount of heat produced in muscle is extremely small during any phase, but is of great importance theoretically and historically. Heat production was first measured by AV Hill in 1939.

1. *Resting heat* in resting condition some amount of heat is produced due to metabolic activity in the muscle, especially for operating sodium pump to maintain resting membrane potential.
2. *Activation heat* is the heat produced in stimulated muscle before shortening. Some authors name this as initial heat. According to some other authors initial heat is sum of activation heat and shortening heat.

   Most likely activation heat is byproduct of energy spent in: (a) release of calcium from terminal cisternae, (b) binding of calcium with troponin and, (c) uptake of calcium by sarcoplasmic reticulum.
3. *Shortening heat* is heat associated with shortening, which depends on degree and velocity of shortening. Since there is no shortening in isometric contraction, there is no shortening heat associated with it. Shortening heat may be byproduct of energy spent on the cross-bridge movement.
4. *Maintenance heat* is heat produced due to activation heat and actin-myosin interaction during tetanus.
5. *Relaxation heat* is heat associated with relaxation. It is due to energy expended associated with uptake of calcium by terminal cisternae and restoring length and tension of the muscle to the level previous to contraction.
6. *Recovery heat* or *delayed heat* is heat produced after shortening and relaxation is over and is above the resting heat. It is due to metabolic activity in muscle for restoring the muscle to precontraction level:
   1. Replenishing the energy stores.
   2. Correction of slight imbalance in sodium and potassium concentration.

Although these processes go on side by side with contraction, they also continue for sometime afterwards, especially in prolonged contraction.

CHAPTER

22

Properties of Skeletal Muscle

The skeletal muscle shows following properties:

1. Excitability and contractility
2. Conductivity
3. Extensibility and elasticity
4. Tonicity
5. Refractory period.

EXCITABILITY AND CONTRACTILITY

Muscle belongs to a group of excitable tissue. Therefore, when stimulated with adequate stimulus, the muscles responds by contracting.

Stimulus

Stimulus–anything which brings about a change in excitable or irritable tissue. The agent which can bring about this can be:

1. Mechanical
2. Chemical
3. Thermal
4. Electrical.

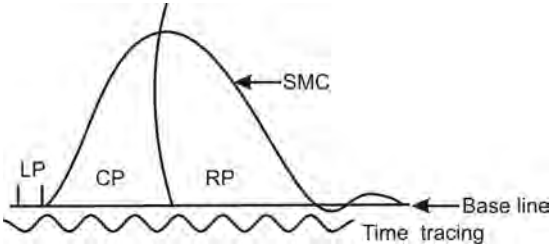
In laboratories, we use electrical stimulus. By using muscle nerve preparation and with electrical stimulation, all properties can be demonstrated.

When excited, muscle contracts, this is followed by relaxation. The whole process is known as *twitch.*

Record of twitch on a rotating smoked drum will produce a curve called as simple muscle curve (SMC) (Fig. 22.1). A strong stimulus produces a stronger contraction as more number of motor units are stimulated.

Simple muscle curve obtained from frogs gastrocneminus muscle has a total duration of 0.1 sec. It consists of three parts

1. *LP or latent period:* Duration 0.01 sec or 10 milliseconds. It is interval between application of stimulus and beginning of contraction.
   Cause of LP—Time taken for propagation of impulse from point of stimulation to sarcolemma of muscle fibers.
2. *CP or contraction period:* The upward stroke of the curve – from beginning of



LP—Latent period (0.01); CP—Contraction period (0.04);
RP—Relaxation period (0.05);
SMC Simple muscle curve (0.1)
[number in bracket indicate duration in sec]

Fig. 22.1: Simple muscle curve

contraction to maximum contraction. Its duration is 0.04 sec or 40 milliseconds.

3. *RP or relaxation period:* Duration 0.05 sec or 50 milliseconds. This phase is represented in the curve from the summit up to the baseline.

Different factors affect excitability and contractility and therefore alter in various ways the nature of simple muscle curve.

Strength and Duration of Stimulus

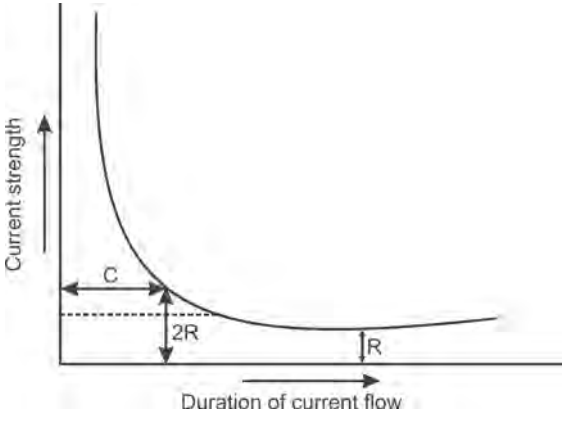
Not any stimulus of any strength can bring about a response (Fig. 22.2).

For response to take place two factors are necessary: (a) minimum strength and (b) an adequate duration of stimulus (These two factors are inversely proportional).

In case of electrical stimulus the weakest strength of galvanic current which when allowed to flow for a variable period will excite the tissue – is called *as Rheobase* (by Lapicque).

The minimum time during which a rheobase current must flow to give a response is known as *utilization time.*

The *shortest duration* of current, which is necessary to excite the tissue when a current of *twice rheobase* is passed – is known as *chronaxie* (by Lapicque) or *excitation time*.



C – Chronaxie, R – Rheobase,
2R – Current of twice Rheobase strength

Fig. 22.2: Strength duration curve

The excitability of different tissues varies widely. Some tissues are highly excitable whereas others are dull.

Chronaxie which includes both standards-strength and duration of current is a definite measure of excitability. The less excitable tissue has a longer chronaxie and more excitable tissue has shorter chronaxie.

1. In practice the weakest strength of stimulus which can bring about a response is known as threshold or minimal stimulus or liminal stimulus.
2. A strength of stimulus which can bring about a maximum response is known as maximal stimulus.
3. Any stimulus above this strength cannot increase the response further and this strength is called supramaximal.
4. Any stimulus value above threshold and below maximum value is submaximal stimulus.
5. Any stimulus below the threshold value is called subthreshold or subliminal stimulus and this fails to evoke any response.

Significance of Chronaxie

Measurement of chronaxie determines the excitability of various tissues, e.g. muscles, nerves, etc.

1. Chronaxies differ in:
   i. Different species.
   ii. In different tissues of same species.
   iii. In same group of tissues in the same body.
2. Chronaxies of various tissues:
   i. Muscles have shorter chronaxies than nerves.
   ii. Adults have shorter chronaxies than infants and children.
   iii. Chronaxies of different muscles differ widely.

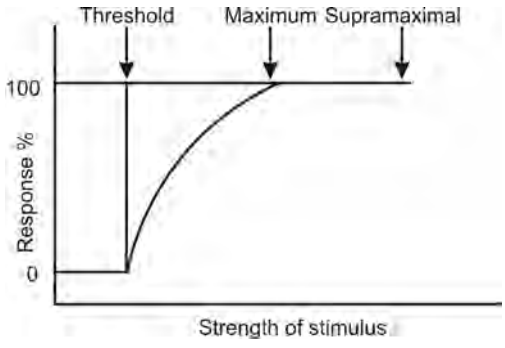


Fig. 22.3: Strength response relationship

a. Voluntary muscles have shortest chronaxies.
b. Cardiac muscle has longest chronaxie.
c. Plain muscles have chronaxies in between.

iv. Pale fibers have shorter chronaxies than red fibers.
v. Conducting tissues of heart have shorter chronaxies than cardiac muscle fibers proper.
vi Myelinated nerves have shorter chronaxies than unmyelinated. Thick nerves have shorter chronaxies than thin. Somatic nerves are thick hence have shorter chronaxies. Autonomic nerves are thin hence have longer chronaxies.

a. *Temperature* – cold increases and heat diminishes it within physiological limits.
b. Tissue injury or degeneration diminishes it.

All or None Law

Individual muscle fibers either contract maximally or do not contract at all. This is all or non law. This is applicable to all excitable tissues. The graded response, which is seen by increasing the strength of stimulus is due to more number of fibers getting stimulated, while each fiber is contracting maximally (Fig. 22.3).

Initial Length of Muscle Fibers

Force of contraction is proportional to initial length of muscle fibers within physiological limits. This is known as *Starling s law.* It has a practical application. Remember position of runner before starting the race. He takes a peculiar position so that his leg muscles are stretched and he can begin to run with a fast speed.

Experiment of *effect of free loaded and after loaded condition proves this fact (Fig. 22.4):*

1. When the weights are hung on the isometric lever and the supporting screw does not touch the lever, it is free loaded condition. In this condition, the muscle gives better performance. In experimental condition, this is shown by - decreased LP and – increased height of contraction.
2. The reason why the *performance is better* in *free loaded* condition is that: (a) in free loaded condition the muscle is in stretched condition and therefore the initial length is longer, (b) Secondly in free loaded condition the series elastic elements are already stretched when the contraction begins. So the contraction is utilized immediately and entirely for moving the load.

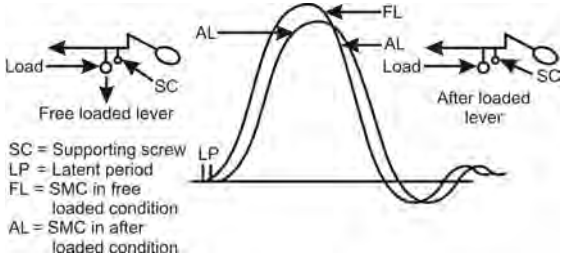


Fig. 22.4: Effect of free loaded and after loaded condition

3. In after loaded condition the initial contraction is utilized for stretching the series elastic elements of the muscle and after that the contraction force is utilized for moving the load.

Effect of Two Successive Stimulation

Effect of two successive stimulation – will depend on the time, when the second stimulus is applied after the application of the first (Fig. 22.5):

1. If second stimulus is applied after sufficient interval so that the 2nd stimulus falls just after the first SMC touches the base line, both 1st and 2nd stimulations will cause contractions and will record 2 SMC. The second curve will be higher than the first. This is due beneficial effect of first contraction.

   Causes of beneficial effect:

   a. Increase in temperature.
   b. Accumulation of metabolites.
   c. Decrease in viscosity of muscle.
2. If the second stimulus is applied in the relaxation period of the first curve summation takes place during relaxation. A wave like curve is obtained in which, the second wave is higher than first. This is known as wave summation. Again height of second curve is more than first due to beneficial effect (Fig. 22.6).
3. If the second stimulus is applied within the contraction period of the first-two curves fuse into one whose height is greater than single stimulation of the same strength. This is known as *summation of contractions (Fig. 22.7).*
4. If the second stimulation applied within the latent period of the first, but after the refractory period, i.e. after 5 milliseconds in case of frogs muscle and 2 milliseconds in case of mammalian muscle, then the effects of two stimulations are added together giving a single SMC of higher height. This is known as summation of stimuli (Fig. 22.8).
5. If 2nd stimulus is given before 5 milliseconds in frog muscle and before 2 milliseconds in case of mammalian muscle, it is ineffective. This period- during which the second stimulus of whatever strength is ineffective, is known as *absolute refractory period (Fig. 22.9).*

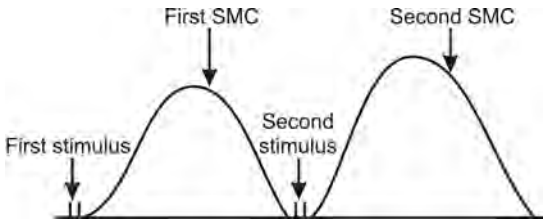


Fig. 22.5: Effect of two successive stimulation (i)

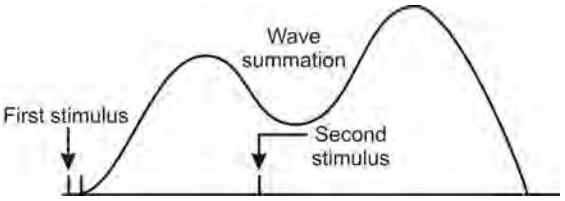


Fig. 22.6: Effect of two successive stimulation (ii)

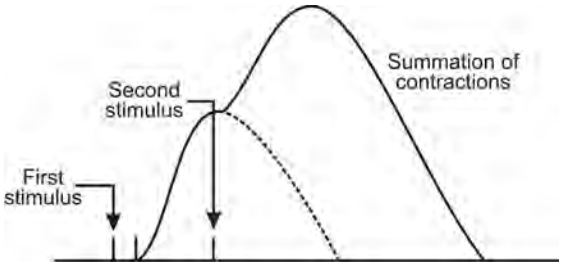


Fig. 22.7: Effect of two successive stimulation (iii)

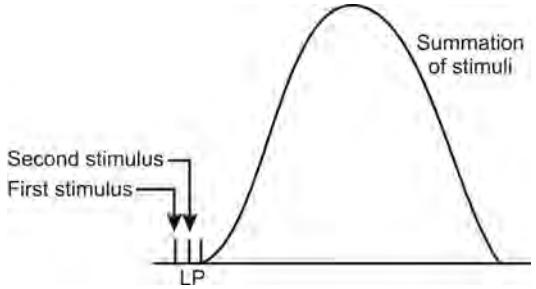


Fig. 22.8: Effect of two successive stimulation (iv)

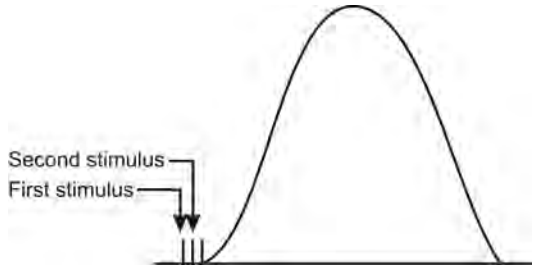


Fig. 22.9: Effect of two successive stimulation (v)

Effect of Repetition of Stimuli (Fig. 22.10)

Depending on frequency following phenomenon are observed:

1. *Staircase:* If a fresh muscle nerve preparation is stimulated with certain strength of stimulus then SMC of certain amplitude is recorded. If 2nd stimulus followed by 3rd, 4th, 5th are applied at short interval of about 1 sec, for 5-6 stimulations gradually increased height of SMC is observed. This stair like rise is known as *staircase* or *treppe phenomenon (Fig. 22.10).* This is due to beneficial effect explained above in effect of two successive stimuli.
2. *Clonus:* When repeated stimuli are applied the type of response will vary with frequency. If the frequency is such that successive stimuli fall within the period of relaxation of the previous curve, the record will show series of oscillations (when recorded on a slow moving drum). This is known as *clonus.* It can be low, mid or high clonus depending on whether the successive stimuli fall late in relaxation period of previous SMC or in middle or early in relaxation period of previous contraction (Fig. 22.11).
3. *Tetanus:* If frequency of stimulation is such that the successive stimuli fall within contraction period of first contraction, the record traces a clear and steady line which rises at first abruptly and then gradually, till maximum is reached (Fig. 22.12). This is called Tetanus.

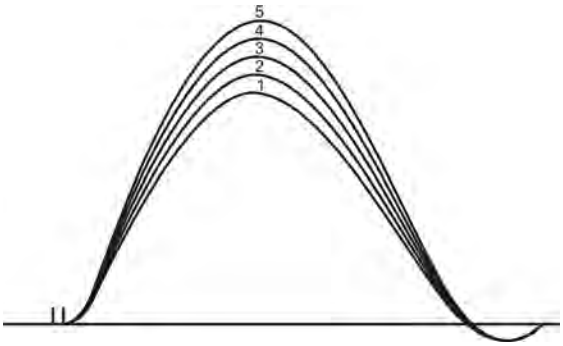


Fig. 22.10: Effect of repitition of stimuli—Staircase or treppe

Here fusion is complete, instead of vibrating the muscle exerts a steady pull. Due to

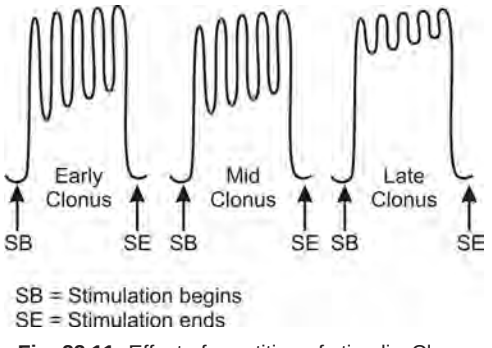


Fig. 22.11: Effect of repetition of stimuli—Clonus

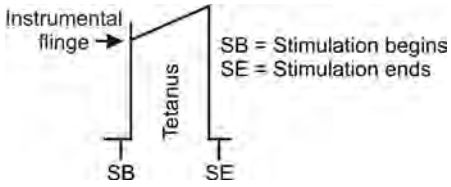


Fig. 22.12: Effect of repetition of stimuli—Tetanus

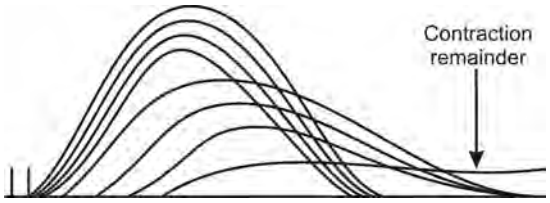


Fig. 22.13: Effect of repetition of stimuli—Fatigue

summation effect the height of titanic contraction is usually higher than single twitch. Frequency of stimulation to produce tetanus varies with muscle.

Fatigue: When repeatedly stimulated, muscle looses its excitability, becomes gradually less excitable and ultimately ceases to respond (Fig. 22.13). This phenomenon is called muscular *fatigue* – which is inability to do further work.

To record: Repeated stimuli are applied through nerve in frogs muscle-nerve preparation over a prolonged period.

Initially for first few contractions staircase phenomenon or treppe due to beneficial effect is observed. Following this subsequent contractions gradually become smaller and their contraction period as well as relaxation period are progressively increased. Ultimately a time is reached when the tracing fails to reach the baseline during relaxation. This is known as *contraction remainder.*

Causes of Fatigue

1. Exhaustion of source of energy in muscle.
2. Accumulation of end products of metabolism in muscle like lactic acid.
3. Decrease in local synthesis of acetylcholine (neuromuscular transmitter) during prolonged exercise.
4. Rise in intramuscular tension hampers passage of blood through muscle.

Fatigue is Reversible

Muscle recovers after rest and supply of oxygen (which normally takes place through blood circulation).

Seat of fatigue - lies in muscle—when directly stimulated:

- Neuromuscular junction—when stimulated through motor nerve.
- In vigorous muscular exercise – synapses.

In human subject fatigue is studied by instrument called ergograph.

Effect of Temperature

Warmth such as application of warm saline up to 40°C – increases the height of contraction - decreases LP, CP and RP (Fig. 22.14). Therefore, total duration of twitch is short.

On the other hand cold such as application of cold saline (4°C) decreases the height of contraction, increase LP, CP and RP. The duration of contractile event is increased.

In other words, heat increase, and cold decreases all phases of contractile event.

Explanation for such behavior is that: (i) heat increases metabolic activity in muscle, and (ii) viscosity of muscle cytoplasm is reduced.

Heat above 40°C causes *heat rigor* = irreversible muscle contraction (contracture) due to coagulation of muscle proteins.

Application of cold: (i) slows down metabolic activity in the muscle and (ii) increases the viscosity of muscle cytoplasm.

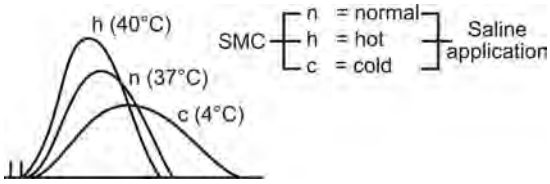


Fig. 22.14: Effect of temperature

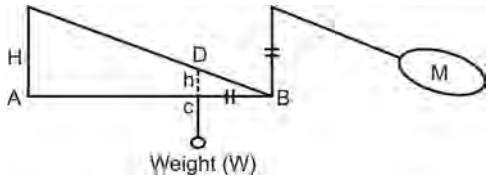


Fig. 22.15: Work done

Effect of Increasing Load

With increase in load there is increased LP, reduced height of contraction and CP and RP are increased.

If work done by the muscle is calculated it is found that it increases with increasing load up to certain limit beyond which it decreases.

Optimum load is the load at which maximum work is done (Fig. 22.15).

Work done = height

through which weight is lifted × weight

h x w (where h is real height through which weight is lifted).

In above arrangement of isotonic lever attached to a muscle.

$$h = \frac{BC \times H}{AB}$$

h x w = work done is given in gm, cm. Multiply this figure by 981 to get work done in ergs.

CONDUCTIVITY

Following adequate stimulus the impulse is carried to the fibers adjacent to neuromuscular junction, which show development of tension followed by shortening. This wave of excitation followed by contraction travels both ways leading to contraction of the whole muscle.

This property of carrying excitation process to the whole muscle is known as conduction.

TONICITY

The muscles in living body are always in slight tension. This is known as tone of the muscle. This is a reflex phenomenon. It helps to maintain posture.

1. In isolated muscle, it is not possible to show tone. *In vivo* if tendon is cut from the bone the muscle shortens.
2. When a loaded muscle is stimulated the first mechanical response during LP is slight lengthening – known as *latency relaxation.* It is partly due to release of resting tension. More marked at longer length of the muscle.

REFRACTORY PERIOD

Skeletal muscle is absolutely refractory during first half of latent period during which muscle will not respond to any other stimulation, however strong it may be. This period is known as *absolute refractory period* (ARP) or effective refractory period (ERP).

In frogs muscle, it is 5 milliseconds and in mammalian muscle, it is 2 milliseconds.

Then the excitability of muscle gradually returns to normal. So that stimulus of greater than threshold intensity will evoke a response, although threshold stimulus is ineffective. This period is known as *relative refractory period* (RRP).

Duration of ERP and RRP varies from muscle to muscle. In fast muscles ERP and RRP are much shorter. Therefore, they respond to higher frequencies of stimulation, e.g. insect flight muscles respond so rapidly that it literally flutters.

CHAPTER

23

Physiology of Smooth Muscle

Smooth muscle is so called because it lacks striations. It is involuntary muscle as it is not under the control of will. It forms contractile element of various organs and tissue (Figs 23.1 and 23.2). Therefore, also called as visceral muscle.

It is distributed in:

1. Walls of digestive tract.
2. Walls of ducts of glands associated with digestion.
3. In walls of respiratory passages.
4. In walls of urinary bladder, ureter, urethra and genital tract.
5. In walls of arteries, veins and large lymphatic ducts.
6. Areola, nipple and ducts of mammary glands.
7. Muscles of scrotum.
8. Prostate gland.
9. Erectores pilorum muscle of skin.

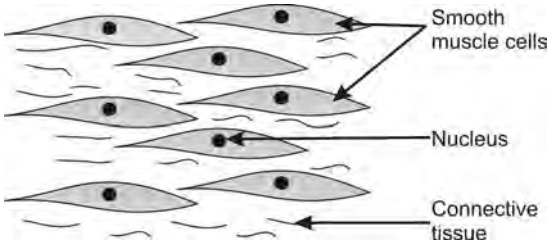


Fig. 23.1: Smooth muscle

FUNCTIONAL ANATOMY

1. It consist of smooth muscle fibers which are fusiform or spindle shaped cells. 2-5 μm in diameter, and 20-500 μm in length.
2. Adjacent muscle fibers are connected to each other by two types of connections:
   i. *Gap junctions*: Which allow ionic movement between cells.
   ii. *Desmosomes:* Which provide stability and cohesiveness to the tissues.
3. Smooth muscle cells are packed with thin actin and thick myosin filaments. Their arrangement is similar to skeletal muscle but not well organized as in skeletal muscle. Number of actin filaments is at least

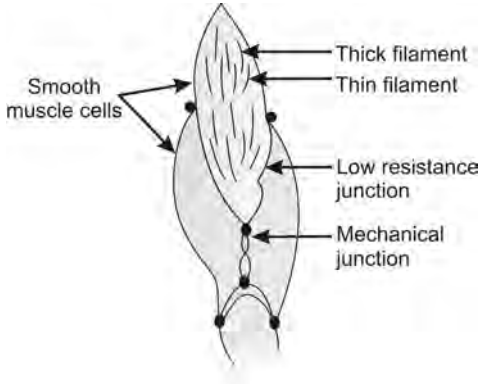


Fig. 23.2: Diagrammatic representation of myofilaments in smooth muscle and their cytoskeleton

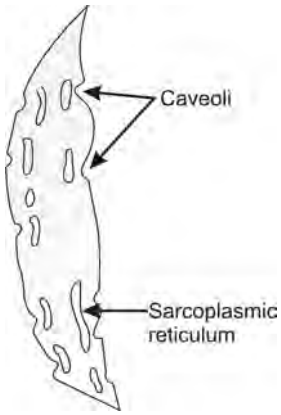


Fig. 23.3: Sarcoplasmic reticulum and caveoli in smooth muscle

10 times that of myosin filament. Muscle contraction takes place by cross bridge movement and sliding filament mechanism. (The thin filaments lack troponin in smooth muscles).

4. Sarcoplasmic reticulum in smooth muscle is poorly developed. Some muscle cells have sac like invaginations called caveoli, corresponding to T tubules (Fig. 23.3). Function of sarcoplasmic reticulum is to concentrate calcium ions as in skeletal muscle.
5. Cytoskeleton is provided by dense bodies of protein alpha actinin, which correspond to Z disks of skeletal muscle. Some of the dense bodies are attached to cell membrane and some are intracellular.
6. Neuromuscular junctions are not well developed in smooth muscle as in skeletal muscle. Efferent nerve fibers (sympathetic and parasympathetic) have multiple varicosities (beaded appearance) along their length, where Schwann cells are interrupted and vesicles of neurotransmitter are present. When nerve fiber is stimulated the neurotransmitter is released at a distance. It diffuses through interstitial fluid and reacts with sarcolemmal receptors to stimulate or inhibit muscle contraction.
7. Smooth muscle activity is regulated by:
   i. Sympathetic and parasympathetic nerves which release norepinephrine and acetylcholine respectively.
   ii. Intrinsic nerve plexus.
   iii. Hormones.
   iv. Other physiochemical factors, e.g.
      a. Local factors like pCO_2, pH.
      b. Concentration of adenosine, prostaglandin, histamine and serotonin.
      Physical factors, e.g. stretch.
8. Smooth muscles are of two types:
   i. Single unit smooth muscle or visceral smooth muscle.
   ii. Multiunit smooth muscle.

Electrophysiology (or Electrical properties)—vary from site-to-site, but the basic principles are same as in other excitable tissue.

1. Resting membrane potential (RMP)—smooth muscle cells are characterized by unstable membrane potential and there is no true RMP. Smooth muscle membrane is more permeable to ions even at rest than the skeletal muscle membrane. As a result, RMP is about –60 mv and it is unstable.
2. Initiation of spontaneous activity
   i. RMP can reach threshold for excitation with a weak stimulus or even spontaneously.
   ii. Pacemaker potentials are generated in multiple foci that shift site.
3. RMP may show rhythmical variation, which may result in rhythmic variation in tone of smooth muscle or variation may reach the threshold for excitation.
   Cause: It may be due to rhythmic changes in membrane permeability to sodium and calcium ions.

Difference between Single Unit and Multiunit Smooth

Main differentiating features are:

Single unit or visceral smooth muscle	*Multiunit smooth muscle*
1. Entire muscle mass is single unit. Gap junctions between cells are many. So the impulse can spread rapidly from one cell to other. It acts like functional syncytium.	1. Each individual muscle fiber has independent nerve supply. Activation of a muscle fiber does not lead to activation of neighboring fibers. Therefore, nonsyncytial.
2. Present in gut, uterus, ureters.	2. Present in ciliary muscles of eye, pilomotor muscles of skin, blood vessels, vas deference.
3. Slow spontaneous activity in certain areas called pace makers is present.	3. Automaticity is much less.
4. Rhythmic contraction and relaxation of these muscles is independent of their innervations. Nervous influence modulates their activity.	4. These contract in response to stimulus through their nerves by releasing chemical transmitters like acetylcholine, norepinephrine to which, they are very sensitive.
5. If these muscles are stretched, there is contraction.	5. These muscles do not respond to stretch.

4. Action potentials in smooth muscle may be brief—called as spikes, as in skeletal muscle, or prolonged with a plateau as in cardiac muscle.

   Duration of spikes of smooth muscle is 10-50 ms, which is considerably longer than that of skeletal muscle.

   Ionic basis: Depolarization phase is predominantly due to calcium influx and only to a small extent due to sodium influx. Repolarization is due to decrease in influx of calcium and sodium and efflux of potassium ions. Calcium influx also triggers contraction process.

MECHANICAL PROPERTIES

1. It shows continuous irregular contractions that are independent of its nerve supply. This maintained partial state of contraction is called tonus or tone. It is myogenic in origin, i.e. inherent property of the smooth muscle.
2. **Mechanical event:** There is diversity of relationship between membrane potential and force of contraction of smooth muscle:
   i. Each action potential is followed by mechanical response (Fig. 23.4).
   ii. Membrane potential shows rhythmic

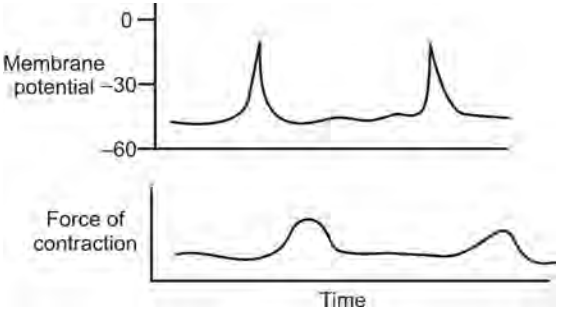


Fig. 23.4: Each action potential is followed by mechanical response

change and there is burst of action potentials. Each burst of action potential is followed by mechanical response (Fig. 23.5).

iii. Membrane potential shows slow fluctuations, which are associated with synchronous fluctuation in tone (Fig. 23.6).

3. *Excitation contraction* coupling is very slow process because muscle starts to contract approx 200 msec after the start of the spike. (i.e. 150 msec. after the spike is over).
4. Unique feature of visceral smooth muscle is—*it contracts when stretched* in absence of any innervations. Stretch causes:
   a. Decrease in membrane potential
   b. Increase in frequency of spike and
   c. Increase in tone.

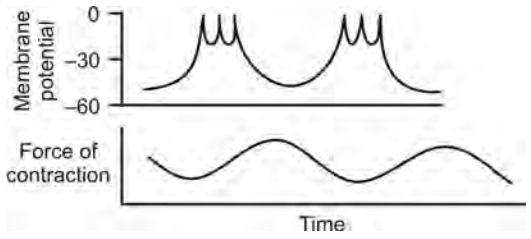


Fig. 23.5: Each burst of action potential is followed by mechanical response

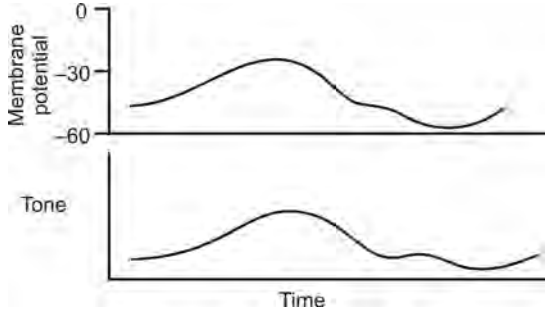


Fig. 23.6: Fluctuations in membrane potentials are associated with synchronous fluctuation in tone

5. *Length tension relationship*—(relationship between initial length of muscle fiber and tension is called property of *plasticity*).
   Another unique character of smooth muscle is the variability of the tension it exerts at any given length of muscle fiber.

If a piece of visceral smooth muscle is stretched it first exerts increased tension. However, if the muscle is held at greater length after stretching, the tension gradually decreases. Sometimes, it falls to level below that exerted before the muscle was stretched, e.g. urinary bladder tension.

NERVE SUPPLY TO SMOOTH MUSCLE

Smooth muscles have dual nerve supply from two division of autonomic nervous system (Fig. 23.7):

1. Sympathetic.
2. Parasympathetic nerve fibers.
   i. In some organs, sympathetic stimulation increases and parasympathetic stimulation decreases smooth muscle activity.
   ii. In other organs, reverse is seen.
   iii. In smooth muscles, nerve fibers run along the length of the muscle fibers and groove it. During their course they show varicosities or beaded appearance, which contain neurotransmitter. Release of chemical transmitter acts on many muscle fibers. But for stimulation of whole organ repeated stimuli are required.

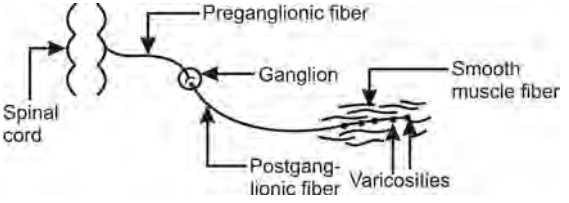


Fig. 23.7: Nerve supply to smooth muscle

EXCITATORY JUNCTIONAL POTENTIAL (EJP)

In smooth muscle in which sympathetic stimulation is excitatory, stimulation of the adrenergic nerve produces discrete partial depolarization called EJPs. These potentials summate with repeated stimuli. Similar EJPs are seen in tissues excited by cholinergic discharges.

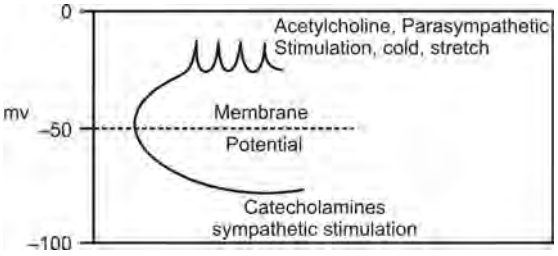


Fig. 23.8: Effect of various agents on membrane potential of intestinal smooth muscle

DENERVATION HYPERSENSITIVITY

Smooth muscle does not atrophy when denervated, but it becomes hypersensitive to chemical mediator, that normally activates it. This is known as denervation hypersensitivity. It is limited to smooth muscle fibers innervated by destroyed neuron.

CAUSE

There is an increase in the number of active receptors for the transmitter.

Effect of various agents on the membrane potential of intestinal smooth muscle as shown in Figure 23.8.

Effect of Catecholamine

Epinephrine and norepinephrine act via both α and β adrenegic receptor.

1. Action on α receptor increases Ca^{2+} efflux.
2. Action on β receptor stimulates cAMP —causing increase in intracellular binding of Ca^{2+}.

Both the actions: (a) increase membrane potential (hyperpolarization), and (b) decrease in spike frequency which leads to: (i) decrease in muscle tension (tone). Baseline shifts downward, and (ii) decrease in rhythmic muscle contraction.

Therefore, there is more relaxation. Same effect is produced by sympathetic stimulation which cause release of norepinephrine at their nerve endings.

Effect of Acetylcholine

It increases Na^+ and Ca^{2+} influx, producing decrease in membrane potential (= depolarization) and increase spike frequency. So the muscle tension increases and baseline shifts upwards. There is increase in rhythmic muscle contraction. Similar effect is seen by stimulation of parasympathetic nerves, which causes release of acetylcholine at their nerve endings.

Cold and Stretch

Stretch and cold—also produce effect similar to effect of acetylcholine or parasympathetic stimulation.

CHAPTER 24

Physiological Anatomy and Innervations of Digestive System

Human beings get their nutrition from complex organic substances known as food, which undergoes chemical changes within the body to meet the body's needs. So a complicated system was evolved to receive the food, where it is suitably broken down for absorption into body fluids. This complex system, concerned with: (i) receiving, (ii) breaking down, and (iii) absorption of food material is known as digestive system or alimentary canal or gastrointestinal tract (GIT). This system also includes the associated glands: (i) pancreas, and (ii) liver.

The breaking down process of food material (i.e. chemical changes undergone by the food stuff in digestive tract) is known as digestion, which is brought about by digestive juices secreted into alimentary tract.

The final products of digestion such as monosaccharides, amino acids across the membrane of the intestine and enter the circulation. This process is known as absorption.

As the process of digestion and absorption is going on, the food stuff progresses along the digestive tract aided by its movements and finally there is elimination of unabsorbed remains, from the anal canal defecation.

It should be remembered that the alimentary canal, though located within the body is physiologically outside the body because its wall separates it, from the body fluids.

It is unique in the sense that it communicates with the exterior with two openings (i) mouth, and (ii) anus and has access to body fluids by its intimate contact with (i) blood, and (ii) lymphatics.

The basic function of gastrointestinal system is to transfer food and water from external environment to internal environment.

GENERAL PLAN AND ACTIVITIES OF ALIMENTARY CANAL

Alimentary canal is long and muscular tube lined on inner side by mucous membrane and outside by serous membrane, in most of its course.

Blood vessels, nerve and lymphatic actively supply the tube.

The layers from outside-inwards are (Fig. 24.1):

1. Outer—serous coat

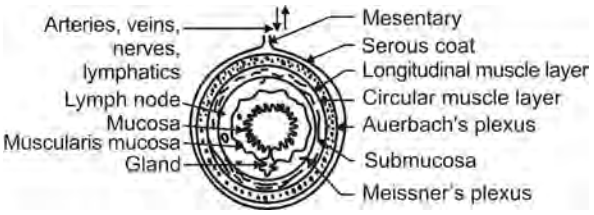


Fig. 24.1: Cross-section of GIT showing different layers of its wall

2. Muscular layer:
   i. Outer layer of longitudinal muscle.
   ii. Inner layer of circular muscle (This layer is thicker at sphincters).

   Both layers of muscle help in mixing and forward propulsion of contents of the gut.
3. Submucous layer in which is a small circular muscle layer known as muscularis mucosa.

MUCOUS COAT

It is thrown into folds and is lined by cells specialized to secrete digestive juices.

Note:

1. In submucous layer is connective tissue, blood vessel plexus and lymphatics.
2. Intrinsic nerve plexuses are:
   i. Myenteric plexus (Auerbach's plexus) lies between longitudinal and circular smooth muscle layers.
   ii. Meissner's plexus (submucous plexus) lies between submucous layer and inner circular smooth muscle layer.

Alimentary canal stretches from mouth to anal canal and is divided into:

1. Mouth or buccal cavity
2. Pharynx
3. Esophagus
4. Stomach
5. Small intestine — Duodenum, Jejunum, Ileum
6. Large intestine
   i. Cecum
   ii. Ascending colon
   iii. Transverse colon
   iv. Descending colon
   v. Sigmoid colon (pelvic colon)
   vi. Rectum
   vii. Anal canal

Mucous membrane of GIT (1) contain innumerable glands. These are specialized epithelial structures. Their secretions are known as digestive juices, which are rich in enzymes, water and salt (Fig. 24.2).

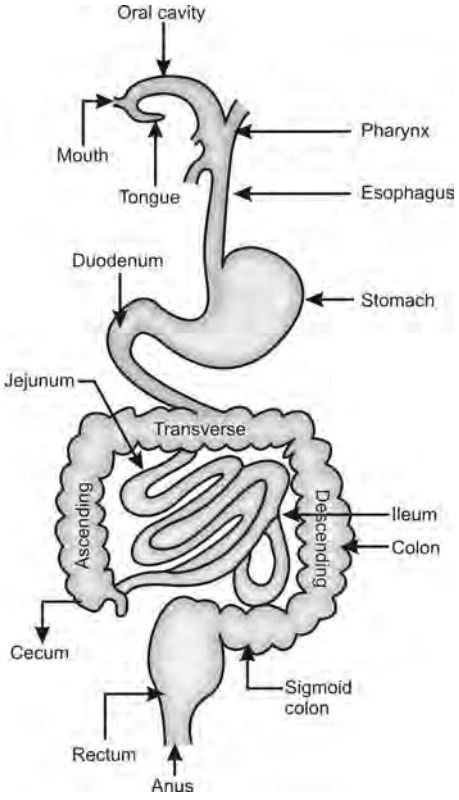


Fig. 24.2: Digestive system

The digestive juices, specially its enzyme content catalyze the breakdown process of consumed food.

2. Mucous membrane of *small intestine* is specially adapted for absorption, so as to provide huge area.
   i. The mucosal surface of small intestine, from the point of entry of bile duct, is thrown into numerous folds, approximately 1 mm in height—they are called as *villi.*
   ii. Villi are covered by a layer of columnar cells, which posses brush border consisting of microvilli (1 µm in length and 0.1 µm width) (Fig. 24.3).

Each villus contains the following in its core (Fig. 24.4).

1. A lymph vessel (lacteal) continuous with lymphatic plexus of submucosa.
2. Smooth muscle fibers continuous with muscularis mucosa.
3. An arteriole and venule with its capillary plexus.
4. A nerve net which has connections with submucosal and myenteric plexuses.
   i. Villus having the brush border is lined on the luminal side by an amorphous layer called the *glycocalyx*, which is rich in neutral and amino sugars and serves as protective function.

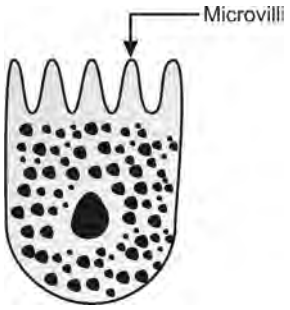


Fig. 24.3: Villus cell with brush border

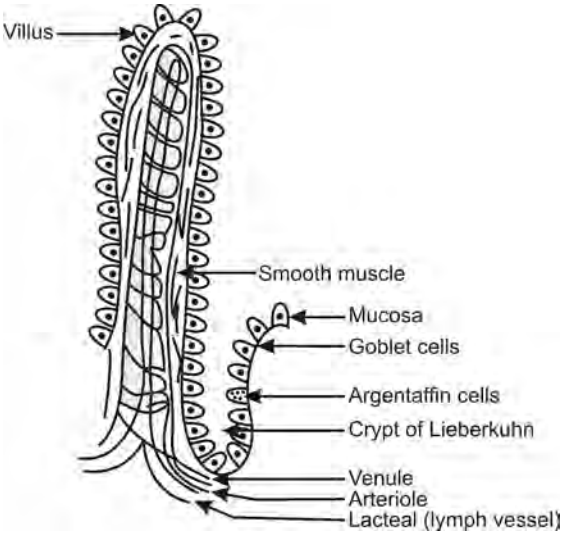


Fig. 24.4: Villus

   ii. In between the villi are the intestinal glands which are called crypts of *Lieberkuhn*. They are simple glands lined by low columnar epithelium, which show active mitosis and replace the cells shed from the tip of the villi rapidly, so that the intestinal lining is replaced every three days.
   iii. *Crypts of Lieberkuhn contain:*
      a. Goblet cells—which secrete mucus.
      b. Argentaffin cell—which secrete -
         – Secretin
         – 5HT (5 hydroxytryptamine) which stimulates intestinal movement
         – Paneth cells which secrete various enzymes.
   iv. *Smooth muscle of villi* - help in contraction of the villi.
3. Mucous membrane of *duodenum* show glands—Brunner's glands. They are tortuous, long and penetrate the muscularis mucosa. At rest, these glands show small basal secretion. Ingestion of fatty food or secretin, produces large volume of thick

alkaline mucous secretion, which probably helps to protect duodenal mucosa from the gastric acid.

Innervations of GIT is divided into:

1. Intrinsic, and
2. Extrinsic—network of nerve fibers that innervate the GIT.

1. *Intrinsic innervations*: There are two intrinsic nerve plexuses:
   i. *Myenteric plexus*—(Auerbach's plexus)—is mainly motor in function, and it increases the:
      a. Tone of the wall of GIT.
      b. Intensity of rhythmic contraction.
      c. The rate of rhythmic contraction.
      d. Velocity of conduction of excitatory waves along the wall of GIT. Thus, it mainly controls the peristaltic activity of the GIT.
   ii. Submucous plexus (Meissner's plexus) is mainly sensory and control secretions of GIT.
2. *Extrinsic innervations:* Two divisions of autonomic nervous system namely:
   i. Parasympathetic, and (ii) sympathetic nerve fibers.
      a. *Parasympathetic nerve fibers*: Liberate acetylcholine at their nerve endings. The parasympathetic supply of GIT comes from two sources:
         – Cranial nerve (X or vagus), and
         – Sacral outflow

         Vagus: Descends from Dorsal nucleus of vagus. Their ganglion cells are situated in Myenteric and Meissner's plexuses and parasympathetic fibers (postganglion) supply:
         - Gastric and intestinal glands.
         - Smooth muscle of GIT up to junction of proximal 2/3rd and distal 1/3rd of transverse colon.

         Sacral outflow: Comes from segments 2, 3 and 4 of sacral nerves (as nervi erigents).

         Their ganglion cells are situated in hypogastric ganglia and post ganglionic parasympathetic fibers supply rest of large intestine.

         Stimulation of parasympathetic nerves to GIT produces:
         - Increase in tone
         - Increased motility
         - Increased secretions from Stomach (mainly enzymes) and of the intestines
         - Relaxation of sphincters.
      b. *Sympathetic nerve fibers*: Release epinephrine at their nerve endings.

Sympathetic fibers that supply GIT comes from:

1. *T6 - L2 segments: Chiefly* these fibers supply abdominal viscera. Their ganglion cells are situated in upper abdominal ganglia, e.g. superior mesenteric and celiac, etc. Postganglionic fibers travel along the blood vessels to reach their destination.

b. *L1 - L2 segments: Chiefly* these fibers supply pelvic viscera. Their ganglion cells are situated in hypogastric ganglia. Postganglionic fibers travel along blood vessels and hypogastric nerves to reach their destination.

Stimulation of sympathetic nerves to GIT produce:

1. Decrease in tone
2. Decrease in motility
3. Contraction of sphincters
4. Inhibition of secretions from stomach and intestine.

MAIN FUNCTIONS OF ALIMENTARY CANAL

1. To receive food material.
2. Digest the food and make it ready for absorption and absorb it.
3. After absorption, excrete the residues.
4. As the canal communicates with outside it contains innumerable bacteria (specially the large intestine). These bacteria synthesize vitamins and also bring about putrefactive changes on food which escapes digestion. In human beings it does not serve any useful purpose but in herbivorous animal, proteins are synthesized by this putrification.

FUNCTIONS OF DIFFERENT SECTIONS OF ALIMENTARY CANAL

1. *Mouth and buccal cavity*: It receives food and with the help of tongue and teeth, grind it into small fragments. Then with saliva it forms a bolus, which is semi-solid globular mass consisting of food and saliva intimately mixed together.
2. *Pharynx*: In conjunction with soft palate help onward passage of bolus into esophagus by a process known as deglutition or swallowing.
3. *Esophagus*: Quickly carries food to stomach.
4. *Stomach:* (a) whose main job is to act as reservoir of food and (b) it slowly sends it into duodenum.
5. *Duodenum and jejunum*: These are mainly concerned with digestive function, with the help of bile and abundant juices rich in enzymes. Only small amount is absorbed here.
6. *Ileum*: Finishes the digestion and completes the absorption. The portion, which escapes digestion and absorption passes into large intestine.
7. *Large intestine*: It absorbs anything, which is useful to body and finally residue is discarded as faeces.

Note:

1. Onward movement of food is facilitated by complex movements of alimentary canal which also help digestion mechanically.
2. All these complex functions of reception, digestion and absorption of food stuff are coordinated by the action of nervous system, so that the process is smoothly accomplished without any clash with each other.

CHAPTER

25

Movements of Digestive System

MASTICATION AND DEGLUTITION

Ingestion of food is determined by hunger and appetite.

Mastication and Chewing

Mastication and chewing is a process to which food is subjected before swallowing. In this process, the teeth and muscles of mastication help.

1. *Teeth:* The anterior teeth have strong cutting action. The posterior teeth have grinding action.
2. Muscles of mastication:
   i. The movements of lower jaw against the upper jaw is brought about by these muscles.
   ii. Chewing can be carried out voluntarily but for the most part it is a reflex act.

The muscles of mastication are:

i. Masseter
ii. Temporalis
iii. Internal and external pterygoid

Supplied by mandibular division of trigeminal (V) nerve

iv. Buccinator—supplied by facial (VII) nerve

Functions of Chewing

1. It makes digestion easier because:
   i. It increases the surface area on which digestive enzymes can act later.
   ii. The cellulose covering of the plant food is broken and the nutrient within is exposed to digestive enzyme action.
2. The food is broken down into fine particles so the excoriation of alimentary canal is prevented (Only the mouth and esophagus are lined by the stratified epithelium and rest by columnar epithelium).
3. It facilitates formation of bolus by reducing food to fine particles and mixing with saliva. Bolus is easily swallowed.
4. It prevents overeating to some extent, as chewing itself satisfies hunger to some extent. Satiation depends on time taken to consume a meal. If food is well chewed naturally less food will be consumed.

Swallowing or Deglutition

Swallowing starts as a voluntary act but it soon becomes involuntary. Swallowing occurs in three stages:

1st stage: Voluntary (Buccal phase or oral phase).

2nd and 3rd stage: Involuntary or are produced reflexly.

Oral Phase (1st Stage)

After mastication food is rolled into a bolus which lies in the curve of the tongue. Mouth is closed. Swallowing commences by voluntary contraction of mylohyoid and styloglossus muscles, which throw the bolus back between the pillars of the fauces on the posterior pharyngeal wall. This part is richly supplied by sensory nerve fibers from glossopharyngeal nerve.

2nd and 3rd Stage

When they are stimulated, afferent impulses are setup, which go to deglutition center in medulla and reflex coordinated movements occurring in involuntary phases of swallowing follow, which result in following events:

1. Soft palate is elevated and thrown against posterior pharyngeal wall to close nasopharynx.
2. Vocal cords are approximated and breathing is momentarily inhibited reflexly (deglutition apnea), no matter what is the phase of respiration.
3. Larynx begins to rise as bolus passes over the back of the tongue. Epiglottis guards the laryngeal opening and aspiration of food in respiratory passages is also prevented by associated reflex apnea.

Pharyngeal Phase

Since pharynx communicates with both esophagus and trachea, the movements occurring in this stage are designed to allow the bolus to enter esophagus, while avoiding air passages.

1. The tongue moves back like a piston towards posterior pharyngeal wall and forces the bolus back against epiglottis.
2. Entrance of larynx is closed by sphincteric action of girdle of muscles surrounding it. The food passes along the lateral edges of epiglottis in two streams in part of pharynx immediately posterior to larynx.
3. At this moment the Cricopharyngeus muscle, which forms the upper esophageal sphincter (UOS) relaxes briefly and bolus enters the upper esophagus.
4. Now the larynx drops to its original position, the vocal cords open and epiglottis quickly resumes its initial position. Rhythmic breathing begins.
5. Then the cricopharyngeous muscle contracts. This is the end of second stage.

Esophageal Phase

The esophagus is normally relaxed but closed, above and below, by sphincters. The lower esophagal sphincter (LOS) cannot be defined anatomically, but there is functional sphincter present in lower esophagus.

After a swallow a single peristaltic wave of contraction moves down the esophagus (can be seen radiologically after Barium swallow).

The wave passes down at a rate of 2-4 cm/sec.

1. It is faster in lower half of esophagus.
2. Liquids in erect posture pass quickly down the esophagus under the influence of gravity, well in advance of peristaltic wave.
3. More solid food forms a bolus, which is actively pushed by peristaltic wave.
4. During swallowing LOS reflexly relaxes and remains so until the peristaltic wave has passed over it. Then, it closes and rest of the esophagus relaxes.

Normally, lower part of esophagus is below diaphragm, and is in abdomen, where abdominal pressure keeps it closed. In pregnancy, it is brought up in thorax, gastric contents regurgitate resulting in heartburn.

LOS—Neural Control

1. Cholinergic—excitatory
2. Vagal fibers—inhibitory
3. Extrinsic excitatory—noradrenergic fiber
   a. Sensitive to hormone gastrine, so that tone is high after a meal
   b. Low sphincter pressure—predisposes to reflux of gastric content into esophagus causing heartburn.

MOVEMENTS OF STOMACH

In fasting condition two types of movements are seen in stomach (Fig. 25.1):

1. *Tonus*: In fasting, the walls are in opposition and fasting stomach show rhythmic variation in tone (rate about 3 per minute).
2. *Hunger contractions:* At intervals a series of strong contractions occur involving the whole stomach lasting for about 30 seconds. Since these contractions are associated with sensation of hunger, they are called hunger contractions.

After Meal

Two different kinds of movements are seen in two halves of the stomach, after the entry of food into it. The pyloric part has different kind of movement than the fundus and body of the stomach.

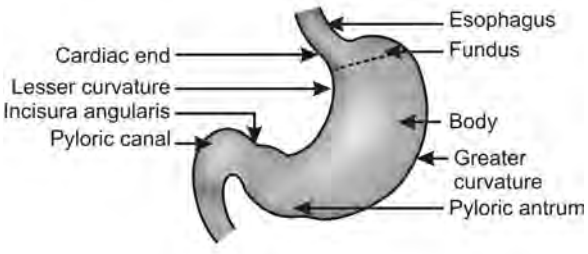


Fig. 25.1: Stomach

Movements of the Fundus and Body

Peristaltic wave follows basic electrical rhythm (BER) of stomach.

1. Basic electrical rhythm is rhythmical cyclical potential change.
2. Starts in longitudinal muscle of greater curvature and passes over body, antrum and pylorus.
3. Rate is about 3/minutes.

Peristalsis: It is contraction preceded by relaxation of a hollow viscera. It takes 1 minute to travel to pylorus. It ends in pyloric canal or the pyloric sphincter will contract if the wave goes ahead.

Frequency and rate of progress depends on nervous and humoral factors.

Rate of progress in body 1 cm/sec.

In antrum 3-4 cm/sec.

Character: It is gentle, surface of stomach is merely moulded, indentations deepen when pylorus is reached.

MOVEMENTS OF THE PYLORUS

The pylorus contracts with the arrival of wave in their region—this is known as systolic contractions, with the result:

1. Viscous contents of stomach are pressed into terminal part of antrum by the peristaltic wave.
2. The antral pressure rises which overcomes the pressure of pylorus and antral contents pass into the duodenum. The passage of chyme into the duodenum is stopped suddenly by the contractions of pylorus.
3. The contraction of the last portion of antrum continues, so that now the contents move in oral direction (because the contents cannot go in duodenum as pylorus is closed).
4. This reflux of chyme help in mixing the food with gastric juice.
5. Finally the terminal part of antrum and pylorus relax till next peristaltic wave comes.

CAUSE OF MOVEMENTS

In man, peristaltic contractions in stomach are coordinated by BER. The spread of electrical activity is myogenic involving direct conduction from cell to cell.

1. Intrinsic nerve supply by Auerbach's and submucous (Meissener's) plexuses are involved in perfect coordination of movements of two parts.
2. Their activity is modified by extrinsic autonomic nerves — vagus and sympathetic.

Sympathetic Stimulation

Inhibit gastric movement and constricts sphincter.

Vagal Stimulation

Stimulates movements and relaxes sphincter:

1. Agents that stimulate contractions of smooth muscles of stomach are gastrin, histamine, acetylcholine, nicotine, barium and K^+.
2. Agents that inhibit contraction of smooth muscle of stomach are enterogastrone, epinephrine, norepinephrine, atropine and Ca^{2+}.

Control of Gastric Emptying

Gastric emptying results from progressive wave of contraction which involve contraction of antrum, followed by contraction of pyloric region, followed by the duodenum. Therefore, all these three function as a unit (gastro-duodenal pump).

1. Force of gastroduodenal pump is decreased and gastric emptying time is greatly increased after bilateral vagotomy, which is often performed to reduce gastric acid secretion in man.
2. Volume and composition of gastric contents:

   Water: Passes out immediately.

   Liquid food: It is emptied more rapidly than solid.

   Larger meals: Require longer emptying time.

   Carbohydrates Leave early. Proteins take intermediate time.

   Fats: Are retained for maximum time as they inhibit gastric movements. They release a hormone called enterogastrone from the mucous membrane of intestine. This inhibits the gastric motility.

   With normal mixed diet stomach completely empties in about 3 ½ hours, with rich fatty diet in about 4 ½ hours.
3. Products of protein digestion and acid in duodenum act by stimulating receptors in the duodenal mucosa and decrease gastric emptying. This is neurally mediated reflex called enterogastric reflex.
4. *Size of duodenal osmoreceptors:* The hyposmolar chyme in duodenum causes distention of *osmoreceptors*, which cause mild inhibition of gastric emptying. While hyperosmolar chyme in duodenum cause shrinkage of osmoreceptors, which cause marked inhibition of gastric emptying. These effects are neural.
5. *Distention*: According to Laplace law, tension (T) on wall of an organ is a direct function of its radius (R). Therefore, tension in stomach wall acts as the adequate stimulus for peristalsis.
6. *Other factors*
   i. Gastric emptying is inhibited by GIP (gastric inhibitory peptide), CCK, secretin. (CCK and secretin collectively called enterogastrone, is released from duodenum).
   ii. Gastric emptying is stimulated by gastrin.
   iii. Emotional factors emotional state of subject has great influence on emptying time and motility.

Fear: inhibits, and food remains in stomach for 12 hours.

Excitement: Reduces emptying time.

MOVEMENTS OF SMALL INTESTINE

Different movements of small intestine are:

1. *Peristalsis:* Propulsive movement
2. Segmentation, and
3. Pendular movements — are mixing movements
4. Antiperistalsis

Rhythmic Segmentation

In this type of movement a portion of intestine is divided into several segments by rings of contraction (Fig. 25.2).

Contraction is followed by relaxation and next maximum contraction occur at the place of previous maximum relaxation.

Pendular Movement

Pendular movements are so called because they toss the food alternatively on one side and then the other.

Cause

Both are due to outstanding property of smooth muscle, i.e. rhythmicity. The smooth muscle responds to stretch by contracting. They are myogenic in nature and are independent of nerves.

Function

1. Cause proper mixing of food with digestive juices, thus help in digestion.
2. *Help in absorption:*
   i. By constantly changing the layer of fluid in contact with mucosa.
   ii. By change of pressure.
   iii. By improving intestinal circulation.

Peristalsis: Consists of a ring of contraction in one segment and receptive relaxation in the immediately distal segment. This results in propulsion of the contents from contracted segment to the relaxed segment. This is promptly followed by contraction of the segment which was earlier relaxed and relaxation of the segment distal to it. This results in propulsion of contents:

1. *Two types of contraction:* Segmentation and peristalsis occur simultaneously. Peristalsis is superimposed on segmentation (Fig. 25.2).
2. Peristaltic wave travel for varying distance some few centimeters and others few meters depending on intensity of stimulus.
3. Peristaltic wave induced by strong stimulus may sweep over the entire length of small intestine called as rush wave or peristaltic rush.

Basic electrical rhythm (BER): A cyclical change in the electrical potential occurs in duodenum near the entrance of bile duct. Frequency of BER declines progressively from duodenum to ileum. 11-12/min in duodenum and 8-9/min in ileum.

Therefore, the frequency of movements is inversely proportional to the distance from the stomach.

LAW OF INTESTINE

Peristaltic wave moves aborally and not orally. Since, frequency of contraction is similar to the

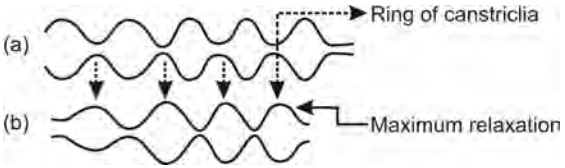


Fig. 25.2: Segmentation

frequency of BER and frequency of BER decreases from duodenum to ileum. Therefore, peristaltic wave moves away from mouth.

Cause

It is activity of longitudinal and circular layers of smooth muscle. When stimulus is applied to a given point on the intestinal wall - causes contraction locally and relaxation below the stimulated point. It is a local reflex which depends on intrinsic plexuses (Myenteric reflex). Presence of food in intestine will lead to constriction above and relaxation below. So the contents are pushed, then this segment contracts. Local nerve plexuses help in coordination. Vagal stimulation increase peristalsis, sympathetic stimulation decrease it.

Function

Mainly propulsive and also help in digestion and absorption like mixing movements.

Antiperistalsis

In every respect is same as peristalsis but direction is opposite. It moves in oral direction.

Present in only: (i) 2nd and 3rd part of duodenum-helps in thorough mixture and causes duodenal regurgitation, (ii) In terminal part of ileum-prevents rapid passage of contents in cecum. Intestinal movements are affected by a number of reflexes of physiological importance.

Gastroileal Reflex

Intake of food increases secretary and motor activity of stomach. This increases motility of ileum and relaxes ileocecal sphincter. Purpose is to empty the small intestine as it is going to be filled again.

Ileogastric Reflex

Distention of ileum leads to a decrease in gastric motility. This reflex is useful in preventing further distention of ileum.

Intestino-intestinal Reflex

Distention of one segment of the ileum leads to relaxation in rest of the intestine. This will help in relieving distention, or stop further movements, till cause of distention has been removed. This reflex is dependent on extrinsic innervation.

MOVEMENTS OF LARGE INTESTINE

Food reaches the various parts of large intestine in following number of hours after a meal:

1. Cecum 4 ½ hours
2. Hepatic flexure 6 hours
3. Splenic flexure 9 hours
4. Descending colon 11 hours
5. Pelvic colon 12-18 hours (= Sigmoid colon)

From pelvic colon to the anus, transport is much slower.

Rhythmic Variation in Tone

Occur over all parts of large intestine. They do not propel the contents onwards but serve to mix them and aid absorption of water. Colonic movements are more sluggish by night than by day.

Segmentation

Segmentation is major mixing movement occur at a frequency of 2-3 per minute. These contractions are much stronger than small intestine and divide the large intestine into very distinct segments called haustra. The consistency of luminal contents changes from liquid to semisolid in large intestine. Therefore,

the contractions should be strong. Semisolid contents take more pressure for mixing. Continued mixing ensures homogenecity.

Mass Peristalsis

Propulsion of large intestinal contents accelerates following a meal:

1. Mediated by gastrine and CCK (two gastrointestinal hormones).
2. It is known as gastrocolic reflex.
3. Occurs 1 to 3 times per day for 10 to 30 minutes at a time and empties a large segment.
4. This is powerful peristaltic movement and contents are pushed to pelvic colon which is a storehouse.
5. Because of their scale of operation, they are called mass peristalsis.

Defecation

Defecation reflex is induced by distention of rectum. This information is conveyed to spinal cord. During defecation reflex a propulsive wave is set up in distal part of colon from descending colon to rectum and relaxation of internal anal sphincter takes place.

1. Simultaneously during defaecation reflex pudendal nerve is also activated which leads to contraction of external anal sphincter.
2. External anal sphincter is a voluntary muscle under voluntary control.
3. When the conditions are appropriate the reflex contraction of external anal sphincter is voluntarily inhibited, allowing defection.
4. If the conditions are unsuitable, reflex contraction of external anal sphincter is voluntarily reinforced, and postponement of defecation is achieved.
5. During the act deep breath is taken, which results in descent of diaphragm and increased abdominal pressure.
6. Contraction of abdominal muscle also raises the abdominal pressure.
7. Urination which presses urinary bladder against rectum, raising the intrarectal pressure.

All these maneuvers raise the intrarectal pressure to a sufficient level to result in defection.

Defection is a matter of habit so that it can be performed fairly regularly at a convenient time everyday. It is a sort of conditioned reflex, starting off when appropriate accompaniments are present.

Pathway

S2, S3 and S4 and pudendal nerve.

CHAPTER

26

Salivary and Gastric Secretion

SALIVARY SECRETION

There are three pairs of salivary glands:

1. *Parotid glands:* Lie in front of ear. Secretion passes through Stensen's duct, which opens in mouth opposite the site of second motor tooth.
2. *Submandibular glands:* Lie medial to mandible in the submaxillary triangle. Its duct (Wharton's duct) opens into the floor of the mouth at the side of frenulum linguae.
3. *Sublingual glands:* Lie immediately beneath the mucosa of floor of the mouth. Numerous ducts collect and discharge the sublingual secretion into sublingual part of the mouth.

Besides several minor glands are there, which are scattered throughout the mouth and pharynx.

Salivary glands contain mainly two types of cells mucus cells and serous cells which are arranged in the form of acini:

Parotid glands: Purely serous (watery secretion—contain ptyalin).

Submandibular glands: Contain both type of cells but predominantly serous.

Sublingual glands: Also mixed but predominantly mucous (viscous secretion - contain mucin).

Sublingual glands and minor salivary glands serve to keep the mouth moist even when no food is taken.

The acini and the ducts are surrounded by myoepithelial cells, which help in squeezing the secretions into the mouth (Fig. 26.1).

Nerve Supply of Salivary Glands

All glands receive both sympathetic and parasympathetic nerve supply (Fig. 26.2). Parasympathetic innervation is most important.

Parasympathetic Supply of Salivary Glands

Parotid glands: Receive parasympathetic fibers from cells of inferior salivary nucleus. They are preganglionic nerve fibers which course via tympanic plexus and tympanic nerve to otic ganglion, and synapse with ganglion cells. Postganglionic fibers reach parotid gland via auriculotemporal nerve.

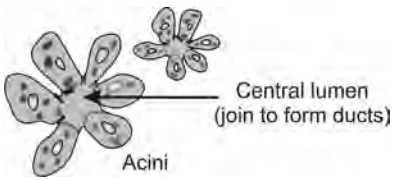


Fig. 26.1: Acini

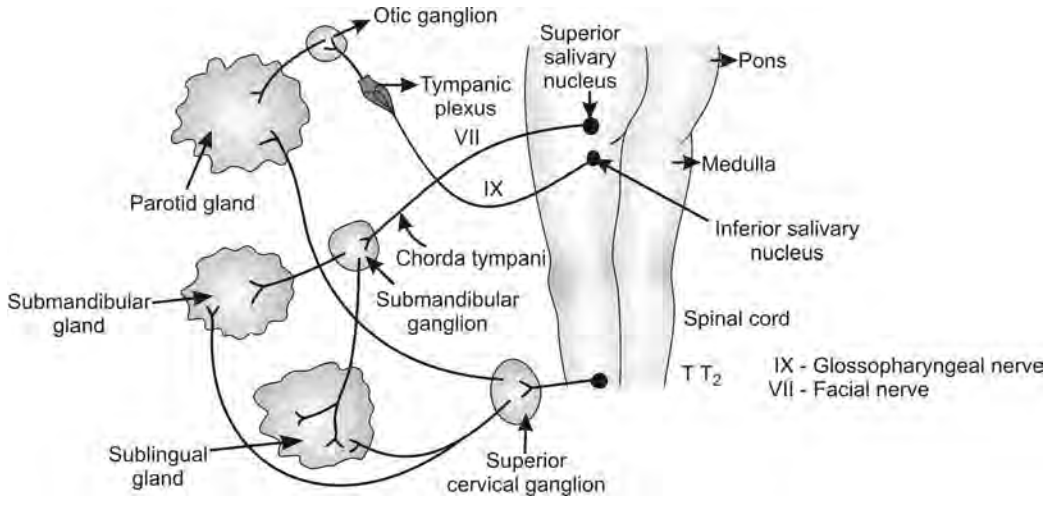


Fig. 26.2: Sympathetic and parasympathetic supply of salivary glands

Submandibular and sublingual glands: Receive their parasympathetic nerve supply from superior salivary nucleus. Preganglionic fibers course in facial nerve and leave by its chorda tympani branch to reach lingual nerve. They synapse with ganglion cells scattered in vicinity of submandibular and sublingual glands. Postganglionic fibers are supplied to both these salivary glands.

Sympathetic supply: Preganglionic fibers come from the upper 2 thoracic segments of the spinal cord, which synapse with superior cervical ganglion. Postganglionic fiber from superior cervical ganglion reach the secretory cells.

Mechanism of Secretion of Saliva

There are two main ways of controlling secretion of digestive glands: (1) Through nervous system, and (2) By means of hormones.

In case of salivary glands the control is exclusively through nervous system by reflex path.

Reflex Path

Any reflex has an afferent path, center and an efferent path. Stimuli will reach the center (Fig. 26.3) through afferent path, and the effect will be carried out by the efferent path, which supplies in this case the salivary glands.

Afferent path is formed by:

1. Branches of chorda tympani (which supply anterior 2/3 of tongue).
2. Glossopharyngeal nerve (which supply posterior 1/3 of tongue).
3. Vagus.
4. Branches of trigeminal nerve.
5. Other sensory pathways - (olfaction, sight, hearing).

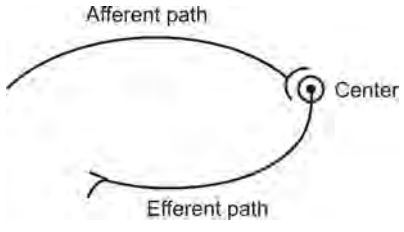


Fig. 26.3: Reflex path

Center is formed by salivary nuclei - superior and inferior salivary nuclei in brain-stem (i.e. pons and medulla).

Efferent path is formed by:

1. Fibers of IXth cranial nerve.
2. Fibers of VII–nervous intermediary fibers in chorda tympani.

   Normally reflex secretion of saliva occurs in two ways:

   i. Presence of food or other substance in mouth.
   ii. Stimulation of special sense organs (other than taste buds),

   Like - sense organ of sight.

   Sense organ of smell.

1. Presence of food or other substance in mouth- stimulates mucous membrane; impulses are carried by afferent fibers supplying the area of contact.

   This reflex is present from birth. Therefore, it is named as unconditioned reflex.
2. Stimulation of sense organ like sight, smell, etc. cause salivation even when no food is taken.

   This is acquired reflex and is conditioned reflex. Pavlov established this by sounding a bell just before giving food to a dog. After continuing this procedure for a few days, he found that salivation took place with the sounding of bell even without giving any food to the dog. Sound of bell acted as a stimulus for the conditioned reflex.

In man sight, smell or even thought of food causes salivary secretion, i.e. makes the mouth water.

1. Tasty substances are more effective than bland ones – for a copious secretion.
2. Dry substances or acids – produce more watery secretion.
3. Even movement of tongue or jaw (chewing) will lead to salivation due to irritation of nerve endings.

Basic Mechanism of Salivary Secretion

1. The acini form a 'primary secretion'.
2. Then it is modified by the ducts.

At high rates of secretion less time is available for modifying the primary secretion, Therefore, saliva resembles primary secretion.

1. Primary secretion is isotonic with plasma.
2. As the primary secretion flows along the ducts sodium and chloride ions are re-absorbed from it and much smaller amount of potassium and bicarbonate ions are secreted into it.
3. Bicarbonate ions are synthesized from blood-carbon dioxide as well as local carbon dioxide.
4. To catalyze - carbonic anhydrase is present in the ductular cells.
5. The changes that take place in the ducts make saliva hypotonic.

Composition of Saliva

1. Mixed saliva is — colorless
   — viscous
   — opalescent
2. Quantity — 1-1.5 L/day
3. pH— slightly less than 7.0 therefore acidic
4. Normal contribution of submandibular-glands — 70% (of resting volume of saliva)
   i. Parotid glands — 25%
   ii. Sublingual gland — 5%
5. Contains water—99.5%.
6. *Solids*—0.5%
   i. 2/3 organic
   ii. 1/3 inorganic.

Organic Solids

1. Two main substances are mucin (glycoprotein) makes saliva viscous
   – Enzyme ptyalin known as a amylase.
2. Other enzymes
   i. Maltase
   ii. Lysozyme (bactericidal)
   iii. Kallikrein (Proteolytic enzyme)
   iv. Lipase (lipolytic enzyme).

   Antibodies
   IgA-which give local immunity.
3. *Blood group substances:* In some individuals called secretors (whether a person is secretor or nonsecretor is genetically determined).

Other organic contents: Urea, uric acid, creatinine, free amino acids.

Inorganic solids: Electrolyte composition of mixed saliva depends on rate of salivary secretion.

1. Na - as the rate of secretion rises the concentration of Na rises.
2. K - concentration constant.
3. Bicarbonates - high concentration at high rate.
   This makes saliva alkaline (while the pH of basal mixed saliva is slightly less than 7.0).
4. Chloride
5. Calcium
6. Phosphate - traces
7. Bromide - traces.

A rise of pH produced by loss of CO_2 or by bacterial action causes precipitation of salivary constituents and their deposition on the teeth as tartar.

Functions of Saliva

Mechanical Functions

1. *Moistening action*: Keeps mouth moist and assists in speech.
2. *Lubricating action:* Helps in chewing of foodstuff, preparation of bolus and swallowing.
3. *Protective action:* Protects mouth from injurious effect of hot irritating substances by diluting it.
4. *Cleansing action:* It washes down any remnant of food particles to keep mouth clean.
   i. Bacterial effect of enzyme lysozyme helps.

Digestive Function

1. Starchy food is acted upon by ptyalin or salivary α amylase. It is a weak amylase.
   i. It requires chloride ions for its maximum activity.
   ii. Acts best in neutral or faintly acidic medium (optimally at pH [6.5]).
   iii. Destroyed in more acid medium.
   iv. Can act on boiled starch.
   v. Breaks polysaccharides only up to disaccharides, e.g. starch to maltose.
   vi. It cannot act on cellulose. Therefore, cellulose coated grains must be boiled to split up cellular coat.

   Food remains for a short period in mouth. In stomach salivary digestion can continue for sometime inside the bolus, till acidity rises, which inactivates ptyalin.
2. **Maltase:** Only trace is present which forms glucose by action on maltose.

Excretory Functions

1. Salts of heavy metals - like lead, arsenic, bismuth, iodide.
2. Viruses responsible for rabies (hydrophobia) and anterior poliomyelitis.

Solvent Function and Taste Sensations

Helps taste by dissolving edible substances. The taste buds are only stimulated when substance is in solution.

Maintenance of Water Balance

Water loss from body, e.g. in diarrhea, depresses salivation, resulting in drying of mucous membrane of mouth and pharynx. Afferent impulses are sent to hypothalamic center to be recognized as thirst.

Buffering Action

As salivary flow increases during meal concentration of bicarbonates also increases. This helps to keep pH in mouth optimum for the activity of salivary amylase.

GASTRIC SECRETION

Stomach

Gastric mucosa contains deep glands in pyloric and cardiac region, which secrete mucus (Fig. 26.4).

In fundus and body of the stomach the glands contain (Fig. 26.5):

1. *Parietal or oxyntic cells:* Which secrete hydrochloric acid
2. *Chief or peptic cells:* Which secrete pepsinogen.

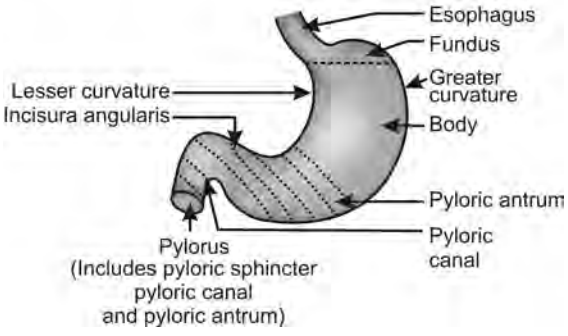


Fig. 26.4: Stomach

These secretions are mixed with mucus secreted by the necks of the gland. Several glands open on a common chamber that opens in turn on the surface of the mucosa (gastric pit).

Stomach has rich blood and lymphatic supply.

Nerve Supply

1. Parasympathetic— comes from vagi.
2. Sympathetic— from cardiac plexus.

Regulation of Gastric Juice Secretion

It is regulated by two mechanisms: (1) Neural, and (2) Humoral (by hormones) mechanisms. Classically, secretory response of stomach to ingested meal is considered to be in three phases.

1. Cephalic phase → Neural phase
2. Gastric phase
3. Intestinal phase } → Humoral phases

These phases are not distinctly separate or independent phases, but overlap and are closely related.

Neural control of gastric secretion is mediated via *vagus nerve*.

Vagus supplies secretory fibers to glands, and influences the secretion of all three glandular elements:

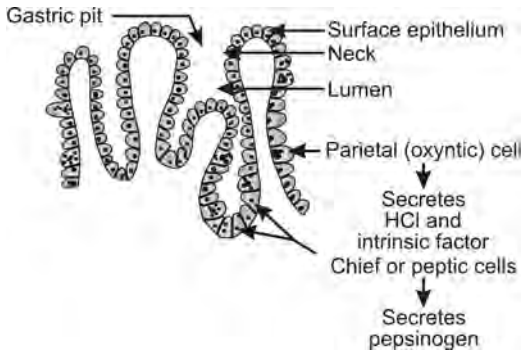


Fig. 26.5: Structure of main gastric glands

1. Parietal cells
2. Peptic or chief cells
3. Mucus cells.

Therefore, stimulation of vagus causes secretion of hydrochloric acid, pepsinogen and mucus.

Vagal effect is due to release of acetylcholine at its nerve endings. Vagus exerts three types of influences on stomach:

1. Directly activating the parietal cells.
2. Releasing gastrin from G cells (gastrin is hormone, secreting gastric juice).
3. By general supporting action - increasing responsiveness of gastric cells to other stimuli.

Humoral Mechanism

1. It is due to release of a hormone—Gastrin from G cells - present in pyloric antrum - by presence of food in stomach. Gastrin is absorbed in blood and is carried to glands, which secrete gastric juice rich in acid and contain less pepsin.
2. Gastric juice secretion is increased by histamine. Histamine receptors are found on parietal cells. Cimetidine—an H_2 receptor antagonist, reduces gastric secretion. Source of histamine: (i) Food, e.g. meat, cabbage. (ii) Cells in gastric mucosa that resemble mast cells contain histamine.

c. Gastric juice secretion is inhibited by hormone enterogastrone, released from duodenum in response to fats and increased acid in it also release inhibitory hormones like gastric inhibitory peptide (GIP).

Cephalic Phase

Just as salivary secretion, gastric secretion is also initiated before the food enters the stomach.

1. Sight, smell or even thought of appetizing food can initiate the secretion of gastric juice → conditioned reflex.
2. Presence of tasty food in mouth causes gastric juice secretion. This is unconditioned reflex.

Cephalic phase of gastric secretion was first demonstrated by Pavlov. He showed in dog having esophageal fistula, when food is given by mouth, gastric juice is secreted. The process is known as Sham feeding, as although animal eats the food, no food reaches the stomach.

Gastric juice secretion in cephalic phase is principally mediated by vagus nerve. The phase is so called because secretion is initiated by food not is stomach but in mouth or awareness of food in brain by thought, smell, sight, etc. Therefore, the juice secreted in this phase is known as appetite juice or psychic juice.

Characteristics of Cephalic Juice

1. Rich in HCl and pepsin and copious.
2. Hunger profoundly influences its secretion.
3. Food agreeably flavored attractive in appearance and prepared in pleasing way, helps secretion.
4. Congenial surroundings and friendly company on dining table helps.
5. Disagreeable food, disgusting appearance, foul odor, unfriendly company, depress the secretion.

Gastric Phase

Presence of food in stomach itself is capable of causing continued secretions of gastric juice. This is gastric phase.

During this phase two types of stimuli operate:

1. *Mechanical stimulation due to distention:* operates through vagus nerve, which have both afferent and efferent fibers. Afferent

fibers convey the information about distention to the center. Efferent impulses along vagal fibers result in gastric secretion.

2. *Chemical stimulation*: Most potent is partially digested proteins and amino acids. Protein digestion products act mainly by stimulating G cells to release gastrin.

Characteristics: Secretion in gastric phase is rich in acid and contains less pepsin. It must be remembered that, neither gastrin alone nor vagal stimulation alone, can cause maximal stimulation of gastric glands. Maximum secretion is obtained only when both act simultaneously.

Intestinal Phase

Products of protein digestion peptides and amino acids in small intestine cause secretion of small amount of gastric juice secretion.

While intestinal phase plays only a minor role in stimulation of gastric secretion, presence of food in the intestine plays a major role in its inhibition. With entry of food into the duodenum gastric secretion starts slowing down. Acid, fat and hyperosmolarity in intestine, inhibit gastric juice secretion. These factors act partly by neural and partly by hormonal mechanisms.

CHAPTER 27

Composition of Gastric Secretion and Mechanism of Gastric Acid Secretion

COMPOSITION OF GASTRIC JUICE

1. Daily secretion—2.5-3 liters/day
2. pH 1-2, acidic due to presence of HCl.

Electrolytes

Cations – Na^+, K^+, H^+, Mg^{2+}.

When rate of secretion is low, concentration of Na^+ is high and concentration of H^+ is low, but as acid secretion increases, Na^+, concentration falls.

Anions – Cl^-, HCO_3^-, HPO_4^{2-}, SO_4^{2-}

Enzymes

1. Pepsinogen is converted to pepsin,* (which is active) in presence of HCl (optimum pH = 2) helps digestion of proteins.
2. *Renin:* Present only in infants and animals; it curdles milk, so that its rapid passage from stomach is prevented.
3. *Gelatinase:* Liquefies gelatin. Gelatin is a protein contained in connective tissues.
4. *Gastric lipase:* Weak fat splitting enzyme. Optimum pH 4-4.5, inactive at pH 2.5.
5. *Lysozymes:* Bactericidal enzymes.
6. *Carbonic anhydrase:* Present in small amounts.

Mucus of two types:

1. *Soluble mucus*: Secreted by pyloric and cardiac tubular glands.
2. *Visible mucus:* Secreted by surface epithelium of gastric mucosa.

Intrinsic Factors

It helps in absorption of vitamin B_{12}.

MECHANISM OF GASTRIC ACID SECRETION

Secretion of hydrochloric acid takes place from parietal cells of the stomach (Fig. 27.1). Parietal cells are conical in shape. Apex is facing the lumen.

For secretion of HCl, H^+ ions are concentrated four million fold in the parietal cells. This requires enormous energy. The cells contain large number of mitochondria, which produce ATP to supply energy. Oxygen consumption, of parietal cells is high and is an index of the rate of acid secretion.

1. The ultrastructure of parietal cells shows characteristic features depending upon whether the cell is resting or secreting.

*Pepsin also causes further conversion of pepsinogen to pepsin.

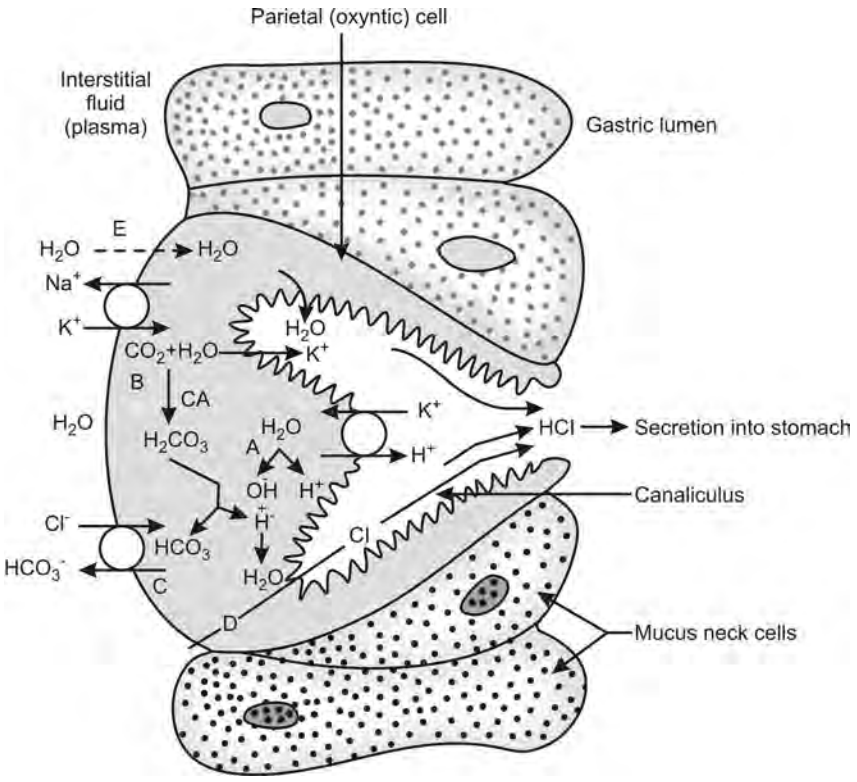


Fig. 27.1: HCl secretion by parietal cells in the stomach CA = carbonic anhydrase

2. *The nonsecreting cells* show many vesicles in the cytoplasm, which contain H^+ - K^+ ATPase in inactive form. The canaliculi become distended and loose their microvilli and opening.
3. The *secreting cell* shows a system of intracellular canaliculi, which open into the lumen. The walls of the canaliculi as well as apex of the cell show numerous microvilli, which increase the surface enormously. In Figure 27.1.

A → $H_2O \rightarrow OH^- + H^+$

B → $CO_2 + H_2O \xrightarrow{CA} H_2CO_3 \rightarrow HCO_3 + H^+$

C → HCO_3 actively removed from the cell in exchange for Cl

D → Cl- secreted in canaliculi

E → Water enters the canaliculi.

HCl secreted

The Basic Process of Acid Secretion

1. Intracellular water is ionized into Hydrogen and hydroxyl ions.
   $H_2O \rightarrow H^+ + OH^-$
   Hydrogen ions (H^+) are actively secreted into the lumen. H^+ Pump is activated by H^+- K^+ATPase. H^+ - K^+ ATPase is Mg^{++} dependent and is highly specific to parietal cells. H^+ - K^+ ATPase is localized in the canalicular membrane and K^+ is merely recycled.
2. The hydroxyl ions (OH^+) might raise the intracellular pH to lethal levels. Therefore, they need to be neutralized.

Neutralization of OH^+ is done by H^+ ions generated by ionization of carbonic acid (H_2CO_3). Carbonic acid is formed by CO_2 produced from cell metabolism or diffused from blood. Since, CO_2 is poorly soluble in water, required quantity of H_2CO_3 is produced by catalyzing the reaction by carbonic acid.

$$CO_2 + H_2O \xrightarrow[\text{anhydrase}]{\text{carbonic}} H_2CO_3 \rightarrow HCO_3^- + H^+ \downarrow + OH^- \downarrow H_2O$$

3. Bicarbonate ions are actively removed from the cell at basolateral membrane of parietal cell by a pump which is activated by HCO_3 ATPase. HCO_3 diffuses in blood in exchange of Cl^- which diffuses from blood into the interstitial fluid and from there into parietal cell.

   Secretion of HCO_3^- into the bloodstream is responsible for the alkaline tide associated with acid secretion (postprandial alkaline tide). Associated with it are:
   i. Passage of alkaline urine.
   ii. Breathing is slightly depressed and alveolar.

   PCO_2 is increased.
4. The Cl^- that enter the parietal cell in exchange for HCO_3 - are secreted into the canaliculi down its electrochemical gradient.

   The Cl^- accompany the H^+ secreted in step (A) to form hydrochloric acid (HCl).
5. Water enters the canaliculi down the osmotic gradient created by movement of HCl.

Regulation of HCl Secretion (Fig. 27.2)

1. Increased by:
   i. *Histamine:* Histamine bind H_2 receptors on the parietal cell. This increases adenyl cyclase activity and intracellular cAMP.
   ii. *Acetylcholine:* Secreted by postganglionic cholinergic nerve endings innervating parietal cells. These nerve endings are carried in vagus nerve. They increase intracellular free calcium.
   iii. *Gastrin:* Secreted by G cells of pyloric antral glands, reaches parietal cells via circulation. Gastrin binds with gastrin receptors on parietal cell and increase the intracellular free calcium.

   Cyclic AMP and Ca^{++} act via protein kinase which will increase the transport of H+ into the gastric lumen by H^+- K^+ ATPase.

   The intracellular events interact. Therefore, activation of one receptor type potentiate the response of another receptor to stimulation.
2. *Decreased by:*
   Prostaglandin (PGE_2)—Its acts via Gi receptors and decreases adenyl cyclase

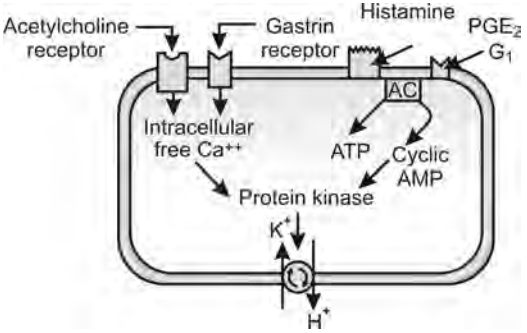


Fig. 27.2: Regulation of gastric acid secretion, AC = Adenyl cyclase

activity and intracellular cyclic AMP. All factors which affects HCl secretion, cause release of these agents namely, acetylcholine, histamine, gastrin or PG E_2 .

GASTRIC FUNCTION TESTS

Gastric function tests are done mainly to investigate acid secretion.

Fractional Test Meal

1. Intubation is necessary to study gastric acid production. A nasogastric a tube made up of soft plastic with bore of 2 mm is used for intubation. The blind gastric end of the tube is round and weighted with metal to render it radiopaque. This end is perforated also. The lubricated tube is passed via a nostril and then swallowed. For study of gastric secretion it should lie in the most dependent part of the stomach (confirmed by screening).
2. After the overnight fast, person is intubated. The resting gastric secretion is removed with the help of a syringe. Then, stomach is washed with distilled water.
3. Approximately 400 gm of thin gruel (starch) is swallowed.
4. 10 ml of gastric contents are aspirated every 15 minutes – until stomach is empty.
5. Each sample is examined to determine its 'free and total acidity'. Findings are plotted on chart in the form of a curve.
6. **Findings**
   Normally:
   i. *Free HCl* in fasting contents is between 1.5 to 2 mEq of HCl. After the gruel is taken the acidity is reduced by dilution almost to zero and combination with organic substances is also responsible for reducing the free HCl. Free HCl then steadily rises and becomes 40-50 meq of HCl in 2nd hour. Value is 3 times in peptic ulcer. In hypochlorhydria values obtained are always under 20 (subacidity). Absence of free acid is called achlorhydria or anacidity.
   ii. Then, acidity declines gradually by neutralization of acid gastric contents by regurgitated intestinal juices and alkaline secretion of pyloric glands.
   iii. *Combined acidity:* This includes HCl combined with protein, mucus, and organic acids – such as lactic acid, produced by fermentation.
   Normally, it varies from 10 to 55 mEq of HCl. In hypochlorhydria or achlorhydria, rate of fermentation is more so that this figure is high.
   iv. *Total acidity:* This is sum total of (1) free HCl + organic acid + combined HCl + acid salts. Curve for total acidity rises a short-time after a test meal and after 1 ½ hours reaches its peak level. Subsequently – usually curve declines gradually.
   v. Curve for free acidity runs more or less parallel to total acidity but at a lower level.
7. Samples are also tested for starch and sugar, bile, blood, mucus and physical characteristics like color, odor.

Starch and sugar: Indicate that stomach has not yet completely emptied. Their absence determines emptying time. Normally they are not found after 10-11th sample.

Presence of bile is indicated by yellow or green color of stomach contents and indicates duodenal regurgitation. It also shows that pyloric sphincter has opened and gastric emptying has begun.

Generally bile first appears in 2nd hour. Absence of bile indicates pyloric obstruction.

Blood: Its presence shows ulcer or other hemorrhagic condition of stomach or carcinoma.
Mucus: Excess indicates inflammation.

Note: Clinical value of fractional test meal is limited due to availability of other reliable tests.

Histamine Test

After overnight fast, in the morning stomach is emptied by aspiration, then washed with distilled water. Then 0.5 mg histamine acid phosphate is given subcutaneously and gastric juice is aspirated for one hour. Normally 200 ml of gastric juice is secreted in one hour with acidity equivalent to 180 ml HCl.

Augmented Histamine Test

By increasing the dose of histamine in a stepwise manner, the parietal cell can be stimulated to produce 'maximal' secretory response. This response is proportional to number of parietal cells in gastric mucosa.

Average size of parietal cell population is 1.18 billion in male and 0.64 billion in female.

In patients, with duodenal ulcer parietal cell population increases to 1.8 billion in male and 1.52 billion in female.

In patients, with gastric ulcer it decreases to 0.8 billion irrespective of sex.

Pentagastrin Test

After overnight fast, the patient is intubated in the morning. All resting fluid from the stomach is removed with help of a syringe.

Then secretion is collected over next one hour by continuous aspiration. In normal persons it is few ml per hour, containing 10 mEq of HCl. This is basal acid output (BAO), i.e. 10 mEq/hour.

Pentagastrine which is synthetic gastrine is given-dose is 6µg/kg body weight, subcutaneously.

This causes maximal acid secretion. Gastric juice is collected for one hour after injection. The total acid secreted in this hour is the maximal acid output (MAO). In normal persons, MAO may reach a maximum of 27 mEq/hour in males and 25 mEq/hour in females. In patients with duodenal ulcer, MAO increases up to 50 mEq/hour.

In patients, suffering from gastric ulcer or carcinoma stomach, its values are less than normal or equal to normal.

Insulin Test

IV infusion of insulin 0.04 units/kg per hour causes hypoglycemia, which in turn stimulates vagal nuclei. Impulses pass down and increase gastric secretion rich in acid and pepsin (vagal juice). Gastric aspiration is carried out for 2 hours. A rise of acid secretion to 20 mEq/hour or more above basal unstimulated value indicate incomplete vagotomy. Vagotomy operation is performed when patient develops a recurrent peptic ulceration.

Plain Radiography

X-ray of abdomen with patients in supine and erect posture are useful in diagnosis of perforated gastric or duodenal ulcer. Gas may be seen under the diaphragm usually on right side in such cases.

Barium meal: Used for diagnosis of gastric and duodenal ulcer and a gastric carcinoma.

In gastric ulcer: Barium filled ulcer crater is present.

In duodenal ulcer: No definite ulcer crater but duodenal cap is deformed.

In gastric carcinoma: In early stage – filling defect, in barium filled organ due to tumor growth.

In late stage: Hour glass constriction of stomach.

Intrinsic Factor Secretion

IF is measured by immunological assays. It decreases due to big gastric ulcer and carcinoma stomach.

Endoscopy and Biopsy

By use of flexible fiberoptic gastroscopes, it is possible to see the whole of the esophagus, stomach and duodenum. The instrument carry a channel through which a biopsy forceps or a brush can be introduced to obtain specimens for histological and cytological examination.

CHAPTER

28

Functions of Liver

Liver is the largest organ in the body, where metabolism of all nutritional material takes place, e.g. carbohydrate, fat, protein, vitamins and minerals. Liver is both secretory and excretory organ.

Physiological Anatomy of Liver

It is situated in the upper abdomen on right side. It is a mass of cells traveled by tunnel systems. Eighty-five percent of cells are parenchymal. It consists of several *lobes*, each lobe consists of several *lobules* which are hexagonal in shape (Fig. 28.1). In connective tissue between the lobules there are *mast cells*.

Each *lobule* consists of rows of polygonal cells. These are parenchymal cells radiating from centre. At the centre is *central vein*. At the periphery of lobule there is *portal triad*, which contain: (i) Bile ductule, (ii) hepatic arteriole, and (iii) radicle of portal vein. Hepatic arteriole and radicle of portal vein are connected to central vein by thin walled *sinusoids*, which lie in between the rows of hepatic cells. Walls of sinusoids are of endothelial cells and phagocytic cells belonging to R.E. system, called *Kuffer cells*. Sinusoids drain in central vein. Thus, blood from hepatic artery and portal vein drain in *central vein*. It receives sinusoids from all sides and passes through long axis of the lobule. It leaves at the base. There it is joined by other central veins to form *sublobular vein*. This ends in large *hepatic vein*, which drain into *inferior vena cava*.

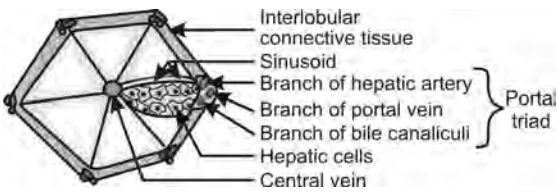


Fig. 28.1: Structure of hepatic lobule (cross-section)

Row of hepatic cells has on one side a vascular sinusoid going to join the vein and on other side a *bile capillary* going out of the lobule to join bigger bile channel. Bile capillary has no definite wall and blood sinusoid has very thin wall, so that intimate contact is there between blood and hepatic cells but blood and bile are kept separate.

Excretory System of Liver

Starts with bile canaliculi. These are intercellular spaces bound by two or more rows of hepatic cells. Bile is formed in minute vacuoles in true hepatic cells, which are discharged into fine intercellular bile canaliculi. Canaliculi form network around

individual liver cells and form *cholangioles*, which enter *bile ductule* in portal triad.

Blood Supply of Liver

Blood enters liver through: (i) Hepatic artery 20%, and (ii) Portal vein 80%.

Blood leaves liver via hepatic vein, which drains into inferior vena cava.

Blood supply per minute is 1500 ml.

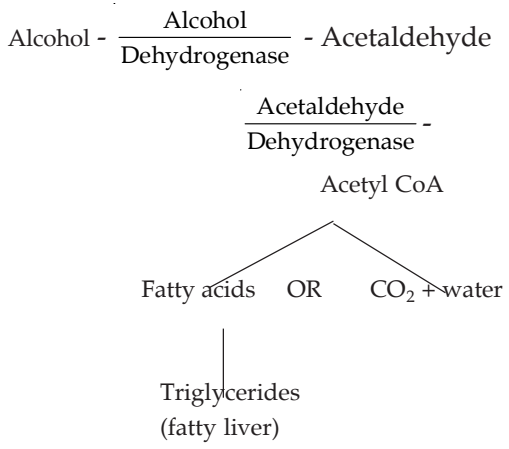
FUNCTIONS OF LIVER

Functions of liver are many. It is mainly concerned with production and storage of essential material that are required for the survival of organism and elimination of others that are unwanted—these are metabolic functions.

Classification

Functions are described under 1 to 10 heads.

1. *In Connection with Blood and Circulation*
   i. RBC formation in fetal life.
   ii. RBC destruction in adult life – by Kuffer cells.
   iii. Store house of blood and regulation of blood volume.
   iv. In relation with blood clotting: (i) Synthesis of *fibrinogen* and *prothrombin* and factors V, VII, IX and X are synthesized: (ii) mast cells produce *heparin*.
   v. Site for production of most of the *plasma proteins - mainly albumin*.
   vi. Stores iron, B_{12} and copper and helps in formation of *Hb and RBC*.
   vii. Formation of lymph
   viii. In liver hepatic and portal blood mixes.
2. *Manufactures Bile*
   Liver is the site for synthesis of bile acids from cholesterol which helps (or is essential for) fat digestion.
   i. Bile is route for excretion of substances, which are poorly excreted by kidney – bile pigments.
   ii. Heavy metals, e.g. Bi, arsenic, lead.
   iii. Bacteria (e.g. typhoid).
   iv. Bacterial toxins, viruses.
   v. Cholesterol.
3. *In Relation with Carbohydrate Metabolism*
   Liver helps in synthesis, storage and release of glucose by following processes:
   i. Glycogenesis—glycogen is formed from glucose and stored in liver.
   ii. Glycogenolysis—liver glycogen is broken down to glucose.
   iii. Gluconeogenesis—formation of glucose from noncarbohydrate sources, e.g. amino acids, fatty acids, lactic acid, pyruvic acid and glycerol. (i), (ii), and (iii) help regulation of blood glucose level by the liver.
   iv. Liver also converts nonglucose monosaccharides to glucose and glycogen. For example, fructose, galactose.
   v. *Alcohol metabolism:*



4. *In Relation with Fat Metabolism*
   i. Liver is a fat depot – neutral fat accounts for 5% of its bulk.
   – *Fatty liver*—develops (a) when diet is rich in fat but deficient in lipotropic factors e.g. choline,

methionine, (b) in starvation, (c) in diabetes mellitus.

ii. Liver is a site of:
   a. β-oxidation – which occurs in mitochondria which oxidized triglycerides to produce ATP.
   b. Nonesterified *fatty acids* are esterified to form *triglycerides* in the liver.
   c. Synthesis of saturated fatty acids from acetate via Krebs's cycle within the mitochondria.

iii. Synthesis of cholesterol and phospholipids (e.g. lecithin, cephalin, sphingomyelin, etc.).

iv. Enzyme liver lipase—hydrolyzes – neutral fats to glycerol and fatty acids.

v. Fat soluble vitamins ADEK are stored in liver.

5. *In Relation to Protein Metabolism*
   i. Liver is a site for synthesis of plasma proteins – albumin, fibrinogen and prothrombin.
   ii. Liver produces proteins – important in binding of hormone.
   – in binding inorganic ions.
   iii. Degradation of amino acids in liver to produce
   – α-keto acids
   – ammonia.
   iv. Ammonia is converted to urea.
   v. Deamination and transamination.
   vi. Synthesis of some amino acids.

6. *Hormone Metabolism*
   i. Liver is a site for degradation of steroid hormone.
   ii. Inactivation of hormones like ADH, Insulin, glucagons, anterior pituitary tropic hormones.

7. *In Relation with Vitamins*
   i. Liver manufactures prothrombin with the help of vitamin *K*.
   ii. Forms vitamin A from carotene.
   iii. Stores vitamin *A,D,E,K*.
   iv. Stores vitamin B_{12}.
   v. Liver converts folate to tetrahydrofolate, which is storage form of folic acid.

8. Excretory Function
   i. Certain heavy metals are temporarily fixed in liver and then excreted in bile.
   ii. Toxins, viruses, bacteria are excreted in bile.
   iii. Drugs, iv. Cholesterol } are excreted by liver in bile
   v. Bile pigments are also excreted in bile.

9. *Detoxicating and Protective Function*
   Liver is the site of detoxication of different toxic substances either produced in body or taken along food.

   Detoxication is a process by which toxic substances are rapidly made excretable through biochemical changes. Detoxication can be done by oxidation, hydrolysis, reduction and conjugation *or* by complete destruction.

Conjugation examples are:
1. Glycine + benzoic acid forms hippuric acid.
2. Glucuronic acid + drugs or steroid hormones.
3. Sulfate with phenolic substance to form ethereal compound.
4. Acetic acid with aromatic amino compounds.

10. *Synthetic Function of Liver*

   This function is already described under various headings above. That which is left out is synthesis of enzymes, e.g.
   1. Alkaline phosphatase.
   2. Serum glutamic oxaloacetic transaminase (SGOT).
   3. Serum glutamic pyruvic transminase (SGPT).
   4. Serum isocitrate dehydrogenase (SICD) takes place in liver.

LIVER FUNCTION TESTS

When there is any disease of liver there occur metabolic disturbances, which serve as diagnostic aid to hepatic disease because liver has many functions there are many tests:

They can be classified in following groups:

1. Tests based on secretory and excretory functions of liver.
2. Conjugation tests.
3. Tests based on metabolic functions of liver.
4. Enzyme studies.
5. Miscellaneous tests.

Tests-based on Secretory and Excretory Functions of Liver

Estimation of *serum bilirubin* (van den Bergh test).

Principle: Bilirubin is formed from degradation of hemoglobin, which (bilirubin) circulates in plasma bound with α-globulin. Therefore, it is soluble in plasma and globulin prevents its excretion in urine. In liver, it is conjugated to form bilirubin glucuronide, which is soluble in water.

When jaundice is of hemolytic type, i.e. due to destruction of RBC, increased quantity of bilirubin is formed and bilirubin level in blood is increased, because liver is unable to deal with so much bilirubin. This bilirubin is not water soluble but soluble in alcohol and gives indirect van den Bergh's test positive (unconjugated bilirubin is increased).

Whereas, when jaundice is due to obstruction to passage of bile, the bilirubin is conjugated bilirubin, which is increased. This is soluble in water and gives direct van den Bergh test positive.

In liver insufficiency as well, conjugated bilirubin increases which gives direct van den Bergh test positive.

Note: *Jaundice* is yellow color of skin, conjunctiva and other tissues, caused by excessive bilirubin in plasma and tissue fluid.

Excessive bilirubin can result from three causes:

1. Excessive breakdown of RBC— Hemolytic jaundice (jaundice is prehepatic).
2. Infective or toxic damage of hepatic cells - Hepatic or hepatocellular jaundice. (jaundice is hepatic).
3. Obstruction of bile ducts—obstructive jaundice (jaundice is posthepatic).

Normal total bilirubin (which includes both conjugated and unconjugated bilirubin) = 0.2 mg – 0.8 mg%.

Urine Bilirubin

Normally absent, increases in liver insufficiency producing 'bilirubinuria'. This occurs when serum bilirubin exceeds 2 mg%.

Urine Urobilinogen

Normal value < 4 mg/day when urine flow is 1 ml/min. In liver insufficiency it is mildly increased initially. Later on absent from urine as liver is swollen and liver cells block bile canaliculi and prevents excretion of conjugated bilirubin in bile.

Note: Urobilinogen is formed by bacterial degradation of bilirubin glucoronide when it enters intestine. It is absorbed in blood and via blood reaches back to liver.

Fecal Stercobilinogen

Normal value—20-250 mg%. In liver insufficiency, initially increases producing dark brown stools, later decreases causing pale stools.

Note: Urobilinogen formed in intestine when excreted in stools is known as stercobilinogen.

Conjugation Tests

Hippuric Acid Excretion Test

Six gm of sodium benzoate is given orally. It gets conjugated in liver with glycine to form hippuric acid. Normally, 2.7-3.5 gm of benzoic

acid is excreted in urine as hippuric acid in next 4 hours (i.e. urine collection is done for 4 hours following ingestion of sodium benzoate. Urine is then analyzed).

In liver insufficiency, hippuric acid excretion decreases due to decreased conjugation in the liver.

Bromsulphalein (BSP) Excretion Test

Ability of liver to remove this BSP is measured, this indicates efficiency of liver.

Dye used is tetrabromphthalein disodium sulphonate.

Procedure: Dye is injected intravenously (5 mg/kg body weight). Samples are withdrawn 5 and 45 minutes after. Concentration of the dye during injection is 100%:

1. After 5 minutes it is 85%
2. After 45 minutes it is 5%.

If blood concentration of dye is > 10%, it indicates liver insufficiency.

Tests-based on Metabolic Function

For Carbohydrate Metabolism

1. *Blood glucose estimation:* Normal fasting blood glucose level is 50-90 mg%, it decreases in liver insufficiency.
2. *Galactose Tolerance Test*
   Principle: Normal liver is able to convert galactose into glucose. Therefore, normally galactose concentration of blood does not rise after oral ingestion of galactose. In liver insufficiency after oral ingestion of galactose, its blood concentration increases.
   Procedure: After 12 hours fast 40 gm of galactose in 400 ml of water are given by mouth. Blood galactose is determined after ½, 1, 1½ and 2 hours interval. The normal galactose index (= sum of galactose level in mg% in all four samples) is 68 to 160 mg%.

   In normal subjects, galactose level in blood rises slightly, in liver damage it increases markedly. Liver insufficiency is directly proportional to galactose index.

For Protein Metabolism

1. Estimation of plasma proteins concentration by electrophoresis.
   Normal values

Total plasma protein concentration	=	6.4-8.3 gm%
Serum albumin	=	3-5 gm%
Serum globulin	=	2-3 gm%
Serum fibrinogen	=	0.3 gm%
Serum prothrombin	=	40 mg%

   Normal albumin globulin ration = 1.7:1
   In hepatic insufficiency, S albumin decreases and serum globulin increases (Globulin increases because it is synthesized in R-E system. The increase is called compensatory increase) and there is reversal of albumin globulin ratio.
2. *Test for reversal of albumin globulin ratio:* Thymol turbidity test – 0.05 ml serum + 3 ml thymol solution stand for 30 minutes. Turbidity is developed which is read in colorimeter against barium sulfate standard.

   Turbid solution is obtained when ϒ globulin level is increased.

   Negative thymol turbidity test in presence of jaundice is useful to distinguish between hepatic and extrahepatic jaundice.
3. *Prothrombin time:* Measurement of prothrombin time (normal 11-16 sec) is useful test of liver function. In impairment of liver function plasma prothrombin time is increased to 22-150 sec and if it persists even after administration of vitamin K, indicates severe liver damage.
4. *Blood urea estimation:* (Normal = 20-40 mg%) decreases in liver insufficiency.
5. *Blood ammonia:* (Normal = 20-80 µgm%) increases in liver insufficiency.
6. *Urine ammonia:* (Normal 350-1200 mg/day), increases in liver insufficiency.

For Fat Metabolism

	Normal level	*In liver insufficiency*
i. Serum cholesterol	150-240 mg%	Decreases
ii. Plasma free fatty acids or nonesterified fatty acids	10-30 mg%	Increases
iii. Serum phospholipids	150-300 mg%	Decreases
iv. Serum triglycerides	30-150 mg%	Decreases
v. Total lipids	350-800 mg%	Decreases
vi. Serum ketone bodies	0.7-1.5 mg%	Increases

Tests-based on Enzymes Studies

1. *Serum alkaline phosphatase:* (Normal = 5 –13 KA unit) moderately increases in liver cell damage and markedly increases in biliary obstruction.
   Cause: This enzyme is normally excreted in bile.
2. Certain enzymes appear as a result in bile breakdown, which occurs in hepatocellular disease.
   i. Serum lactic dehydrogenase SLDH – Increased in both
      a. Hepatitis
      b. Obstructive jaundice.
   ii. Serum glutamic pyruvic transaminase (SGPT)—increased in hepatitis.
      Note: SGOT increases in myocardial infarction.
   iii. Serum isocitric dehydrogenase – SICD
      increased in – hepatitis.
      normal in – cirrhosis
      – and extrahepatic obstructive jaundice

Miscellaneous Tests

Isotope Scan

A substance, which is rapidly taken up by the liver cells and Kuffer cells and emits γ-rays is chosen (e.g. A radioisotope of ^{99}technetium or colloidal gold or ^{131}I Rose Bengal or micro-aggregated albumin), is injected IV. The γ-rays can be detected by a suitable counter. A gamma camera is used to show size and shape of liver. Filling defects (i.e. areas which fail to show isotope) is seen in hepatic tumors, liver abscess and liver cysts.

Ultrasound Scan

A probe emitting ultrasonic pulses is used and these pulses are passed across the liver and surrounding areas. Echoes detected from within the patient are received with a transmitter, amplified and suitably displayed. Useful in diagnosis of fluid filled lesions, e.g. liver cysts, liver abscess.

CAT Scanning

Means computerized axial tomography. It is used to produce cross-sectional images of the liver. It is popular and all types of liver lesions can be diagnosed.

Liver Biopsy

Small piece of liver tissue is removed for histocytological studies.

CHAPTER 29

Secretion of Bile, Pancreatic Juice and Succus Entericus

SECRETION OF BILE

Bile is a mixture of secretory and excretory products of liver. It is continuously formed by liver. Bile first passes along the bile capillaries then the hepatic and cystic ducts to the gall-bladder where it is stored and concentrated (Fig. 29.1). The expulsion of bile from the gallbladder and its passage along the common bile duct into the duodenum is intermittent, related in time to the arrival of food in intestine. When food enters the mouth, the sphincter of Oddi relaxes and when food enters the upper part of small intestine, release of secretin and CCK-PZ from duodenum causes the gallbladder to contract.

Composition of Bile

Daily secretion is 500 to 1000 ml. Transparent, alkaline and light golden yellow in color.

pH	– 7.3-7.7
Water	– 97%
Bile salts	– 0.7% (120-180 mg%)

These are sodium and potassium salts bile acids:

Lecithin (phospholipid)	– 0.1% (140-810 mg%)
Bile pigments	– 0.2%.

These include biliverdin and bilirubin and its derivatives:

Fats	– 0.1%
Fatty acids	– 0.15%
Cholesterol	– 0.06% (60-170 mg%)

Enzyme alkaline phosphate and inorganic salts.

Bile Electrolyte

Electrolyte composition of bile is related to flow rate. In turn, flow rate depends on availability of bile salts. More the bile salts more is the flow rate (85-90% of bile salts excreted in the bile are reabsorbed and return to liver for re-excretion. This secretion absorption and resecretion is known as Enterohepatic circulation).

- Principle cations are sodium and potassium
- Principle anions are bicarbonate and chlorides.

With increase in bile flow, there is increase in bicarbonate concentration and pH. Chloride concentration also increases with increase in flow rate.

Bile Salts

Liver synthesizes bile salts from cholesterol by action of liver enzyme.

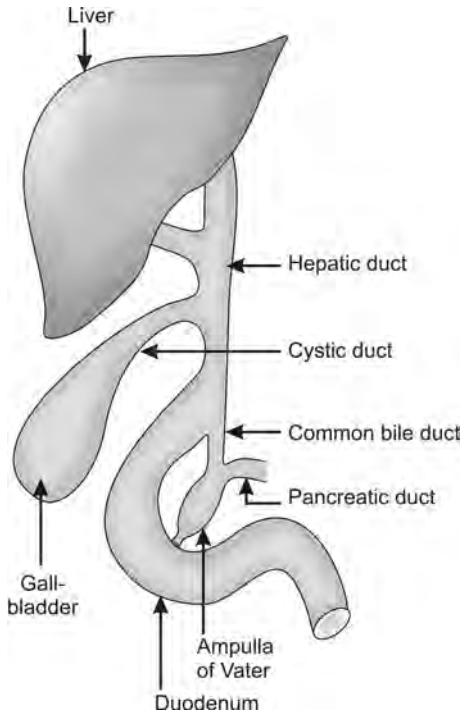


Fig. 29.1: Biliary tract

1. Cholesterol is converted to cholic acid and chenodeoxycholic acid.
2. Both are bile acids, proportion is 2:1.
3. Bile acids are conjugated with glycine and taurine in ratio of 3:1 before secretion.
4. Conjugated bile acids then combine with Na or K to form bile salts. Important one are—Na taurocholate and Na glycocholate.
5. Bile salts have hydrophilic (water attracting) and hydrophobic (water repelling and fat attracting) regions. This accounts for the characteristic property of bile salts, i.e. lowering of surface tension of aqueous solution. Thus, formation of emulsion of fatty material is possible. Thus:
   i. Bile salts, combine with lipids to form cylindrical disks called 'micelles' i.e. water soluble complexes from which the lipids can be more easily absorbed.
   ii. Bile salts by decreasing surface tension are responsible for emulsification of fats which is a prerequisite for digestion and absorption of fats.
   iii. Bile salts also play a role in activating lipase in intestine.
   iv. Emulsification of fats increases the surface area for action of lipase.

Note: Bile salts are reabsorbed from terminal ileum and returned to liver by portal blood. They are then resecreted into bile (enterohepatic circulation).

Bile acid pool remains relatively constant as synthesis is balanced against excretion. Approximately 3.5 gm of bile salts comprises the pool of circulating bile, which recycles.

Bile Pigments

Bile pigments are bilirubin and biliverdin. Bilirubin is chief pigment, biliverdin is oxidative derivative which is present in small amount in bile. These are formed from globin portion of hemoglobin after the destruction of old RBC in R.E. cells (or system):

1. They give color to bile.
2. They are only excretory products and have no digestive function.

Cholesterol in Bile

Bile salts are formed from cholesterol; in this process cholesterol is also excreted from bile. There is no known function of cholesterol and is byproduct of bile salt formation and secretion.

Cholesterol is insoluble in water and is kept in solution with combination with bile salts and lecithin.

In gallbladder, the bile is concentrated. So concentration of cholesterol also increases in bile and in hypercholesterolemia, cholesterol crystals are formed, which become nuclei for

deposition of bile pigments and calcium salts —gallstones are formed.

Functions of Bile

1. *Functions of bile salts:*
   i. Help in digestion and absorption of fats, as above.
   ii. Help in absorption of fat soluble vitamins.
2. *Neutralization of acid* as bile is alkaline it neutralizes the acid chyme from stomach.
3. *Excretion*—many drugs, toxins, bile pigments and various inorganic substances are excreted through bile.
4. Large quantity of cholesterol present in the bile is kept in solution by bile salts and prevents it from precipitation.

Regulation of bile secretion by two mechanisms:

1. Nervous mechanism, and
2. Humoral mechanism.

Nervous Mechanism

Vagal stimulation increases bile secretion by

1. Contraction of bladder (i.e. gallbladder) and by
2. Relaxation of sphincter of Oddi.

Humoral Mechanism

Choleretic substances are the substances which increase secretion of bile from liver, e.g. bile acids and bile salts. *Cholagogues* are substances that cause contraction of gallbladder, e.g. fatty acids, acid in small intestine, products of protein digestion , Ca^{++}, etc.

These substances cause release of CCK-PZ from the duodenum, which in turn cause contraction of gallbladder.

Most potent stimuli for liberation of CCK-PZ are fats and products of protein digestion, whereas acid in the duodenum is major stimulus for secretin release. These hormones, i.e. secretin and CCK-PZ increase biliary secretion by contraction of gallbladder.

After meal flow of bile increases within 30 minutes, peak secretion in 3-5 hours. Both nervous and hormonal mechanisms are responsible for initiation of bile secretion in intestine.

Later tone of sphincter of Oddi increases and bile is prevented from entering intestine. But the enterohepatic circulation of bile salts causes continuous secretion of bile from liver during rest of the digestive phase.

PANCREATIC JUICE

Pancreas is situated in abdomen and extends from inner curvature of the duodenum to the spleen. Pancreas has double functions namely exocrine and endocrine functions (Fig. 29.2):

i. The portion of the pancreas which subserve exocrine function consists of secretory acini which secrete pancreatic juice. The cells of acini contain zymogen granules at apices, which are secreted in pancreatic duct by process of exocytosis.

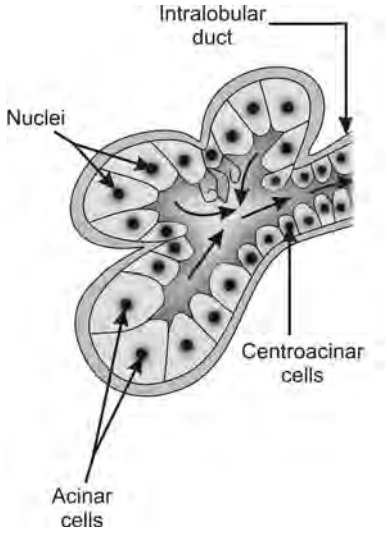


Fig. 29.2: Acini and duct cells of pancreas

The pancreatic juice, which contains enzymes and electrolytes, passes in bigger and bigger ducts—intralobular and interlobar ducts—to join *main excretory ducts* → named: (a) duct of Wirsung and (b) duct of Santorini, which is an accessory pancreatic duct (Fig. 29.3).

Duct of Wirsung: Joins common bile duct to form ampulla of Vater. The ampulla opens through duodenal papilla and its orifice is encircled by sphincter of Oddi.

Duct of Santorini: Opens in duodenum 2 mm higher than ampulla of Vater.

ii. The portion of gland which subserve endocrine function consists of islets of Langerhans, which forms three types of hormones insulin, glucagon and somatostatin.

Nerve Supply

Pancreatic acini receive vagal innervations. Preganglionic vagal fibers synapse with ganglion cells embedded in pancreatic tissue. Postganglionic fibers innervate both acinar cells and smooth muscles of duct.

Vagal stimulation increases pancreatic juice secretion.

Composition of Pancreatic Juice

Daily secretion—1200-1500 ml, transparent, colorless and isotonic with plasma.

pH —pancreatic juice is alkaline. pH = 7.8 to 8.4. It has high bicarbonate content 4-5 times that of plasma. Bile and intestinal juice are also alkaline. So that 3 juices neutralize the gastric acid. Failure to neutralize will result in development of duodenal ulcer.

Electrolytes: cations – Na^+, K^+, Ca^{2+}, Mg^{2+}, Zn^{2+}.

Anions: HCO_3^-, Cl^- and traces of SO_4^2, HPO_4^{2-}

Concentration of bicarbonate: The centroacinar cells are the cells, which line the finest pancreatic ductules. These cells contain carbonic anhydrase and they form and secrete bicarbonate into the lumen of the duct. The primary pancreatic secretion contains bicarbonate, but as the juice traverses the ducts, some bicarbonate is exchanged for chloride. Slower the rate of secretion, more is the time available for exchange.

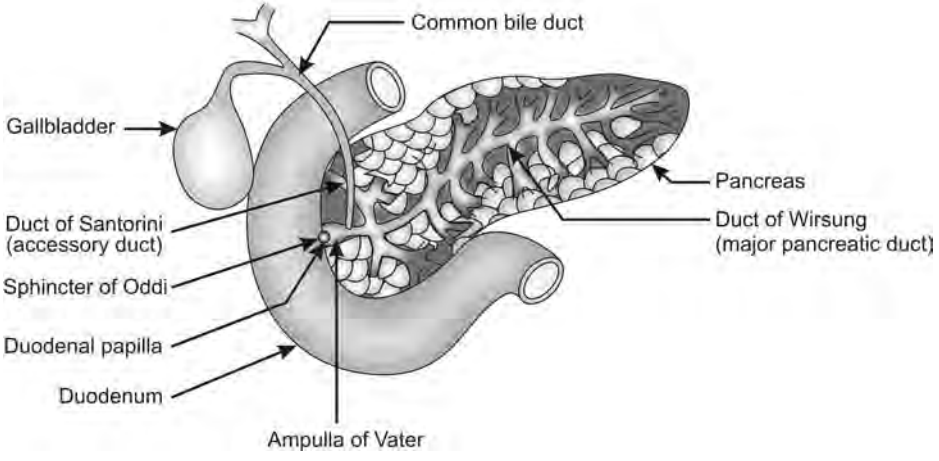


Fig. 29.3: Pancreas and its structure

Enzymes

1. *Pancreatic amylase:* It is stable in pH 4-11 and digests starch (both boiled and unboiled) and glycogen to maltose. Amylase activity depends on presence of Cl ions. Optimum pH for its activity = 6.5 to 7.2.
2. *Pancreatic lipase:* It hydrolyzes neutral fats—to glycerol and esters of fatty acid. pH range of activity is 7-9. Its activity is greatly increased by bile salts.
3. *Phospholipase A and Phospholipase B:*
   Phospholipase A—splits fatty acid from lecithin or cephalin. It is secreted in inactive form and gets converted to active form by trypsin.
   Phospholipase B—splits fatty acid from lysolecithin and lysocephalin.
4. Pancreatic esterase—converts cholesterol esters to cholesterol.
5. *Pancreatic proteolytic enzymes:* These are powerful protein splitting enzymes in pancreatic juice and are secreted as inactive proenzymes.
   i. Trypsinogen (inactive)—converted to trypsin (active) by enterokinase secreted by duodenal mucosa and by trypsin itself.
      Trypsin is more active proteolylic enzyme of pancreatic juice and proteins are digested by it mainly to small polypeptides.
   ii. Chymotrypsinogen (inactive)
      $\xrightarrow{\text{trypsin}}$ chymotrypsin (active). It digests protein to small polypeptides.
   iii. Procarboxypeptidase A and B (inactive)
      $\xrightarrow[\text{trypsin}]{\text{enterokinase}}$
      carboxypeptidase A and B (active)
      It splits polypeptide and it removes amino acids from the free carboxyl group at the end of the chain.
   iv. Ribonuclease and deoxyribonuclease
      They split nucleic acids into nucleotides
   v. Proelastase $\xrightarrow{\text{trypsin}}$ Elastase
      (inactive) (active)

It converts elastin and some other proteins into simplified substances.

Regulation of Pancreatic Secretion

Its secretion is regulated by both:
1. Nervous, and
2. Humoral mechanisms.

Nervous Mechanism

Stimulation of vagi produces enzyme rich pancreatic juice—experimentally.
1. Sight smell, taste or even thought of food, particularly palatable food stimulates pancreatic secretion—this *conditioned reflex* is mediated by vagus nerve.
2. Chewing and swallowing of food—causes secretion of pancreatic juice. This is unconditioned reflex.

Humoral Mechanism

The chyme that enters duodenum is acidic and also contains nutrients including proteins that have been partially digested by pepsin in the stomach. These stimuli release two hormones: (a) secretin, and (b) CCK - PZ (cholecystokinin – pancreozymin) from the duodenum. These hormones potentiate each other's effect and release copious pancreatic secretion after they reach pancreas via systemic blood.

Stimulant effect of secretion and CCK-PZ is potentiated by simultaneous vagal stimulation.

Secretin

It is polypeptide. Molecular weight 5000, first hormone to be discovered. Consist of 27 amino acids. Produced by argentaffin cells in the crypts of mucosa of upper part of small

intestine, duodenum and jejunum. It is secreted as prosecretin (inactive) and is converted into secretin by HCl and salts of fatty acids. It produces watery flow, rich in bicarbonate but contains less enzymes.

Secretin also secretes bile and potentiates the effect of CCK-PZ on pancreas.

CCK-PZ and secretin cause contraction of pyloric sphincter. Thus, preventing reflux of duodenal contents in the stomach.

CCK-PZ

Previously it was thought two hormones are released from duodenal mucosa, CCK causing contraction of gallbladder and PZ causing secretion of pancreatic juice. But now it is known that a single hormone is released from duodenal mucosa, which acts on both sites. Therefore, it is known as CCK-PZ.

It is polypeptide containing 33 amino acids.

It acts chiefly on acinar cells to produce pancreatic juice rich in enzymes.

Note: Acid in duodenum causes more of secretin liberation and less of CCK-PZ.

Products of carbohydrate, fats and protein digestion in small intestine (especially peptides, amino acids) cause more of CCK-PZ release.

Interaction of Stimuli

Pancreatic secretion is initiated by vagal stimulation, which also releases gastrin from pyloric antrum. Gastrin causes more quantity of acid secretion from gastric parietal cells. Acid enters duodenum and causes secretion of secretin and CCK-PZ.

Pancreatic digestion rapidly diminishes when upper part of intestine becomes empty as the products of digestion pass on to lower parts of intestine, the mucosa of which contain very little secretin or CCK-PZ.

The volume and quality of pancreatic juice vary according to the diet to which animal is accustomed.

1. *High carbohydrate:* Juice is rich in amylase poor in trypsin
2. *High proteins:* Rich in trypsin poor in amylase
3. *High fat:* Lipase is not increased but amylase is diminished.

Mechanism for Regulation of Volume

1. Acidity of duodenal content stimulates secretin release which causes copious supply of bicarbonates in pancreatic juice. So self-regulatory mechanism exists for neutralization of acid chyme.
2. Fat digestion products—depress gastric emptying and also gastric secretion by release of enterogastrone.
3. But it also stimulates release of secretin and pancreozymin, which causes secretion of pancreatic juice, moderate in volume and rich in enzyme.

Total Removal of the Pancreas

Total removal of the pancreas—in man is indicated in carcinoma of pancreas. It will result in:

1. *Diabetes mellitus:* Due to deficiency of insulin (which is secreted by β cells of islets of Langerhans).

ii. *Digestive disturbances*: Mostly affecting fat and protein digestion. Carbohydrate digestion and absorption is unaffected.

   i. Incomplete protein digestion results in increase in fecal nitrogen to 4-8 gm/day (normal 1 gm/day).
   ii. Fecal fat content is increased because fats are lost in feces (as their digestion is imperfect and absorption poor). Feces become bulky, pale, greasy and foul smelling (steatorrhea).

Normal fat content of feces is 5 gm in cases of complete removal of pancreas it becomes 40-50 gm.

Tests for Pancreatic Function

1. *Estimation of serum amylase levels*: Its levels are markedly increased in acute pancreatitis. Normal value 50-120 units/L.
2. *Fecal fat excretion test*: Person is given a diet containing 100 gm of fat/day. Stools are collected for 3-5 days and estimated for fat contents. Normal is 5-6 gm/day. In patients with pancreatic exocrine insufficiency it may increase to 40-50 gm/day.
3. *Lundh test*: Indirect stimulation of pancreas is done by ingestion of meal. Pancreatic juice is collected by duodenal intubation. Mean trypsin activity of < 6IU/L indicates presence of pancreatic exocrine insufficiency.
4. *Secretin and CCK-PZ stimulation test:* IV injection of secretin and CCK-PZ is given. Continuous duodenal aspiration is done. Bicarbonate, enzyme and volume of secretion in response is estimated.

SUCCUS ENTERICUS

Small Intestinal Secretion

Small intestine is so called because its diameters is smaller than that of large intestine. Small intestine is 7 meters long in adult.

It has three divisions:

Duodenum – first part, C shaped
Jejunum – proximal 2/5th part
Ileum – distal 3/5th part

The chyme delivered to duodenum is well ground and mixed with ample quantity of water. This physical state is ideal for chemical reactions.

1. Small intestine is major site for *digestion* of variety of nutrients. Pancreatic juice, bile and intestinal juice with their enzymes act on the nutrients and complete their digestion.
2. Small intestine is also a site for *absorption* of various nutrients. Small intestine is presented with 9L of fluid/day, of which 2L comes from dietary sources and 7L from GIT secretions. Only 1-2 L passes into the colon.

Composition and Functions

1. *Duodenal juice:* Special submucosal mucous glands are present in duodenum, which resemble gastric pyloric glands known as "Brunner's glands". They are tortuous, long and penetrate muscularis mucosa. Their ducts empty into the crypts of Lieberkuhn. They are numerous in first part of duodenum and very less below common opening of bile and pancreatic duct.
2. *Brunner s glands* secrete small amount of basal secretion at rest. It is rich in *mucus* and is *alkaline.* Stimulation of vagus, fatty food or secretin, produces large amount of thick alkaline mucous secretion, which help *to protect* the duodenal mucosa from gastric acid.

   Crypts of Lieberkuhn, which are present in whole of small intestine continuously form the cells which migrate up the villus and secrete the *intestinal juice* also called *succus entericus.*

Daily secretion—3 liters, colorless, slightly cloudy (because mixed with mucus)

pH — alkaline 7.6

Contain two parts:

1. Protective secretion of *mucus.*
2. Large quantity of serous fluid containing *water, electrolytes* and *enzymes.*

   Water – 98.5%
   Solids – 1.5%

a. Inorganic – 0.7%
   Cations – Na^+, K^+, Ca^{2+}, Mg^{2+}
   Anions – Cl^-, HCO_3^-, PO_4^{2-}

b. Organic – 0.8% enzymes.

Enzymes

Enzymes are secreted from luminal brush border of the epithelial cells:

1. *Enterokinase* (enteropeptidase): It activates trypsinogen to trypsin.
2. *Proteolytic enzymes:*
   - Peptidases, which act principally and rapidly on polypeptides and peptones and convert them to amino acids.
   - Nucleotidases and nucleosidases and nucleases which breaks down nucleic acids – to liberate purine and pyramidine bases.
3. *Lipase*—which hydrolyze fats.
4. *Amylase*—to hydrolyze starch.
   Both lipase and amylase are in traces in intestinal juice and are not of great importance in normal digestive process because great quantities of these enzymes are secreted by pancreatic juice.
5. *Invertase* (= sucrase) converts cane sugar to glucose and fructose.
6. *Maltase* breaks maltose in two molecule of glucose.
7. *Lactase* converts lactose into glucose and galactose.
   Last three enzymes are important because they convert disaccharides into monosaccharides and are essential for final digestion of carbohydrates.
8. Cholesterol esterase converts cholesterol esters to cholesterol.
9. Lecithinase converts phospholipids (lecithin and lysolecithin) to simpler phospholipids.
10. Alkaline phosphatase, converts organic phosphate to free phosphate.

Control of Secretion of Intestinal Juice

Chyme enters the small intestine and causes distention, peristalsis and irritation of mucosa.

Local reflexes are set up by mechanical stimuli or chemical irritation and copious secretion of intestinal juice occurs.

Local reflexes through myenteric plexuses are at work. The flow of intestinal juice is slight during first 2 hours but it is markedly increases in third hour.

Ingestion of meal causes flow of intestinal juice, which is most obvious at the upper end of gut.

CHAPTER

30

Large Intestine and Absorption in GI Tract

LARGE INTESTINE

Caliber of large intestine is greater than small intestine. The transverse measurements being greater in the cecum, and becoming narrower towards rectum.

The longitudinal muscle is gathered in three longitudinal strands, which since they are shorter than the other coats, produce, sacculated appearance.

Mucous coat is smooth *without villi* and *glands* are long and closely packed and are composed largely of mucous secreting goblet cells. Mucous cells are continuously and rapidly regenerated.

Lymph nodes are present in proximal part of colon and especially in vermiform appendix.

Principal functions of colon are absorption, fermentation, storage and defecation. Of these the first-two are primarily the functions of the proximal colon and last two are those of the distal colon. Proximal colon conserve the water and electrolytes, which escape absorption in the small intestine.

Functions of Large Intestine

1. Main function of colon is *absorption of water* and main sites of water absorptions are cecum and ascending colon.

   Approximately 1-2 L of isotonic chyme passes through ileocecal valve each day. Of this only 100-150 ml of water reaches rectum per day.

   Retention of water in body is important for fluid equilibrium. Persistent diarrhea, i.e. loss of large quantity of water leads to dehydration and loss of electrolytes, especially potassium, which may be quickly fatal especially in elderly persons and infants.
2. *Absorption of electrolytes glucose and vitamins:* Large intestine can absorb Na^+, K^+, Cl^-, glucose and certain vitamins. Na^+ is actively absorbed from colon and water follows osmotically (i.e. along the osmotic gradient).
3. *Mucus secretion:* The mucosa of large intestine contain numerous longitudinal glands. Cells are almost entirely goblet cells secreting mucus. Therefore, only significant secretion in large intestine is *mucus secretion.*

Rate of secretion in large intestine is regulated mainly by:

i. Direct, tactile stimulation of the goblet cells on the surface mucosa.
ii. Local nervous reflexes to goblet cells in crypts of Lieberkuhn.

iii. Stimulation of parasympathetic nerve fibers increase secretion of mucus, which occurs along with increase in mobility.

Mucus in large intestine protects large intestine against:

- Excoriation, mucus lubricates and facilitates passage of contents.
- Provides adherent qualities for holding fecal matter together.
- Protects intestine from great amount of bacterial activity that take place inside the feces.
- It increases the alkalinity of secretion so that acids formed deep in feces cannot attack the mucous membrane of large intestine (alkalinity nutralize the acid).

Whenever a segment of large intestine becomes intensely irritated, such as occurs in bacterial infection of intestine (gastroenteritis). Mucosa secretes large quantities of water and electrolytes in addition to normal viscid mucus secretion, which dilutes the irritating material and moves it towards anus, resulting in diarrhea, with loss of large quantity of water and electrolytes.

4. *Bacterial activity:* At birth colon is sterile but the colonic bacterial flora becomes established early in life. The microorganisms present in colon are '*Escherichia coli*, enterobacter, aerogens and gas gangrene bacilli. Some of them are beneficial and others are harmful. The beneficial effects of colonic bacterial flora are:
   i. Synthesis of vitamin K (important because the ingested vitamin K is not enough).
   ii. Synthesis of vitamins of B group, e.g. B_{12}, thiamine, riboflavin, folic acid, biotin, and pantothenic acid.
   iii. Gases are formed as a result of bacterial activity—such as carbon dioxide (CO_2), hydrogen sulfide (H_2S) and methane, which contribute to flatus. The smell is mainly due to presence of H_2S. However, most of the flatus passed through rectum is nitrogen from the air swallowed. About 200 ml of gas is found in normal human GIT and 500 to 1500 ml. Gas is produced in GIT daily. In some individuals gas in intestine causes cramps, borborygmi (rumbling noise) and abdominal discomfort.
   iv. Play a role in cholesterol metabolism by decreasing plasma cholesterol and LDL.
   v. By bacterial action cellulose is digested and give some calories.
   vi. A number of amines are formed in the colon by bacterial enzymes that decarboxylate amino acids.

   Examples:
   a. Histamine, and
   b. Tyramine, which are potentially toxic substances and are to be detoxified by the liver.
   c. *Indole and skatole* responsible for the odor of the feces.

   They can cause intoxication if absorbed into the blood. They are also detoxified by liver.
   vii. Pigments formed from bile pigments by the intestinal bacteria are responsible for brown color of the stool.
   viii. Organic acids formed from carbohydrate by bacteria are responsible for slightly acidic reaction of stools (pH 5 to 7).
5. *Excretory:* (a) waste products from digestive tract is excreted in the form of feces.

(b) some heavy metals like lead, bismuth, mercury, arsenic are excreted in feces.

6. *Propulsive:* Due to its mass peristaltic movement it helps in defecation.
7. *Storage:* The capacity of the colon to store residue for long periods of time is closely related to its absorptive function and motility.

The colon is able to store the material entering it because of its efficient absorptive mechanisms reduces the volume of the contents markedly.

There is retrograde propulsive movement in transverse colon, which gently propel the contents towards caecum. This gives maximum time for the contents to be exposed to the absorptive surface. In distal colon also there is pressure gradient from sigmoid colon towards descending colon. The gradient is only temporarily reversed during defecation.

ABSORPTION IN GIT

Absorption is *mainly the function of intestine*. In *mouth and esophagus* no appreciable absorption of foodstuff occur. Although certain drugs, e.g. steroids, hormones are absorbed through oral mucous membrane.

Absorption through *gastric mucosa* is limited but: (i) small amount of water (ii) simple salts, and (iii) glucose as well as (iv) alcohol may be absorbed.

In colon absorption is confined to: (i) water (ii) water soluble substances of low molecular weight, e.g. glucose and inorganic salts.

Absorption occurs most actively in the upper part of small intestine where the structure of mucous membrane is especially adapted for this purpose.

Absorptive Surface of Intestine

1. Intestinal surface show many folds known as plicae circulares or valves of Kirking or valvulae conniventes (Fig. 30.1), which increase the intestinal absorptive area *3 times*. These folds extend circularly all the way round the intestine and are especially well developed in duodenum and jejunum, where they project about 8 mm into the lumen.
2. Over the entire surface of the small intestine (from the point where the bile duct enters to ileocecal valve there are millions of small villi which project about 1 mm from the surface of the mucosa. About 20 to 40 villi are present per square millimeter of mucosa.

Distribution of villi is profuse in upper part of small intestine.

Distribution of villi is less in distal part of small intestine.

Thus, the presence of villi increases the mucosal surface another *10 times.*

The intestinal epithelial cells are characterized by brush border—as illustrated by electron microscopy. Microvilli of 1 μ length and 0.1 μ in diameter, protrude from each cell. This increases the surface area exposed to intestinal materials another *20 folds.*

The combination of: (i) valvulae conniventes, (ii) villi, and (iii) microvilli increase absorptive area of mucosa about 600 folds. Thus, the total area of entire small intestine is 550 sqm.

The microvillar surface is covered with the fuzzy coat or glycocalyx which consists of branched network of fine filaments, consisting

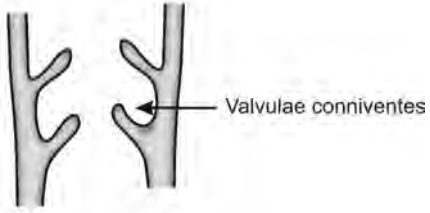


Fig. 30.1: Longitudinal section of intestine

of glycoproteins which are synthesized within the enterocyte. Besides the absorptive cells, the epithelium has goblet cells. These cells secrete mucus which further coats the surface of epithelium.

The microvilli glycocolyx complex, mucus and water together form a viscous barrier, which offers considerable resistance to the passage of molecules through it. The barrier is referred to as the unstirred water layer or the diffusion boundary layer.

The epithelial lining of villi rest upon a basement membrane, underneath it is smooth muscle fibers, continuous with muscularis mucosae. Just beneath the muscle tissue is loose areolar tissue containing innumerable blood vessels encircling the central lymphatic channel (central lacteal).

The smooth muscle in the villi helps in its contraction. For structure of villlus (refer to Figs 23.3 and 23.4).

Mechanism of Absorption

By two mechanisms:

1. Active transport, and
2. Passive diffusion – also can be called as osmotic diffusion. Passive means fluid and dissolved substances diffuse through the intestinal membrane without expenditure of energy by absorbing cells, e.g. water is reabsorbed by osmotic diffusion. Most solutes are absorbed by active transport.

   In active transport energy is imparted to the substance as it is being transported for the purpose of being concentrated on the other side of mucous membrane or for moving it against an electrical gradient.

Absorption of Carbohydrates

1. After hydrolysis of disaccharides and oligosaccharides the concentration of glucose outside is higher than inside the enterocyte (epithelial cell of gut). At this stage, some glucose is transported by *passive diffusion (Fig. 30.2).*
2. But the major mechanism for transport of glucose across the brush border membrane is active and *carrier mediated.*

The carrier molecule has one binding site for *glucose and one for sodium.* Therefore, carrier cotransports glucose and sodium into the enterocyte.

This transport is along the concentration gradient of *Na.* But its intracellular concentration is lower than the interstitial fluid concentration and the transport *across the basolateral membrane is active.* The sodium pump is energized by ATP. As sodium is transported into the intestinal fluid, water and glucose get dragged along passively. This is *facilitated diffusion.*

Note:

1. Galactose absorption from GIT occurs by the same mechanism which transport glucose.

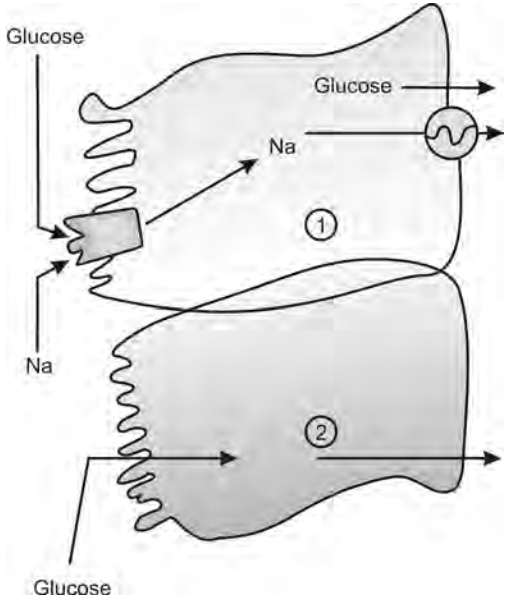


Fig. 30.2: Absorption of glucose (1) Na linked active transport, (2) Simple diffusion

2. Fructose utilizes a different carrier; it is transported by facilitated diffusion. Some fructose is converted to glucose in the mucosal cells.
3. Pentoses are absorbed by simple diffusion.
4. Rate of absorption of monosaccharides is variable. It is fastest with glucose and galactose, intermediate with fructose and slowest with mannose or pentose.

Absorption of Proteins

Although, theoretically the pancreatic juice can break proteins completely into amino acids. Normally the final stages of digestion are significantly assisted by enzymes located in brush border membrane or within the villous cell. 90% of intestinal epithelial cell peptidases are located in the cytoplasm of the cell and much of the: (a) final stages of digestion of peptides takes place at the brush border or within intestinal cells, (b) Desquamated intestinal cells create such a high concentration of peptides in the ileum that some peptides reaching the ileum may be converted into amino acids intraluminally. Thus, all protein is converted into amino acid prior to absorption into the blood stream.

The absorption of amino acids is similar to *that of glucose* but *unique*. The *similarity* is that it is sodium dependent; carrier mediated active process requiring energy.

The *unique feature* of amino acid transport is that: (i) there are *specific protein carriers* which are specific for a *particular class of amino acids*. (ii) Several amino acids are transported by more than one of these carriers. The multiple mechanisms for the transport of amino acids have a special functional significance—body's requirement of essential amino acids is highly specific. Even if one amino acid required for synthesis of a protein molecule is missing, the amino acid chain will come to an abrupt halt at the point where the missing amino acid is to be fixed. Therefore, it is important for survival that every single essential amino acid be absorbed.

The proteins digested in the gut are:

i. Taken in food.
ii. Proteins contained in the desquamated cells which are shed from the mucosal lining, and
iii. Some of the digestive enzymes may be absorbed intact by pinocytosis and resecreted. Proteins from source and are endogenous proteins and their amino acid composition is best suited for synthesis of human proteins.

Note: An Indian diet is generally made up of cereals and pulses. Most cereals are deficient in lysine while pulses are deficient in methionine but mixture provides good quality protein because cereals and pulses make up for each others deficiency.

Carriers for Transport of Amino Acid

1. One type of carrier located in brush border of mucosal cell of small intestine transports levo amino acids. Levo amino acids are most naturally occurring amino acids. D amino acids are absorbed solely by passive diffusion only.
2. Acid or basic amino acid are absorbed by second carrier mechanism, e.g. lysine, cystine, arginine and ornithine.
3. Dicarboxylic acids like glutamic or aspartic are carried by third type of carrier molecule.
4. *Glycine* is carried by fourth type of molecule.

Digestion and absorption of protein goes on throughout the small intestine. A small amount of protein which escapes digestion in small intestine reaches colon and is acted upon bacterial flora of colon.

Note: That proteins in stools are not of dietary origin but come from bacterial and cellular debris.

Absorption of Fats

1. In duodenum triglycerides are emulsified with the help of bile salts and are hydrolyzed by pancreatic lipase into fatty acids and some mono and diglycerides.
2. At this stage emulsion of fat is transformed into water-soluble micelles. Micelles formation and their absorption is helped by bile salts with which they form conjugate. Micelles are taken up by brush border and enter into the cell with the help of bile salts by *passive process.*
3. Bile salts act as shuttle engine carrying micelles into the cell. Subsequently they are extruded out.
4. Most of the fat is absorbed in jejunum but bile salts are not, and they are absorbed in terminal ileum by active process.
5. Micelles are absorbed *mostly* by dissolving themselves (diffusion) in membrane and to a less extent by pinocytosis.

   After absorption fat molecules pass in endoplasmic reticulum where triglycerides are resynthesized. ATP is required.
6. β lipoproteins cover these and render them water soluble when they are called chylo-microns (diameter—0.1 to 3.5 micro meter).
7. Chylomicrons leave the cell to enter lacteals (lymphatic channels), reach thoracic duct and then enter circulation.

Short Chain Fatty Acids

Short chain fatty acids (= having C atoms less than 14) are absorbed by, active process, requiring a carrier Na- dependent, into mucosal epithelium and then into portal circulation. They are not aggregated with micelles.

Note:

1. Pancreatic electrolytes, monoglycerides, fatty acids and bile salts interact spontaneously to form polymolecular aggregate called micelles.
2. Fat absorption is greatest in the upper part of small intestine but appreciable amounts are also absorbed from the ileum.
3. Movements of villi compress lacteals and capillaries, this increases the mobilization of lipids towards thoracic duct and portal vein respectively.
4. Cholesterol, like short chain fatty acids is absorbed directly into lymphatics and esterified as cholesterol esters. Its absorption requires presence of bile, fatty acids and pancreatic juice. It is mainly absorbed from the distal small intestine.

Absorption of Vitamins

1. Fat soluble vitamins ADEK are dissolved in micelles and absorbed alongwith them with the help of bile salts.
2. Water soluble vitamins diffuse through brush border epithelium and absorbed in portal blood.
3. Vitamin B_{12} is exception, because of large molecule. It is absorbed by special mechanism. On entering stomach it combines with a glycoprotein called intrinsic factor secreted from pyloric region of stomach—the complex of vitamin B_{12} and intrinsic factor is absorbed from terminal ileum. Once inside the membrane the intrinsic factor is set free and the membrane the intrinsic factor is set free and diffuses out leaving vitamin $B_{12,}$ which enters portal blood.

   A small amount of vitamin B_{12} is absorbed by pinocytosis.

Absorption of Water and Electrolytes

Chyme is isotonic with plasma in small intestine; sodium ions are absorbed actively by mucosal cells. So, luminal fluid becomes hypotonic. Intestinal mucosa has high capacity to absorb water. Therefore, water rapidly passes from hypotonic solution to plasma. So luminal fluid again becomes isotonic.

Water can pass in both direction. Carbohydrate and protein molecules are osmotically active and during digestion attract water.

When intestinal content becomes hyperosmotic, e.g. when children take lot of candy, etc. (high carbohydrate), water is drawn in and intestinal distention results which can reflexly cause nausea and vomiting.

Ca^{2+}, Mg^{2+}, K^{+} and Cl^{-} absorbed both by diffusion and active absorption.

Cl^{-}—follows Na^{+} ions.

In diseases like cholera, gastroenteritis large amount of fluid comes out as secretion leading to loss of salt and water.

Absorption of Iron

Broadly there are two forms of dietary iron, and they are absorbed differently.

Absorption of Hem Iron

Hem iron is iron present in: (i) myoglobin, (ii) hemoglobin and related compounds—at first hem is released from proteins by proteolytic enzymes of the gut and then haem is converted into hemin. Hemin is taken up by mucosal enterocytes. Iron is released from hemin intracellularly by an enzyme oxygenase. This iron is handled in the same way as nonhem iron. Hem iron absorption is not much affected by other dietary constituents.

Absorption of Nonhem Iron

Nonhem iron is converted into ferrous form before absorption. This is helped by gastric acid and vitamin C. Therefore, vitamin C enhances iron absorption (nonhem type). Animal foods such as meat or fish also enhance nonhem iron absorption. Uptake of iron is impaired by phytates and oxalates present in several plant foods. Also tea reduces its absorption.

Absorption of nonhem iron is by carrier mediated active process.

Calcium enhances iron absorption by forming complexes with phytates and oxalates.

Fate of Iron in Intestinal Mucosal Cell (Enterocyte)

Iron in enterocyte is present in the cytosol:

1. Partly chelated to amino acids (in low molecular weight form).
2. Partly in association with ferritin.

Part of iron present in enterocyte is transported into the blood stream by a passive process involving a receptor on the basolateral membrane.

Part of iron, which remains in the enterocyte is retained mostly as ferritin until the cell is sloughed off.

Note: If iron needs of the body is great; it is transported to the blood from enterocyte. But if the body is well stocked with iron, most of the iron in the enterocyte gets incorporated in ferritin and is lost when the enterocytes are shed into the lumen.

CHAPTER

31

Nutrition and Balanced Diet

NUTRITION

Nutrition is all about the study of food and how our bodies use food as fuel for growth and daily activities.

The food we eat supply energy needed by the body. We need energy for such vital activities like pumping action of heart, respiratory activities, keeping the body warm and for various metabolic activities and so on. These are examples of energy expenditure, which occurs even at rest. Additional energy expenditure occurs during muscular activities or during exposure to a cold.

We also require food for supplying vitamins, essential amino acids, essential fatty acids, etc. which cannot be synthesized by the body. Even for the substances, which can be synthesized by the body, the source of raw material is the food.

For children food is required for growth. In convalescence food provides replenishment of materials lost from the body during sickness.

In short, food mainly serves: (i) supply of energy, (ii) formation of tissues of body (growth , wear and tear), (iii) maintenance of vital activities, and (iv) body temperature maintenance.

Food that we take should be able to fulfill all these purposes, should contain all the macronutrients (protein, carbohydrates and fats) and micronutrients (vitamins and minerals) in right amount and right proportion so that:

1. Caloric need must be satisfied and extra calories are provided for growing children and convalescents.
2. Sufficient fiber or roughage must be supplied.
3. Water intake must be sufficient.
4. It should supply electrolytes and other essential inorganic elements.

Carbohydrates

(4 kcal/gm)
Normally provide major part of the energy in a normal diet.

We obtain most of our carbohydrate from: (i) starches found in cereals root vegetables and legumes, (ii) sugars found in fruits, milk (lactose), and some vegetables, apart from cane sugar (sucrose). They are converted into glucose by our digestive system and absorbed. Glucose is carried around the body in blood and is used by our tissues as source of energy.

When we use glucose in tissue respiration we need oxygen → glucose + O_2 = CO_2 + water + energy. Normally, we respire aerobically. But in heavy muscular activity like running in race, we may not get enough oxygen in blood. So our muscles are utilizing glucose anaerobically producing lactic acid.

How Much Energy should Come from Carbohydrate?

Example: If a man weighing 70 kg requires 2500 kcal/day, 64% of calories, i.e. 1600 calories must come from carbohydrates (approximately).

Carbohydrates are the cheapest of all foodstuffs. However, they produce fermentation in gastrointestinal tract. Among the poorer sections of Indians over 80% of the calorie needs are satisfied by the carbohydrates.

Fats

Fats have a high calorie value (9 kcal/gm). Fats are useful to people with large energy expenditure because fats are used as source of energy. One must have some fat in the diet because it contains *fat soluble vitamins and essential fatty acids.*

They are an insidious cause of obesity for sedentary people.

Advantages of Fats in the Diet

1. Fat yield 9 kcal/gm. Therefore, if the calorie requirement is very high, greater amount of food fat is desirable, as it reduces the bulk of the food.
2. Fat makes the food more palatable.
3. Fat prevents rapid emptying of stomach and thus prevents the need of too frequent eating.
4. As already stated it provides essential fatty acids and fat soluble vitamins A, D, E, K).
5. *Fat stores* are build up to provide energy.

Optimal Requirement of Fats

Few facts should be considered:

1. More of polyunsaturated fats should be consumed (those contained in oils).
2. Less of saturated fats should be consumed, so that they provide less than 10% of energy intake (those contained in butter, ghee).
3. A normal person can take enough fats so that it gives calorie intake of 25% (and not more) of the total. So in our classical example of a man weighing 70 kg, requiring 2500 kcal/day. Fats should provide 625 kcal/day (= 70 gm of fat consumed).

Protein

(4 kcal/gm)

Proteins of satisfactory quality must be present in the diet in sufficient quantity. Because they are preferentially utilized for other specific purposes apart from energy which cannot be served by any other nutrient:

Proteins are required for:

1. Replenishment of lost tissues, lost due to wear and tear.
2. For synthesis of enzymes (all enzymes are protein in nature).
3. For synthesis of protein hormones (e.g. insulin, parathormone, ADH, etc.).
4. Synthesis of breast milk.
5. For forming new tissues during growth convalescence and pregnancy.
6. For maintenance of concentration of plasma proteins.

Besides these reasons protein helps generation of excess heat due to its specific dynamic action (SDA). Therefore, people living in cold environment like to take extra protein in their diet. Causes of SDA (i) deamination, (ii) urea synthesis – which generates heat.

Proteins provide some 20 amino acids of which 10 are essential for normal synthesis of different proteins in the body and for maintaining nitrogen balance in adults, and they cannot be synthesized by the body. Therefore, they are called essential amino acids These are:

Valine	Lysine
Isoleucine	Leucine
Tryptophan	Phenylalanine
Threonine	Methionine

Histidine and arginine are also needed for growth in infants.

The other 10 amino acids can be synthesized in the body from nonprotein sources.

Biological value of different proteins depends on the relative proportions of essential amino acids they contain.

1. Proteins that contain all the essential amino acids (in addition to nonessential amino acids) are called first class proteins.
2. Proteins in whom one or more essential amino acids are missing are called second-class proteins.
3. Proteins of animal origin particularly from eggs, milk and meat are generally of higher biological value than the proteins of vegetable origin, which are deficient in one or more of the essential amino acids.

However, it is possible to have a diet of mixed vegetable proteins–which will give high biological value, e.g. wheat contain 10% protein and is relatively deficient in lysine. Legumes contain around 20% of protein, which is relatively deficient in methionine. If two parts of wheat are eaten mixed with one part of legume, a food results, which contains 13% of protein of high biological value. They supplement each others deficient amino acids. (Supplementary role of proteins). In Indian food, dal and roti gives a protein of good quality.

Quantity of Protein Required

A normal healthy person (adult) requires 1 gm/kg/day of food protein or 10% of total calorie intake.

Protein requirement is more in:

i. *Growing children:* (a) infants require 3 to 5 gm of protein per kg body wt/day, and most of the protein should be animal proteins or protein of vary high biological value, (b) throughout the period of growth, i.e. up to 18 years greater proportion of protein is required. Between 14th and 16th years in boys there is a spurt of growth, heavier quantities of proteins are required.
ii. *Lactation, pregnancy:* The protein requirement is about 1.5 gm/kg body wt/body.
iii. *Convalescence:* Protein requirement is increased.

Proteins Rich Foods

Figures in bracket indicate % of protein:

Meat (20%)	Dal (20%)
Fish (20 %)	Legumes (20%) approx.
Egg (8 %)	Rice (10%)
Cow's milk (3.5%)	Wheat (10%)
Examples of animal proteins	Examples of vegetable proteins Soyabean is another vegetable rich in protein

Energy Requirements

Largest component of energy expenditure is:

1. Basal metabolic rate (BMR)
   i. This increases with lean body mass (which is related to weight and height).
   ii. It declines with age.
   iii. It is less in women than men
2. *Muscular activity:* There is considerable variation of energy expended between individuals of the same size, age, sex and activity.

Approximate daily energy requirements:

Male office worker	– 2700 kcal
Men doing heavy work	– 3500 kcal
Healthy housewives	- 2000 kcal
Rural women	- 2250 kcal

There are two units in use of energy: (i) kilocalories, and (ii) kilo-Joules (1 kcal = 4.184 kJ).

Note: Energy requirement figures are from – Davidson's principles and practice of medicine 16th edition.

Vitamins and Minerals

Vitamins and minerals are needed in very small amounts and are therefore called micronutrients. Vitamins are organic substances in food. They have extensive involvements in metabolic reactions as factors and co-enzymes.

Most of the vitamins cannot be synthesized in the body in adequate quantities. Therefore, must be provided in the diet.

Vitamins are classified into:
1. Fat soluble vitamins A, D, E, K
2. Water soluble vitamins B complex and vitamin C.

Vitamin A (Retinol)

Dietary Sources

1. Retinol is found only in food of animal origin.
2. Herbivorous obtain the vitamin from its precursor or provitamins—some of the carotenoid pigments in plants.

Conversion of the best among these β carotene takes place in the human small intestinal wall (only 30% efficient).

Absorption of both retinol and carotene is facilitated by fats in the diet and bile salts in the duodenum.

Sources of retinol: Milk, butter, cheese, egg yolk, liver (richest source).

Source of carotene: Dark green leafy vegetable.

Yellow and red fruits (carrots rich source), red palm oil.

Functions

1. Vitamin A has a place in the function of retina and is present in rhodopsin and cone pigment.
2. Epithelium-maintenance of the integrity of epithelial tissues.
3. Growth
4. Bone remodeling
5. Reproduction.

Requirement

For adults 600 µg of retinal/day. If taken in the form of β carotene – intake is correspondingly increased (e.g. 100 gm of carrots).

Liver

Stores vitamin A, supply for 50 days.

Deficiency

On the world scale vitamin. A deficiency is one of the seven most common causes of blindness.
1. Night blindness
2. Xerophalmia and keratinization of the cornea and sometimes corneal ulceration in prolonged deficiency.

Vitamin D

Vitamin D is a collective term of which two are important:
1. Ergocalciferol (Vit D_2) – from vegetable source.
2. Cholecalciferol (Vit D_3) – from animal source.

Sunlight converts 7 dehydrocholesterol (a normal constituent of skin) into vitamin D_3.

Sources

1. Liver, eggs, milk, butter, fish liver oils.
2. In tropical countries from skin by irradiation with ultraviolet rays from sun.

Functions

1. It prevents hypocalcemia.
2. Achieves adequate calcium and phosphorus deposition in bones.
   It has actions at three sites:
   i. Intestine—enhance absorption of calcium and phosphorus.
   ii. Kidneys—stimulates reabsorption of calcium and phosphorus.
   iii. Bones—promotes deposition of calcium, at the same time allowing their modeling and remodeling.

Requirements

A person needs about 400 international units (IU) of vitamin D per day irrespective of age. One IU is equal to 0.025 µg of cholecalciferol.

Deficiency Results in

1. *Rickets in children* as bones are poorly calcified weak bones are not able to bear the weight of the body and child develops bowing of legs. Ribs are deformed – swellings at costochondral junctions. (Rachitic rosary = beads).
2. *In adults:* Poorly calcified bones which fracture with even mild trauma condition is known as osteomalacia.

Vitamin E

Group of substances known as tocopherols. The most biologically active member of the group is alpha tocopherol.

Sources

Vegetable oils.

Functions

1. It is an antioxidant. Free radials, which are formed during metabolic reactions and also entering the body from environment are neutralized by antioxidants.
2. Prevents oxidation of (polyunsaturated fatty acids PUFA).

Requirement

10 mg vitamin E/day.

Deficiency

It is very rare as needs are met within any diet.

Deficiency is seen in premature infants and adults having intestinal malabsorption.

Major manifestation is hemolytic anemia.

Vitamin K

Group of chemicals called quinones.

Most important phylloquinone found in plants. It is synthesized by bacteria and found in animal tissues.

Sources

1. Green leafy vegetables.
2. Bacterial synthesis in large intestine.

Vitamin K deficiency-seen in persons having malabsorption or taking antibiotic or taking Vitamin K antagonist like Dicumarol.

Functions

Vitamin K is required for synthesis of prothrombin and coagulation factors VII, IX, X in liver.

Requirement

0.4 µg/kg body weight/day.

Deficiency

Causes bleeding tendency with prolonged prothrombin time and low serum prothrombin level.

Thiamine (Vitamin B_1)

Sources

1. Cereals and pulses, but more than 90% of thiamine in present in husk and germs both of which are removed during milling.
   Repeated washing of rice, soaking of legumes for a long time in water, which is discarded and use of washing soda to hasten cooking of legumes, are all practices which enhance the loss of thiamine from the diet.
2. Vegetables, milk, milk products, various flesh floods (pork).

Functions

Thiamine pyrophosphate (TPP) is essential coenzyme for decarboxylation of pyruvate to acetyl coenzyme A in Kreb's cycle.

Requirements

Depends on intake. An intake of 0.5 mg thiamine per 1000 kcal energy intake is ordinarily quite satisfactory.

Deficiency

1. Cells cannot utilize glucose aerobically, this is likely to affect NS first, since it depends entirely on glucose for its energy requirements.
2. Thiamine deficiency can produce cardiac failure and/or peripheral neuropathy.
3. *Wet Beriberi:* In Singhalese language it means 'I cannot' (said twice), meaning patient is too ill to do anything, occurs in those who eat polished rice mainly.

   Owing to lack of thiamine: Glucose is incompletely metabolized and pyruvic and lactic acid accumulate in tissues and body fluids-cause vasodilatation of blood vessels – resulting in oedema and cardiac failure.
4. *Dry Beriberi:* It is essentially peripheral neuropathy. Nutritional background is similar to wet beriberi. There is degeneration and demyelination of both sensory and motor nerves – there is severe wasting of muscles.

Riboflavin (Vitamin B_2)

It is a compound with an intensely yellow color.

Sources

1. Cereals are good source of riboflavin. Refining of cereals results in loss of up to 60% of their riboflavin content
2. Liver, kidney
3. Milk, yoghurt.

Functions

Riboflavin is a constituent of the flavoproteins, which are concerned with tissue oxidation.

Requirements

Depends on energy intake 0.6 mg/1000 kcal meets the requirements of all age groups satisfactorily.

Deficiency

1. Angular stomatitis cracks are centered around the mouth corners.
2. Cheilosis—lips may be inflamed.
3. Glossitis—tongue may become smooth and purplish red.

Niacin (Nicotinic Acid and Nicotinamide)

Sources

1. In husk of cereals (more than 90%)
2. Legumes
3. Flesh foods
4. It can be synthesized from tryptophan.

Functions

Like thiamine and riboflavin, niacin also plays vital role in utilization of carbohydrates.

Requirements

Depends on energy intake. About 7 mg/per 1000 kcal is satisfactory.

Deficiency

Manifests as Pellagra—affects GIT, skin and nervous system giving rise to the symptom complex of 3 D's – diarrhea, dermatitis and dementia.

Pantothenic Acid

Sources

Widely distributed in plant as well as animal foods. Refining of cereals and heat processing result in appreciable loss.

Functions

Used to synthesize coenzyme A (CoA), from this acetyl CoA is formed with acetate. Acetyl CoA is vital in Kreb's cycle. Pantothenic acid is essential for obtaining energy from carbohydrates fats or proteins. Acetyl CoA- is precursor of triglycerides, cholesterol, hemoglobin and acetylcholine synthesized in the body.

Requirement

4-7 mg/day.

Deficiency

Mild deficiency may give rise to poor resistance to stresses such as infection.

Biotin

Sources

Present in number of different foods and it can be synthesized by intestinal bacteria.

Function

Functions as coenzymes for several carboxylases.

Requirement

100 to 200 µgm/day.

Deficiency

Occurs when raw egg white is taken for long duration. Raw egg white contains a protein – avidin, which binds biotin. Heat denatures avidine. Therefore, cooked egg white does not produce biotin deficiency.

Pyridoxine (Vitamin B_6)

Comprises of group of atleast three related compounds, pyridoxol, pyridoxal and pyridoxamine with similar physiological actions.

Functions

Its active form pyridoxal phosphate, coenzyme for large number of different enzymes involved in the metabolism of amino acids.

Sources

Widely distributed in plants and animal tissue. Liver, whole grain, peanuts and bananas are good source.

Requirements

Depends on protein intake and is about 0.02 mg/gm of dietary protein or 2 mg/day.

Deficiency

Rare, but when occurs it causes poor growth, anemia and neurological symptoms nervousness, irritability, insomnia and convulsions.

Folic Acid

Sources

As name suggests, folic acid (folium = leaf) is abundant in green leafy vegetables.

1. Fruits, wheat germ
2. Liver, kidney, and
3. Yeast

Functions

1. In the form of tetrahydrofolic acid (THFA) is required as a coenzyme for all single carbon transfer reaction of the body.
2. Involved in the synthesis of purines and pyramidines (part of DNA and RNA). Therefore, important for rapidly dividing cells such as blood cells.
3. For synthesis of porphyrin of the hemoglobin molecule.

Requirements

1. 100 µg of folate per day for adult.
2. 300 µg of folate per day for pregnant women.

Deficiency

1. Deficiency is common during pregnancy.
2. Deficiency results in megaloblastic anemia.

Cobalamin (Vitamin B_{12})

It is complex molecule containing cobalt.
Exists in several forms

1. Cyanocobalamin – synthesized by bacteria.
2. Hydroxycobalamin
3. Methylcobalamin
   Found in dairy products.

Sources

1. It is available only in animal foods. It is synthesized by bacteria residing in the rumen of animals, absorbed and stored in tissues.
2. Bacteria residing in colon (of human beings) also synthesize vitamin B_{12} but it cannot be absorbed from there. Therefore, human beings must get their supply of vitamin B_{12} from animal foods – milk, milk products, liver, kidney and other flesh floods.

Functions

Its active form is the cobamide co-enzyme, which can be synthesized from dietary vit B_{12} with the help of riboflavin, niacin and manganese.

Vitamin B_{12} supplies methyl groups for the synthesis of DNA. Therefore, vitamin is important for cell division and its deficiency specially affects rapidly dividing cells such as blood cells.

Vitamin B_{12} has some unique role in neural functions. The role may be related to the participation of vitamin B_{12} in the carbohydrate metabolism in neurons or in lipid metabolism in the myelin sheath.

Requirements

1 µgm/day

- Vitamin B_{12} is stored in liver (about 1 mg). Therefore in well nourished individual this liver store can last 1000 days in case of lack of dietary vitamin B_{12}.

Deficiency

When it occurs it is due to poor absorption or deficiency of gastric intrinsic factor. It manifests as a megaloblastic anemia known as pernicious anemia.

If not treated in time it progresses to a serious form in which central nervous system is involved – subacute combined degeneration of spinal cord, in which there is defective myelination of peripheral nerves and posterior and lateral columns of spinal cord.

Ascorbic Acid (Vitamin C)

Sources

Vitamin C is found only in plant food.

1. Its richest source is amla (emblica officiantes), lime, lemons and oranges.
2. Substantial amount is also present in potato and fresh green vegetables. But heat and oxidation destroys it.

Functions

1. Needed for hydroxylation of proline to hydroproline, the characteristic amino acid of collagen in connective tissue.
2. Needed for formation of dentin in the teeth.
3. Needed for formation of neurotransmitters of CNS – norepinephrine and serotonin.
4. May also function as an antioxidant in the body.

Requirement

40 mg per day.

Extra vitamin C is needed after surgery to facilitate formation of connective tissue during healing.

Deficiency

In severe form is called scurvy:

1. It affects blood vessels – leading to abnormal petechial hemorrhages under the skin.
2. Bleeding of gums is common.
3. Joint pains due to bleeding in joints.
4. Generalized weakness and flaccidity of muscles (frog posture in children).

Minerals

1. These are also needed in small quantities but more than vitamins. They also perform vital functions in the body. More than 20 minerals are now considered essential nutrients. Those required in very small quantities are called trace elements.
2. In general, animal foods are better source of minerals than plant foods. In cereals and legumes the minerals are concentrated in outermost layers, i.e. husk. Therefore, refining of food grains result in their loss. Important ones are Na, K, chloride, Mg, Ca, phosphorus, iron, iodine, zinc, copper, chromium, selenium, manganese and molybdenum and also:
   i. Fluoride—its optimal intake reduces dental carries in man. Source—drinking water containing 1 ppm of water.
   ii. Cobalt is physiologically active only in the form of vitamin B_{12}
   iii. Sulfur is required in the form of amino acid methionine and cysteine.

Copper and chromium- facilitate action of insulin.

Selenium—Soil content varies. Selenium is part of the enzyme – glutathione peroxidase. Helps to prevent accumulation of hydroperoxides in cell membrane.

Sodium, Potassium and Chloride

Between 10 and 15 gm of NaCl are consumed/day. If the supply is short body excrete less sodium.

Excess sodium supply is important because our ability to excrete sodium is not highly satisfactory, and excess sodium in food may help to develop high blood pressure. There are conditions where it is necessary to use a salt free (Na restricted) diet. Foods comparatively

deficient in sodium are rice, wheat, over ripe fruits and sugar.

The daily intake of potassium is between 2-3 gm. Plant foods are rich in K (Potassium), fruits and vegetables. Deficiency of K–may occur in diarrhea, vomiting, heavy sweating (K lost in all)—results—weakness, muscle cramps.

Functions

1. *Sodium* is the principal cat ion of the extracellular fluid (ECF) and is major contributor to the osmotic pressure of these fluids. Therefore, sodium helps regulate total fluid volume of the body as well as the balance between extracellular and intracellular fluids.

   Sodium, as sodium bicarbonate, forms a part of the bicarbonate – carbonic acid buffer system of the body. In this way sodium helps regulate the pH of body fluids. Thus, help to maintain constancy of internal environment. It provides the cells an optimal and relatively constant environment in which they can function normally.
2. *Potassium* is principle cat ion of the intracellular fluid and therefore, is an essential constituent of cells. Therefore it is required during growth.

   Potassium is one of the two major ionic participants in maintenance of resting membrane potential the other participant is sodium. Both help in genesis of action potential.

Calcium

The body of adult normally contain about 1000-1200 gm of calcium 99% of which is in skeleton—bones and teeth.

Sources

1. Best sources are milk and milk products
2. Fish eaten with bones, shell fish
3. Nuts, e.g. almonds, peanuts
4. Vegetables — like chick peas, beans
5. Egg and fortified bread.

Requirements

1. 500 mg/day—adult (WHO)
2. 1200 mg/day—pregnancy and lactation
3. 1000 mg/day—postmenopausal women.

Deficiency

No clear deficiency syndrome, but calcium metabolism shows abnormalities in:

a. Vitamin D deficiency
b. Hypo- and hyperparathyroidism
c. Senile osteoporosis.

Phosphorus

The body of an adult has about 600 gm phosphorus, of which 90% is in bones and teeth.

Sources

Widely distributed in foods. The concentration of phosphorus is particularly high in protein rich foods, milk, aerated soft drinks and processed foods contain considerable amounts of phosphorus. Excessive consumption of these foods may lower calcium/phosphorus ratio of the diet.

Functions

Used in body in the form of phosphates present in all cells. The key molecules involved in energy transactions of the body, ATP, ADP and AMP contain phosphorus.

1. Phosphorylation of enzymes required in action of various hormones, neurotransmitter and neuroactive peptides.
2. Phosphate groups form part of DNA and RNA molecules.
3. More amount of phosphorus is present in the form of calcium salts in bones and teeth.

Requirement

It should be equal to calcium intake.

Deficiency

Does not occur in ordinary circumstances. Renal dialysis and excessive use of antacid containing aluminium hydroxide (which reduces phosphorus absorption) cause deficiency.

Iron

Adult body has about 4 gm iron – 2/3 in the form of hemoglobin and remaining in the form of myoglobin, cytochromes, transferrin, ferritin and storage iron (hemosiderin).

Sources

Leafy vegetables, potatoes, legumes, fruits:
1. Meat, liver
2. Peas, beans and lentils
   In cereals, iron is concentrated in husk.

Daily Requirements

1. In men about 1 mg iron is lost per day.
2. In women about 2 mg iron is lost per day because of menstrual loss.
3. Daily intake should be about 30 times the loss as poor absorption of iron is there from mixed cereal diet.
4. Therefore, as per ICMR for men 28 mg/day iron is needed.
   For women 30 mg/day iron is needed.

Deficiency

Leads to microcytic hypochromic anemia.

Iodine

Iodine metabolism in body is linked with thyroid function.

Sources

Iodine is present in sea, seafoods and soil and water in trace amounts over most of the land.

Iodine is lacking in the major mountainous areas of the world, e.g. Alps, Himalayas. These regions show endemic goiter being present.

To make up for this deficiency salt is iodized in these regions by adding potassium iodide.

Function

In the body in the form of thyroid hormones.

Requirement

1 μg/kg body weight.

Deficiency

May be due to less consumption of iodine or due to presence of goitrogenic substances (= antithyroid substance) in the diet, such as cabbage, turnip, radish.

Zinc

Body contains 2 gm zinc about 75% of which is in bones, rest in skin, hair, testes, RBC.

Sources

Cereals and legumes but absorption from these sources is prevented by phytic acid.
1. Sea foods (oysters), fish, crab
2. Liver, beef, lamb
3. Nuts.

Functions

Zn is a part of several enzymes known as metalloenzymes, e.g. carbonic anhydrase, carboxypeptidase, alkaline phosphatase DNA polymerase and RNA polymerase. It is also cofactor in synthesis of collagen (in enzymic reactions).

Therefore, Zn is essential for normal growth, for reproductive function, for wound healing and for normal activity of sense of smell and taste.

Requirements

Only 25% of dietary Zn is absorbed. For adult requirement is 15 mg Zn per day. Requirement is slightly higher in periods of growth spurt, pregnancy and lactation.

Deficiency

Results in poor growth and slow sexual development, poor wound healing, loss of appetite and diminished activity of sense of smell and taste and skin disorders.

Dietary Fibers and Roughage

Dietary fiber is the natural packing of plant food. It can be defined as those parts of food, which are not digested by human enzymes, hence they increase the bulk of feces and mass peristalsis (i.e. defecation) is favored.

Principal classes of dietary fibers are: cellulose, hemicellulose, pectins and gums—all are polysaccharides. Pectins and gums are viscous not fibrous.

1. Some types of fibers, notably hemicellulose of wheat, increase the water holding capacity of colonic content and the bulk of faeces. They relieve simple constipation and reduce the risk of colonic cancer.
2. Other viscous indigestible polysaccharides like pectin and gum have more effect on upper GIT. They tend to slow gastric emptying, contribute to satiety, and reduce plasma cholesterol.
3. Dietary fiber is in fact partly digested in large intestine by resident bacterial flora with formation of flatus and small volatile fatty acid—absorbed by colonic mucous membrane.

   Recommended intake – 15-20 gm/day.

BALANCED DIET

The balanced diet provides adequate quantities of all essential nutrients – carbohydrates, proteins, fats, vitamins, mineral salts and fiber. It must contain these in correct proportion.

Many vastly different diets can all be balanced diets. For example, there can be a balanced Indian diet, a balanced Chinese diet and a balanced European diet. They look very different but are all balanced because chemically they provide all essential nutrients in adequate quantities.

Knowledge of balanced diet is useful in two ways: (1) To frame a diet, and (2) To evaluate a diet. To frame a diet – we first determine the energy intake, which would be adequate for the individual, depending on age, sex, body, weight and habitual physical activity. Next step is to determine desirable minimum protein intake on the basis of recommended dietary allowance (RDA). For example, for 50 kg moderately active woman a diet should provide 2225 kcal and at least 50 gm protein every day. Remaining 2025 kcal can be obtained from flexible mixture of carbohydrates and fats. The diet should provide at least RDA of vitamins and minerals.

Then depending on likes and dislikes of the person a diet can be prescribed of:

1. Mixture of cereals and pulses as major sources of energy.
2. Vegetables – preferably green and partly raw.
3. Milk and milk products with fats.
4. Fruits.

CHAPTER 32

Physiological Anatomy and Composition of Air

In unicellular organism oxygen—diffuses from watery environments to all parts of cell.

With increase in size and complexity of animal, distance between the surface and tissues is increased. Therefore, special means are required to carry oxygen to individual cells.

In mammals—oxygen is taken up by capillaries in lungs and conveyed by blood to tissues. At the same time the CO_2 produced by tissues is carried to lungs and then leaves the body (Fig. 32.1).

Respiration consist of:

1. External respiration
2. Internal respiration.

External respiration includes:

1. Breathing
2. Diffusion of gases

} Takes place in lungs

Internal respiration includes:

1. Diffusion of gases
2. Oxidation

} Takes place in tissues

In between, external and internal respiration is the transport mechanism.

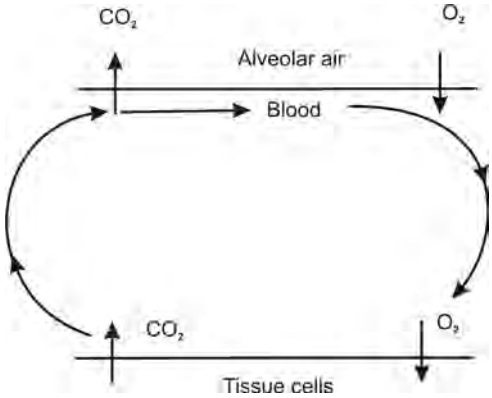


Fig. 32.1: Scheme of respiration

RESPIRATORY TRACT

1. Upper respiratory tract from nares to vocal folds, and
2. Lower respiratory tract below vocal folds.

Nose

Nasal passages are lined by vascular and moist mucous membrane covered by ciliated columnar epithelium except entrance. Functions of nasal epithelium are: (a) it warms the air, (b) removes the dust, and (c) humidification of air.

In the nose the air is warmed, therefore by the time air reaches trachea its temperature rises to body temperature and up to the bifurcation of trachea it is completely humidified.

The Air Passages

Pharynx

Pharynx is used by both respiratory and digestive systems and therefore has attributes of both.

Nasopharynx

Nasopharynx is normally concerned with respiration only. Therefore, it is lined by pseudostratified ciliated columnar epithelium. (Oropharynx and laryngeal pharynx are lined by stratified squamous epithelium—so designed, as it can withstand wear and tear by coarse food).

Trachea

Trachea arises from larynx. It is a circular tube about 16 mm in diameter and 12 cm long. It is kept patent by incomplete rings of cartilages, which are deficient posteriorly, so filled by fibrous, elastic and muscular tissue.

During inspiration its diameter and length is increased.

Trachea subdivides into *two Bronchi,* which subdivides repeatedly and the smallest air passage is *bronchiole,* with every branching they become narrower.

Bronchi are also lined by cartilage rings, but they progressively decrease in extent with every successive branching and the relative amount of smooth muscle increases.

Innermost lining of trachea and bronchi are pseudostratified ciliated columnar epithelium and contains numerous goblet cells, which secrete mucus. The cilia catch the dust particles and other particles. The particulate matter is swept by the cilia towards the pharynx where it is periodically swallowed with saliva. In bronchioles there are *no* goblet cells (Figs 32.2 and 32.3).

1. *Terminal bronchiole:* Opens in respiratory bronchi of equal diameter.
2. *Respiratory bronchiole:* Gives rise to number of short passages called alveolar ducts.
3. Alveolar ducts open into wider alveolar sacs, on the walls of which are located pulmonary alveoli.

The respiratory passages up to and including respiratory bronchiole are purely conducting pathways for passage of air. Respiratory gas exchange does not occur in this region.

Alveoli are also present on the walls of alveolar ducts and few can be seen in the respiratory bronchiole.

The *epithelial lining* – which is of the ciliated columnar type almost throughout the respiratory tract up to the terminal bronchioles, is replaced by cuboidal cells in the respiratory bronchioles and by squamous cells in the alveolar ducts.

Alveoli: There are about 300 million alveoli in the lungs. When fully inflated each has a diameter of 250 to 300 microns.

1. They are lined by continuous lining of extremely flattened epithelium. Many of the cells having long cytoplasmic extensions, are called Type I cells.
2. At the angles of the alveoli are somewhat taller cells with oval nuclei and granular cytoplasm. These corner cells known as type II or septal cells have many mitochondria, are metabolically highly active and secrete surface active material which lines the alveolar surface, known as *surfactant*.
3. The total alveolar surface area is about 100^2 meter. Alveoli are ideal structures for

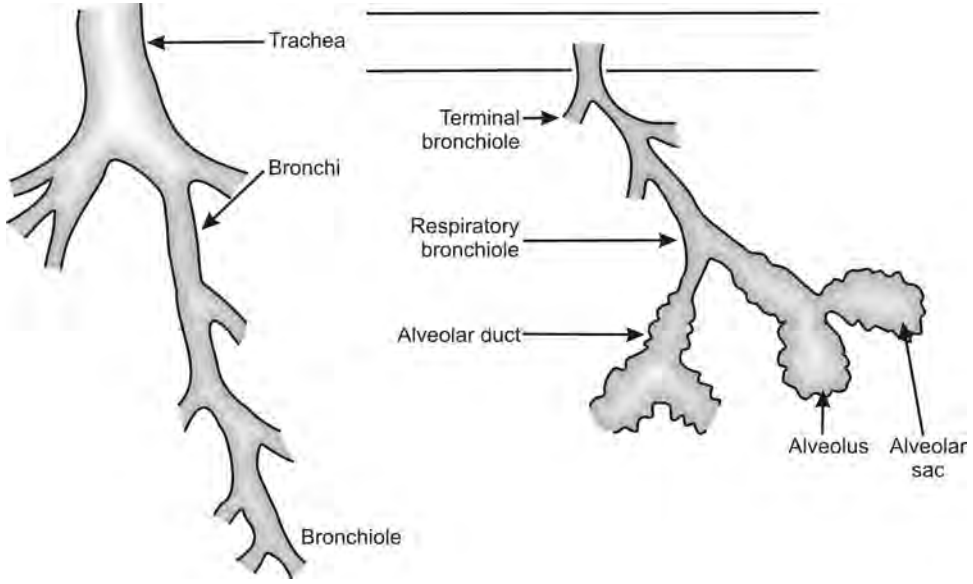


Fig. 32.2: Tracheobronchial tree

bringing about gas exchange because of: (i) enormous surface area, and (ii) thin alveolar wall.

4. Pulmonary alveoli are kept dry because colloid osmotic pressure exerted by plasma proteins is 25 mm Hg and pulmonary capillary pressure is low. When pulmonary capillary pressure increases it results in pulmonary edema.

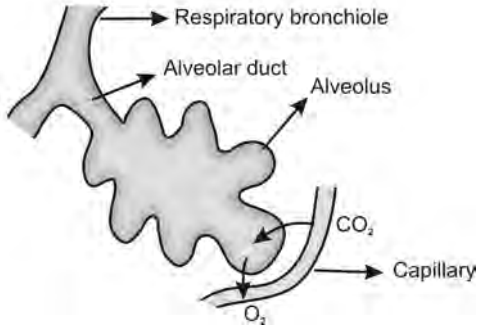


Fig. 32.3: Alveolocapillary gas exchange

BLOOD SUPPLY

Capillaries in the alveolar wall are derived from *pulmonary artery.*

1. Pulmonary artery arises from right ventricle and the entire right ventricular output of 5L per minute flows through the lungs.
2. It is carrying deoxygenated blood. It branches in the lungs like airways.
3. Beyond the terminal bronchiole a dense capillary network is formed on the walls of air sacs, alveoli and in interalveolar septa.
4. Pulmonary capillaries are lined by single layer of endothelial cells.

Nutrition for the lungs is derived from the *Bronchial arteries,* which arises from descending aorta and carry oxygenated blood. They supply bronchial glands and walls of the air passages up to the terminal bronchioles. Blood flow through these vessels is only 2% of the cardiac output.

Bronchial Smooth Muscles

1. Present in submucous coat, form two helical tracts, which run in opposite directions along the bronchial tree.
2. They are innervated by vagus and sympathetic nerves stimulation of vagus causes bronchodilatation.
3. Bronchial smooth muscle shows some degree of tone due to vagal activity.
4. The bronchomotor tone is affected by reflex and humoral factors.

Reflex bronchoconstriction or dilatation may be brought about by stimulation of variety of nerve endings and also by stimulation of receptors present in respiratory tract and chemoreceptors (aortic and carotid).

i. CO_2 excess, O_2 lack } increase bronchomotor tone
ii. Adrenaline (epinephrine) and β adrenergic stimulating drugs cause bronchodilatation.
iii. Atropine causes bronchodilatation by its parasympatholytic effect.
iv. Histamine and acetylcholine cause bronchoconstriction. Bronchoconstriction is associated with increased *airway resistance.*

5. Paroxysmal attacks of dyspnea in *bronchial asthma* are associated with bronchoconstriction. Bronchodilator drugs relieve it.

ALVEOLAR SURFACE TENSION

Surface tension of the fluid lining the alveoli is kept low by a substance called *pulmonary surfactant.* It is secreted by the *type II* alveolar cells and lines the alveolar surface. Lowering of the surface tension by surfactant improves the distensibility: (a) therefore, the first function of surfactant is to reduce the muscular effort required for breathing. (b) it prevents emptying of small alveoli into large alveoli and (c) prevents pulmonary edema.

Chemically, it is *phospholipid dipalmitoyl lecithin.* It appears late in fetal life.

Deficiency

Deficiency of surfactant is responsible for the respiratory distress syndrome of the newborn (hyaline membrane disease).

Pleura

The outer surface of the lungs is covered by delicate serous membrane *visceral pleura,* which is reflected from the roots of the main bronchi on inside of thoracic wall and the upper surface of diaphragm—the *parietal pleura.*

Surface of each layer of pleura is single layer of flattened cells. Parietal and visceral pleura are separated by thin film of serous fluid, which is sufficient to lubricate so that movement of one over another is easy during breathing. So long as film is intact, it exerts a hydraulic traction, making the two layers inseparable under normal conditions and this is an important factor in the mechanics of lung expansion.

Under physiological condition the potential space between two pleurae is called *pleural cavity.* Sometimes, fluid accumulates in it – *hydrothorax* or air accumulates in it—*pneumothorax* or both accumulate in it—*hydropneumothorax.*

COMPOSITION OF INSPIRED, EXPIRED AND ALVEOLAR AIR

1. *Composition* (= % of each gas in the air) *of atmospheric* air is constant. The percentage of oxygen and nitrogen in the air is about 20% and 80% respectively, irrespective of altitude and at sea level.

Carbon dioxide content of air shows slight variation, being more in large cities and industrial areas.

If we know the fractional concentration of a gas in the air, its partial pressure can be easily calculated.

Example:

At sea level atmospheric pressure is 760 mm Hg.

Suppose humidity at that time is such that it exerts pressure of 10 mm Hg.

Therefore, 760-10 is the pressure of all other gases in air (= 750).

If oxygen forms 20% of the air. Then partial pressure of oxygen (PO_2)

$$= 750 \times \frac{20}{100} = 150 \text{ mm Hg.}$$

PO_2 changes with altitude:

Example:
Atmospheric pressure is:
760 mm Hg at sea level and
400 mm Hg at 5000 meters above sea level

$$\text{Hence, } PO_2 \text{ will be } 760 \times \frac{20}{100}$$

$$= 152 \text{ mm Hg at sea level}$$

$$\text{And } PO_2 \text{ will be } 400 \times \frac{20}{100} = 80 \text{ mm Hg}$$

at 5000 meter above sea level.

2. *The composition of inspired air is same as that of atmospheric air. But* by the time air reaches the trachea, it is saturated with water vapor. This water vapor exerts a pressure of 47 mm Hg at 37°C. This causes slight changes of partial pressure of the gases present in air.
3. *The composition of alveolar air:* In the alveoli some oxygen is removed from the air and some carbon dioxide is added to it. Under most conditions, the volume of carbon dioxide added is slightly less than that of the oxygen removed. This is reflected in composition of the alveolar air.
4. *The composition of expired air:* When air is breathed out the portion breathed out first is the air from the airways, which has almost the same composition as the inspired air.

As the expiration proceeds the share of alveolar air increases till finally the end expiratory air is identical with alveolar air. Therefore, mixed expired air has composition midway between inspired and alveolar air (Table 32.1).

Table 32.1: Composition of air in relation to respiratory phases and regions

	Composition of	*Oxygen*	*Carbon dioxide*	*Nitrogen*
i.	Inspired air	20.93%	0.04%	79.03%
ii.	Expired air	16.23%	4.05%	79.72%
iii.	Alveolar air	14.00%	5.60%	80.40%

1. In quiet respiration an adult breaths 6-7 L/min. This is known as pulmonary ventilation or minute ventilation.
2. His breathing rate is about 18/min.
3. Amount of inspired air per breath is 500 ml at rest.
4. An adult uses 250 ml O_2/min.
   And expires 200 ml of CO_2/min.
5. In heavy exercise pulmonary ventilation volume increases.

CHAPTER

33

Mechanics of Respiration

INSPIRATION AND EXPIRATION

A balloon may be filled by pumping air into it at a pressure, higher than existing pressure – or by *positive pressure filling.*

Or a balloon can be stretched to enlarge it, so that the volume of air inside increases but the pressure is reduced. If it is reduced at a pressure lower than the surrounding pressure and if it is in communication with surroundings, air will rush into the balloon – or by *negative pressure filling* the balloon is filled.

This is the method employed by respiratory system to expand the lungs during inspiration.

During inspiration, the chest expands. Expansion of thoracic cage, generates negative pressure in the lungs and air rushes in the lungs.

During expiration the chest becomes smaller, producing positive pressure in the lungs. Therefore, air moves out of the lungs.

Change in the size of the thoracic cage during inspiration and expiration is very important for respiration.

The change in the size of thoracic cage is brought about by: (i) Diaphragm, and (ii) Intercostal muscles.

The rhythmic act of quiet breathing includes:

1. Active inspiratory movement
2. Passive expiratory movement.

Inspiration

Inspiration is brought about by (Fig. 33.1):

1. *Downward movement of the diaphragm* due to its contraction, which increases size of the thoracic cage from above downwards.
   - i. Diaphragm is supplied by motor neurons of C3, 4 and 5 segments of spinal cord. They are excited by impulses descending on them from dorsal respiratory group of neurons (DRG) via phrenic nerve the impulses reach diaphragm.
   - ii. Diaphragm consist of muscle fibers and central tendinous portion.
     Muscle fibers arise from:
     - Xiphisternum,
     - Inner surfaces of lower six ribs,
     - As crura from vertebra, and
     - Arcuate ligament.
   - iii. Normally, it is dome shaped and its fibers converge on central tendon.
   - iv. When it contracts it draws the central tendon down thereby increasing the vertical diameter of the chest.

v. The effectiveness of diaphragm for changing the dimensions of chest depends on (i) strength of contraction, and (ii) to its contour when relaxed.

Strength of contraction as in any muscle depends on number of muscle units activated and synchronization and frequency of their discharge.

vi. Increase in circumference of lower chest by any condition flattens the diaphragm. Extreme obesity, advanced pregnancy and tight abdominal clothing interfere with diaphragmatic mobility.

vii. Descent of diaphragm can be accomplished by displacement of abdominal contents, which is possible by relaxation of muscles of abdomen during inspiration. Abdominal wall moves outward during inspiration.

viii. In normal breathing (eupnea), diaphragm shows excursion of some 1.5 cm. In deep breathing, diaphragm may show as much as 7 cm excursion. Movement can be seen in radiographic screening.

ix. Diaphragm movement accounts for 75% of tidal volume.

x. Descent of diaphragm is similar to *piston movement.*

2. *Inspiration is brought about by:* Second important factor *rib movement*.

Rib movement: The external intercostal muscles arise from the lower border of the ribs, and fibers run downward and medially over the front of the thorax and downward and laterally over the back of the thorax, to be inserted into the upper border of rib below. They are innervated by T_1-T_{12} motor neurons of spinal cord (Fig. 33.1).

Contraction of the external intercostals causes the ribs to be elevated to a more horizontal position and to be rotated upwards and outwards increasing the anteroposterior diameter *(pump handle movement)* and transverse diameter of the thorax *(bucket handle* movement).

i. First pair of ribs is joined between vertebral column and manubrium sterni. In quiet breathing this part of the thorax moves little, but in increased breathing the manubrium sterni moves upwards and upper thorax increases in its anteroposterior diameter.

ii. 2-6th ribs–both inclusive slope obliquely downward and forward from their joints with vertebral column. Each being successively larger and more oblique than its previous neighbor.

In inspiration due to contraction of external intercostal muscles they assume more horizontal position and are rotated upwards and outwards (pump handle and bucket handle movement). Chest expands both anteroposteriorily and transversely.

iii. Lower ribs 7 - 10th ribs swing outward and upward in inspiration and widen transverse thoracic diameter.

The rib movement is not equal in all the ribs. The upper ribs are arcs of smaller circle; therefore the transverse diameter of lower thorax increases more than the upper thorax.

Chief muscles of inspirations are:

1. Diaphragm
2. External intercostal muscles.

Chief muscles of expirations are:

1. Internal intercostals, and
2. Abdominal muscles
   i. External oblique
   ii. Internal oblique
   iii. Transversus
   iv. Rectus abdominis.

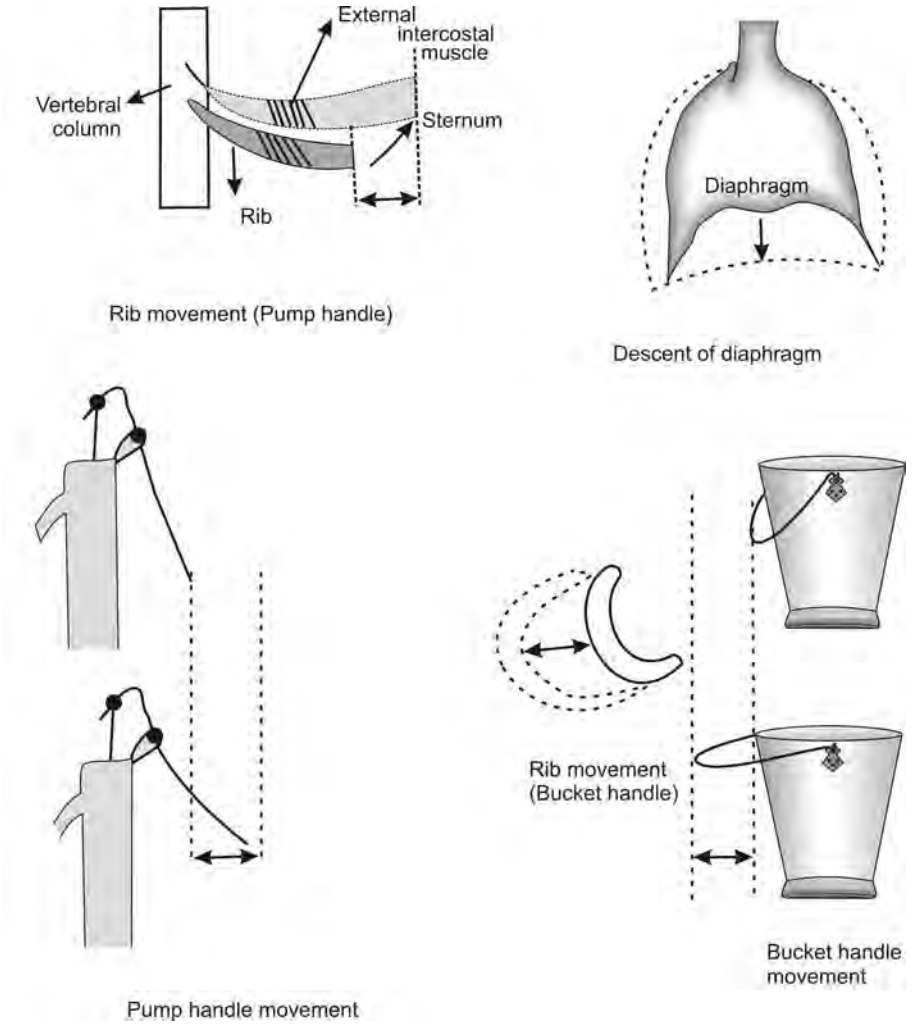


Fig. 33.1: Movements of thoracic cage in inspiration

They are inactive in quiet breathing, but contract vigorously in voluntary expiratory effort. Apart from these there are *other muscles*.

i. *Like scalene, sternomastoid, serrati*: Elevators of scapula, which are called accessory muscles of respiration. Their role in quiet breathing is insignificant, but they assume importance in forced, difficult and static inspiratory and expiratory effort.
ii. *Intrinsic muscles of larynx:* Abductors of vocal cord contract early in inspiration phase.

Adductors of vocal cord contract early in expiration but their contraction is not complete. It seems their main role is protective.

Respiratory pressure changes in lungs and thorax during inspiration and expiration

Intrapulmonary pressure (intra-alveolar pressure): Respiratory muscles cause pulmonary ventilation by alternately compressing and distending lungs, which in turn causes the pressure in the alveoli to rise and fall.

During inspiration intra-alveolar pressure becomes slightly negative to atmospheric pressure (–1 mm Hg). This cause air to flow inward through respiratory passages.

During expiration intra-alveolar pressure increases to about + 1 mm Hg which causes the air to flow outward through respiratory passages.

Note: How little pressure is required to move air in and out of lungs.

INTRAPLEURAL PRESSURE (INTRATHORACIC PRESSURE)

1. The pressure inside the pleural cavity is known as intrapleural pressure (Fig. 33.2). It is generally below the atmospheric pressure and therefore it is called as negative pressure. It should be clearly understood that negativity is in relation to the atmospheric pressure and is not absolute expression of pressure.
2. In the fetus, the thoracic cage is filled with unexpanded lungs and intrapleural pressure is equal to atmospheric pressure. With the first breath at birth the thoracic cage enlarges and the lungs expand and get filled with air.
3. After this first breath the lungs are never again completely empty of air and therefore remain in a slightly expanded state thereafter.
4. The bronchial tree and pulmonary alveoli have abundant elastic tissue and expansion of lungs puts this tissue on stretch and the *elastic recoil* tends to pull the lungs away from the chest wall. This force is not adequate to separate visceral and parietal pleura and fold away the lungs but there is always a *tendency to recoil.* This is responsible for the negative pressure.
5. The greater the stretch of the lungs, greater is the negative pressure. During quiet inspiration it is –5 to –10 mm Hg and during quiet expiration –2 to –4 mm Hg. Negative intrapleural pressure is maintained throughout life because pleural capillaries absorb any fluid or gas in the intrapleural cavity because of low capillary hydrostatic pressure in them (7-8 mm Hg).
6. Intrapleural pressure can be measured by inserting a needle in pleural space and connecting it to the manometer.
7. Intrapleural pressure is negative throughout inspiration and expiration – except:
   - Forced expiration
   - Cough
   - Sneezing.
8. Intrapleural pressure can be greatly changed by artificial respiratory gymnastics. Such as voluntary inspiration or expiration against closed glottis.
9. *Forced expiration* against closed glottis may produce positive intrapulmonary pressure of 100 mm Hg (Valsalva's maneuver).
10. *Forced inspiration* against closed glottis (Muller's maneuver) can reduce the intrapleural pressure to –80 mm Hg.

Advantages of Negative Intrapleural Pressure

1. Venous blood is sucked from abdomen and other parts.
2. Patency of airways is maintained because of radial tension on walls of airway by elastic tissues of lung.

Transpulmonary Pressure

It is the difference between alveolar pressure and pleural pressure, that is to say the difference between intrapleural pressure and intrapulmonary pressure (Fig. 33.2).

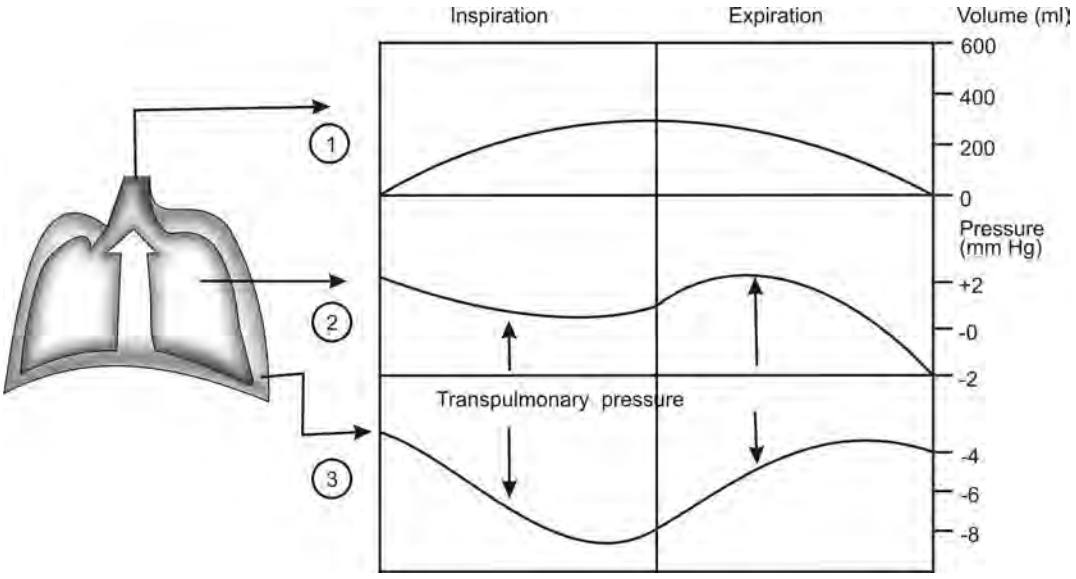


Fig. 33.2: (1) Volume changes in lung, (2) Intrapulmonary pressure changes, (3) Intrapleural pressure changes in quiet breathing

COMPLIANCE

The lungs and thoracic cage both are elastic structures. Expansibility of lungs and thorax is called compliance, and is expressed as change in volume per unit change in pressure ($\Delta V/\Delta P$) (Fig. 33.3).

For example, compliance of lungs is 0.2 L/cm of water.

To avoid certain fallacies such as getting compliance as below normal even when distensibility is normal (a) as in the case of persons in whom one lung is removed surgically, (b) or in children in whom volume is small therefore compliance will be below normal, specific compliance is used. *Specific compliance* is compliance expressed as a *fraction of the functional residual capacity* (FRC). That is specific compliance = compliance/FRC. Since FRC is also proportionately lower in children. Specific compliance is essentially constant irrespective of age.

The compliance of the lungs is 0.2 L/cm of water and the compliance of the thorax is also equal to 0.2 L/cm of water.

But the compliance of the lungs and thoracic cage together is equal to 0.1 L/cm of water.

This is so because the lungs try to pull thoracic cage inwards while the thoracic cage tries to pull lungs outwards. Therefore, it is more difficult to distend the lungs and thoracic cage together than either of them individually.

Normally, the lungs and thoracic cage have to move together.

Measurement of Compliance

1. i. For compliance of lungs the relevant pressure is the difference between intrapleural pressure and intrapulmonary pressure (alveolar pressure). This difference is called the transpulmonary pressure. Change in this difference and the associated change in volume can be used for calculating compliance.

ii. For compliance of *thoracic cage* the relevant pressure is the difference between atmospheric pressure and intrapleural pressure.

iii. For compliance of *thoracic cage and lungs together* or total respiratory compliance, the relevant pressure is the difference between atmospheric pressure and intrapulmonary pressure.

Experimentally, intrapleural pressure is assessed from esophageal pressure and intrapulmonary pressure from airway pressure or mouth pressure when the glottis is open to the pressure-recording device and there is no airflow.

2. The change in *volume* of lungs, the thoracic cage and the total respiratory system (i.e. lungs and thoracic cage) is identical and can be measured by spirometry.

Graph may be plotted for different values of ΔP and associated ΔV.

Graph ideally is a straight line. Compliance can be calculated from any point along the graph (Fig. 33.3).

Note: That compliance is a static measure of lung and chest distensibility.

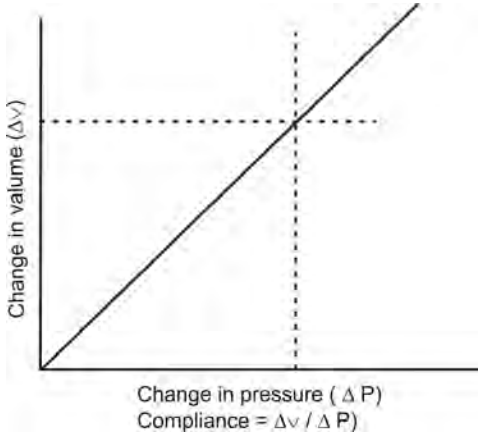


Fig. 33.3: Compliance of lungs and thorax or total respiratory compliance

If the distansibility of lungs and thorax is high the compliance will be high or in other words a small change in pressure leads to higher increase in volume, the lungs are said to be very distensible and compliance is high.

If the little change of volume occurs with great increase of pressure then the compliance is said to be low.

This fact is important because in low compliance work of breathing is increased.

Causes of low compliance of lungs:

i. Edema of lungs
ii. Fibrosis
iii. Block in bronchial tubes.

Causes of low compliance of lungs and thorax together.

Deformities of thoracic cage:

i. Kyphosis
ii. Scoliosis
iii. Fibrotic pleurisy
iv. Fibrotic muscles.

SURFACTANT

It is surface tension reducing agent, which lines the surface of the alveoli, by forming monomolecular layer.

Chemically, it is dipalmitoyl lecithin, is secreted by type two alveolar cells.

Functions of Surfactant

1. Lowering of the surface tension by the surfactant improves the distensibility of the lungs. This reduces the muscular effort required for breathing. Monomolecular layer of surfactant is formed between the fluid lining the alveoli and the air in the alveoli, which prevent water air interface formation.
2. Prevents emptying of small alveoli into large alveoli. Surfactant contributes to stability of alveoli.

3. Surfactant prevents accumulation of edema fluid in the alveoli. Surfactant appears late in fetal life. Deficiency of surfactant in newborn babies especially premature babies leads to respiratory distress syndrome or hyaline membrane disease. In these babies the lung expansion is difficult. Without treatment these babies die soon after birth because of inadequate ventilation.

AIRWAY RESISTANCE

Certain amount of work is required to move the air along the respiratory passages.

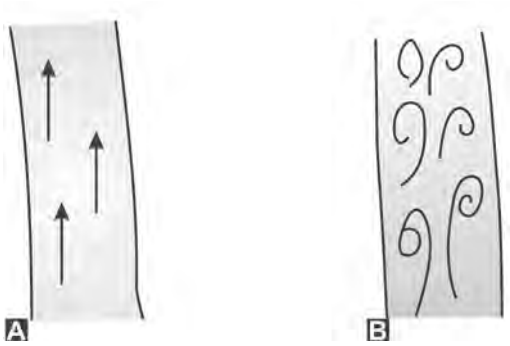
This is less in quiet breathing but in heavy breathing when air must flow through air passages at high velocity, the greater proportion of the work is used to overcome airway resistance.

Also when airway becomes obstructed resistance is increased and extra energy is spent by muscles. For example, in asthma.

Airway resistance depends upon:

Size, shape, number, length, cross-sectional area of air conducting tubes:

1. The medium sized airways offer greater resistance (or seat of airway resistance) and most of the resistance is offered by airways up to seventh generation.
2. Airflow in airways is – partly streamlined and partly turbulent (where branching takes place).



Figs 33.4A and B: (A) Streamlined flow, (B) Turbulent flow

Resistance offered to turbulent flow is much greater than streamlined flow (Figs 33.4A and B).

In Asthma

Airway resistance is the main problem. Bronchoconstriction increases the airway resistance.

CHAPTER

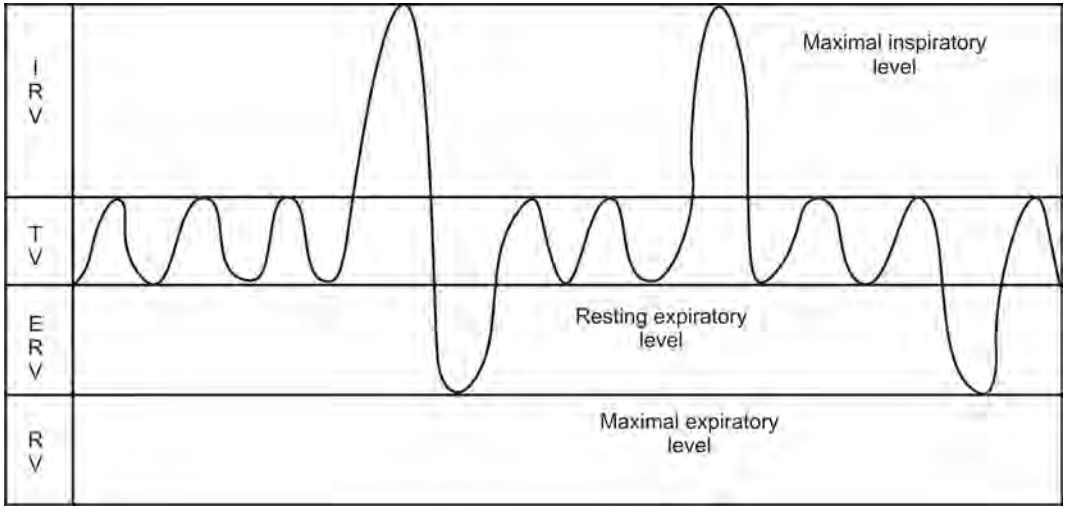
34

Pulmonary Volumes and Capacities/Pulmonary Function Tests

For ease in describing the events in pulmonary ventilation, the air in lungs has been divided in 4 different volumes and 4 capacities.

PULMONARY VOLUMES (FIG. 34.1)

1. *Tidal volume:* It is the volume of air inspired or expired with each normal breath. It amounts to about 500 ml.
2. *Inspiratory reserve volume:* Extra volume of air that can be inspired after normal tidal inspiration.
3. *Expiratory reserve volume:* Maximum volume of air, which can be expired after normal tidal expiration by forceful expiration.
4. *Residual volume:* The volume of air still remaining in lungs after forceful expiration.



IRV = Inspiratory reserve volume, TV = Tidal volume
ERV = Expiratory reserve volume, RV = Residual volume

Fig. 34.1: Pulmonary volumes and capacities

Significance

This volume aerates between expiration and inspiration. If this is not there oxygen and its concentration in blood will markedly fall and rise with each respiration, which would be disadvantageous to respiratory processes (Table 34.1).

The figures given in table are approximate mean values observed in adult Indians and may differ from values in western subjects. It must be remembered that normal values vary widely in different subjects and may deviate from the mean by more than 20%.

Respiratory rate – 14-20/min in adults. Respiratory minute volume – 6-7L/minute (= pulmonary ventilation).

PULMONARY CAPACITIES

In describing events in pulmonary cycle it is sometimes desirable to consider two or more of the volumes together such combinations are called capacities.

1. *Inspiratory capacity:* The amount of air that can be inspired from the resting expiratory level (that is after normal tidal expiration). It consist of inspiratory reserve volume + tidal volume.
2. *The functional residual capacity:* The amount of air remaining in the lungs after normal expiration. It consist of expiratory reserve volume + residual volume.
3. *Vital capacity:* It is the maximum volume of air that can be expired with maximum effort after maximum inspiration. It consist of inspiratory volume + tidal volume + expiratory reserve volume.
4. *Total lung capacity:* Maximum volume to which the lungs can be expanded with greatest possible inspiratory effort.

   Note: All volumes and capacities are less in females than in males.
5. Forced expiratory vital capacity on next page.

Table 34.1: Values observed in adults

	Men (Vol in ml)	*Women*
IRV	1850	1300
TV	600	450
ERV	1450	850
RV	1100	1000
Total lung capacity	5000	3600

IRV = Inspiratory reserve volume.
TV = Tidal volume.
ERV = Expiratory reserve volume
RV = Residual volume.

Significance of Vital Capacity

1. Vital capacity is related to anatomical build of the person.
2. It is increased in swimmers, divers, athletes.
3. It changes with position of body, less when lying down and increased when standing.
   i. *Strength of respiratory muscles:* For example, poliomyelitis (vital capacity decreases).
   ii. *Distensibility of thoracic cage*: Any factor which decreases lung compliance and compliance of thoracic cage, will decrease vital capacity. *For example, tuberculosis.*
   iii. *Pulmonary congestion:* For example, left heart failure causes vascular congestion and edema of lungs and vital capacity is decreased.

   Broadly, three categories or disease affect vital capacity.
4. *Forced expiratory volume or forced expiratory vital capacity:* Important clinical test. The person first inspires maximally then exales into the spirometer with maximum respiratory effort as rapidly and as completely as possible. The total excursion of the record is forced expiratory vital capacity.

The FEVC or FEV is nearly equal in normal and a person with airway obstruction but the difference is in the flow rates. Therefore, it is customary to record expiratory volume that is expired in first second (FEV_1). In normal person the % forced expiratory vital capacity or forced vital capacity (FVC) that is expired in the first second (FEV_1/FVC %) is about 80%. FEV is also known as *timed vital capacity (Fig. 34.2).*

In restrictive lung disorders, VC is much reduced FEV_1% (FEV_1 as a percent of FVC) is quite normal and may even be supernormal (about 90%) (Fig. 34.3).

Restrictive pulmonary diseases are characterized by reduced compliance and obstructive disorders are characterized by increased air way resistance.

Cause

1. Tendency of abdominal contents to press upward against diaphragm in lying position.
2. Increase in pulmonary blood flow which decreases the space available for pulmonary air.

This is applicable to all other volumes and capacities.

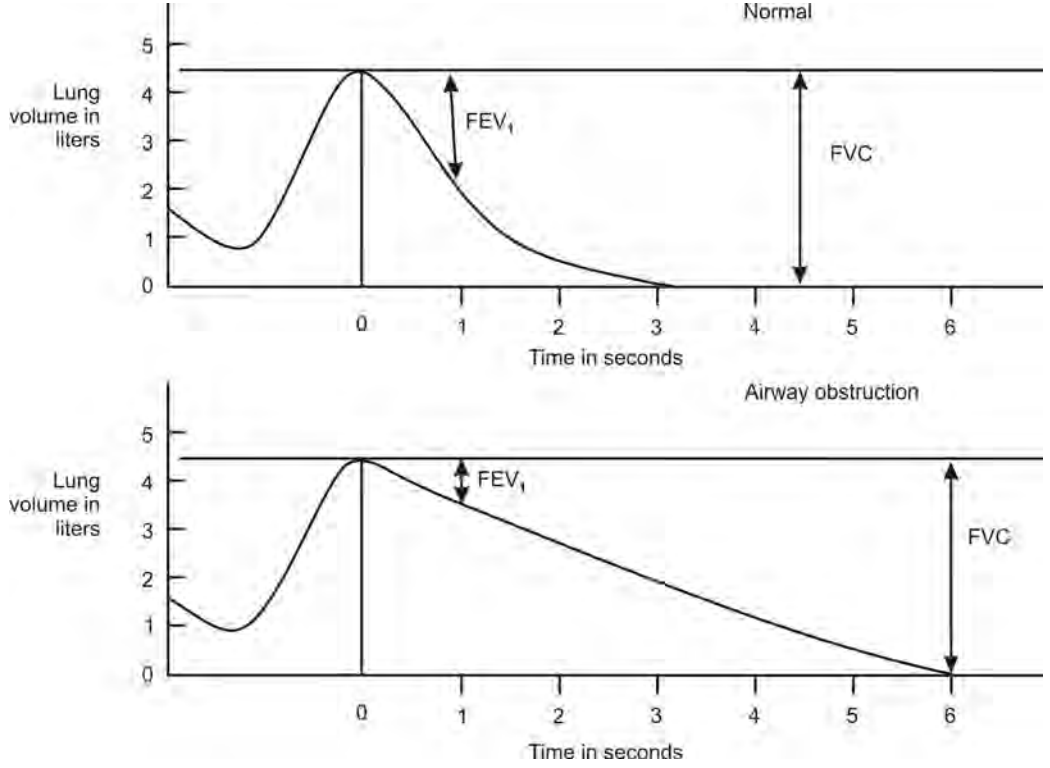


Fig. 34.2: FEV_1 in normal and airway obstruction

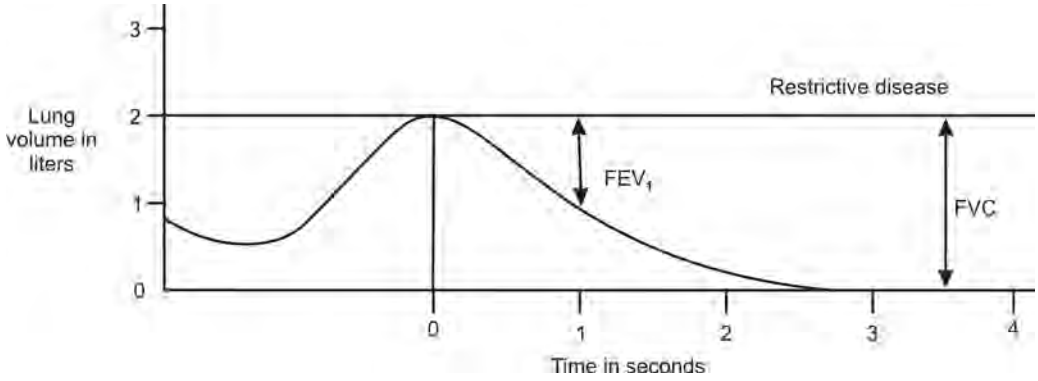


Fig. 34.3: FEV_1 in restrictive pulmonary disease

Measurement of Pulmonary Volumes and Capacities

1. *By simple spirometer:* We can measure tidal volume, expiratory reserve volume and vital capacity.
2. *By closed circuit spirometry:* All, except – residual volume, functional residual capacity and total lung capacity can be measured.

Measurement of Functional Residual Capacity

An increase in functional residual capacity (FRC) takes place through air trapping in disease associated with chronic increase in airway resistance.

It can be measured by *Helium dilution method.*

1. Spirometer of known volume is filled with air mixed with helium at a known concentration.
2. Before breathing from spirometer person expires normally. So that now the remaining air in the lung is equal to functional residual capacity.
3. At this point subject immediately begins to breathe from spirometer and the gases of the spirometer begin to mix with gases of lungs.

   Therefore, the helium becomes diluted by functional residual capacity gases.
4. The volume of the functional residual capacity can be calculated from the degree of dilution of the helium using following formula.

$$FRC = \frac{(CiHe - 1)}{CfHe} \text{ Vispir}$$

CiHe = Initial concentration of helium in spirometer.

CfHe = Final concentration of helium in spirometer.

Vispir = Initial volume of spirometer.

Measurement of Residual Volume

Residual volume

= FRC – Expiratory reserve volume

Measurement of total lung capacity = FRC + inspiratory capacity

Maximum voluntary ventilation – or Maximum breathing capacity (MVV or MBC)

It is the maximum volume of gas that can be moved into and out of the lungs in one minute by voluntary efforts.

Normal value in Indian young adults –

70-140 L in females (mean 100 L).

100-200 L in males (mean 150 L).

It is a good index of ventilatory capacity

It requires cooperation of the subject as well as considerable motivation of the subject.

Measurement of MVV or MBC – It can be measured by closed circuit spirometer or Douglas bag.

Subject is asked to breath as rapidly as he can and as deeply as he can. Expired gases are collected in Douglas bag for 15 sec, which is emptied in gassometer to measure the volume. Calculate for 1 minute.

i. MVV is decreased in airway obstruction and emphysema.
ii. Percentage breathing reserve can be calculated.

$$\frac{MVV - PV}{MVV} \times 100 = \% \text{ breathing reserve}$$

normal = 95%

(PV = Pulmonary ventilation):

When % breathing reserve falls below 60% dyspnea is present at rest. Therefore, known as dyspnea index.

The Dead Space

1. Anatomical dead space.
2. Physiological dead space.

Anatomical Dead Space

Air that fills the respiratory passages in each breath is called dead space air, because it is not available for alveolar ventilation.

In inspiration much of fresh air fills nasal passages, pharynx, trachea and bronchi. During expiration all the air in dead space is expired first before any of the air from alveoli reaches the atmosphere. Therefore, this volume is not available for alveolar ventilation.

Volume of air that fills alveoli with each breath = Tidal volume – Dead space air.

Physiological Dead Space

It is the air that fills the respiratory passages + volume of air in alveoli which have no blood supply.

In normal persons physiological and anatomical dead space is nearly equal because all the alveoli are functional, but in persons with partial nonfunctioning alveoli physiological dead space is more.

Measurement of Anatomical Dead Space Volume (Fig. 34.5)

It involves nitrogen analysis in the expired air following single deep breath of 100% oxygen:

1. Subject first breaths normal air.
2. Then suddenly takes inspiration of 100% oxygen which fills entire dead space and some oxygen mixes with alveolar air.
3. Then person expires rapidly through a flow meter and a nitrogen analyzer so that the flow rate and continuous nitrogen analysis are both available.
4. The first portion of expired air contains pure oxygen, then the air from alveoli starts coming out, which is mixture of: (i) oxygen breathed in, (ii) Air already present in alveoli, (iii) and the gas exchange going on there.

   Therefore, expired air at first has 0% nitrogen then the nitrogen curve rises to about 60% and then levels off.

Volume of dead space =

$$\frac{\text{Area of dots} \times \text{Total volume expired}}{\text{Area of hatching} + \text{Area of dots}}$$

Example - area of dots 30^2 cm
area of hatching 70^2 cm
Total volume expired = 500 ml.

$$\text{Then volume of dead space} = \frac{30}{30 + 70} \times 500$$

$$= 150 \text{ ml}$$

Normal dead space volume in young male is 150 ml.

This increase slightly with age.

Measurement of Physiological Dead Space Volume

It is based on the fact that all the carbon dioxide expired is derived from the alveoli, which alone indulge in gaseous exchange.

Hence, volume of expired air x PCO_2 in expired air =

Volume of the air from the alveoli per breath x mean PCO_2 in the alveoli

(Arterial PCO_2 gives the most satisfactory value for the mean alveolar PCO_2).

Let tidal volume be = 500 ml

and $\times$ = Volume of dead space air

Then $(500 - \times)$ = Volume from alveoli per breath

Suppose PCO_2
in expired air = 28 mm Hg
and arterial PCO_2 = 40 mm Hg.

$$(500 \times 28) = (500 - \times)\ 40 + (X \times 0)$$

$$\times = 150 \text{ ml}$$

Maximum Expiratory Flow Rate

Flow rate during breathing are indicators of airway resistance. Expiratory flow rates are more informative because during expiration raised intrathoracic pressure compresses small airways, therefore airway resistance is higher than during inspiration.

The measurement can be done from same record as for FEV_1. The expired volume can be divided into four parts and flow rate is calculated for middle 2 parts (i.e. middle half). This rate is termed as the maximum mid expiratory flow rate. The normal value for MMFR is greater than 3.5 $L.s^{-1}$. A decrease in MMFR indicates an increase in airway resistance.

Flow Volume Curve (Fig. 34.4)

The rate of air flow during breathing can be continuously monitored using a pneumotachograph.

Subject starts to expire maximally and forcefully at the end of deep inspiration.

To start with lungs have about 5-6 L of air and flow rate is O. During expiration flow rate rapidly peaks to maximum forcing out some air and thereby reducing lung volume, then the flow rate falls slowly till at the end of expiration it is O again. At the end of maximal expiration the lungs contain only the residual volume.

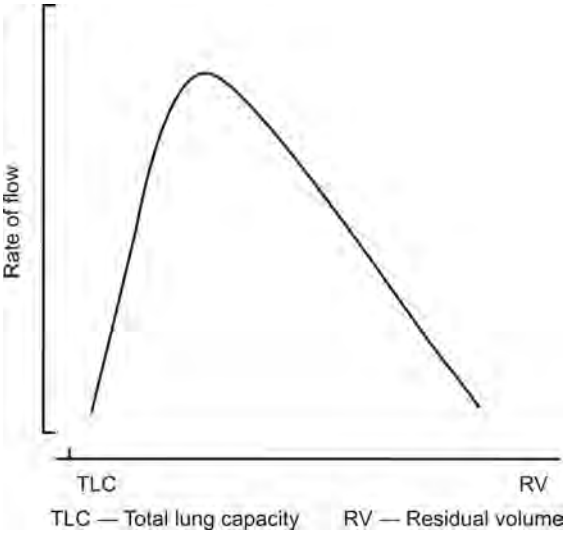


Fig. 34.4: Flow volume curve

Curve alters both in obstructive and restrictive diseases. In obstructive diseases:

1. There is trapping of air in the lungs, and
2. Flow rate is low due to airway obstruction.

In restrictive diseases:

1. The lung volumes are low due to restriction to expansion.
2. Flow rates are low, but
3. Curve is smooth than in obstructive lung disease.

Measuring Inequality of Ventilation

It is important to know if the ventilation in different parts of lungs is uniform.

Radioactive Xenon Method

Following inhalation of radioactive xenon, radioactivity is measured over the chest. Normally ventilation is greater at the bases than at the apices of lungs, but if ventilation is uniform transition should be smooth.

Breath Nitrogen Test—Single Breath Technique

Patient is asked to take single maximal inspiration of pure oxygen and then to breathe out maximally at a slow and steady space. A similar graph of N_2 concentration. in expired air is plotted as for determination of anatomical dead space. If ventilation is uneven the plateau is not there, instead there is a steady rise in nitrogen concentration (Fig. 34.5). This happens because in poorly ventilated alveoli not enough oxygen can enter in inspiration.

Uneven ventilation is seen in both restrictive and obstructive diseases of lung.

Note: Measurements mentioned above are pulmonary function tests for ventilation.

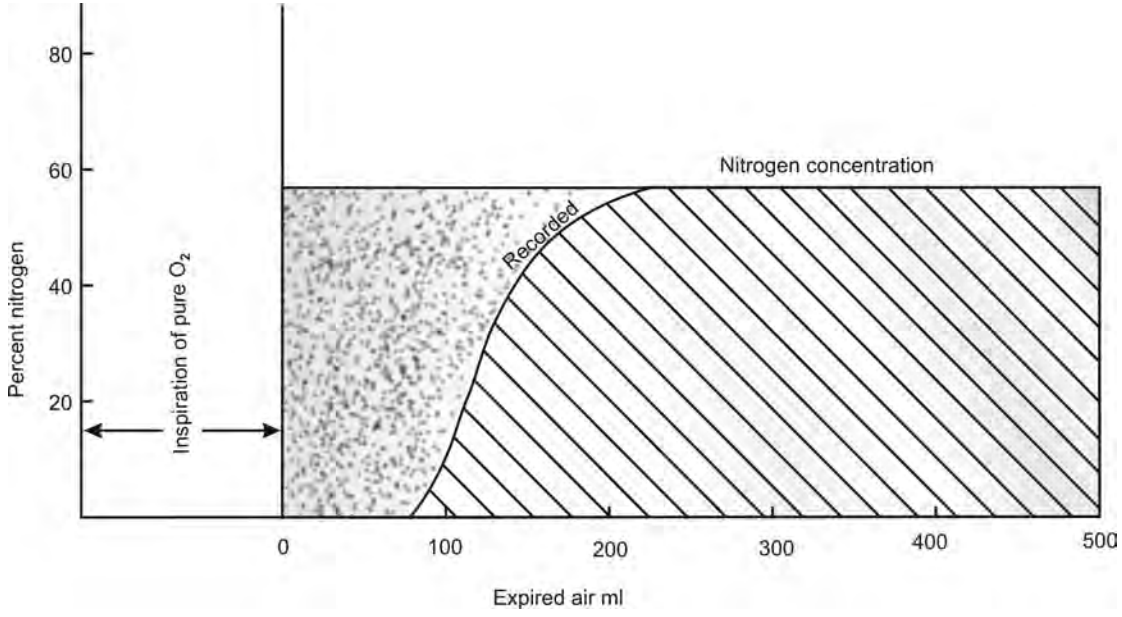


Fig. 34.5: Nitrogen concentration curve after inspiration of pure O_2

PULMONARY FUNCTION TESTS FOR DIFFUSION

The amount of gas diffusing in unit time per unit pressure gradient is called diffusing capacity of the lungs for that gas.

Therefore, to measure the diffusing capacity for a gas we should know the amount of gas diffusing in a given time and the pressure gradient.

The pressure gradient is equal to the difference in the partial pressure of the gas in the alveoli and in pulmonary capillaries.

It is very difficult to determine partial pressure of oxygen or carbon dioxide in pulmonary capillaries. Therefore, we determine diffusing capacity of *carbon monoxide* instead of normal respiratory gases.

Carbon monoxide is a lethal gas and therefore very low concentration should be inhaled.

In single breath technique the subject takes one breath of a gas mixture containing 0.2 – 0.3% CO and holds his breath for 10 seconds to allow transfer of alveolar CO to blood. The larger the diffusing capacity the greater is the amount of CO transferred during this period. An infrared analyzer is used to measure CO concentrations.

Diffusing capacity for CO =

$$\frac{\text{ml co transferred from alveoli to blood in one minute}}{\text{Mean alveolar PCO} - \text{Mean pulmonary capillary PCO}}$$

CO has such a high affinity for Hb that at very low concentrations of CO used, almost all CO in blood is in combination with Hb and its partial pressure in pulmonary capillary blood can be considered zero.

Normal diffusion capacity of CO (DCO) is 15-20 ml/min/mm Hg and diffusing capacity of oxygen is

= 1.23 × DCO

= 20 to 25 ml/min/mm Hg

Diffusing capacity of lungs increases markedly during exercise and decreases in diseases characterized by thickening of the alveolar capillary membrane.

Tests for End Result of Respiration

The ultimate purpose of respiration is to supply adequate oxygen to the tissues and to efficiently get rid of carbon dioxide produced in the tissues.

If both these functions are adequate it is reflected in arterial PO_2, PCO_2 and pH.

1. Nowadays PCO_2, PO_2 is measured in arterial blood samples using O_2 and CO_2 electrodes and we can detect.
   i. Hypoxia (ii) hypo- or hypercapnia.

   Normal PO_2 of arterial blood is about 100 mm Hg.

   Normal PCO_2 of arterial blood is about 40 mm Hg.
2. Determination of pH along with PCO_2 helps to distinguish between acidosis or alkalosis of respiratory origin or metabolic origin. pH is determined by pH meter.

CHAPTER

35

Oxygen Carriage

The mechanism by which atmospheric oxygen is provided to the tissues has three main components.

1. Diffusion of oxygen from pulmonary alveoli to pulmonary capillaries (Fig. 35.1).
2. Transport of oxygen in blood
3. Transfer of oxygen from blood to the tissues.

Oxygen diffuses from the alveoli into pulmonary capillaries; it is transported principally in combination with hemoglobin to the tissue capillaries, where it is released for use by the cells.

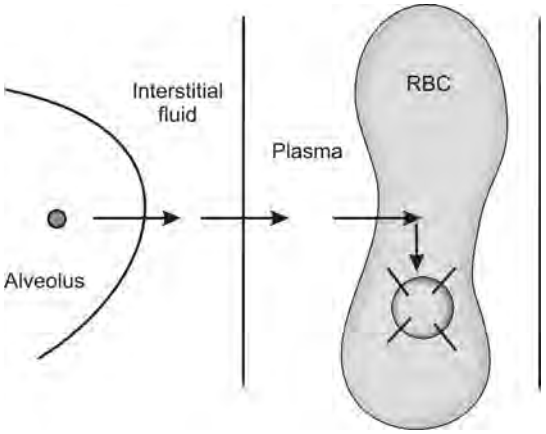


Fig. 35.1: Path of diffusion of oxygen

LUNGS—DIFFUSION OF OXYGEN

1. When venous blood enters the pulmonary capillaries the PO_2 is 40 mm Hg, because large amount of oxygen is removed from this blood as it passes through the tissue capillaries.
2. PO_2 in alveoli at sea level is 100 mm Hg.
3. Because of this pressure difference, the diffusion normally is so rapid that the PO_2 in alveoli and capillaries become nearly equal by the time the blood has traversed only one-third the length of the pulmonary capillary.
4. Extremely rapid diffusion of oxygen is possible by two important anatomical features of the lung:
   i. The large surface area of alveoli, average 70 sq meters, and
   ii. Extreme thinness of the alveolar capillary membrane, average is only 0.6 μm and at some places 0.2 μm.

Consider (3) and (4) in Exercise:

Normally, PO_2 in alveoli and capillaries becomes nearly equal when blood has travelled only 1/3 length of pulmonary capillaries. This gives great safety factor hence in exercise even with short stay of

blood in pulmonary capillaries (due to increased heart rate) rapid diffusion takes place. Secondly as the venous blood PO_2 is less in exercise therefore the amount of oxygen transferred from alveoli increases.

In exercise, breathing is deeper therefore, lungs are inflated more in inspiration. Hence, the surface area becomes even larger and the thickness of alveolar-capillary membrane is further reduced.

5. Hemoglobin has a great affinity for oxygen. It combines with oxygen *reversibly.* As the blood comes across increased concentration of oxygen (or PO_2) more and more oxygen combines with hemoglobin. Therefore, as the oxygen diffuses in blood it combines with hemoglobin. However, the oxygen, in combination with hemoglobin does not contribute to the PO_2 of blood (PO_2 depends on dissolved oxygen in plasma).
   The sequence of events are:
   i. PO_2 of RBC fluids is the same as in the plasma.
   ii. Oxygen diffuses from the alveoli into the plasma due to the PO_2 gradient, which raises plasma PO_2.
   iii. Now there is a gradient between PO_2 of plasma and PO_2 of RBC fluids.
   iv. So, oxygen diffuses from plasma to RBC fluid.
   v. As soon as oxygen enters the RBC it combines with hemoglobin. Hemoglobin mops up oxygen and does not allow PO_2 of RBC fluid to rise.
   vi. The process continues till hemoglobin cannot pick up any more oxygen.
   vii. Then the PO_2 of RBC fluids rises, to equal that in the plasma and diffusion from plasma to RBC stops.
   viii. After that PO_2 of plasma rises to equal that in the alveoli, therefore diffusion from alveoli to the plasma stops.

   The entire process takes only 0.25 seconds.
6. Alveolar-capillary (or respiratory) membrane is studied under electron microscope. While diffusing from alveoli to the blood, oxygen passes through the following layers:
   i. Fluid lining the alveoli
   ii. Alveolar epithelium
   iii. Epithelial basement membrane
   iv. Interstitial fluid
   v. Capillary basement membrane
   vi. Capillary endothelium
   vii. Plasma
   viii. RBC membrane.

   In areas where alveolar capillary membrane is very thin, interstitial space may not be seen and capillary basement membrane and alveolar basement membrane may appear fused even under electron microscope.
8. Every molecule of oxygen has to dissolve in the fluid lining the alveoli, then in the plasma and finally the RBC fluids, before it combines with hemoglobin. Further, since the direction of flow of oxygen depends on the PO_2 gradient and PO_2 depends on the concentration of dissolved oxygen. *Therefore, concentration of dissolved oxygen is very important.*
8. The pulmonary vein blood has PO_2 95 mm Hg as compared to 100 mm Hg in alveoli. This is because some blood passing through lungs circulates to areas such as bronchioles where gas exchange is impossible or through poorly aerated alveoli. This blood has low PO_2 and these vessels are called shunts. This blood mixes with blood from well-aerated alveoli and brings about fall in PO_2 to 95 mm Hg.
9. *Ventilation perfusion relationship:* An appropriate alveolar ventilation perfusion (VA/Q) ratio is essential for optimal respiration function. At the apices of the lungs both perfusion as well as ventilation

is low as compared to bases of the lungs. The gas tensions at apical alveoli are quite close to those of inspired air, which are favorable environment for growth of bacteria responsible for tuberculosis.

OXYGEN TRANSPORT IN BLOOD

Oxygen is carried in blood in two forms:

1. The dissolved form or in physical solution (3%), and
2. Combined with hemoglobin (97%).
   a. In dissolved form or physical solution = 0.3 ml/100ml.
   b. Combined with hemoglobin—loosely and reversibly – with the hem portion of hemoglobin. Where PO_2 is high, as in pulmonary capillaries oxygen binds with hemoglobin, but where PO_2 is low, as in tissue capillaries oxygen is released from the hemoglobin.
      i. One gram of hemoglobin when fully saturated combines with 1.34 ml of oxygen. Therefore, on average hemoglobin in 100 ml of blood (normally 15 gm) can combine with 20 ml of oxygen when hemoglobin is 100% saturated.
      ii. In arterial blood oxygen, bound with hemoglobin, which is 97% saturated, is approximately 19.4 ml/100 ml at PO_2 95 mm Hg. On passing through tissue capillaries this amount is reduced to 14.4 ml/100 ml at PO_2 40 mm Hg.
      Thus, under normal condition 5 ml oxygen is given away to tissues by 100 ml of blood.
      iii. Oxygen combines with the iron in the porphyrin part of hemoglobin. Each molecule of hemoglobin contains 4 atoms of iron in the ferrous form and each iron atom combines with one molecule of oxygen.

Thus, each molecule of hemoglobin (Hb4) combines with 4 molecules of oxygen ($O_2 \times 4$) and oxyhemoglobin can be represented as $Hb4O_8$.

The combination with O_2 of one iron atom increases the affinity of Hb for oxygen and facilitates the combination of O_2 with next iron atom. The process of combination and deoxygenation occurs very rapidly, taking less than 0.01 sec.

The iron remains in ferrous state, therefore chemical combination is oxygenation not oxidation and compound formed is known as oxyhemoglobin. The combination is loose and the compound is not stable.

Oxygen Dissociation Curve of Hemoglobin

It is S shaped or sigmoid shape. It is also known as oxyhemoglobin dissociation curve (Fig. 35.2).

It can be seen from the graph that at PO_2 of 100 mm Hg hemoglobin is about 97% saturated and contains 19 ml oxygen. When the PO_2 is 40 mm Hg the Hb is only 70% saturated and contain 14 ml% oxygen. This corresponds to venous blood at rest. In

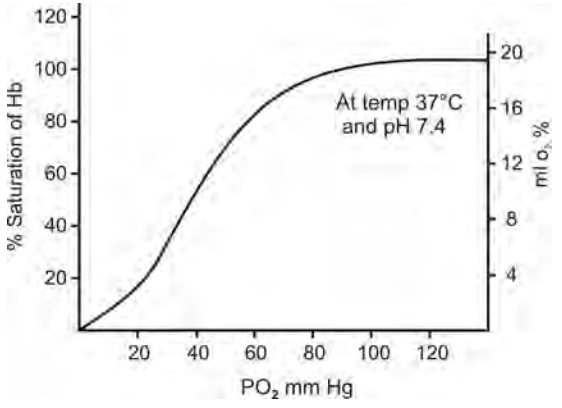


Fig. 35.2: Oxygen dissociation curve or oxyhemoglobin dissociation curve

exercise, there is further fall in PO_2 and % saturation of Hb is markedly reduced. That means more oxygen is given away to the tissues.

In other words lungs where PO_2 is high oxygen uptake is favored but in the tissues where the PO_2 is low, oxygen is released from combination.

Factors that Help Oxygen Uptake in Lungs

1. Gradient of PO_2: PO_2 is high in alveolar air than venous blood therefore, oxygen diffuses in pulmonary capillaries.
2. As CO_2 is evolved in the lungs its tension in blood falls and pH increases or blood tends to become alkaline. Oxyhemoglobin being stronger acid than reduced hemoglobin, Oxyhemoglobin is formed to combat with increased pH. This means evolution of CO_2 favors formation of oxyhemoglobin (Haldane effect).
3. Pulmonary temperature is low because large amount of heat is passed out in expired air. This favors oxygen intake.

IN THE TISSUES—OXYGEN TRANSFER

Transfer of oxygen from blood to tissues takes place in tissue capillaries. It depends on the difference in PO_2 .

PO_2

PO_2 at arterial end of capillaries is 95 mmHg and that in interstitial fluid in the tissues is about 40 mmHg (but it depends on metabolic activity of tissues).

PO_2 of intracellular fluid is highly variable —it is affected by: (a) level of tissue activity, and (b) distance of the cell from capillaries.

Intracellular PO_2 is generally 20 mm Hg. Some cells survive even at 1 mm Hg PO_2 and normal PO_2 is much higher than this, again there is great safety factor.

Thus, there are large gradients of PO_2 at the tissue level,

(i.e. 95 mm Hg $\rightarrow$ 40 mm Hg $\rightarrow$ 20 mm Hg).

PO_2 of arterial blood in capillary tissues	PO_2 of interstitial fluid in capillary tissues	PO_2 of intracellular fluid of tissue cells

1. This ensures that adequate oxygen is delivered even when PO_2 is low as in the diseases characterized by impaired diffusion at lungs or at high altitude.
2. At PO_2 of 40 mm Hg hemoglobin is still 70% saturated and if interstitial PO_2 falls still further enough oxygen can be delivered to tissues (steep portion of oxyhemoglobin dissociation curve).

FACTORS AFFECTING OXYGEN TRANSFER OR OXYGEN DISSOCIATION

1. PO_2—when metabolic activity of tissue is high its PO_2 is low. So in metabolically active tissue oxyhemoglobin dissociates to a greater extent.

   Thus, more oxygen is made available to the tissue.
2. Low pH
3. High temperature
4. High PCO_2

   } Affect oxyhemoglobin dissociation curve in such a way that oxygen delivery to tissues is increased.

And these 3 factors shift the oxyhemoglobin dissociation of curve to right (Fig. 35.3). This increases the amount of oxygen delivered to tissues at given PO_2.

The rightward shift of the curve brought about by an increase in PCO_2 is called *Bohr effect*.

The effect of increased PCO_2 may be due to increase in hydrogen ion concentration. Hydrogen ions bind with hemoglobin ions.

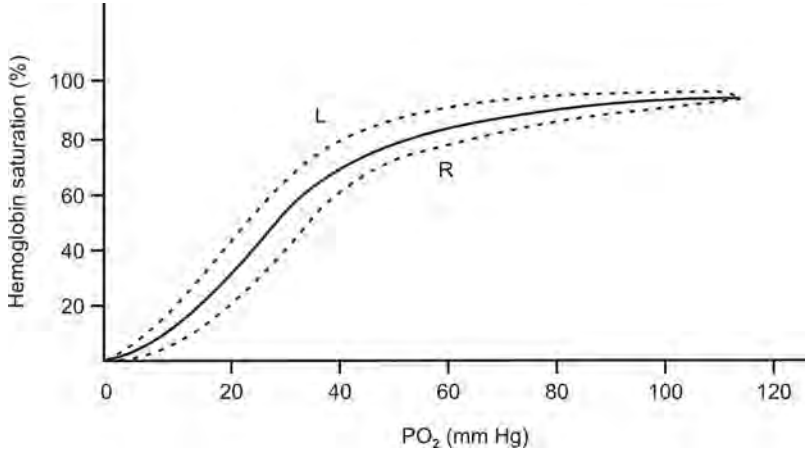


Fig. 35.3: Factors affecting oxyhemoglobin dissociation curve

The binding changes the configuration of hemoglobin in such a way that the accessibility of oxygen to hem groups is reduced. Therefore, in presence of more hydrogen ion less oxygen can bind with hemoglobin and the oxyhemoglobin dissociation curve shifts to right.

1. Shift to right (R) is cause by:
   i. Fall in pH
   ii. Increase in PCO_2, and
   iii. Increase in concentration of 2,3 DPG in red cells.
2. changes in opposite direction shifts the curve to left (L).

5. Concentration of 2,3 diphosphoglycerate (DPG) in RBC—2,3 DPG is isomer of 1,3 DPG formed in glycolytic pathway (optionally). 2,3 DPG binds with hemoglobin (Hb) but not with oxyhemoglobin (HbO_2). Therefore, when 2,3 DPG increases, oxygen is released more from oxyhemoglobin and the curve shifts to right.

$$Hb\ O_2 + 2,3\ DPG = Hb\ 2,3\ DPG + O_2$$

This factor is of physiological importance as 2,3 DPG concentration in RBC increases when:

i. There is increased oxygen demand. *For example* – Exercise.
ii. Oxygen supply is reduced. For example – *High altitude*
iii. Oxygen carrying capacity of blood is reduced. For example, *Anemia.*

Note:

2,3 DPG does not combine with fetal hemoglobin—is one of the reasons why fetal hemoglobin has more affinity for oxygen than adult hemoglobin. This is again important for transfer of oxygen from maternal blood to fetal blood.

CHAPTER

36

Carbon Dioxide Carriage

Tissues utilize oxygen and produce carbon dioxide, which is a waste product and has to be eliminated from the body to maintain constancy of internal environment.

Carbon dioxide, produced in the tissues enters the bloodstream in tissue capillaries, is transported to lungs, where it is liberated and expelled.

Elimination of carbon dioxide involves three processes:

1. Transfer of carbon dioxide from tissues to blood
2. Transport of carbon dioxide
3. Expulsion of carbon dioxide from lungs.

TRANSFER OF CARBON DIOXIDE FROM TISSUES TO BLOOD

Carbon dioxide is continuously formed in tissue cells. Therefore, PCO_2 in cells is increased (PCO_2 in cells is about 46 mm Hg) and PCO_2 in interstitial fluid is less (about 45 mm Hg). PCO_2 of arterial blood entering the tissue capillaries is 40 mm Hg. Because of this gradient of PCO_2, carbon dioxide diffuses out into the interstitial fluid and from there into the capillary blood and PCO_2 of capillary blood increases to 45 mm Hg.

Thus, PCO_2 gradient is

46 mm Hg in intracellular fluid of tissue cells → 45 mm Hg in interstitial fluid in tissues → 40 mm Hg in arterial blood in capillary

40 mm increases to 45 mm at venous end in capillary

Although, the PCO_2 gradient is only of 5 mm Hg between interstitial fluid in tissues and arterial end of the capillary; which is much less than PO_2 gradient for oxygen even then almost equal volume of carbon dioxide diffuses. This is due to the fact that carbon dioxide is much more soluble than oxygen and carbon dioxide diffuses 20 times faster than oxygen.

CARBON DIOXIDE TRANSPORT

Carbon dioxide diffused from tissue cells to the blood is transported or carried in three forms:

1. In dissolved form or physical solution (7% = 2.7 ml/100 ml blood).
2. As chemical compounds—70%

i. Bicarbonates
   [Bicarbonates of sodium in the plasma]
   [Bicarbonates of potassium in RBC]
ii. Carbamino compounds–[20%
   [carbamino hemoglobin in RBC]
   [carbamino proteins in plasma (small extent)].

DISSOLVED CARBON DIOXIDE

Although, carbon dioxide is fairly soluble in water the dissolved form accounts for only about 7% of the carbon dioxide transported. This is because amount of dissolved carbon dioxide *depends on* PCO_2. The difference between arterial and venous blood is 5 mm Hg and total carbon dioxide of arterial blood is 48 ml/100 ml and that of venous blood is 52 ml/100 ml. Each 100 ml of venous blood carries 4 ml more carbon dioxide than arterial blood. Out of 4 ml only 0.3 ml is carried in dissolved state per 100 ml.

CARBON DIOXIDE TRANSPORT AS BICARBONATES

Carbon dioxide transport as bicarbonates is major mechanism for carbon dioxide transport (Fig. 36.1). RBCs contain carbonic anhydrase, therefore play major role in this mechanism.

1. Carbon dioxide diffuses from tissue cells into the interstitial fluid, from there into the plasma and from plasma into the RBC fluids, following a PCO_2 gradient.
2. In RBC fluid, carbon dioxide dissolves to form carbonic acid. This process is accelerated enormously by carbonic anhydrase, therefore reaction occurs in fraction of a second.
3. Carbonic acid dissociates to form hydrogen ions and bicarbonate ions, in another fraction of a second.

$$CO_2 + H_2O = H_2CO_3 \rightarrow H^+ + HCO_3$$

   The dissociation is 99.9% so that only a small fraction of carbonic acid remains in undissociated form.
4. Hydrogen ions are buffered partly by hemoglobin and partly by plasma proteins.

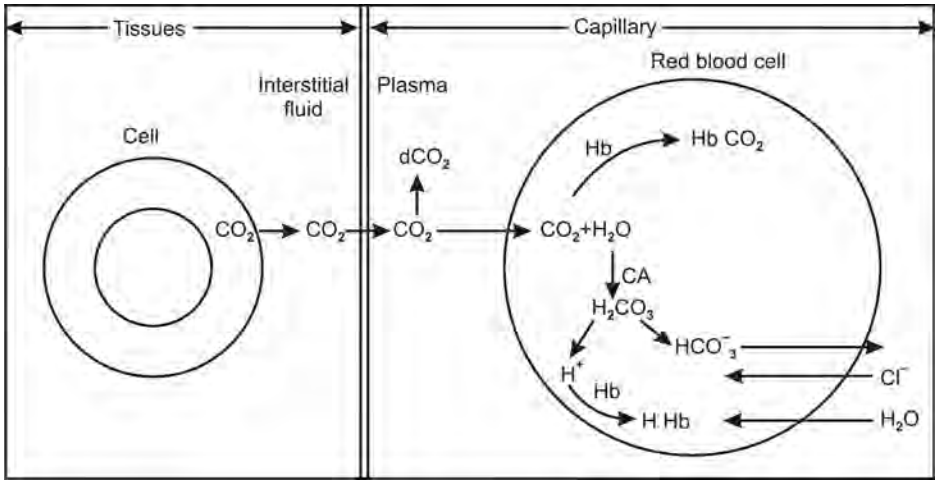
   Oxyhemoglobin which is a stronger acid gives up its oxygen and gets converted to reduced hemoglobin, which is less strong acid, also it combines with hydrogen ions. Even then pH of venous blood falls slightly.
5. Bicarbonate ions diffuse out of RBC because of concentration gradient.
6. Exit of bicarbonate ions from RBC is not accompanied by exit of cations because RBC membrane is relatively impermeable to cations.
7. Therefore, an electrical gradient is created across RBC membrane.
8. With the result passive transport of some chloride ions from plasma into the RBC takes place (chloride shift).

   The degree of chloride shift is governed by Gibbs-Donnan equilibrium.
9. Efflux of bicarbonate and influx of chloride is facilitated by bicarbonate/chloride carrier protein in the RBC membrane.
10. Formation of bicarbonate ions and entry of chlorine ions increases osmotic pressure of RBC. Therefore, water moves passively from plasma to RBC.

    Therefore, RBC of venous blood becomes rounded (i.e. less biconcave) as compared to arterial blood.
11. Overall reaction:

$$CO_2 + H_2O + HbO_2 \xrightarrow{\text{tissues}} HCO_3^- + \underset{\text{Lungs}}{\overset{CA}{\leftarrow}} HHb + O_2$$

(CA = carbonic anhydrase)



CA = Carbonic anhydrase

Fig. 36.1: Transport of carbon dioxide: (i) as dissolved CO_2 (dCO_2 —7%), (ii) as carbamino hemoglobin (Hb-CO_2—20%), (iii) as bicarbonate (HCO_3^- — 70%)

does not go to completion in either direction but the conditions in tissues shift it to right and conditions in lungs shift it to left. At lungs, oxygen tends to drive out CO_2 and at tissues CO_2 tends to drive out oxygen.

Conversion of carbonic acid into carbon dioxide and water is also catalyzed by carbonic anhydrase. Therefore, carbonic anhydrase inhibitors inhibit carbon dioxide collection from the tissues as well as discharge in the lungs and lead to raised PCO_2 in tissues as well as blood.

Carbonic Anhydrase

1. It is present in red cells in plenty—also present in pancreas, stomach, intestinal mucosa, renal cortex, brain, spleen, red muscles and salivary gland.
2. It accelerates the reaction $CO_2 + H_2O \rightleftarrows H_2CO_3$, 500 times.
3. It is a protein of low molecular weight.
4. Contains zinc.
5. Its action is inhibited by acetazolamide, cyanide, etc.

CARBON DIOXIDE TRANSPORT AS CARBAMINO COMPOUNDS

1. Transport in this form accounts for only 20% of carbon dioxide transport.
2. Carbon dioxide combines with: (a) hemoglobin in red cells (2.6 ml/100 ml of blood and (b) several plasma proteins in plasma (1.1 ml/100 ml of blood).
3. Hemoglobin is most abundant protein in blood therefore, carbamino hemoglobin is major compound formed.
4. This combination is reversible and occurs with very loose bond.

CARBON DIOXIDE DISSOCIATION CURVE

The relationship between PCO_2 and volume of carbon dioxide carried by blood in all the three forms together is expressed in carbon

dioxide dissociation curve. The position of the curve is affected by *PO_2 significantly.*

1. In venous blood, PO_2 is 40 mm Hg and carbon dioxide content of venous blood is 52 ml/100 ml.
2. In arterial blood, *PO_2 is nearly 100 mm Hg* and its carbon dioxide content is 48 ml/100 ml.

The carbon dioxide dissociation curve changes with PO_2 of blood. This effect is known as Haldane effect and carbon dioxide picked up in tissues is doubled because of effect of PO_2 on carbon dioxide dissociation curve (Fig. 36.2).

Note: Arterial blood enters tissues at PO_2 100 mm Hg and PCO_2 40 mm Hg (Point A). Tissues have PCO_2 46 mm Hg. Therefore, CO_2 diffuses from tissues to blood. If this was the only process going on in tissues the blood carbon dioxide content will change from B and C (i.e. from 48-50 ml/100 ml). But simultaneously the blood PO_2 falls (from 100 mm Hg to 40 mm Hg) in the venous blood (V) and because the carbon dioxide dissociation curve is different at PO_2 40 mm Hg, the CO_2 picked up in blood changes from B to V (i.e. from 48 to 52 ml/100 ml) which is double—Haldane effect.

In the same way the amount of carbon dioxide released in the lungs is also doubled by the Haldane effect because: (i) PO_2 changes from 40 to 100 mm Hg while (ii) PCO_2 fall from 46 mm Hg to 40 mm Hg.

Expulsion of Carbon Dioxide

PCO_2 of venous blood is 45 mm Hg while that of alveolar air is 40 mm Hg. Thus, there is a gradient of 5 mm Hg, which makes carbon dioxide diffuse into the alveoli till the pulmonary capillary PCO_2 falls to 40 mm Hg. Carbon dioxide is finally expelled from alveoli during expiration.

Alongwith diffusion of carbon dioxide from pulmonary capillary to alveoli, oxygen exchange is also going on simultaneously, which raises the pulmonary PO_2 from 40 to 100 mm Hg. This will cause Haldane effect in opposite direction (Fig. 36.2). Rise of PO_2 of pulmonary capillary blood effectively doubles the amount of carbon dioxide eliminated from the capillaries of lungs.

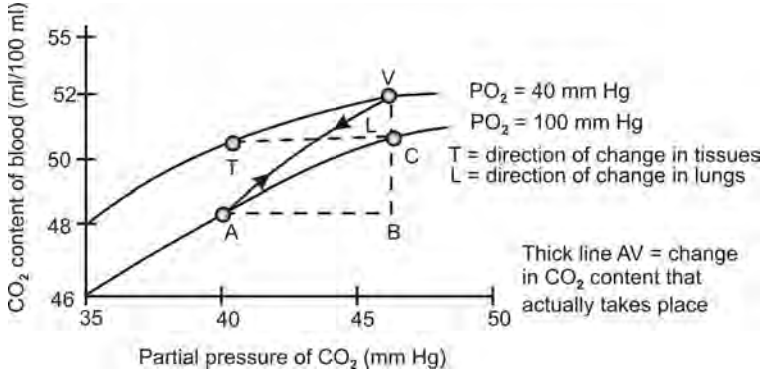


Fig. 36.2: Carbon dioxide dissociation curve showing Haldane effect

MECHANISM OF HALDANE EFFECT

Transfer of carbon dioxide from tissues to blood generate H^+ ions. Deoxygenated hemoglobin is a better hydrogen ion acceptor. Therefore, deoxygenation of hemoglobin in the tissues helps the carriage of extra carbon dioxide by mopping up hydrogen ions.

$HbO_2 \longrightarrow Hb + O_2$ – in tissues forward reaction takes place

In tissues $Hb + H^+ \rightleftharpoons$ Hb. H-deoxygenated Hb mops up hydrogen ions

$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$ – H^+ are mopped up

Therefore, forward reaction is promoted.

The overall reaction is $CO_2 + H_2O + HbO_2 \overset{CA}{\rightleftharpoons} HCO_3^- + H.Hb + O_2$

In tissues, this facilitates picking up of carbon dioxide and opposite sequence of events facilitates expulsion of carbon dioxides in the lungs. Besides oxyhemoglobin is stronger acid therefore, it displaces carbon dioxide in blood in two ways:

i. $H Hb + O_2 \longrightarrow H^+ + HbO_2$

In lungs

combines with bicarbonates

$H^+ + HCO_3^- = H_2CO_3 =$

$H_2O + CO_2 \longrightarrow$ expelled from lungs

ii. Oxyhemoglobin is highly acidic therefore, it has less tendency to form carbamino hemoglobin. Therefore, carbon dioxide is released also from carbamino hemoglobin.

Liberation of CO_2 from plasma bicarbonates:

i. CO_2 in physical solution is evolved first.

ii. Carbamino compounds break and liberate CO_2 further.

iii. → (i) and (ii) favor oxygenation of blood therefore, HHb is converted into HbO_2. HbO_2 is a stronger acid and cell reaction tends to become acidic. To prevent this Cl^- from KCl in cell comes out and chloride shift is reversed. Cl^- reacts with $NaHCO_3$ of plasma.

$Cl^- + NaHCO_3 = NaCl + HCO_3^-$

$HCO_3^- + H^+ = H_2CO_3^-$

Dissociates in presence of carbonic anhydrase

$CO_2 + H_2O$

CO_2 is expelled.

CHAPTER

37

Regulation of Respiration

Respiration is involuntary function, which can be influenced voluntarily.

Rate and depth of respiration change appropriately in response to metabolic demands without any voluntary effort on our part.

Yet the respiratory muscles can be made to contract voluntarily or relax voluntarily to achieve a desired pattern of breathing.

NEURAL CONTROL OF BREATHING

Two separate neural mechanisms regulate respiration:

1. Responsible for voluntary control, and
2. Responsible for automatic control.

1. Voluntary control system is located in cerebral cortex and sends impulses to respiratory motor neurons via corticospinal tract.
2. Automatic control system is located in pons and medulla and sends impulses to respiratory motor neurons via fibers (tracts) located in white matter of spinal cord between lateral and ventral corticospinal (or pyramidal) tracts.

These fibers (tracts) synapse with motor neurons of respiratory muscles:

Apart from these there are:

i. *Intrinsic muscles of larynx*—supplied by recurrent laryngeal nerve.

Respiratory muscles of *inspiration* are:	Respiratory muscles of *expiration* are:
1. Diaphragm—supplied by phrenic nerve arising from anterior horn cells of C_3, C_4 and C_5 segments of spinal cord. 2. External intercostals—their motor neurons are located in anterior horn cell of T_1 to T_{12} thoracic segments of spinal cord.	1. Internal intercostal muscles. They do not take part in quiet breathing but in hyperpnea (= increased breathing) they serve as expiratory muscles. 2. Abdominal muscles: i. External oblique ii. Internal oblique iii. Transversus iv. Rectus abdominis Inactive in quiet breathing. Contract vigorously in voluntary expiratory effort.

Abductors of vocal cords contract in inspiratory phase.

Adductors of vocal cords begin to contract in early expiration but their contraction is not complete. It seems to have protective function.

ii. The scalene and sternomastoids and anterior serrati.

Play little part in quiet breathing but take part in voluntary static inspiratory or expiratory effort. For example, when one wants to hold breath after inspiration or expiration.

It is important to note that motor neurons supplying the expiratory muscles are inhibited when those supplying the inspiratory muscles are active and vice versa—example of reciprocal innervation.

Medullary Respiratory Group

There are two principal areas in the medulla oblongata which are concerned with respiratory regulation:

1. *Dorsal respiratory group (DRG)*
   i. Has predominantly inspiratory neurons.
   ii. Extends length of medulla on dorsal side.
   iii. It occupies nucleus of tractus solitarius and the neighboring reticular formation.
   iv. These neurons are active during inspiration and remain inactive during expiration and then activity starts building up again during next inspiration.
   Thus, normal rhythm of quiet breathing is generated in DRG.
   v. Activity in DRG gradually increase corresponding to increase in force of contraction of inspiratory muscles = Ramp signal. Expiration is passive.
2. *Ventral respiratory group (VRG)*
   i. Has predominantly expiratory neurons.
   ii. These neurons are silent during quiet breathing.
   iii. They get activated only when the breathing becomes more forceful as during exercise.
   iv. Principal role of VRG is possibly bring about active expiration by contraction of abdominal muscles.
   These two centers in medulla generate the basic rhythm of respiration.

Pontine Respiratory Centers

Although rhythmic discharge of medullary neurons concerned with respiration (DRG and VRG) is spontaneous it is modified by (Fig. 37.1):

1. Neurons in the pons and
2. Afferents in the vagus from receptors in airways and lungs (Fig. 37.2).

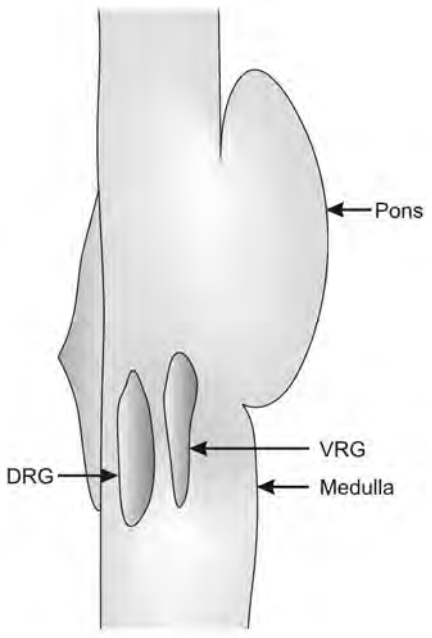


Fig. 37.1: Medullary centers

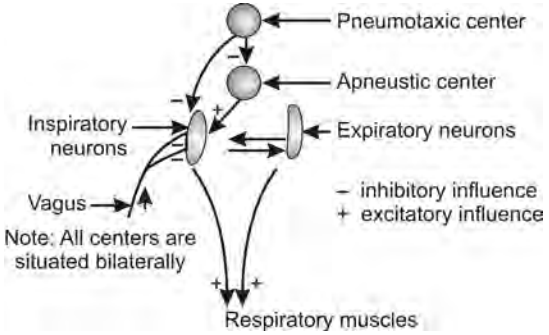


Fig. 37.2: Interaction of respiratory center and vagus

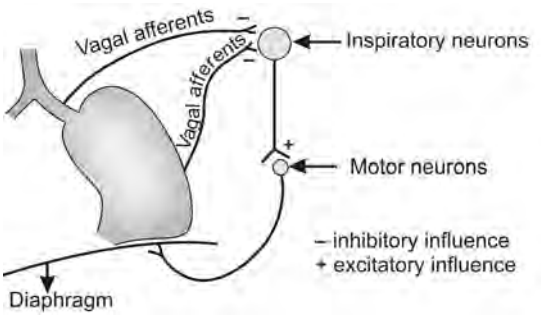


Fig. 37.3: Mechanism—underlying Hering Breuer reflex (Diagrammatic)

1. *Neurons in the pons:*
   i. Pneumotaxic center—situated in upper pons, dorsally in nucleus parabrachialis (NPBL). It has inhibitory effect on inspiratory neurons (DRG).
   ii. Apneustic center—situated in lower part of pons.

   It has excitatory effect on inspiratory neurons.

   The basic rhythm established by medullary centers is spoilt by strong inspiratory drive originating in apneustic center. The rhythm is restored by two influences which inhibit inspiratory drive originating in the apneustic center:
   a. Pneumotaxic center, and
   b. Vagal afferent impulses.
2. *Vagal afferent activity*: When lungs are stretched during inspiration, this is detected by group of receptors located in (a) tracheobronchial tree and (b) *Visceral pleura*. Because these receptors are sensitive to degree to which lungs are stretched, they are often called as pulmonary stretch receptors (pulmonary because they are stimulated when lungs are stretched).

The information is conveyed to CNS by vagus nerve. Activation of vagal fibers leads to inhibition of inspiratory neurons in DRG. Inspiratory neurons act by stimulating motor neurons, which supply inspiratory muscles (for example, diaphragm). When they are inhibited inspiration is cut short and expiration begins which is a passive process. This reflex is known as Hering Breuer reflex (Fig. 37.3).

HIGHER NEURAL INFLUENCES

1. *Cortical influences on respiration* are there, therefore, we can bring about changes in the pattern of breathing voluntarily.
2. *Limbic system and hypothalamus*—effect of emotions on respiration are brought about via limbic system and hypothalamus.

   Influences of higher centers are superimposed on pontomedullary respiratory center.

Respiratory Reflexes

1. *Hering Breuer Reflex*
   i. Already described, is Hering Breuer inflation reflex.
   ii. Hering Breuer deflation reflex: When stretch receptors are unstretched during expiration, impulses from these receptors cease, which allows next inspiration to begin.

2. *Head s paradoxical reflex:* When vagi are partially blocked by cooling to 5°C, at this temperature *conduction* in vagal fibers, which mediate Hering Breuer reflex is blocked and inflation of lungs promote more inflation useful in newborn.
3. *Intercostal and phrenic proprioceptive reflexes:* In skeletal muscles are located receptors, which are stimulated by stretch (= stretch of muscle as a whole). They are called as muscle spindles. Intercostal muscles contain numerous muscle spindles and diaphragm contains few.

   The response is contraction of the muscle, which neutralizes the stretch. Contraction of muscle initiated by stretch is known as stretch reflex (Fig. 37.4).

   The stretch reflex is observed to control the activity of intercostals muscles and diaphragm.

   If there is increase in the mechanical load of respiratory muscles (i.e. if there is resistance to contraction) the spindles in them are stimulated leading to increased strength of contraction.
4. *J reflexes:* These reflexes are due to stimulation of J receptors discovered by AS Paintal in 1954, an eminent Indian physiologist.

   J receptor is abbreviated version of juxtapulmonary capillary receptors because they are located very close to pulmonary capillaries. They are innervated by unmyelinated vagal fibers (Fig. 37.5).

   Natural stimulus for them is pulmonary congestion which cause increase in interstitial fluid volume. Collagen tissues soak water and swell. These collagen fibers are closely associated with the receptors. Therefore, when they swell they stimulate J receptors.

   Reflex response in physiological circumstances is tachypnea (= increased rate of breathing), physiological role of J receptors—is that they are stimulated by increase in pulmonary capillary pressure that occurs during exercise: (a) which increase rate of respiration causing dyspnea, and (b) inhibit stretch reflexes in skeletal muscle. Both these factors discourage exercise and thereby protect us from exercise reaching a level, which might precipitate pulmonary edema.

   When phenyl diguanide is injected into right atrium or right ventricle in

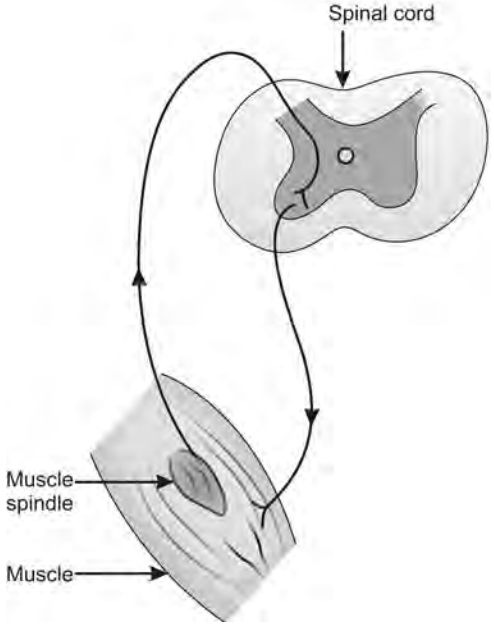


Fig. 37.4: Stretch reflex

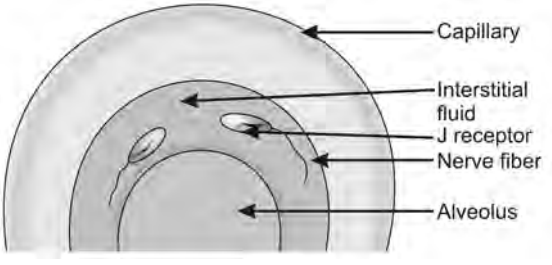


Fig. 37.5: J receptor (location)

anesthetized animals—in the same way it stimulates J receptors and the response is: (a) apnea, (b) hypotension, and (c) bradycardia.

5. *Reflexes originating in irritant receptors*
   Irritant receptors are present in:
   i. Trachea
   ii. Major airways, and
   iii. Also in intrapulmonary airways.
   Highest concentration is in *larynx* and at *point* where trachea bifurcates called the carina.

   They are stimulated by:
   – Cold air
   – Mucus
   – Dust
   – Any other particles.

   Information reaches CNS from receptors via vagal afferent fibers and response is:
   – Bronchoconstriction
   – Hyperpnea, and
   – Cough.

   Cough is protective reflex, which prevents obstruction of the airways by unwanted matter. During cough unwanted matter is thrown out.
6. *Sneezing:* Sneeze is evoked by irritation of the nasal mucosa. It is similar to cough but during sneeze the air is also expelled partly through nose so that the irritant is blown out.

   In both cough and sneeze first there is deep inspiration, the closure of glottis in early expiratory effort and then finally when glottis opens the expiration is explosive.
7. *Hiccup*: A reflex manifestation associated with stimulation of sensory endings in the GIT or other tissues of abdominal cavity through irritation. There is a sudden inspiration caused by spasm of diaphragm during which the glottis is closed so that further air cannot enter. The characteristic sound is there due to vibration of air against closed glottis.
8. *Yawning:* Prolonged inspiration, possibly due to boredom, fatigue and drowsiness. Stretching of jaw muscles may help to relieve these. Yawns sometimes have purely psychological reasons.
9. *Swallowing reflex:* During swallowing respiration is inhibited in whatever phase of respiratory cycle is there. It is protective against aspiration of foodstuff in respiratory passages.
10. *Chemoreceptor reflex:* Afferent impulses pass from carotid and aortic bodies. These are composed of special cells, which are stimulated by CO_2 excess and oxygen lack and also by increase in hydrogen ion concentration.
11. *Baroreceptor reflex:* Baroreceptors specially present in carotid sinus and aortic arch are stimulated when blood pressure is increased.

    Increase of blood pressure—inhibits respiration (in anesthetized animals).

    When blood pressure falls respiration is stimulated.
12. *Pain afferents reflexly stimulate respiratory center:* Therefore, in newborn attempt is made of initiate breathing by slapping.
13. *Afferent impulses from joints*: Reflexly stimulate breathing. Therefore, increased breathing in exercise is partly due to reflexes originating from joints.
14. *Effect of body heat on respiration*: Thermoreceptors present in periphery, also those present in hypothalamus stimulate respiration.

CHEMICAL REGULATION OF RESPIRATION

Chemical signals, which regulate respiration are sensed either by peripheral or central chemoreceptors.

Major signals are PO_2, PCO_2 and pH. pH depends on PCO_2.

Central Chemoreceptors

The respiratory centers, none is affected directly by changes in blood CO_2 concentration or H ion concentration.

Instead, an additional neuronal area is a very sensitive, *chemosensitive area* is located *bilaterally* lying less than 1 mm beneath the ventral surface of medulla (Fig. 37.6).

1. The primary stimulus for the receptors in central chemosensitive area is an increase in hydrogen ion concentration. When stimulated by an increase in hydrogen ion concentration, the effect is increase rate and depth of respiration.
2. Increase in hydrogen concentration is the result of increase in PCO_2. Because hydrogen ions cannot cross blood-brain barrier, increase in blood hydrogen ion concentration does not change hydrogen ion concentration in immediate vicinity of chemosensitive neurons.
3. Carbon dioxide being lipid soluble can easily diffuse out of blood or CSF and can dissolve in ECF which surrounds these neurons to raise its hydrogen ion concentration. Thus, effect of increased blood PCO_2 is to increase in hydrogen concentration, which will stimulate central chemoreceptors.

PERIPHERAL CHEMORECEPTORS (FIG. 37.7)

Chemoreceptors located peripherally that is in the:

1. (a) Carotid body and (b) aortic body regulate respiration. They contain special cells called glomus cells with high dopamine content.

   Information from carotid body is sent by glassopharyngeal nerve and from aortic body by vagus nerve to dorsal group of medullary neurons (DRG).
2. Blood flow to these receptors is highest in the body → 2000 ml/min/100 gm of tissue.

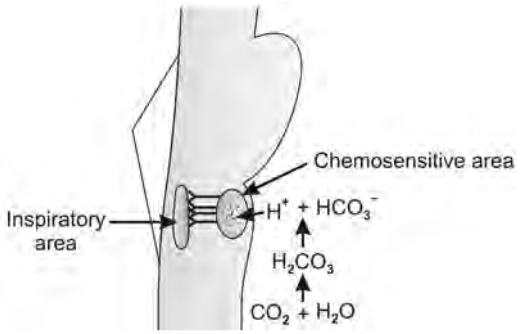


Fig. 37.6: Stimulation of (Inspiratory area) by chemosensitive area

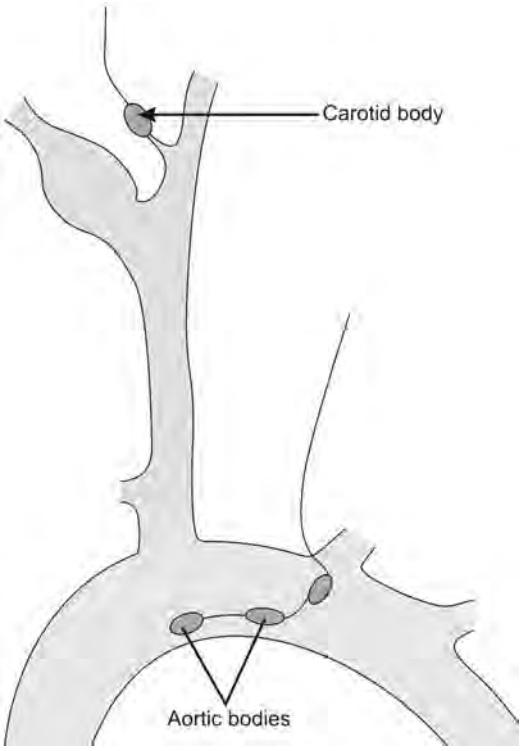


Fig. 36.7: Peripheral chemoreceptor and their innervation (diagrammatic)

Inspite of very high metabolic rate they hardly remove any oxygen from the blood supplied to them.

There is negligible oxygen difference in the arterial blood supplying them and venous blood drained away from them. Therefore, they are ideally built to sense changes in arterial PO_2.

3. Most potent stimulus for peripheral chemoreceptors is low arterial PO_2 (maximum stimulation between 30 and 60 mm Hg).
4. Other stimuli, which activate peripheral chemoreceptors are: (i) high arterial PCO_2 or (ii) increase in arterial hydrogen ion concentration.
5. *Response of activation of peripheral chemoreceptors is*—increase in pulmonary ventilation by increase in rate and depth of respiration.

Integrated Chemoreceptor Response

The combined effect of low PO_2 and high PCO_2 on respiration is greater than the sum of their individual effects.

In vigorous exercise increased oxygen consumption leads to low PO_2 and because CO_2 is also increased in exercise, the combined stimuli of low PO_2 and high PCO_2 may explain the hyperventilation associated with exercise to a considerable extent.

CHAPTER

38

Hypoxia and Acclimatization to High Altitude

HYPOXIA

Hypoxia is inadequate supply of oxygen to tissues.
Hypoxemia refers to reduction of oxygen content of blood.

Types of Hypoxia

Hypoxic Hypoxia

Hypoxic hypoxia is characterized by:

i. Lower than normal oxygen tension in blood (PO_2 is low). Hemoglobin is not saturated with oxygen to the normal extent; therefore,
ii. Oxygen content is low. It may be due to:

1. *Low oxygen tension in inspired air examples*:
   i. High altitude. PO_2 in air may be as low as 50 mm Hg (Normal is 100 mm Hg) because of rarefied atmosphere due to low atmospheric pressure than at the level of sea.
   ii. Admixture of atmospheric air by other gases—for example, carbon monoxide, nitrous oxide.
2. *Lung failure (gas exchange failure) examples:*
   i. Pulmonary fibrosis.
   ii. Any pathology in the lungs, which does not allow proper diffusion of gases.
3. *Respiratory pump failure*—can be due to:
   i. Fatigue of respiratory muscles in conditions in which the work of breathing is increased or due to
   ii. A variety of mechanical defects such as pneumothorax or bronchial obstruction.
4. *Venous to arterial shunts*—in many congenital conditions of heart such as:
   i. Patent interventricular septum
   ii. Patent foramen ovale
   iii. Fallot's tetralogy.

All are cyanotic congenital heart diseases in which large amount of unoxygenated venous blood bypass the pulmonary capillaries and are mixed in systemic arteries; this results in chronic hypoxic hypoxia and cynosis.

Anemic Hypoxia

In which: (a) arterial PO_2 is normal, but the amount of hemoglobin available to carry oxygen is reduced, (b) therefore, oxygen carrying capacity and oxygen content is low; examples are: (i) anemia where hemoglobin content is low, (ii) carbon monoxide poisoning. Small amount of carbon monoxide (CO) are formed in the body, and this gas may function as a chemical messenger in the brain and elsewhere.

In larger amounts it is poisonous. Outside the body it is formed by incomplete combustion of carbon. CO is toxic because it reacts with hemoglobin to form carbon monooxyhemoglobin (Carboxyhemoglobin, COHb). COHb cannot take up oxygen. The affinity of hemoglobin for CO is 210 times its affinity for oxygen. Also, when COHb is present, the dissociation curve of remaining HbO_2 shifts to left decreasing the amount of O_2 released.

Symptoms of CO poisoning are those of any type of anemia, headache and nausea but there is little stimulation of respiration, since in the arterial blood PO_2 remains normal and the carotid and aortic chemoreceptors are not stimulated.

The cherry red color of COHb is visible in the skin, nail beds and mucous membrane. Death results when 70-80% of circulating Hb is converted to COHb.

Treatment

1. Immediate termination of exposure to carbon monoxide.
2. *Oxygen inhalation:* Hyperbaric oxygen is useful in this condition.
3. In overdosage of drugs like nitrites, chlorates and sulfonamides, hemoglobin is oxidized to methemoglobin and functioning Hb is reduced.

Stagnant Hypoxia

In stagnant hypoxia: (a) oxygen tension and (b) oxygen content is normal, but the supply to the tissues is reduced due to diminished rate of blood flow through the tissues as happens in *cardiac failure.*

Other examples are:

- Shock
- Hemorrhage
- Cold exposure, etc.

It is also known as hypokinetic hypoxia. Due to slow circulation the CO_2 content of the tissues is increased, as it is not removed fast. This favors oxygen dissociation. Secondly, more time is also available for extraction of oxygen and these factors to some extent minimize oxygen lack at rest. But requirements during activity are inadequate.

Histotoxic Hypoxia

In this condition: (a) oxygen tension and (b) oxygen content are normal and supply to tissues is adequate but the cells are unable to utilize the oxygen due to inhibition of tissue oridative proceses. It is most commonly the result of cyanide poisoning. Cyanide inhibits cytochrome oxidase and possibly other enzymes.

Effects of Hypoxia

The effects of hypoxia depend on the: (i) rapidity of onset (ii) severity, and (iii) duration of hypoxia.

The organs most susceptible to hypoxia are: (i) brain, and (ii) heart.

Nervous System

1. If the onset of hypoxia is rapid and severe, there is sudden loss of consciousness. On recovery the subject feels that he has been knocked down by a blow.
2. When the onset is gradual the symptoms simulate alcohol intoxication.
   i. Individual may be depressed and apathetic or there may be excitement, elation and a sense of well being.
   ii. There is general loss of self-control and the subject may become talkative, quarrelsome, ill tempered and rude.
   iii. There is dyspnea, easy fatigability, muscular weakness and incoordination.
   iv. Pain may be dulled.

v. Disorientation may take place and subject may not know where he is.
vi. Memory is impaired and mental tasks are performed with less efficiency.
vii. *But inspite of all this* the subject feels confident that he has clear mind and fails to appreciate dangers and may fail to take suitable safety measures.
viii. Visual and auditory acuity is diminished. There may be retinal hemorrhage.
ix. Brain is highly susceptible to hypoxia and there is danger of permanent brain damage.

Respiratory System

1. When hypoxia is very rapid and severe, for example, inhalation of inert gas with no oxygen—there is brief period of initial hyperpnea followed by inhibition of respiration.

   Loss of consciousness occurs within a minute. Breathing ceases due to failure of respiratory center activity.
2. The effects of a less acute deprivation of oxygen—when oxygen content falls from normal *21%* to about *14%*. Now, there is: (i) *increased breathing*—which becomes, (ii) *periodic* with respirations waxing and waning.

   If oxygen content continues to fall and when it reaches a very low level (below 5%) there is (iii) *depression of breathing* followed by loss of consciousness and *failure of respiration*.
3. If hypoxia is of very gradual onset as in ascending gradually to high altitudes, sufficient time is available for the compensatory changes, and sufficient time is available for oxygen lack to stimulate breathing and maintain pulmonary ventilation at adequate levels, up to certain limits of hypoxia.

Cardiovascular System

i. There is an increase in rate and force of cardiac contraction.
ii. Cardiac output increases.
iii. Blood pressure is increased
iv. Constriction of cutaneous and splanchnic vessels is there:

All changes are due to reflex stimulation of cardiac and vasomotor centers.

Constriction of cutaneous and splanchnic blood vessels shifts large amount of blood from nonvital to vital organs, for example, brain and heart. So that they are supplied with adequate oxygen.

Increased cardiac output and increased blood pressure also help to increase the flow through the cerebral and pulmonary vessels.

Effects of hypoxia may persist for sometime even after the restoration of oxygen supply.

i. Brain takes time to recover depending upon the severity and the duration of hypoxia.
ii. Prolonged and severe exposure will finally cause irreversible damage to the brain tissues.
iii. *Sometimes delayed effects also occur* nausea, vomiting, depression, muscular weakness and impairment of mental faculties may appear several hours after exposure to hypoxia.

Oxygen Therapy

Oxygen therapy is of definite value in some pulmonary and cardiac disorder and when given to patients in whom, it is indicated; dramatic improvement occurs and the general condition of the patient becomes better.

Oxygen is administered through:
- Nasal catheter
or – face mask
or – by placing patient in oxygen tent.

Place of Oxygen Therapy in Different Types of Hypoxia

Administration of oxygen can be of considerable benefit in certain forms of hypoxia.

Hypoxic Hypoxia

1. At high altitudes where partial pressure of oxygen is low, breathing oxygen greatly increases the arterial oxygen content. Oxygen inhalation increases the alveolar and arterial PO_2. In fact, beyond heights of 6,000 meters inhalation of pure oxygen is essential.
2. In pulmonary diseases associated with:
   i. Impaired diffusion
   ii. Hypoventilation or
   iii. Airway obstruction, the increase of alveolar PO_2 favors better oxygenation of pulmonary capillary blood.
3. *In venoarterial shunts* oxygen is not of much value, since that portion of blood passing through the lungs is already well saturated and further improvement of PO_2 is not of much help.

Anemic Hypoxia

1. In carbon monoxide poisoning administration of oxygen is of great value, as a high concentration of oxygen helps to release carbon monoxide from its combination with hemoglobin.
2. In anemia, the hemoglobin content of the blood is reduced, but the available hemoglobin is well saturated with oxygen. Therefore, administration of oxygen will not significantly increase the O_2 combined with Hb, but it increases the quantity of dissolved oxygen by about 2 ml percent. Because it is under high pressure, this oxygen diffuses to the tissues and the peripheral supply of oxygen is improved.

Stagnant Hypoxia

The arterial oxygen content and tension are normal. Here again the small increase in dissolved oxygen may improve the oxygen supply to tissues.

Histotoxic Hypoxia

Oxygen is of no value as there is no oxygen deficit and the symptoms are due to the fact that the tissues are unable to utilize oxygen supplied to the cells.

Hyperbaric Oxygen Therapy

Administration of oxygen under pressure has been found to be definitely useful in the treatment of: (i) carbon monoxide poisoning, and in (ii) gas gangrene.

In carbon monoxide poisoning, the high oxygen pressure expedites the removal of carbon monoxide from HbCO.

Surgery for certain forms of congenital heart disease is sometimes carried out in high-pressure tanks.

The patient is placed in a special pressurized chamber and exposed to oxygen at 2 or 2 ½ atmospheres for short period. If given for a prolonged period or at higher pressures oxygen toxicity will result. Therefore, limits of exposure are less than 5 hours and pressures to 3 atmospheres or less. *Oxygen toxicity* O_2 is necessary for life, is also toxic. Toxicity seems to be due to: (i) production of superoxide anion (O_2^-, which is a free radical) and (ii) H_2O_2.

1. When 80-100% oxygen is administered to humans for period of 8 hours or more—the respiratory passages are irritated, causing substernal discomfort, nasal congestion and coughing with sore throat.
2. Clinically, the tissues most susceptible to oxygen toxicity seems to be central nervous system and lungs. Neurological symptom

of toxicity is *convulsions*. Prolonged administration of high concentration of oxygen produces *pulmonary fibrosis* leading to diffusion defect.

3. In premature infants, prolonged stay in oxygen tent is associated with: (i) development of blindness due to retrolental fibroplasia.

ACCLIMATIZATION

Acclimatization has come from French word Acclimater.

Definition

The changes in the responses of the organism produced by continued alteration in the environment.

At high altitude, the percentage of oxygen in the atmosphere is the same as at sea level but the barometric pressure is low and therefore, the partial pressure of oxygen is proportionately reduced and with increase in altitude, the barometric pressure and the partial pressure of oxygen progressively fall.

In aeroplanes flying at high altitude pressurized cabins are provided to enable the crew and passengers to travel without ill effects.

The alveolar PCO_2 depends upon the metabolic and respiratory activity and not upon the barometric pressure. The alveolar PCO_2 which is 40 mm Hg at sea level fall to 35.5 mm Hg at 3,000 meters, 32.5 mm Hg at 4500 meters and 30 mm Hg at 6,000 meters.

Mountain Sickness

Mountain sickness is not due to low barometric pressure but due to resulting low oxygen content of blood due to reduced partial pressure of oxygen. The height at which the mountain sickness appears varies with different climbers and depends upon: (i) physical fitness and previous training, (ii) rapidity of ascent and muscular effort used.

Effects

1. Headache
2. Dizziness
3. Nausea vomiting
4. Tachycardia
5. Impairment of mental faculties
6. And errors of judgement and other effects (described under effects of hypoxia) may occur.

Acclimatization at High Altitude

If sufficient time is available, compensatory mechanisms of the body come into play to improve the oxygen supply to tissues.

Immediate changes

1. *Hyperventilation:* Pulmonary ventilation is increased due to increased rate and depth of respiration.

   Increase in rate and depth of respiration is due to oxygen lack stimulating the respiratory center reflexly by stimulating carotid body chemoreceptors.

   Because of increased ventilation more CO_2 is washed out and blood becomes alkalemic.

   i. Initially the fall in PCO_2 tends to depress respiration through the central chemoreceptor mechanisms. Thus, low PO_2 tends to stimulate respiration and the resulting low PCO_2 tends to inhibit respiration. The net result of these opposing influences is an increase in pulmonary ventilation by up to 65%.

   ii. But within 3-4 days there is further increase in ventilation. Minute volume

may eventually increase by 500%. It increases due to mainly increase in tidal volume.

Mechanism: Wash out of carbon dioxide tends to produce respiratory alkalosis, and alkalosis is compensated by *renal excretion of bicarbonates.*

Therefore, blood and CSF carbonic acid/bicarbonate ratio and hence, pH of CSF are maintained at normal level. Central chemoreceptors are affected primarily by pH of CSF, and they no longer inhibit respiration inspite of carbon dioxide wash out.

Secondly, there is evidence of increased sensitivity of central chemoreceptor mechanisms to hypoxia and carbon dioxide. Therefore, hypoxia stimulates respiration to a greater extent and PCO_2 even at low level can stimulate them.

2. *Physiological polycythemia:* Hypoxia is potent stimulus for erythropoiesis via erythropoietin mechanism. Tissue hypoxia causes release of erythropoietin from the kidneys. Erythropoietin is a hormone carried by blood to bone marrow where it stimulates red cell production by acting on several precursors of erythrocytes. *RBC count may increase* to 6 - 8 millions/cmm.

   Therefore, within a few weeks of stay at high altitude the Hb concentration rises.
3. *Hemoglobin concentration of blood rises*
4. The red cell mass expands therefore, *Blood volume also expands.*
5. *Increase in hemoglobin increases the oxygen carrying capacity of blood.* Therefore, in spite of low saturation of hemoglobin due to low PO_2 the amount of oxygen carried at high altitude may be same as at sea level.
6. Increase in red cells leads to *increased viscosity* of blood, which will *increase peripheral resistance.*
7. *Increased vascularity of tissues:* At high altitude more number of capillaries open up therefore, blood flow to tissues is increased and more oxygen is supplied.
8. *Improved ability of tissues to use oxygen:* There are also compensatory changes in tissues. The mitochondria increase in number and there is an increase in myoglobin that facilitates the movement of oxygen in the tissues. There is also an increase in tissue content of cytochrome oxidase.
9. Within hours of exposure to high altitude or hypoxia due to any other cause, the *DPG (2, 3-diphosphoglycerate) concentration of red blood cells increases.*

   This reduces the affinity of hemoglobin for oxygen. The phenomenon is advantageous at tissue level because more oxygen dissociates from hemoglobin for a given fall in oxygen tension or PO_2.
10. *Total volume of lungs increases* so that lungs hold more volume of air, causing more stretching of alveolar epithelium, which is thinned out and facilitates gaseous exchange. Associated with this there is increase in pulmonary capillary blood flow. Both these factors help *greater transfer of oxygen from lungs to blood.*
11. *Cardiovascular changes: Cardiac acceleration, increase in cardiac output and increase in blood pressure* is only for few days. Blood flow to muscles, heart and brain is increased but to skin and kidneys is reduced.

Natives of High Altitude

1. Chests are barrel shaped their vital capacity is increased.
2. Marked polycythemia.
3. Low alveolar PO_2, but in most other ways they are remarkably normal.

CHAPTER

39

Abnormal States of Respiration

Normal quiet breathing is called *Eupnea. Tachypnea* is increased rate.

HYPERPNEA (HYPERVENTILATION) — INCREASED BREATHING

Any increase in the quantity of air breathed per minute is known as hyperventilation or hyperpnea due to increased rate or depth of breathing or both.

Causes

1. Voluntary
2. Impulses from cerebral cortex to respiratory center for example emotions.
3. Impulses from hypothalamus to respiratory center as in increased temperature.
4. Reflexly by stimulation of general sensations – for example, pain, heat, cold receptors in skin.
5. All conditions that increase metabolic rate, for example, muscular exercise.
6. Factors causing dyspnea.
7. Initially at high altitude.

Effects of Voluntary Hyperpnea or Hyperventilation

If continued for 3 minutes, breathing is stopped for sometime (*apnea*).

Causes

Washing out of excessive carbon dioxide (hypocapnia), therefore, arterial PCO_2 falls and PO_2 increases slightly. The fall in PCO_2 depresses respiration. Therefore, the urge to breathe is diminished after voluntary hyperventilation. In apnea, PCO_2 increases and PO_2 falls.

1. Apnea is followed by breathing for sometime, again apnea is there. Therefore, for sometime *periodic breathing* is there. Then respiration gradually comes back to normal.
2. *Alkalosis:* Because of washing out of more CO_2 blood becomes more alkaline and alkaline urine is passed as more bicarbonates are excreted and H^+ ions secretion is low by tubule.
3. Presence of *keto acids* in urine.
4. *Skin vessels* constrict and skin becomes white and cold.
5. *Cardiac output* and *blood pressure* is increased slightly.
6. *Dizziness* and *paresthesias* are felt and consciousness becomes blurred. Cause of this is reduction of cerebral blood flow because of direct vasoconstrictor effect of hypocapnia on cerebral blood vessels.
7. Plasma level of *ionic calcium falls* and due to hypocapnia individual develops

carpopedal spasm, positive Chvostek's sign and other signs of tetany.

Same will be effects of hypocapnia (= reduction in CO_2 content of blood).

DYSPNEA

Dyspnea is distressed breathing or difficult breathing

Normally breathing goes on without being conscious of it and dyspnea is consciousness of the necessity for increased respiratory effort. Hyperpnea means increased breathing without discomfort. For sometime hyperventilation may not impinge on our consciousness and hyperpnea is a stage preceding dyspnea and height of hyperpnea – where dyspnea occurs is called *dyspnea point.*

Normal person will develop discomfort when ventilation is increased four times.

Breathing reserve is maximum ventilation volume minus resting minute ventilation

Normal MVV—100 L/min
RVV—5 L/min
100 – 5 = 95 L/min is breathing reserve at rest

% breathing reserve or dyspneic index =

$$= \frac{MVV - RMV}{MVV} \times 100$$

$$= \frac{100 - 5}{100} \times 100$$

= 95% at rest

If this value falls below 60% dyspnea is present at rest. Therefore, called as dyspneic index.

Different factors often enter into the development of the sensations of dyspnea:

1. Abnormality of respiratory gases in body fluids specially hypercapnia and to less extent hypoxia.
2. Amount of work performed by respiratory muscles to provide adequate ventilation.
3. State of mind (abnormal) – results in neurogenic dyspnea or emotional dyspnea.
4. Altered discharge from airway receptors, lung receptors or respiratory muscle proprioceptors.

ORTHOPNEA

In congestive heart failure or left ventricular failure the lungs are congested therefore, patient is dyspneic. The breathlessness is more pronounced in lying down position. Patient feels comfortable in sitting posture. This type of postural dyspnea is called orthopnea.

Cause

1. Lungs are much more congested in lying down posture. In erect posture gravity clears the congestion except at the bases.
2. Elevation of diaphragm in lying down position.

APNEA

Temporary cessation of breathing is known as apnea may be seen in various conditions:

1. During periodic breathing – short periods of apnea are followed by breathing.
2. Low PCO_2 of blood as occurs after voluntary hyperpnea.
3. *Reflex apnea:*
   i. *Deglutition apnea:* During swallowing there is apnea, duration 1.5 sec. After swallowing respiration starts from the point at which it was arrested.
   ii. *Adrenaline apnea:* After injection of IV adrenaline respiration may become very shallow and almost cease.
   Cause: Rise of blood pressure stimulates baroreceptors present in carotid sinus and aortic arch. Impulses pass through vagus and glossopharyngeal

nerve to the medullary centers–vasomotor and respiratory. These impulses are inhibitory to the neurons of VMC and as respiratory neurons are intermingled, respiratory neurons are also depressed. Actual apnea is observed in anesthetized animals.

iii. *Vagal apnea:* Stimulation of central cut end of vagus in anesthetized animals causes apnea. This simulates inhibitory neurons as exaggerated Hering Breuer reflex.

iv. *Oxygen apnea:* Occurs during oxygen therapy in patients of hypoxia. It may be alarming especially during anesthesia. Before oxygen administration in such patients respiratory centre was driven by hypoxia stimulating peripheral chemoreceptors. As oxygen administration abolishes this source of stimulation, apnea occurs.

v. *Sleep apnea:* Sometimes healthy subjects during sleep show alternate apnea and hyperpnea.

Periodic Breathing

This term is applied to uneven breathing. There is alternate apnea and hyperpnea.

Two types of periodic breathing can occur:

1. *Cheyne-Stokes breathing* is a form of periodic breathing in which, breathing is shallow to begin with, increases gradually to a maximum amplitude and diminishes gradually to cease for a short time. This cycle is repeated. Each cycle lasts for about one minute. Alternate waxing and waning of respiration without definite apnea can also occur sometimes (Fig. 39.1A).
2. *Biot s breathing* is another form of periodic breathing in which, varying periods of apnea alternate with hyperpnea. The change from one to another is abrupt. Gradual increase and decrease of respiratory amplitude being absent (Fig. 39.1B).

Biot s breathing occurs in (i) meningitis and (ii) lesions and injuries to the brain.

Cheyne-Stokes breathing occurs in:

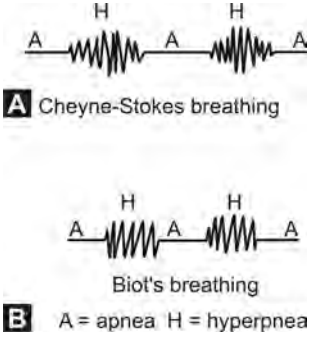
i. Premature infants.
ii. Unacclimatized person at high altitude and sometimes in
iii. Healthy subjects during sleep and sometimes after
iv Prolonged periods of hyper-ventilation.

Pathologically it occurs in:

i. Advanced cardiac and renal diseases
ii. Raised intracranial pressure
iii. Morphine poisoning.

Its occurrence in disease is a serious sign and indicates respiratory depression.

Main cause of periodic breathing appears to be central hypoxia causing depression of respiratory center – PO_2 falls. Respiration and breathing becomes deeper – this increases oxygen supply and washes out more CO_2 – Improved oxygen supply reduces chemo-receptor drive and lowered PCO_2 inhibit respiratory center and shallow breathing and apnea follows. The cycle is repeated.



Figs 39.1A and B: Periodic breathing

Administration of O_2 relieves periodic breathing.

Breath holding time or apnea time—after a maximal inspiration, ranges from 40 to 80 sec in normal subjects. In some persons it may be more due to training or as an effect of will.

During apnea, PO_2 falls and PCO_2 increases and both hypoxia and hypercapnia powerfully stimulate respiration so a "breaking point" is reached when it becomes impossible to hold breath any longer.

Breath holding can be prolonged by: (a) breathing pure oxygen (initial alveolar PO_2 will be more) or (b) prior voluntary hyperventilation (initial alveolar PCO_2 will be less).

ASPHYXIA

Improper aeration of blood if continued for sometime in an intact animal produces a series of pathological manifestations ultimately leading to death.

Definition

Asphyxia is combined effects of acute oxygen lack (hypoxia) and increased PCO_2 (hyper = capnia)

Examples:

1. Drowning
2. Respiratory arrest due to:
   i. Electrocution
   ii. Overdose of anesthetic or narcotic drug.

In drowning ˇ sequence of events:

i. Oxygen lack for one minute produces loss of consciousness and respiration is stimulated.
ii. *Within another minute or two*
   a. Respiratory center ceases to function.
   b. Vasomotor center is more resistant.
   Therefore, continues to function for sometime and tone of the blood vessels is maintained—Asphyxia livida.
   c. It then fails → peripheral vasodilatation and fall of blood pressure → Asphyxia pallida.
iii. Most important of all heart, unlike skeletal muscle or smooth muscle, can function normally only for a short while in absence of oxygen. It has no anaerobic metabolism to fall back on.
   a. The force of contraction of heart beat in severe hypoxia rapidly weakens and all chambers dilate greatly.
   b. Output to blood vessels is reduce to a trickle and then acute asphyxia presents a combination of respiratory, circulatory and nervous system failure.
iv. Therefore, treatment employed must be effective if it is to be successful. Most important treatment is *artificial respiration.*

Effects of general asphyxia are divided in three stages:

Whole episode from onset to death is about 5 minutes.

First stage: Stage of hyperpnea.

1. *Duration:* 1 minute.
2. *Manifestations:* Rate and depth of respiration increases. At first both inspiration and expiration increase and animal becomes dyspneic.
   i. Then expiratory effort becomes more pronounced than inspiratory. This feature makes the end of first stage.
3. *Cause:* Respiratory stimulation is due to increase PCO_2, although oxygen lack is there, it is not severe enough to exert its effects.

Second stage: Stage of expiratory convulsion or stage of central excitation.

1. *Duration:* 1-2 minutes
2. *Manifestations*
   i. In experimental animal stage of hyperpnea is followed by unconsciousness.
   ii. Expiration becomes still more pronounced and with each expiration almost whole body convulsion takes place.
   iii. All signs of central excitation are present.
   For example
   iv. Vasoconstriction causing BP to increase.
   v. Constriction of pupil.

   [*Cause:* Action of increased PCO_2, on vasoconstrictor area and secretion of adrenaline is increased].

   vi. Exaggerated reflexes.
   vii. Salivary secretion and vomiting.
   viii. Heart rate and intestinal movements may increase or decrease depending on predominance of sympathetic or parasympathetic stimulations.
3. *Cause*– i. CO_2 accumulates still more.
   ii. Oxygen lack by this time is more pronounced by stimulating peripheral respiratory centre reflexly.
   iii. Due to convulsions lactic acid appears in blood and produces acidosis.

These three factors combine together to stimulate respiratory as well as other nervous centers, therefore, maximum excitation is seen in this stage.

Third stage: Stage of slow deep inspiration or stage of central depression.

Manifestations: Expiratory convulsions cease and are replaced by slow deep inspiration. Inspiration becomes spasmodic and with each inspiration the animal stretches itself out and opens its mouth widely as if gasping for breath.

1. Signs of central depression appear.
2. Pupils dilate
3. Reflexes abolish
4. Vasodilatation
5. Fall of blood pressure
6. Interval between successive inspirations become longer, animal takes few gasping breath and at the end dies.

Causes

1. Central depression of respiratory center due to oxygen lack.
2. All the factors which were present in second stage are still present but they fail to stimulate the centres because they are exhausted, therefore, oxygen lack exerts its direct depressant effect on respiratory center.

DECOMPRESSION SICKNESS (CAISSON'S DISEASE, THE BENDS) OR DYSBARISM

Decompression sickness is a condition which occurs when subjects exposed to high atmospheric pressures are suddenly brought to low atmospheric pressure.

It occurs in deep sea divers and workers in caisson when they return to surface too rapidly from depths of water to the surface.

Caisson is a water tight chamber used for carrying on construction under water. It can occur in aviators who ascend too rapidly from sea level to altitudes of over 9000 meters.

For a depth of every additional 10 meters of sea water there is an additional pressure of one atmosphere.

For example: Barometric pressure at the depth of 30 meters is (1 + 3) = 4 atmosphere.

1. When divers descend to depths, they are exposed to high atmospheric pressures and larger volumes of gases go into *solution* in plasma and the tissues.
2. If the return to the surface is *slow*, the gases that come out of solution diffuse into the blood and are eliminated by lungs.
3. If the decompression is *rapid*, the escape of gases from the solution is *quick* and *bubbles* are formed in tissues and blood.
4. This causes *damage to the tissues* and obstructs the flow of blood in small blood vessels (air embolism).
5. *Nitrogen* is particularly important in this respect as it is *highly soluble in fatty tissues* for example:
   i. Subcutaneous fat
   ii. Bone marrow
   iii. Adrenal cortex
   iv. Myelin sheath

   and it cannot be used by tissues (whereas oxygen is used by tissues). Symptoms commonly appear 10-30 minutes after diver resurfaces.
6. Symptoms *initially* are pain in the muscles and joints of the limbs, flexion of joints, therefore, called as 'bends'.

   Cause: Bubbles in sensory nerves – therefore, pain and 'bends'.
7. Symptoms *later* are:
   i. Paresthesias (cause bubbles in sensory nerves)
   ii. Motor weakness and
   iii. Paralysis

   Cause: Bubbles in motor nerves.
8. There may be:
   i. Dyspnea that divers call 'chokes' (cause bubbles in pulmonary capillaries).
   ii. Small running pulse (feeble pulse).
   iii. Unconsciousness.
   iv. Myocardial damage (cause bubbles in Coronary arteries).
   v. Cyanosis.
9. The important factor in production of symptoms is not the absolute decrease but the percent reduction of pressure. A rapid reduction of 50% is safe but below 45% dangerous.
10. Decompression sickness can be *prevented* by slow decompression, but this may be inconvenient and tedious.

    Therefore, rapid decompression may be done in *stages*.

    A subject may be rapidly brought from 8 to 4 atmospheres and after an interval to establish gaseous equilibrium, pressure may be reduced to 2 atmospheres and again after suitable interval to 1 atmosphere.
11. If symptoms are already set in: (a) rapid compression followed by slow decompression, (b) hyperbaric oxygen, along with recompression is found to be very beneficial.

CYANOSIS

Cyanosis is diffuse bluish discoloration of skin and mucous membrane. Reduced hemoglobin has a dark color and cyanosis appears when the reduced hemoglobin concentration of blood in the capillaries is more than 5 gm/100 ml.

1. Cyanosis may be general in distribution but is more evident over the lips, and the fingers above the base of the nails, earlobes where the skin is thin and the mucous membrane.
2. It is clearly distinguishable in individuals who are fair.
3. Cyanosis depends upon the absolute amount of reduced hemoglobin and not on proportion of reduced to oxygenated hemoglobin.
4. Capillary insaturation may be increased due to:
   i. Increase in arterial insaturation as in hypoxic hypoxia. This form is called

central cyanosis as the cause of insaturation is central.

ii. Increase in venous insaturation as in stagnant hypoxia. This is called peripheral cyanosis.

5. Cyanosis does not occur in:
   i. Anemic hypoxia when the total hemoglobin is low.
   ii. Carbon monoxide poisoning because the color of reduced hemoglobin is obscured by cherry red color of carbon monoxyhemoglobin.
   iii. Histotoxic hypoxia because blood gas content is normal.
6. A discoloration of the skin and mucous membrane similar to cyanosis is produced by high circulating levels of methemoglobin.

Cyanosis occurs in:

1. Pulmonary disorders
2. Congenital heart diseases with right to left shunts, and
3. Cardiac failure, and at
4. High altitudes.

HYPERCAPNIA

1. Is increase in CO_2 content of blood.
2. Occurs in conditions associated with *hypoventilation.*
3. Respiration is stimulated and dyspnea results.
4. Headache, dizziness, depression and fine tremors.
5. Tachycardia, rise of blood pressure and flushing of skin due to vasodilatation.
6. pH of blood is reduced.
7. As CO_2 concentration further increases - fainting.
8. Muscular rigidity.
9. Generalized convulsions.
10. Depression of respiration
11. Loss of consciousness occur.

SECTION VI: CARDIOVASCULAR SYSTEM

CHAPTER 40

General Considerations

The primary functions of cardiovascular system are:

1. To provide an adequate supply to all cells of our body of materials needed for their proper functions—for example:
   i. Oxygen
   ii. Nutrient substances, such as:
      – Carbohydrates
      – Fats
      – Amino aids
      – Hormones
      – Immunological substances.
2. To carry away waste products of their metabolism.
3. To transport heat to the surface of the body from where it is lost. Thus, helps to regulate temperature of the body. In cold heat loss is prevented by decreasing blood supply to skin.

It is a well organized *transport system* of the body by which blood is being circulated within a *closed system* under *different pressure gradients* created by the pumping mechanism, where heart acts as a *central pump*. The size of the pump (heart) is that of a clenched fist. No engineer has yet devised a pump, which has a long-term performance as that of the heart. In 70 years (which is the average lifespan of human being) output of two ventricles exceed 400 million L in resting conditions.

Heart and blood vessels together form cardiovascular system which includes:

i. Heart.
ii. Arteries – which are distensible.
iii. Arterioles – which offer resistance.
iv. Capillaries, and
v. Veins.

All of them differ in their structure as well as in function.

The volume of blood in our body is limited (5-6 L) but it has to perform unlimited work continuously. Therefore, it automatically comes that the same quantity of blood must be used over and over again. In other words blood must circulate.

Heart comprises of two pumps:

i. Right side, and
ii. Left side of the heart and vascular system comprise of two sets of distensible vessels.
   a. Pulmonary blood vessels, and
   b. Systemic blood vessels.

   They offer resistance to the flow of blood.

Venous blood is received by right atrium, which pumps it in right ventricle. Right ventricle pumps it into pulmonary artery. The resistance in pulmonary artery is low and the mean pressure in pulmonary artery is only 15-20 mm Hg. After oxygenation in pulmonary capillaries the blood returns via pulmonary veins (4 pulmonary veins) to left antrium and from there to left ventricle. The ventricle pumps blood into systemic circulation via the aorta. The systemic circulation offers greater resistance to the flow of blood and the mean pressure in systemic arteries is much higher than in pulmonary blood vessels. In systemic arteries a mean pressure of 100 mmHg is usually attained (= P_1 in Fig. 40.1)

After traversing the systemic arterioles and capillaries the blood returns at low pressure to the heart.

FUNCTIONS OF THE HEART

1. Heart pumps blood out in the pulmonary and systemic circulation intermittently.

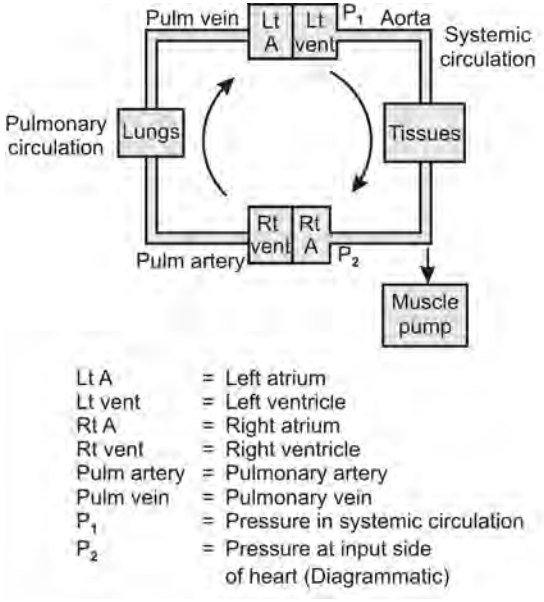


Fig. 40.1: Organization of cardiovascular system

2. Heart is a pump, which transfer blood from the venous side through the lungs to the arterial tree, as fast as it arrives.
3. The heart may be considered to comprise of two pumps working in series.
4. The heart provides the pressure for the circulation (the blood flows from the heart to the periphery and from there via the veins back to the heart only because of pressure gradient).
5. The two atria serve mainly as temporary storage chambers.

PRESSURE GRADIENTS IN SYSTEMIC CIRCULATION

The blood ejected by left heart flows round the systemic circulation to the right atrium because of the continuous pressure gradient that exist along the route which it traverses.

Pressures exist in the blood vessels as the blood is ejected into them from behind. Therefore, pressures are the manifestations of 'vis a tergo' (= force from behind).

'Vis a tergo' is a predominant factor responsible for circulation of the blood.

The *volume flow* through the systemic circulation depends directly on pressure difference $P_1 - P_2$ (Fig. 40.1).

P_1 is about 100 mm Hg in normal supine subject at the heart level and arterial pressures fluctuate about this value. Heart ejects blood intermittently. Therefore, there is pressure fluctuation. During systole it is more and during diastole it is less.

1. Increase of pressure during systole is limited (damped) by elasticity of aorta and large central arteries because they expand when blood is pumped into them by the heart. During diastole when pressure tends to fall the arterial walls recoil, and fall of pressure is limited and it also gives driving pressure to blood during diastole (Fig. 40.2).

Thus, initially the kinetic energy is stored as potential energy and during diastole the stored potential energy is reconverted back to kinetic energy.

2. Blood escapes through arterioles and capillaries, which are much less in diameter. So they offer resistance to the passage of blood, and blood is retained in the blood vessels even during diastole when no blood enters the aorta and big arteries from the heart. This determines the diastolic pressure (Fig. 40.2). By means of two factors (1 and 2) that means:
   i. Elasticity of large blood vessels, and
   ii. Resistance of small blood vessels the intermittent input which the arteries receive from the heart is converted to a steady flow from the capillaries.

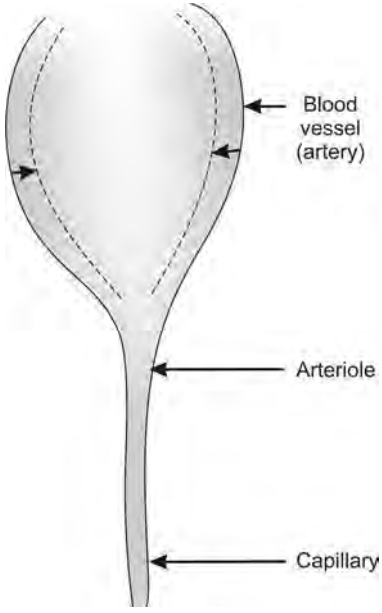


Fig. 40.2: Elasticity of large blood vessel and resistance of small blood vessel

RESISTANCE TO THE FLOW (R)

Resistance to the flow of blood is offered mainly by arterioles and to a less extent by capillaries. Arteries and veins have relatively large diameter and have low resistance.

The main resistance to the flow lie in arterioles. The greatest pressure drop occurs therefore, in traversing them (Fig. 40.3).

Arterioles are normally in a state of *partial constriction* due to tonic activity by *sympathetic vasoconstrictor nerves,* which supply them.

1. This vasoconstriction can be *increased* by increasing sympathetic discharge, e.g. hemorrhage (moderate). In hemorrhage volume flow is much reduced but mean pressure (P_1) may be sustained by increase in resistance.
2. Sympathetic discharge to arterioles may be *diminished,* e.g. at raised body temperature (reflex vasomotor response).

The walls of the arterioles are susceptible to chemical effects also, e.g. in exercise *local accumulation of metabolites* causes marked vasodilatation in the muscle.

PRESSURE AT THE INPUT SIDE OF THE HEART (P_2)

Under normal conditions P_2 is kept at very low level. So that heart transfers blood from venous to arterial side as fast as it returns. Cause is thin walled atria and veins are distensible. P_2 varies rhythmically with intrathoracic pressure during respiration and there are additional small fluctuations of P_2 due to mechanical action of the heart.

1. When the subject is recumbent the difference of pressure between that at the venous end of capillary (P_3) and at the heart (P_2) is responsible for the return of blood from the periphery to the heart (Fig. 40.3).

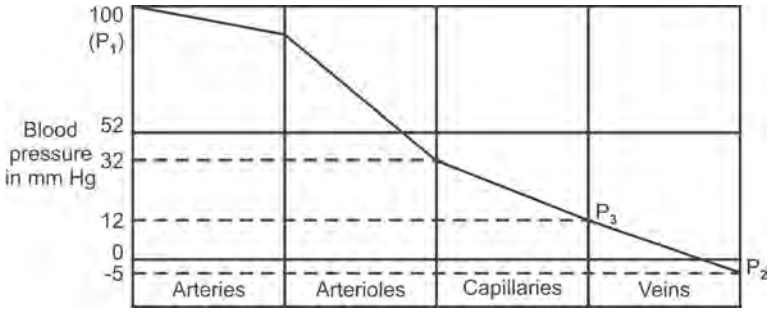


Fig. 40.3: Pressure changes in systemic circulation

2. In erect posture the venous pressure in feet is increased. The venous return is aided by:
   i. *Venous valves:* Thoracic and abdominal veins have no valves. Only the veins in the limbs possess them (Fig. 40.4). These valves permit flow only in one direction that is towards the heart.
   ii. *Compression of the venous segments* by surrounding muscles— forces blood from segment to segment towards heart and valves prevent backward flow into the segments emptied, and transmitted pressure from capillaries-(vis a tergo) causes refilling of the emptied segments.
   iii. Venous valves prevent over distention of thin walled veins. When the valves become incompetent, the veins become over distented – varicose veins.

*In heavy muscular exercise t*he cardine output increases 4 to 5 times. Normal cardiac output is 5 L/min, which increases to 20-25 L/min in heavy muscular exercise. Obviously this increase must be caused by *increase in the rate of circulation* and greater volume flow in circulation is caused by three factors:

i. An increase in P_1 or mean arterial pressure (by increasing rate and force of contraction of heart).
ii. The reduction of peripheral resistance (R) by chemical vasodilatation in the blood vessels of muscles, and
iii. The booster action of muscle pump.

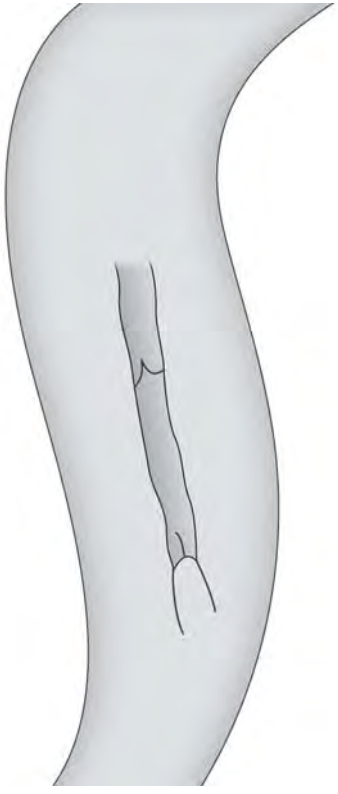


Fig. 40.4: Venous valves in veins of leg

VIS A FRONTE

1. During ventricular systole when the atrioventricular valves are closed the descent of the base of heart lowers the pressure P_2—thus, increasing the rate of flow of venous blood towards the heart.
2. During diastole, when atrioventricular valves are open the ventricles appear to suck as they relax (i.e. the intraventricular pressure is lower than the central vein). This lowering of the value of P_2 by the activity of the heart itself is called Vis a fronte (Fig. 40.5).

Thus, increased cardiac pumping not only increases P_1 but also lowers P_2.

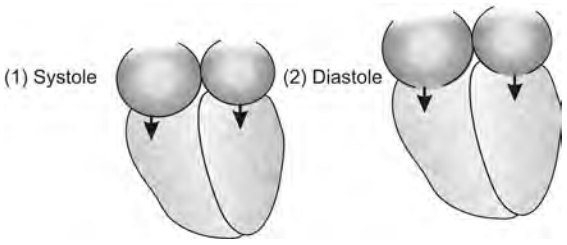


Fig. 40.5: Vis a fronte

BLOOD VESSELS

We can think of blood vessels as arranged in a large member of circuits in parallel. Thus, there will be one circuit for the renal circulation, one for skin circulation one for muscle circulation and so on (Fig. 40.6).

Each of these individual circuits consist of a number of sections, arranged in series:

1. The chief function of the *first section* of each circuit is to damp the huge pressure fluctuations generated by the heart to give fairly steady driving pressure. Anatomically these damping blood vessels correspond fairly closely with the *arteries* – aorta and its branches—*windkessel vessels*.
2. *Second section* is composed of vessels, which offer a high and variable resistance to the flow of blood around the circuit. They act as taps which regulate the flow in any particular circuit. They may be referred to as *resistance vessels* and correspond anatomically to *arterioles* and *precapillary sphincters*.
3. *Third section* in each circuit is composed of the vessels, which permit exchange of material by diffusion across their walls. These may be referred to as the *exchange*

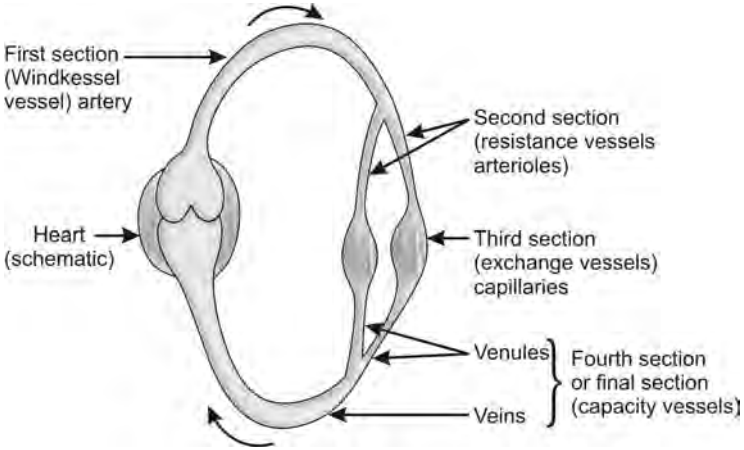


Fig. 40.6: Organization of blood vessels

vessels and correspond anatomically to *capillaries.*

4. *Final section* of each circuit consists of thin walled venules. The final section of each circuit consists of the vessels that contain the bulk of blood volume. These are referred to as *capacity vessels* and correspond anatomically to *veins and venules*. By altering their dimensions they adjust the capacity of the circulation to meet variations in the volume and distribution of blood in the circulatory system.

Important point is that the vessels perform all other functions to some extent, e.g. all blood vessels offer some resistance to the flow of blood but the greater part of the resistance lies in the arterioles. Similarly, all vessels have the capacity to hold the blood but a very large fraction of the blood volume is contained in the venules and veins.

CHAPTER

41

Structure and Properties of Heart Muscle

STRUCTURE OF HEART MUSCLE

The fibers of cardiac muscle are striated and show cross striations (Fig. 41.1). It differs from skeletal muscle in many respects.

1. Cardiac muscle fibers are rectangular. They bifurcate and join with adjacent fibers.
2. Fibers are made up of separate cellular units joined end to end by intercalated disks.

Intercalated Disks

1. Runs transversely across the fiber.
2. Is made up of multiple convolutions of adjacent sarcolemma.

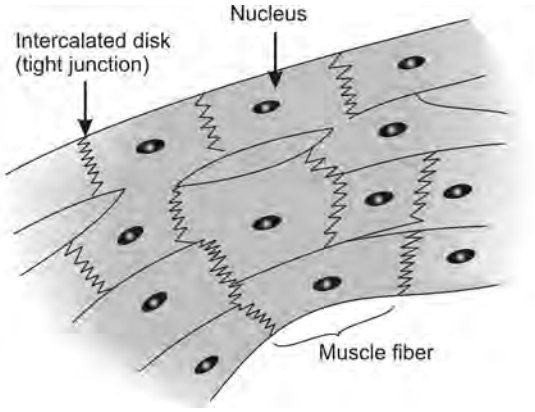


Fig. 41.1: Cardiac muscle fibers

3. It is tight junction of low electrical resistance, which transmits rapidly, depolarizing impulse from one cell to adjacent cells.

Therefore, although cardiac muscle fibers are separated from each other, they act as functional syncytium.

a. Gap junction (nexus) are present along the sides of adjacent myocardial cells.
b. Cardiac muscle fibers show nucleus in center, well-developed sarcoplasmic reticulum with plenty of cytoplasm, mitochondria and are rich in glycogen.

Electron Microscopic Appearance

Same as in skeletal muscles. There is presence of myosin and actin filaments, tropomyosin and troponin.

Sarcotubular system: (a) well-developed, but the T-tubule penetrates at the Z line. Therefore, in cardiac muscle, there is only one triad per sarcomere, (b) T tubule also stores calcium along with L tubule.

Heart is lined by:

- Epithelium on inside known as endocardium, and
- Membrane on outside known as pericardium.

Structure of Cardiac Chambers

The heart contains four chambers:

1. Right atrium and left atrium are 2 thin walled *atria* separated by interatrial septum.
2. Right ventricle and left ventricle are 2 thick walled ventricles separated by interventricular septum.

Left ventricle is thicker – because it has to pump blood against greater pressure.

Right ventricle is less thick – because it pumps blood in pulmonary circulation, which is a low-pressure system.

Atria and ventricles are connected by atrioventricular fibrotendinous ring, which can be called as skeleton of the heart. Cardiac muscle is attached to this ring like skeletal muscle is attached to bone. Therefore, the atrioventricular ring cannot conduct impulses.

Between right atrium and right ventricle is *tricuspid valve*.

Between left atrium and left ventricle is *bicuspid valve or mitral valve.*

Valves

Valves consist of flaps or cusps attached at the periphery to ring. To the free edges of the cusps are attached chordae tendineae, which are attached to papillary muscle from inner wall of ventricles and act as support (Fig. 41.2).

The right ventricle pumps blood to pulmonary artery and the opening is guarded by *semilunar valves. It consists of three cusps* and is known as *pulmonary valve*.

The left ventricle pumps blood to aorta and the opening is guarded by *semilunar valves, consisting of 3 cusps* and is known as *aortic valve*.

Semilunar valves are so named because they are shaped like half moon.

They open during ejection phase of ventricular systole and close at the beginning of ventricular diastole.

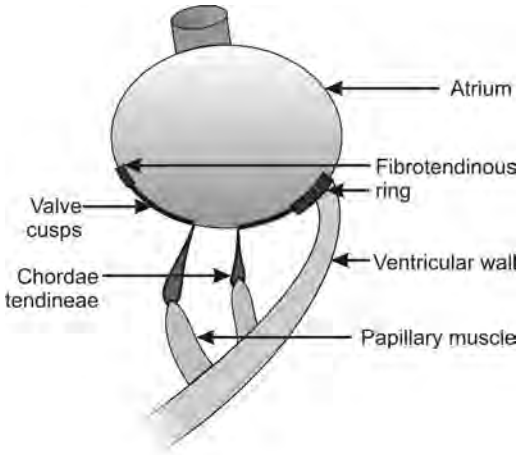


Fig. 41.2: Arrangement of valve cusps chordae tendineae and papillary muscles

Special Junctional Tissues of the Heart or Pacemaker Tissues of Heart

This term is used to describe *certain tissues of the heart*, which are concerned with the initiation and propagation of the heartbeat (Fig. 41.3). It consists of specialized fibers of modified structure, which can conduct the impulse faster than typical cardiac muscle fiber.

They include:

1. Sinoatrial node (SA node).
2. Atrioventricular node (AV node).
3. Atrioventricular bundle or bundle of His.
4. Right and left branches of bundle of His.
5. Purkinje fibers – these are:
   i. Terminal ramifications of bundle of His, below the endocardium
   ii. Terminal fibers, which penetrate the ventricular muscle.
6. Internodal conducting pathways of right atrium and Bachmann's bundle.

Pacemaker tissue can generate rhythmic impulses. Pacemaker and conduction tissue are made up of modified cardiac muscle, which is not so well striated.

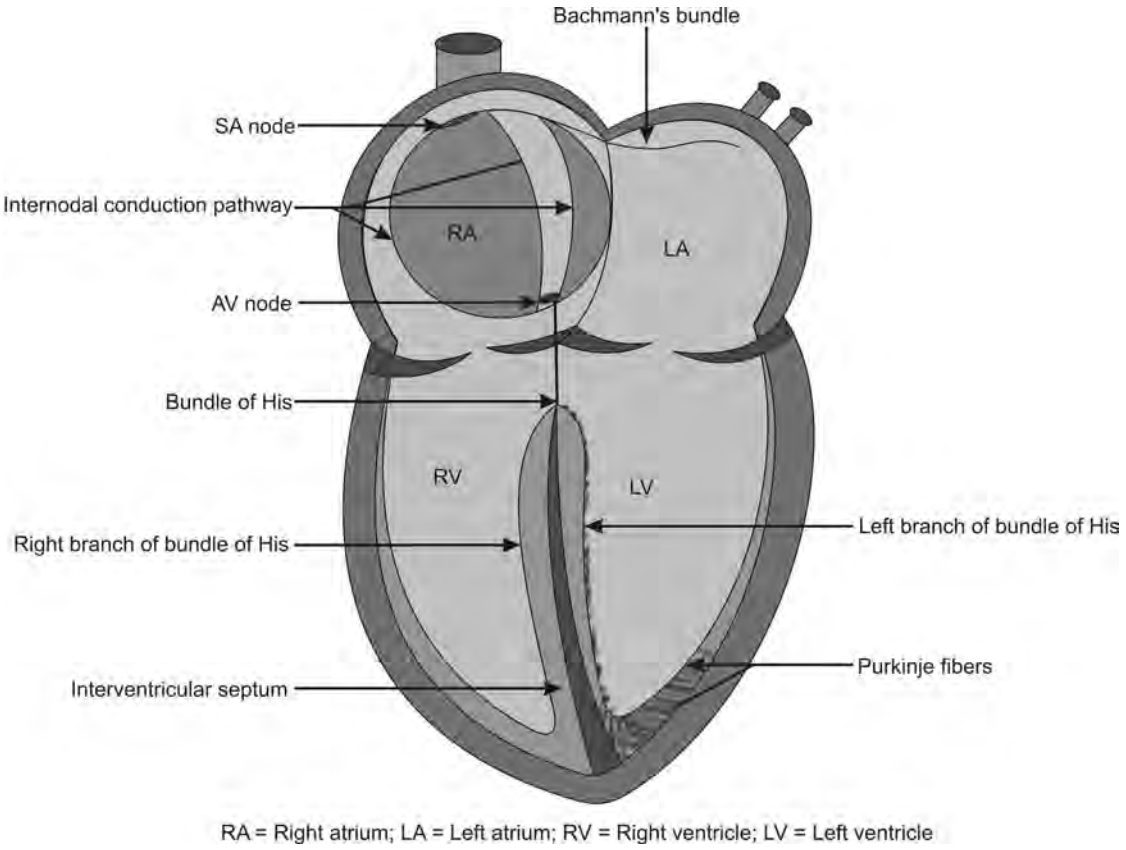


Fig. 41.3: Special junctional tissues (Pacemaker tissues) of the heart

Pacemaker tissue generates impulses and conduction tissue conducts and spreads impulses via specific, sequential and appropriate pathway.

SA Node

1. It is *situated* in wall of the right atrium at the junction of the superior *vena cava* and free border of right atrial appendix and extends along sulcus terminalis for a distance of 2 cm. (Sulcus terminalis is same as crista terminalis on endocardial surface).
2. It has rich blood supply and nerve fibers are abundant.
3. Its fibers are thin and long. They interlace with each other in plexiform manner. Connective tissue is abundant.
4. There is distinctive type of cells known as *P cells* related to pacemaker activity, which are stellate in appearance with larger centrally located nucleus.
5. Thus, two types of cells are present – P cells and transitional cells.

The transitional cells connect P cells to:

1. Atrial myocardial fibers
2. Internodal tract
3. Interatrial path.

Function

The fibers of SA node normally *initiate the heart beat*. Therefore, it is known as *pacemaker*. The whole heartbeats at the rate of SA node, which is about *60-80 beats per minute* in the adult. This is called as *sinus rhythm*.

AV Node

1. It is situated in right posterior portion of interatrial septum, near the mouth of coronary sinus.
2. It is another pacemaker tissue.

Function

1. It receives the impulses from the SA node through the atrial muscles and internodal pathways and transmits through the bundle of His to the ventricles.
2. It can generate its own impulse but at a slow rate that is 40-60/min, when SA node fails. This is known as *nodal rhythm*.
3. Impulses coming to AV node from SA node pass at slow velocity through AV node.

   Note: SA node is right sided structure, developing from tissue which lies at the entrance of the primitive right great vein (which later becomes superior vena cava). It receives nerve supply from right vagus nerve.

   AV node is left sided structure, developing from the tissues in the vicinity of the left great vein (which later becomes the coronary sinus). It receives its nerve supply from left vagus.

   Internodal tracts and Bachmann's bundle– These are specialized conduction paths for the impulses from SA node to:
   a. Left atrium, and
   b. AV node.

They are three in number:

1. *Anterior internodal tract* divides into 2 branches on the left –
   i. One of these branches extends along the dorsal aspect over to the left atrium constituting the specialized path known as *Bachmann s bundle.*
   ii. Another courses along interatrial septum, reaches AV node and merge with other conducting tissue.
2. *Middle internodal tract* arises from SA node, travels along inter atrial septum, reaches AV node. This tract is known as *Wenckebach s tract.*
3. *Posterior internodal tract* arises from SA node passes along crista terminalis to reach right upper border of AV node. This tract is known as *Thorel s tract.*

   The internodal pathways constitute preferential routes of conduction from SA nodes to AV node and from SA node to left atrium. Their conduction velocity is more rapid than atrial cells but not as rapid as Purkinje fibers.
4. *Bundle of His:* This is *the only* functional link between atria and ventricles.
   i. 1-2 mm thick
   ii. Arises from AV node.
   iii. Bundle fibers consist of fusiform parallel fibers with scanty striations and heavy store of glycogen.
   iv. Bundle of His divides at the anterior part of the membranous interventricular septum:
      a. Left division pierces the membrane and then courses on left side of septum through the subendocardium divides in anterior and posterior fascicle.
      b. Right branch passes down the right side of the septum.

   The right bundle branch is a smaller prolongation of the common bundle, whereas left bundle branch is a large fascicle.

The functions are given below:

i. *Conduction:* It transmits impulses received from atria to both ventricles.
ii. When SA node and AV node fails it can generate its own impulses. The rate is less than 40/min and the rhythm is known as *idioventricular rhythm.*

5. *Purkinje tissue:* The right and left bundle branches are continued as an arborization of fibers under the endocardium of both ventricles from which terminal fibers penetrate the ventricular wall. These are called Purkinje tissue.
   i. They are modified cardiac fibers, striated but has indistinct boundaries, and granular cytoplasm with several nuclei.
   ii. Rich in glycogen.
   iii. Longer and thicker than cardiac muscle fibers.
   iv. Conduct impulses at fast rate.

PROPERTIES OF HEART MUSCLE

Excitability and Contractility

1. Heart muscle is excitable that is it responds to external stimuli by contracting.
2. It obeys *all or none law* – so if the external stimulus is too weak no response is obtained, if the stimulus is adequate the heart muscle responds to the best of its ability.
3. In this respect the atria and ventricles behave as a single unit so that stimulus is adequate the heart muscle responds to the best of its ability and adequate stimulus normally produces a full contraction of atria and ventricles.
4. *Force of contraction depends on:*
   i. Initial length of muscle fiber.
   ii. Duration of previous diastolic pause.
   iii. Nutrition and oxygen supply–lack of oxygen decreases excitability.

Initial Length of Muscle Fiber

Greater the initial length greater is the force of contraction within physiological limits. This is known as *Starling s law*, which states that force of contraction varies directly with initial length of muscle fiber within physiological limits.

Duration of Previous Diastolic Pause

If the diastolic pause is greater there is greater venous filling and heart muscle fiber is stretched and according to Starling's law force of contraction is greater. If the diastolic pause is short, there is less time for filling – less stretch and lesser will be the force of contraction.

Refractory Period

1. Throughout the period of contraction heart muscle is absolutely refractory and does not respond to external stimuli at all. However, strong the external stimulus is. This is known as absolute refractory period.
2. Shortly after the contraction is over the heart muscle is relatively refractory during which very strong stimuli are effective, but stimulus of lesser intensity has no effect and force of contraction is also subnormal during this period. Finally, full recovery occurs.

Conductivity

This is the property of all heart muscle fibers but it is specially developed in bundle of His and its branches and Purkinje fibers.

Conduction

1. In Purkinje fibers it is at rate of 2 meters/sec.
2. In atrial wall is 1 meter/sec.
3. In ventricular wall 0.4 meter/sec and - in AV node 0.2 m/sec.

Table 41.1: Law of heart muscle

Cardiac fiber	*Size*	*Glycogen*	*Rate of conduction Meters/sec*	*Refractory period and rhythmicity*
1. Nodal fibers	• Fine	• Present	0.2	• Highest
2. Ventricular fibers	• Broader	• Higher than nodal fibers	0.4	• Higher than atrial fibers
3. Atrial fibers	• Broader than ventricular fibers	• Higher than ventricular fibers	1	• Higher than Punkinje fibers
4. Purkinje fibers	• Broadest	• Highest	2	• Short and slowest

If there is disorders of bundle tissue:

— Due to infection
— Depletion of calcium
— Blockage of blood supply.

There is sudden block in conduction. The ventricles stop beating for sometime. After a short time the ventricles start beating at their own rhythm of 30-35 beats/minute. This is described as idioventricular rhythm.

Rhythmicity

Heart has a power of initiating its own impulse at regular interval resulting in rhythmical contractions. This is most important property of heart muscle. The generation of impulse is regular and is transmitted at regular interval. The rate is about 60-80 beats/minute.

This is vital for pumping out blood into the circulatory channels. Normally impulses are generated at SA node, but under exceptional circumstances the heartbeat may be initiated for long periods by the AV node or other parts of junctional tissue. Rhythmicity is present in decreasing order.

1. At SA node the rate of impulse generation is maximum. This rhythm is known as sinus rhythm. The rate is 60-80 beats/min.
2. At AV node the rate of impulse generation is less than SA node. This rhythm is known as nodal rhythm. The rate is 40-60 beats/min.
3. Ventricles generate impulse at slowest rate. This rhythm is known as idioventricular rhythm. The rate is 30-35 beats/min.

Tonicity

Heat muscle exerts constant tone on its contents. Thus, it regulates the volume during the filling of the ventricles (during diastole).

Law of Heart Muscle—States

As the size of cardiac fibers increase – glycogen content increases, rate of conduction increases but rhythmicity and refractory period increase in opposite order (Table 41.1).

CHAPTER

42

Origin and Spread of Cardiac Impulse

CARDIAC EXCITATION

Resting membrane potential (RMP) in cardiac muscle:

1. When microelectrode with tip diameter of 0.5 to 1 μ is introduced in cardiac muscle fiber, inside is found to be –60 to –90 mv as compared to outside.
2. This negativity is called resting membrane potential (RMP).
3. RMP varies in different tissues of the heart.
   In pacemaker tissue like SA node it varies from –60 to –40 mv.
   In Purkinje fibers it varies from –95 mv to –80 mv.
4. *Cause of RMP*—like all other tissues is distribution of ions specially – potassium, sodium and chloride across the cell membrane.
5. Genesis of RMP—RMP is mainly the result of following factors (which are same for all excitable tissues):
   i. Difference between intracellular and extracellular potassium concentration.
   ii. Impermeability to protein ions.
   iii. Poor permeability of membrane to sodium ions.
   iv. Sodium pump.
6. Under resting condition cell membrane is more permeable to potassium ions than to sodium ions.
   Inside the cardiac fibers concentration of ions in mEq/L.
   i. K^+ — 155 mEq/L
   ii. Na^+ — 31 mEq/L
   iii. Cl^- — 10 mEq/L.
   Outside the cardiac fibers concentration of ions in mEq/L.
   i. K^+— 4 mEq/L
   ii. Na^+—145 mEq/L
   iii. Cl^- —110 mEq/L.
7. To protein ions, which are negatively charged, the cell membrane is impermeable.
   i. For potassium ions, concentration gradient favors its outward movement but the electrical gradient does not.
   ii. The protein ions refuse to move out with potassium as the cell membrane is impermeable to protein ions.
   iii. Therefore, just a small quantity of potassium leaks out and still more negativity develops inside which does not allow further movement of potassium ions.

a. For sodium ions, both electrical and concentration gradient favor its movement into the cell but the cell membrane is relatively poorly permeable to sodium ions.
b. The cell membrane has Na-K pump which constantly pumps sodium ions out in exchange for potassium ions in.
   — Energy is released by breakdown of ATP.
   — Carrier for pump is Na-K ATPase. That means Na and K ions bind with protein carrier which acts as enzyme which breaks down ATP.
   — Exchange is unequal 3Na ions move out and 2 K ions move in.
   This is example of carrier mediated active transport mechanism.
   — Role of chloride ions is passive. Chloride ion concentration is high outside and less inside. Membrane is highly permeable to chloride ions. Although the concentration gradient favors inward movement of chloride ions, electrical gradient does not.

Therefore, chloride ions are distributed passively in accordance with Gibbs Donnan equilibrium

$$\frac{K\ inside}{K\ outside} = \frac{Cl\ outside}{Cl\ inside}$$

But RMP of cardiac muscle is mainly dependent on concentration of potassium ions across the membrane.

RMP of pacemaker cells is slightly different from cardiac muscle cells. RMP of pacemaker cells is unstable also.

It shows a steady change till the threshold for a action potential is reached. The steady change is due to gradual decrease in permeability to potassium ions. Decrease in permeability means that the potassium ions will be held back inside. The potassium ions are positively charged ions. Therefore, when they are held back the negativity will be reduced.

Gradual decrease in polarization across the membrane during resting stage constitutes *pacemaker potential or prepotential (Fig. 42.1).*

ACTION POTENTIAL

Action potential is change in RMP associated with activity. It consist of depolarization followed by repolarization.

1. It shows all or none law
2. It is propagated.

Ionic Basis of Action Potential

Pacemaker regions show a *slow and steady* depolarization called *prepotential* or *pacemaker potential* (Figs 42.2 to 42.6).

1. When it reaches a threshold level — an action potential is fired. Because when depolarization reaches a threshold level the membrane permeability to sodium ions increases suddenly. Na^+ influx takes place, which reverses the polarity. That means inside becomes positive and outside becomes negative.

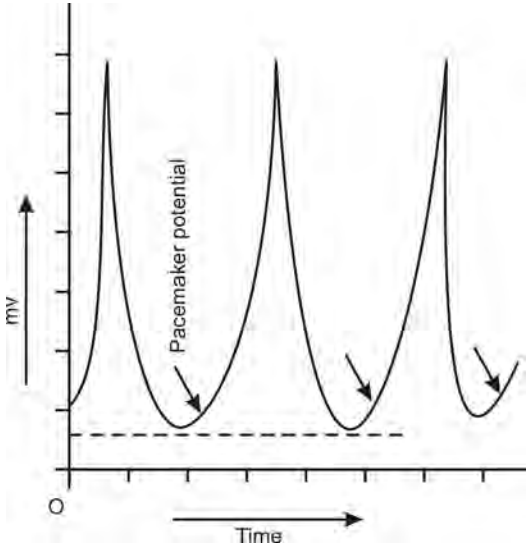


Fig. 42.1: Pacemaker potential

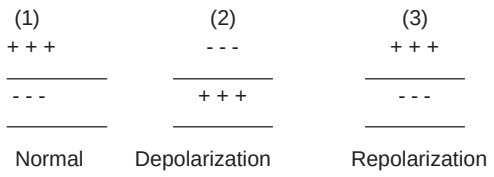


Fig. 42.2: Membrane potential during action potential

2. Then there is K^+ ions efflux due to increased permeability. Simultaneously Na^+ permeability decreases.
3. K^+ ion permeability decreases.
4. And lastly Na-K pump comes into play. (Fig. 42.3).

To understand better, action potential in cardiac muscle fibers is divided into five phases:

Phase 0: It is the spike of action potential - due to sudden increase in sodium permeability. That leads to positivity inside resulting in depolarization.

In SA node depolarization is less than in Purkinje fibers.

Phase 1: Phase 0 is followed by Phase 1. Phase 1 is slight fall in membrane potential mainly recorded from Purkinje fibers and ventricular fibers. Phase 1 is absent in SA and AV node.

Cause: Cesation of Na^+ influx (due to inactivation of sodium channels coupled with passive inward movement of Cl^- ions).

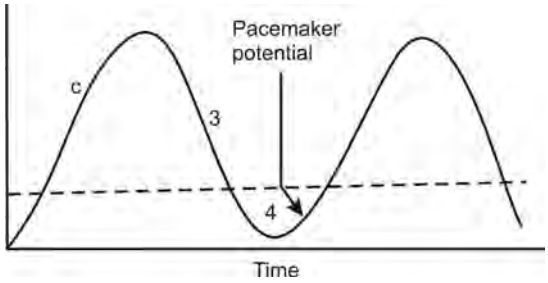


Fig. 42.4: Action potential in nodal fibers

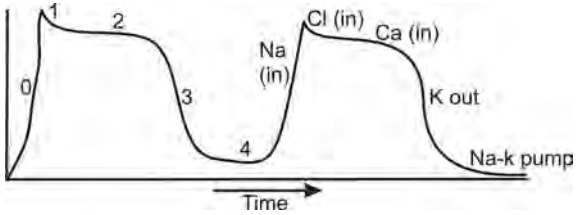


Fig. 42.5: Action potential in ventricle fibers

Phase 2: Phase of prolonged and sustained depolarization known as *plateau phase.* Duration of this phase in atrial fibers is less.

Cause: (i) increase permeability to Ca, (ii) permeability for potassium continues to be low (delayed increase in K^+ ion permeability).

Phase 2 is absent in SA and AV node.

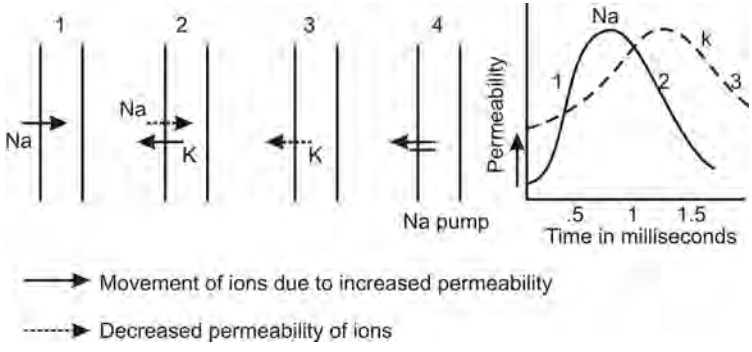


Fig. 42.3: Sequential change in ionic permeability during action potential

Phase 3: It is rapid repolarization phase.

Cause: (i) it is due to increase permeability to K^+ ions. K^+ efflux results in repolarization, (ii) rapid simultaneous closure of calcium and sodium channels.

Phase 4: Na – K pump is activated again to restore ionic composition across membrane.

Phase 4 in pacemaker tissue, that is SA and AV node is not steady. Slow depolarization takes place during resting stage.

Rate of slow depolarization during resting stage determines heart rate.

If it is fast—heart rate is increased.

If it is slow—heart rate is decreased.

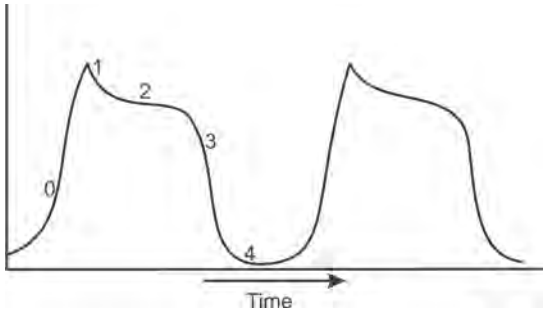
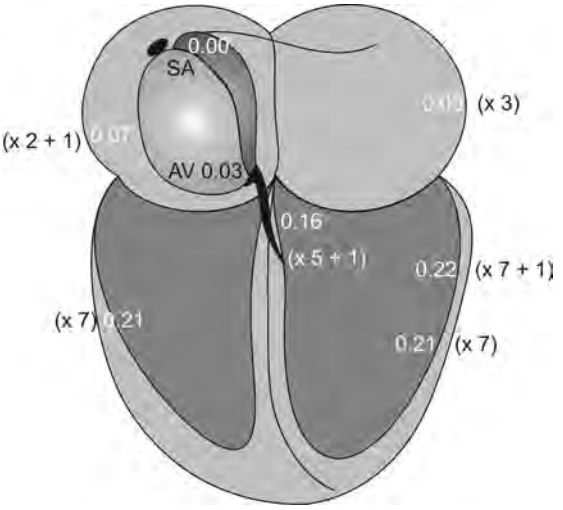


Fig. 42.6: Action potential in atrial fibers

CONDUCTION OF CARDIAC IMPULSE

1. Cardiac impulse originate in the SA node. Since, the cardiac muscle is a functional syncytium the impulses spreads to atria like ripples in a pond (Fig. 42.7).
2. Three specific conduction pathways:
   i. Anterior
   ii. Middle
   iii. Posterior
   — internodal conducting pathways

   Spread the impulse faster.
3. To left atrium, impulse is conducted faster by Bachmann's bundle.
4. After spreading to the atria the impulse reaches the AV node. AV node has thin, slow conducting fibers. Therefore, conduction is slow. So the impulse is delayed at AV. This delay is known as (A-V delay). AV delay is 0.1 sec.
5. After it spreads to ventricles through bundle of His and its branches and finally through Purkinje fibers.
6. In ventricles septum and endocardial surface depolarizes before the epicardial surface.



(To remember take time at AV node as standard time and multiply by factors in bracket and add 1 where given)

Fig. 42.7: Time in sec required for spread of impulse to different chambers of heart

7. Also depolarization of right ventricle is complete about 10 m sec before that of the left ventricles because of its smaller muscle mass.
8. The sequence of repolarization is not exactly the same as depolarization. The outer surface repolarizes first.

CHAPTER

43

Cardiac Cycle

DEFINITION

Changes that occur in the heart during one beat are repeated in the same order in the next beat. The cyclical repetition of various changes in heart from beat-to-beat is called *cardiac cycle (Fig. 43.1)*.

DURATION OF CARDIAC CYCLE OR CARDIAC CYCLE TIME

If the heart rate is 75/min, the duration of cardiac cycle is $\frac{60}{75}$ = 0.8 sec. Same events are repeated at interval of 0.8 sec.

1. Duration of cardiac cycle depends on heart rate.
2. Higher is the heart rate less is the duration of cardiac cycle.
   For example, if heart rate is 120 beats per minute—duration of cardiac cycle will be $\frac{60}{120}$ = 0.5 sec.

Phases of cardiac cycle – cardiac cycle has two main phases:

1. *Atrial events*—consisting of atrial systole and atrial diastole.
2. *Ventricular events*—consisting of ventricular systole and ventricular diastole.

Atrial events and ventricular events during cardiac cycle can be represented in a *circular diagram* where *inner circle* represents the atrial *events* and *outer circle* represents the *ventricular events*. Both circles are divided into eight equal parts where each part denotes 0.1 sec.

PHASES OF CARDIAC CYCLE

Cardiac cycle has two main phases:

I. Atrial events consisting of: (1) atrial systole, and (2) atrial diastole.
II. Ventricular events consisting of: (1) ventricular systole, and (2) ventricular diastole.

ATRIAL EVENTS

1. Atrial systole—0.1 sec, and
2. Atrial diastole—0.7 sec.

Cardiac cycle begins with atrial systole, which is followed by atrial diastole. Atrial diastole is overlapped by ventricular systole, and partly by ventricular diastole.

Atrial Systole

1. Duration—0.1 sec.
2. Both atria contract simultaneously.

   Although, contraction wave first starts in right atrium and then to left atrium, the

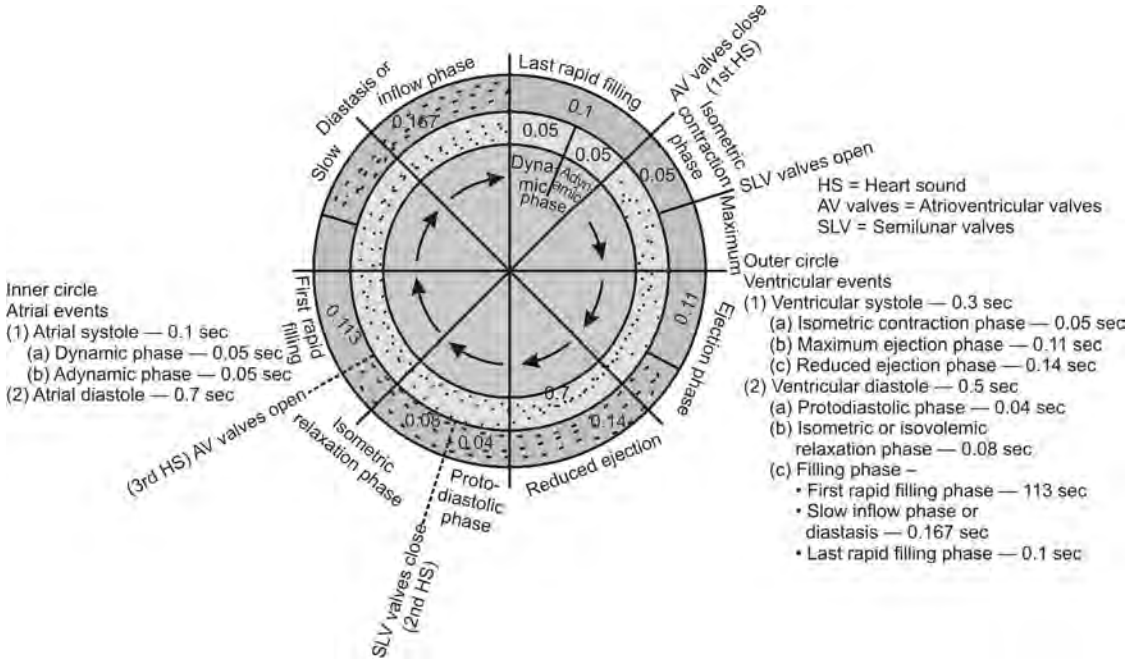


Fig. 43.1: Cardiac cycle

difference between the time of contraction is negligible for all practical purposes. Contraction wave first starts in right atrium because SA node is the pacemaker of the heart and is situated in the right atrium.

3. *Comprises of two phases:*
   i. *First half*—maximum contraction of atria takes place. Therefore, it is known as dynamic phase (0.05 sec).
   ii. *Second half*—is known as adynamic phase (0.05 sec).
      - The force of contraction is less in this phase as some fibers are relaxing.

Atrial Diastole

i. Duration—0.7 sec.
ii. The first 0.3 secs of atrial diastole are overlapped by ventricular systole.
ii. At the beginning of atrial diastole the AV valves close—giving rise to First heart sound, which indicates beginning of ventricular systole and beginning of atrial diastole.
iv. During diastole atria are filling with blood, coming from vena cava and the pulmonary veins.

After 0.3 sec the ventricular diastole begins. AV valves (atrioventricular valves) open and blood passes from atria to ventricles and fill them.

Thus, during atrial diastole—atria collect blood in first half and—atria empty in last half.

VENTRICULAR EVENTS

1. Ventricular systole—0.3 sec.
2. Ventricular diastole—0.5 sec.

Ventricular Systole

1. At the beginning of ventricular systole AV valves close because the ventricular

contraction increases the pressure in the ventricles and AV valves close with a sharp sound. This prevents regurgitation of blood from ventricles into atria.

Semilunar valves (SL valves) are still not open. So ventricles are contracting as closed cavity. Therefore, this phase is known as *Isometric contraction phase or isovolemic phase* (0.05 sec). As no blood goes out of ventricles, this prevents shortening of the ventricular muscle fibers. Therefore, this phase of contraction is known as *isometric contraction phase.* This phase leads to sharp rise of pressure, which increases above the pressure in the aorta and pulmonary artery. So semilunar valves open.

2. *Ejection phase*—maximum ejection phase and - reduced ejection phase.

   During ejection phase blood from both ventricles pass in aorta and pulmonary artery.

   Maximum ejection phase: In first part of ejection phase maximum blood passes from ventricle to arterial system because:

   i. The force of contraction of ventricle is maximum.
   ii. Maximum pressure difference between the ventricle and arterial system exists.
   iii. *Duration* of this phase is 0.11 sec and
   iv. 80% blood leaves ventricles.

   Reduced ejection phase—follows maximum ejection phase.

   During maximum ejection phase most of the blood, from ventricle to aorta and pulmonary artery has passed. The pressure in aorta and pulmonary artery (Fig. 43.2) increases, so that:

   i There is less pressure gradient between the two systems. This is called reduced ejection phase.
   ii. 20% blood leaves ventricles.
   iii. *Duration* is 0.14 sec.

Ventricular Diastole

Consists of:

1. Protodiastolic phase.
2. Isometric or isovolemic relaxation phase.
3. Filling phase
   i. First rapid filling phase.
   ii. Diastasis or slow filling phase.
   iii. Last rapid filling phase.

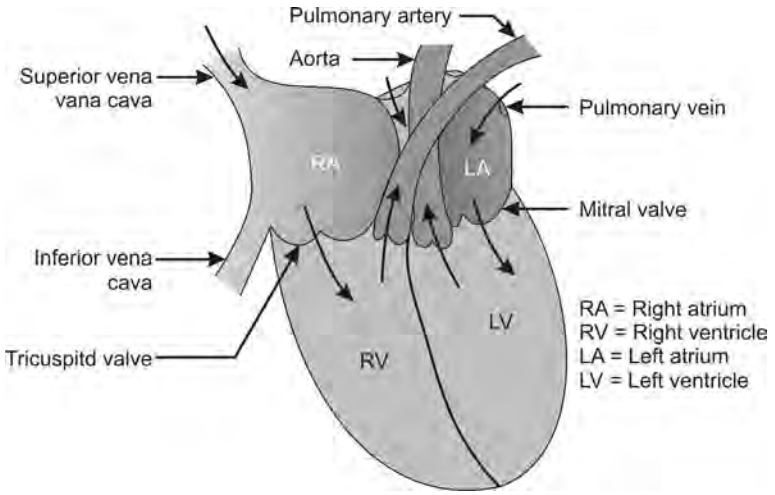


Fig. 43.2: Circulation of blood (shown by arrows) in different chambers during cardiac cycle. (The valves open at appropriate time in cardiac cycle)

a. *Protodiastolic phase*: As the ventricles relax the pressure in ventricles fall below that of aorta and pulmonary artery. So blood tends to flow back, which is prevented by closure of semilunar valve as its cusps get filled with blood - which causes 2nd heart sound.
   Duration of this phase 0.04 sec.
b. *Isometric relaxation phase:* With closure of semilunar valves, the ventricles are turned into closed cavity, because AV valves are still closed. Pressure in the closed relaxing ventricle falls steeply, which falls below atrial pressure. Atrial pressure was rising in the atrial diastole due to filling. Therefore, AV valves open.
   Duration of this phase is 0.08 sec.
c. *Filling phase:* When ventricular pressure falls below atrial pressure AV valves open giving rise to 3rd heart sound and blood passes from atria to ventricles—filling phase begins.

Filling phase is divided in three phases:
1. First rapid filling phase.
2. Diastasis.
3. 2nd rapid filling phase or last rapid filling phase.

1. *First rapid filling phase:* In first part of filling phase, there is rapid filling of ventricles because there is maximum pressure difference:
   i. Ventricular pressure is very less because of previous isometric relaxation phase, and
   ii. Atrial pressure is high because of previous filling.

   About 70% blood comes in ventricle during this phase.
   Duration—0.113 sec.
2. *Diastasis*—with maximum blood leaving the atria, pressure in atria falls and because of filling, pressure in ventricles rises. So pressure difference is less, only 10% blood trickles down from atria to ventricle.
   Duration—0.167 sec.
3. *Last rapid filling phase:* This is due to atrial systole or atrial contraction. 20% blood passes from atria to ventricles.
   Duration—0.1 sec. Blood is forced from atria to ventricles which gives rise to fourth heart sound.

FUNDAMENTAL RULE

1. Atrial and ventricular systole never overlaps.
2. Diastole of atria and ventricles always partly overlaps.

IMPORTANT FEATURE OF VENTRICULAR SYSTOLE

1. Begins with closure of AV valves—which gives first heart sound.
2. Ends with closure of semilunar valves which gives second heart sound.

IMPORTANT FEATURE OF VENTRICULAR DIASTOLE

1. Begins with closure of SL valves.
2. Ends with closure of AV valves.

CHAPTER

44

Pressure Changes in Heart and Blood Vessels During Cardiac Cycle

1. Pressure changes in heart in man during cardiac cycle (Fig. 44.1), can be studied by *Cournand s method* of intracardiac catheterization.

   Thin *catheter* tube is inserted through antecubital vein. It is gradually pushed up through bigger and bigger veins into right atrium and then into right ventricle. Pressure changes transmitted through this are recorded by suitable apparatus.
2. Pressure changes in right atrium can be indirectly studied through jugular venous pressure (JVP) record.

   Jugular pressure can be recorded without catheterizing the vein by using suitable transducer, applied to the skin of the neck.

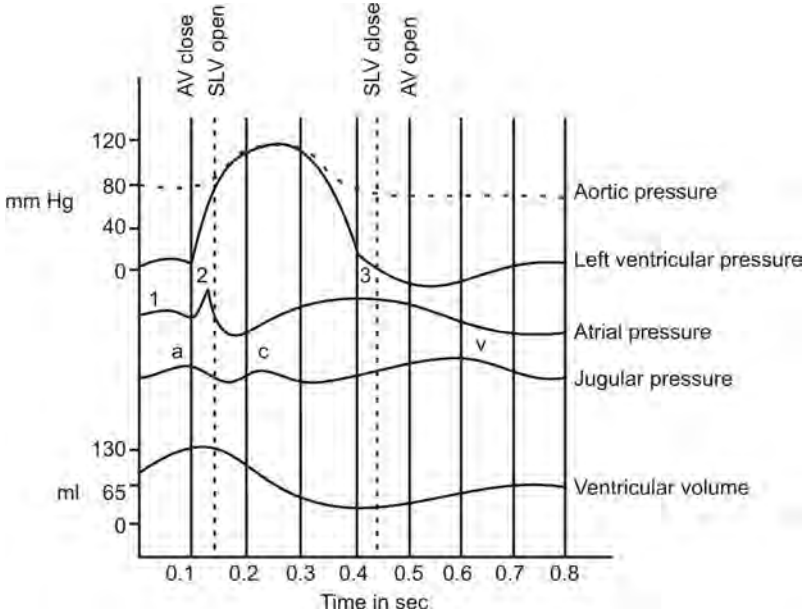


Fig. 44.1: Pressure and volume changes during cardiac cycle

VENTRICULAR PRESSURE CHANGES

Peak left ventricular pressure is about 120 mm Hg and peak right ventricular pressure is 25 mm Hg or less.

During Systole

1. In isometric contraction phase both valves remain closed. Blood cannot leave ventricles and ventricles forcibly contract upon locked up blood. Therefore, intraventricular pressure increases steeply.
2. *Maximum ejection phase:* Blood is leaving ventricles. Therefore, ventricular pressure should fall but pressure rises gradually because force of ventricular contraction is greater than the rate of outflow. Gradually force of contraction and rate of outflow becomes equal hence a horizontal plateau is produced at the top.
3. *Reduced ejection phase:* Force of contraction is much reduced than before and is less than rate of outflow, therefore pressure falls.

During Diastole

1. *In protodiastolic phase:* Pressure continues to fall, because ventricular relaxation starts.
2. *In isometric relaxation phase:* Both valves are closed, therefore, ventricles relax as closed cavities and intraventricular pressure sharply drops. This continues till AV valves open.
3. As soon as AV valves open atrial blood rushes into ventricles (1st rapid filling), but pressure continues to fall gradually for sometime as rate of relaxation is more than filling.
4. *Diastasis or slow inflow phase:* Ventricles: are no more relaxing blood continues to accumulate in it therefore, pressure rises.
5. In last phase of ventricular diastole, which corresponds to atrial systole (last rapid filling phase) there is small but sudden rise of ventricular pressure. Ventricular systole comes again and the changes repeat.

INTRA-ATRIAL PRESSURE CHANGES

There are three positive and three negative waves (Fig. 44.1):

1. During *atrial systole* atrial pressure rise causing *first positive wave.*

In later, half of atrial systole pressure falls because in adynamic phase of atrial systole, some atrial fibers have started relaxing.

2. In *atrial diastole* atria are relaxing and pressure should fall but instead there is a sharp rise of pressure causing *second positive wave* – as in isometric contraction phase of ventricles the AV valves are closed and are pushed in atria in dome shaped manner (Fig. 44.2).
3. This is followed by sharp fall in atrial pressure, which corresponds to maximum ejection phase of ventricles.

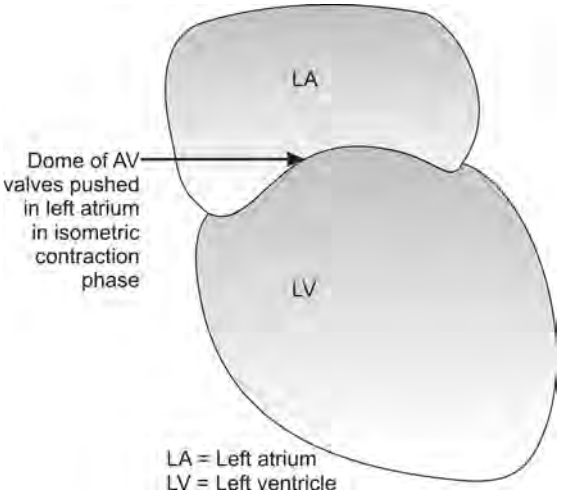


Fig. 44.2: Isometric contraction phase of ventricle

Cause

i. Atrial relaxation continues, as it is atrial diastole.
ii. As ventricle shortens it pulls AV ring down, this increases the volume of atrium and atrial pressure falls.
iii. Ventricular volume decrease due to contraction, therefore mediastinal pressure falls, because of this, thin walled atria dilate causing further fall of atrial pressure.

4. In later part of ventricular systole the:
   i. Atria accumulate blood and atrial pressure rises slowly – resulting in *third positive wave,* AV valves remaining closed. This rise continues until AV valves open.
   ii. In isometric relaxation phase AV ring rises up increasing the pressure further.
5. As soon as AV valves open blood rushes from atria into ventricles and atrial pressure falls. This fall of atrial pressure continues till diastasis. Atrial pressure then slowly rises.

After this there is atrial systole.

INTRA-AORTIC PRESSURE CHANGES (SEE Fig. 44.1)

1. In isometric contraction phase there is slight rise of pressure as there is bulging of semilunar valves in aorta.
2. With opening of semilunar valves blood enters the aorta and aortic pressure rises smoothly with ventricular pressure.
3. In reduced ejection phase, aortic pressure falls.

   Cause

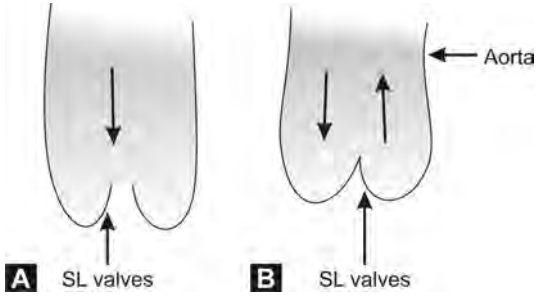
   i. Ventricles are contracting with less force.
   ii. Therefore, less blood is coming in aorta.
   iii. More blood running out to periphery than its entry because of reflex vasodilatation through sinuaortic mechanism.
4. With onset of ventricular diastole ventricular pressure decreases causing backward flow of blood to ventricle. Therefore, aortic pressure drops causing *incisura* (which corresponds to dicrotic notch of radial pulse). Blood column is reflected back by sudden closure of semilunar valve (Fig. 44.3).

Few vibrations in aortic pressure tracing are due to after vibration.

Aortic pressure continues to fall. *Cause* is continuous passage of blood to peripheral blood vessels – propelled by elastic recoil of aorta and arteries.

Fall of pressure continues till ventricles contract again.

1. Aortic pressure changes are similar to ventricular pressure changes but pressure is lower.
2. Diastolic pressure in aorta is maintained at 80 mm Hg.
3. Aortic pressure is lower than ventricular pressure at the summit.



Figs 44.3A and B: Aorta: (A) Beginning of ventricular diastole blood flow reversed, (B) Blood rebounds

JUGULAR PRESSURE (PULSE) TRACING OR JUGULAR VENOUS PRESSURE (JVP) CHANGES

Right jugular vein is direct continuation of superior vena cava and jugular pressure follows atrial pressure.

Therefore, there are three positive waves (a,c and v waves) and 3 negative waves (x, x_1 and y). (See Fig. 44.1) These waves are recorded later than atrial waves.

1. *First positive wave (a wave):* It is due to atrial systole. As atrium contracts pressure in atrium rises and jugular vein cannot empty. Therefore, pressure in jugular vein rises. Sleeve of muscle surrounds the opening of great veins. When atria contract this also contracts and closes the opening of great vein like pulse string.
2. *First negative wave (x wave):* It is due to fall of pressure in atria in adynamic phase of atrial systole.
3. *Second positive wave (c wave):* During isometric contraction phase of ventricles – bulging of AV valves in atria, increases the pressure in atria.

   a-c interval indicates the conduction time of bundle of His.
4. *Second negative wave (x_1 wave):* It is due to corresponding fall of pressure in atria.
5. *Third positive wave (v wave):* It is due to: (a) graded filling of atria which is reflected as increase in pressure in jugular vein, and (b) return of AV ring to original position.
6. *Third negative wave (y wave):* It is due to fall of atrial pressure after opening of AV valve.

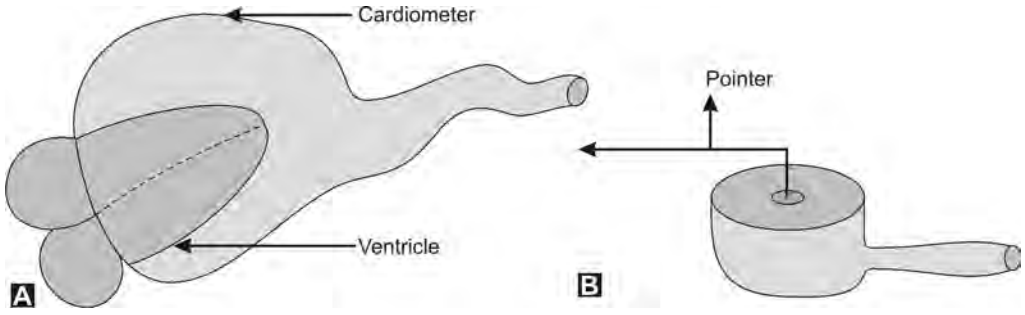
Summit of v wave indicates end of ventricular systole.

Much information regarding the condition of heart in health and diseases may be obtained from jugular tracing.

Ventricular Volume Changes during Cardiac Cycle

In animals, it can be studied by *cardiometer*— It is a rounded funnel. The heart of the animal is so fitted inside the funnel that ventricles remain inside and atria outside and its fitting around the atrioventricular groove is airtight.

When ventricles contract – pressure in funnel falls and when it relaxes pressure rises. Pressure changes are transmitted to Marey's Tambour by rubber tubing and recorded on moving drum, which represent volume changes in ventricles (Figs 44.4A and B).



Figs 44.4A and B: (A) Cardiometer, (B) Marey's Tambour

1. During atrial systole the ventricular volume increases due to last rapid filling phase of ventricular diastole which overlaps atrial systole.

   This rise is maintained as plateau during isometric contraction phase of ventricular systole because no blood goes out.
2. As soon as ejection starts the ventricular volume smoothly and continuously falls up to the end of systole.
3. In isometric relaxation phase, ventricular volume remains same because no blood enters.
4. In the next phase, the ventricular filling starts and its volume rises rapidly corresponding to first rapid filling phase of ventricular diastole.
5. After this during diastasis the ventricular volume gradually increases.

CHAPTER

45

Heart Sounds, Pulse, and Radial Pulse Tracing

HEART SOUNDS

1. Two classical sounds of heart are known as first and second heart sounds. They can be easily detected with Stethoscope.
2. Two other heart sounds have been described—third and fourth heart sounds, which are difficult to detect clinically but are constantly found in phonocardiogram (graphic record of heart sound).
3. First and second heart sounds are close, that means second occurs quickly after first heart sound but after second heart sound there is a longer pause.
4. So the sequence is:
    i. First heart sound
    ii. Second heart sound, pause

Biophysical Principle

Underlying the occurrence of sound in the heart or in circulation.

Generally, the blood flows under most conditions in a streamline fashion, which is silent and must not be noisy. But under certain conditions the streamline flow is changed into turbulent flow then the noise may be produced.

Causes of Heart Sounds

1. *Valvular:* Most important cause is closure of valves, which produces vibrations.
2. *Vascular:* Due to occurrence of turbulence in the blood flow, which occurs due to:
    i. Rapid rush of blood for example, from atria to ventricle.
    ii. Back flow and bouncing of blood against closed valves. For example, during ventricular contraction there is backflow of blood against AV valves causing them to bulge, then back-surging due to bouncing.
3. *Muscular:* Contraction of thick musculature of ventricles contribute to production of heart sounds.

First and second heart sounds occur due to closure of valves and the vibrations which are caused by the closure are transmitted from the valve area to the apices of ventricles—as in the case of first heart sound and along the arteries - aorta and pulmonary artery, in case of second heart sound.

Third heart sound occurs due to turbulence produced, which is caused due

to rapid rush of blood from atria to ventricles after opening of AV valves.

Fourth heart sound is due to rapid rush of blood from atria to ventricles during contraction of atria.

Method of Study

1. Clinical stethoscope is most common instrument, which is used to hear sounds. First and second heart sounds are easily detected. Third heart sound is detected occasionally and with difficulty and fourth heart sound is not heard as a rule.
2. They may be graphically recorded by a chest suction microphone or intracardiac microphone connected via an amplifier to an oscillograph. Such record is known as phonocardiogram (Fig. 45.1). Reading is facilitated by simultaneous record of jugular pressure (which is also known as jugular pulse tracing) and electrocardiogram (ECG).
   i. First heart sound is manifested by a prominent set of vibrations just before onset of c wave of jugular pulse tracing.
   ii. Second heart sounds manifested by a set of vibrations not so prominent as the previous one, corresponds with notch on ascending limb of v wave.
   iii. Third heart sound is manifested by a small set of vibrations and corresponds with end of descending limb of v wave.
   iv. *Fourth heart sound* is manifested by another set of vibrations which coincides with a wave of jugular pulse tracing.

First Heart Sound (Fig. 45.2)

Characteristics

i. Prolonged, low pitched, dull
ii. Like a word Lubb, precedes the c wave of jugular pulse tracing

Duration - 0.01 to 0.17 sec.

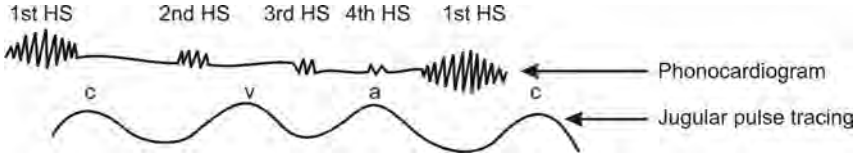


Fig. 45.1: Phonocardiogram (HS = Heart Sound)

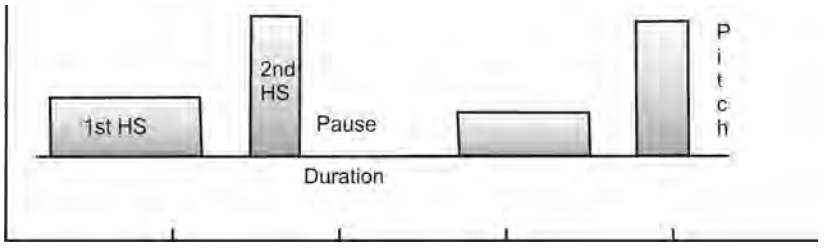


Fig. 45.2: Diagrammatic representation of heart sounds

Cause

1. Due to rapid closure of AV valves (both mitral and tricuspid) at the beginning of ventricular systole (Fig. 45.3).
2. Ejection of blood in aorta and pulmonary artery.
3. Contraction of thick musculature of ventricles.

(In graphic record—1st heart sound has 2 sets of vibrations—first set due to isometric contraction phase and second set is due to maximum ejection phase. Frequency 25 to 45 Hz and there are 7-13 vibrations).

Clinical Identification

1. By its characteristic—prolonged, low pitched, dull like a word Lubb.
2. Best heard over left 5th intercostal space, 1.25 cm (1/2") medial to midclavicular line (Mitral area) and fourth intercostal space on right side close to sternum (Tricuspid area) (Fig. 45.3).
3. It coincides with apex beat and carotid pulse.
4. Comes just after pause.

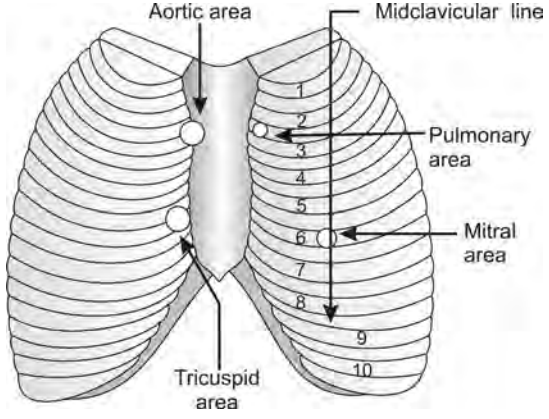


Fig. 45.3: Location of mitral, tricuspid, aortic and pulmonary areas over the chest

Significance

1. Indicates onset of systole of ventricles.
2. Duration and intensity of first heart sound, indicates the condition of the myocardium. In hypertrophied heart, it is more loud (accentuated).
3. Clear first heart sound indicates AV valves are closing properly.

Second Heart Sound

Characteristics

1. Short, sharp and high pitched
2. Like a word DUP
   Duration: 0.1 to 0.14 sec.

Cause

1. Caused by sudden closure of semilunar valves.
2. Vibrations in the blood column after closure of semilunar valves (In graphic record 2nd heart sound has 3-4 vibrations of 50 H_z frequency).

Clinical Identification

1. By its characteristics short, sharp, high pitched like word Dup.
2. Occurs just after carotid pulse.
3. By its relation with first heart sound and pause. It is preceded by first heart sound and followed by pause.
4. Coincides with notch on ascending limb of v wave.
5. Best heard in second intercostal space close to sternum on left side (pulmonary area) and on right side 2nd costosternal junction (aortic area)(Fig. 45.3).

Significance

1. It indicates end of systole and beginning of diastole.

2. Pitch is directly proportional to pressure in blood vessels.
3. Clear sound indicates that semilunar valves are closing properly.
4. Interval between 1st and 2nd heart sounds is clinically taken as systole and between 2nd and 1st is taken as diastole (which is the pause and therefore longer).

Careful auscultation (hearing with stethoscope) will show second heart sound to be split or reduplicated in most normal subjects due to the fact that pulmonary and aortic valves do not shut absolutely simultaneously, especially during inspiration (physiological splitting). Splitting also occurs in many diseases, for example, increase of diastole, pressure in pulmonary artery or aorta.

Third Heart Sound

1. It is soft, low pitched sound.
2. May be heard by careful auscultation in many normal young subjects with bell of the stethoscope placed near cardiac apex.
3. *Duration* 0.04 sec.
   Cause: Rush of blood from atria to ventricle, after opening of AV valves, setting up vibrations which coincide with descending limb of v wave (1 to 2 vibrations with frequency 30 Hz).
4. Heard at apex after exercise in recumbent position because venous return increases and it intensifies the sound.

Fourth Heart Sound

1. Not heard in normal subjects.
2. Recorded graphically as a group of vibrations which are caused by atrial systole.
3. It coincides with a wave of jugular pulse.
4. ***Cause:*** Last rapid filling of ventricles due to atrial systole and impact of blood on ventricular wall.

Murmurs and Bruits

Murmurs and bruits are abnormal sounds heard in various parts of the vascular system.

Blood flows silently as long as the flow is smooth. However, if blood strikes:

1. An obstruction or passes through a narrow opening (orifice) at high speed, swirling vortices are set up that generates vortical sounds.
2. Turbulent flow may also generate sound — examples of sound outside the heart:
   i. *Large highly vascular goiter*—a bruit can be heard over it.
   ii. *Murmur heard over*
   - an aneurysmal dilatation of one of the large arteries,
   - or arteriovenous fistula
   - or patent ductus arteriosus.

   Major cause of cardiac murmer is—disease of heart valves but it is not the only cause.

For example:

1. When a valve is stenosed (i.e. valve leaflets are glued together due to inflammation or other causes) and the opening is narrowed blood flow through it in normal direction is turbulent.
2. When a valve is incompetent (not closing properly) blood leaks through it in wrong direction (= regurgitation or insufficiency).

   A murmur is generated which is due to a disease of a particular valve.
   - It may be systolic or diastolic.
   - Best heard in a particular region
   - And there are other aspects such as:
     i. Duration
     ii. Character of murmur
     iii. Accentuation and
     iv. Transmission of the sound that help to localize its origin in one valve or the other and also one can tell whether it is due to stenosis or incompetence.

PULSE

The rapid rise of pressure following the ejection of 60-70 ml of blood from the left ventricle at each systole, expands the aorta and a pressure wave or pulse passes along its wall. The pulse is not due to passages of blood along the arteries.

1. The blood travels at only 0.5 m per sec speed.
2. But a pressure wave travels at about 7 m / sec speed.

Due to systolic ejection the next section of artery is stretched so that a wave of pressure travels along the vessel wall without involving the actual transmission of blood. The stretch is followed by elastic recoil (Fig. 45.4).

Pulse Wave Velocity

If the pulse is recorded simultaneously from the carotid and radial arteries, the velocity of the pulse wave is found to be 5 m per sec at 5 years of age and 8 m per sec at 60 years of age. The difference in the velocities is due to the fact that arteries become stiffer with increasing age.

Pulse Rate

Pulse rate can be counted for one minute by palpating the radial artery. Normal pulse rate varies from 68 - 72/minute.

In heart disease, when the cardiac rhythm is irregular (atrial fibrillation or premature beats) the rate of the heart may exceed the pulse rate because the volume of some of the systolic discharges to promote a pulse wave is insufficient. In such cases the difference between the heart rate and the pulse rate is known as pulse deficit.

Radial Pulse Tracing (Fig. 45.5)

1. It is electronically recorded tracing of the pulse.
2. Tracing shows an upstroke—anacrotic limb and a downstroke—catacrotic limb.
3. Upstroke is due to rise of pressure during maximum ejection phase of ventricles and downstroke is due to fall of pressure in reduced ejection phase and ventricular diastole.
4. The tracing shows:
   i. Primary wave or percussion wave.
   ii. Dicrotic wave.
   iii. Tidal wave (recorded in central pulse tracing).
   iv. Pre and post dicrotic waves.

Primary or percussion wave: Extends from beginning of the pulse wave up to dicrotic notch. Upstroke is due to maximum ejection phase and downstroke is due to reduced ejection phase.

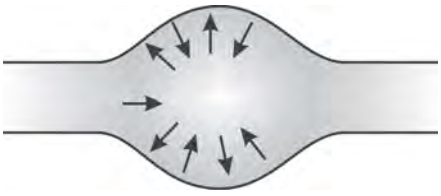


Fig. 45.4: Stretch and elastic recoil of section of artery due to systolic ejection—creating a pressure wave along the wall of artery

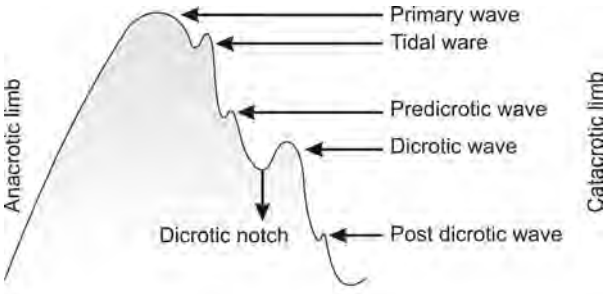


Fig. 45.5: Radial pulse tracing

Dicrotic notch: It is due to fall of pressure at the beginning of ventricular diastole when blood column reverses its direction.

Dicrotic wave: It is due to rebound of blood column in aorta on the closed semilunar valves.

Pre- and postdicrotic waves: Are due to reflected waves from periphery.

Tidal wave: It is recorded in central pulse tracing and is due to reflected waves from periphery.

Causes of large primary wave:

i. Large cardiac output
ii. Slow heart rate
iii. Low peripheral resistance.

Causes of small primary wave:

i. Small cardiac output
ii. High peripheral resistance
iii. Increased heart rate.

RADIAL PULSE TRACINGS

Collapsing or Water Hammer Pulse (Fig. 45.6)

Pulse in aortic insufficiency is called collapsing or water hammer pulse (water hammer is an evacuated glass tube half filled with water that was a popular toy in the 19th century. When held in hand and inverted, it gives a short, hard knock).

This type of pulse tracing is found in aortic insufficiency and the characteristics of the pulse tracing are:

i. Great amplitude
ii. Abrupt upstroke
iii. Rapid fall, and
iv. No dicrotic wave.

Anacrotic Pulse or Plateau Pulse

Characteristics are:

i. Small amplitude
ii. Sloping upstroke (plateau pulse)
iii. Tidal wave well developed and often higher than percussion wave.

This type of pulse tracing is found in aortic stenosis (Fig. 45.7).

Dicrotic Pulse (Fig. 45.8)

It is found in condition where pulse rate is increased such as fever exercise, etc.

Characteristics:

1. Rate of pulse is fast.
2. There is prominent dicrotic wave (due to events taking place in fast succession

Fig. 45.7: Anacrotic pulse (in aortic stenosis)

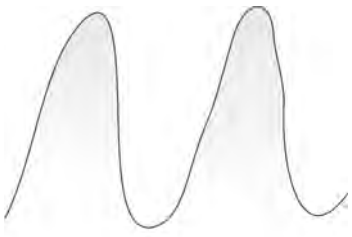


Fig. 45.6: Collapsing or water hammer pulse (in aortic insufficiency)

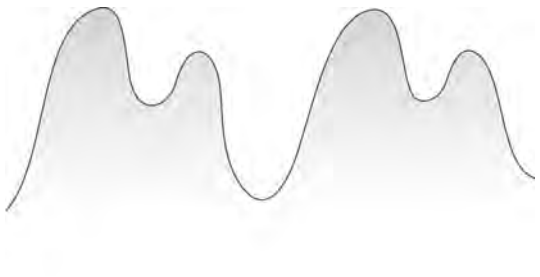


Fig. 45.8: Dicrotic pulse

during cardiac cycle especially rebound of blood column or close semilunar valves at the beginning of ventricular diastole).

Pulsus Alternans (Fig. 45.9)

There are alternate large and small beat in radial pulse tracing.

It occurs in:

- Myocardial damage
- Hypertension
- Left ventricular failure.

Fig. 45.9: Pulsus alternans

Pulsus Paradoxus (Fig. 45.10)

Normally pulse is large in inspiration when person breaths deeply.

- In conditions like pericardial effusion and constrictive pericarditis pulse is small in inspiration (as during inspiration venous return decreases).

Fig. 45.10: Pulsus paradoxus

CHAPTER

46

Cardiac Innervation—Heart Rate and Its Regulation

Heartbeats rhythmically even after complete separation from the animal, because it is inherently rhythmic, but in intact animal its action is continuously under control of nervous impulses from the nerves (Fig. 46.1).

1. Vagus
2. Sympathetic.

VAGUS

1. Convey fibers belonging to—parasympathetic division of autonomic nervous system.
2. From a center in the medulla—dorsal motor nucleus of vagus which is part of nucleus ambiguous, which is under cortical and limbic control.
   i. Vagus nerve in cardioinhibitory.
   ii. This action was discovered by Weber brothers in 1845.
3. The cardiac fibers separate in neck and go towards heart and form superficial and deep cardiac plexus with fibers of sympathetic.
4. Finally they reach atrial muscle and synapse with ganglion cells which are mostly found in the vicinity of SA node and AV node.
5. Postganglionic fibers supply:
   i. Both nodes
   ii. Atria
   iii. Base of ventricles
   iv. Coronary blood vessels.
6. Right vagus supplies—SA node and atrial muscle of fibers
   Left vagus supplies
   – AV node, and
   – Upper part of bundle of His.
   – No vagal fibers are distributed to ventricles.
7. In intact animal vagal motor fibers of heart carry a tonic stream of inhibitory impulses. That is vagi exert a tonic inhibitory control over all parts of the heart.
8. Acetylcholine is released at the postganglionic fibers on stimulation of dorsal motor nucleus of vagus (which is part of nucleus ambiguous. It acts as cardioinhibitory center).
9. It receives afferent impulses from baroreceptors of cardiovascular system, which arise by pulsatile distention of cardiovascular structures occurring with each heartbeat.
10. This normal state of affairs in resting condition is responsible for what is called

as *vagal tone*, which allows resting heart rate of 68 to 75 beats per min.

11. *Atropine* prevents action of acetylcholine on cardiac muscle and when atropine is given it increases heart rate to 160-180/min. This proves that there is constant inhibitory influence exerted by vagus on heart.

Stimulation of Vagus Causes

1. Slowing of *heart rate* even it may stop. This is caused by reduced rhythmic activity of SA node known as *negative chronotropic effect*.
2. *Conductivity* of bundle of His is reduced producing various types of heart blocks. This effect is known as *negative dromotropic effect*.
3. *The force of contraction is diminished*. This is called as *negative inotropic effect*.
4. *Excitability of heart is reduced*, which is known as *negative bathmotropic effect*.

Vagal Escape

In animal, stimulation of vagus by titanizing current causes slowing and stoppage of heart. But after a while ventricles resume rhythmic contraction in spite of continuous vagus stimulation. This phenomenon is known as vagal escape. Many explanations have been put forward to explain vagal escape:

1. It may represent inherent rhythmicity of ventricular muscle itself (as ventricles are cut off from normal pacemaker influence, due to vagal depression of conduction). This rhythm is called idioventricular rhythm.
2. It may be due to escape of SA node from the influence of vagal stimulation as central venous pressure and atrial pressure rises and as the nodal tissue is stretched.

CARDIAC SYMPATHETIC NERVES

1. From the cell bodies in the lateral horn of upper five thoracic segments of spinal cord preganglionic fibers pass into sympathetic trunk to superior, middle and inferior cervical ganglia. From these ganglia the postganglionic fibers course in superior, middle and inferior cardiac sympathetic nerves to the heart (Fig. 46.1).
2. They supply
   i. Nodal tissue
   ii. Bundle of His
   iii. Atrial and ventricular muscle
   iv. Vasodilator fibers to coronary arteries.

   Fibers from right side supply SA node and fibers from left side supply AV node and upper bundle of His.
3. Sympathetic nerves exert a *slight tonic accelerating action* on human heart, because excision of 1st to 6th thoracic ganglia cause slowing of heart rate.
4. Noradrenaline is released by postganglionic sympathetic fibers on stimulation.
5. *Of the two nerves* – vagus and sympathetic nerves, *vagus exerts much stronger influence* on the heart than sympathetic.

Stimulation of Sympathetic Nerves Cause

1. *Increase in the heart rate:* This is known as *positive chronotropic effect.* This is due to innervation of SA node by sympathetic postganglionic fibers.
2. *Increase in the force and speed of contraction of myocardium.* This effect is known as positive *inotropic effect* and it is due to innervation of atria and ventricles by sympathetic postganglionic fibers, which can be demonstrated histologically.
3. *Increase in the excitability of heart.* This is known as *positive bathmotropic effect* and may cause *extrasystoles.*

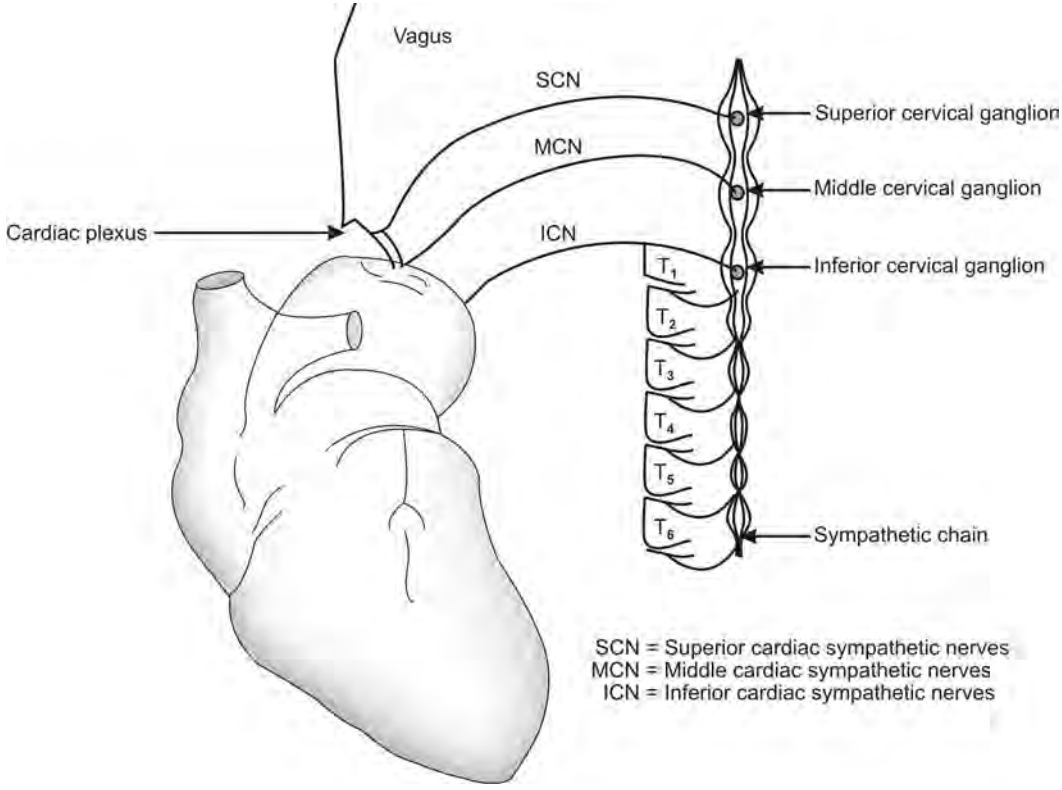


Fig. 46.1: Cardiac nerves

4. *Increase in conductivity.* This is known as *positive dromotropic effect* on myocardium and bundle of His.

On the whole sympathetic is taken as accelerator and augmentor of heart.

HEART RATE

1. Average heart rate in resting man is about 68 to 75/min. Variations are present, for example:
   i. Muscle training tends to reduce heart rate. Therefore, in athletes the heart rate is equal to 50-60/min, frequently cause is increase of vagal tone.
   ii. In some healthy persons, heart rate is 80-90/min.
2. Heart rate diminishes progressively from birth (130/min) to adolescent age (70-80/min). Heart rate increases slightly in old age.
3. Heart rate is inversely proportional to surface area. Bigger the size, lesser is the heart rate. For example:
   i. Elephant's heart rate is 25/min.
   ii. Bird's heart rate is 250/min (Nepoleon had a resting heart rate 40/min).
4. Physiological conditions – in which heart rate increases temporarily:
   i. Muscular exercise
   ii. Emotional excitement
   iii. High environmental temperature
   iv. Digestion.

5. Physiological conditions in which heart rate is decreased temporarily:
   i. Sleep – 55-60/min
6. Pathological conditions, which increase heart rate temporarily:
   i. Hemorrhage
   ii. Shock (surgical)
   iii. Hyperthyroidism
   iv. Fever–heart rate increases by 10 beats with 1°F rise of body temperature.
   v. Cardiac arrhythmias
      a. Paroxysmal tachycardia
      b. Atrial fibrillation.
7. Pathological conditions in which heart rate decreases:
   i. Heart block
   ii. Myxedema.
8. Tachycardia = increase in heart rate above normal average

   Bradycardia = decrease in heart rate below normal average.

REGULATION OF HEART RATE

Heart rate can be adjusted according to needs of the body. For example, heart rate rises during exercise and falls during sleep.

Mechanism of regulation of heart rate includes:

1. Local control
2. Nervous control
3. Chemical control.

Local Control

Any factor which acts on SA node and junctional tissue and alter it's rhythmicity affects the heart rate. For example, when SA node is warmed, its rate of discharge increases.

Nervous Control

This includes:

1. Cardioinhibitory center connected with vagus
   i. Cardioaccelerator center connected with sympathetic nerves.
2. Afferent pathways along which impulses are conveyed to these centers.
3. Efferent pathways in vagus and sympathetic nerves. Vagus exerts tonic inhibitory control.

Sympathetic nerves exert tonic accelerating control over the heart. Out of the two, vagus exerts strong action. Vagal tone is maintained by baroreceptors of the cardiovascular system. Variations in the heart rate may be brought about under normal physiological conditions by alterations in the tone of vagus.

Cardioinhibitory Center

1. Dorsal motor nucleus of vagus, which is part of nucleus ambiguous, acts as cardioinhibitory center. It is situated in the floor of fourth ventricle in medulla (Fig. 46.2).
2. Afferents to this center come from baroreceptors and chemoreceptors (Fig. 46.3).

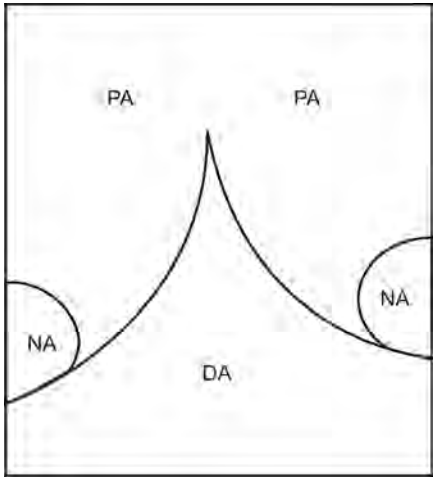


Fig. 46.2: Simple diagram of floor of 4th ventricle in medulla showing: Pressor area (PA), Depressor area (DA), Nucleus ambiguous (NA)

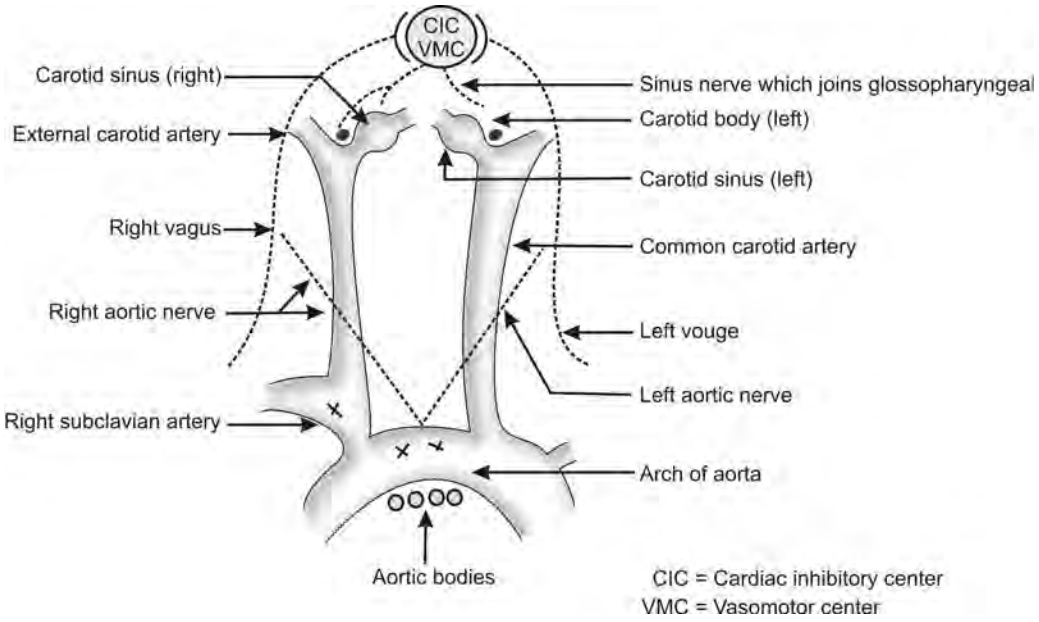


Fig. 46.3: Baroreceptors and chemoreceptors of systemic arterial tree

3. For example, rise of systemic blood pressure will stimulate the baroreceptors and cardioinhibitory center is stimulated. It will increase vagal tone (i.e. it will increase impulse discharge through vagus). Therefore, *bradycardia* will occur.

On the other hand fall of systemic pressure results in tachycardia due to withdrawal of vagal tone (as vagal tone is maintained reflexly by stimulation of baroreceptors).

Cardioaccelerator Center

1. Situated in lateral horn cells of upper thoracic segments of spinal cord T_1 to T_5 or 6. Functions of cardioaccelerator centre in spinal cord is modified by higher centers – in (a) medulla, (b) hypothalamus, and (c) cerebral cortex.
2. Higher center situated in medulla is: Vasomotor center which has (a) pressor area or (b) depressor area (Fig. 46.4).
   - Excitatory fibers from pressor area descend on sympathetic preganglionic

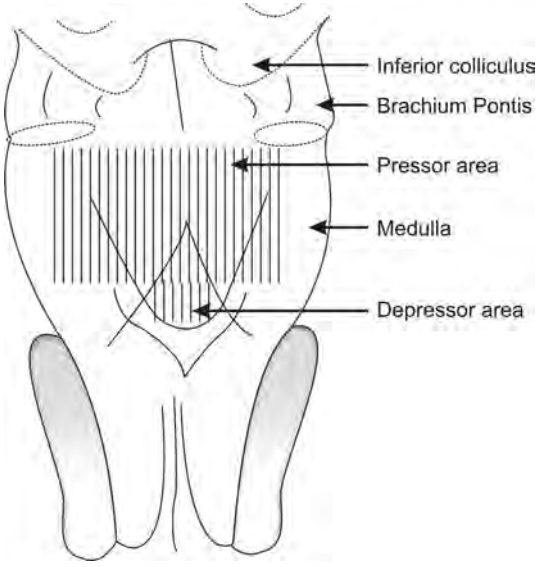


Fig. 46.4: Vasomotor center showing pressor and depressor areas

neurons in lateral horn cells of spinal cord.

- Increased activity of pressor area – increases the sympathetic activity and pressor effects on cardiovascular system are produced which include:
  1. Increase in heart rate
  2. Increase in stroke volume
  3. Increase in systolic blood pressure
  4. Vasoconstriction.

  (note – stimulation of depressor area produces opposite effects).

Vasomotor center – functions with superior control of:

a. Hypothalamus, and
b. Cerebral cortex.

3. *Posterior hypothalamic nuclei* act as cardioaccelerator center. Sympathetic activity to heart is increased following stimulation of these centers.
4. These centers have connections with motor and premotor areas of cerebral cortex.

Impulses from Higher Centers

In general stimuli, which increase the heart rate, also increases the blood pressure, whereas those which decrease the heart rate, lower the blood pressure. Thus, for example:

Emotions

(i) Anger and excitement are associated with tachycardia and a rise of blood pressure, whereas, (ii) pain and grief are usually associated with bradycardia and hypotension.

Emotional stimuli converge through hypothalamus on cardioinhibitory center and exert their effects on heart rate by increasing or decreasing its tone.

Exercise

Heart rate increases promptly at the start of exercise and sometimes even in anticipation of it. Increased heart rate is due to excitatory impulses from the cerebral cortex relayed via the hypothalamus to the – cardioinhibitory center and vasomotor center, so that there is increased activity of cardiac sympathetic nerves and decreased vagal tone appears to be involved.

Effect of Respiration

In most adults, heart rate does not alter during quiet breathing. When respiration is deepened voluntarily, the heart quickens during inspiration and slows during expiration. In children quiet breathing is associated with cardiac acceleration during inspiration and heart rate slows during expiration. This variation is termed as *sinus arrhythmia.* It is due to alteration in vagal tone, which occurs during the phases of rhythmic respiration. Three factors contribute:

1. During inspiration motor impulses from inspiratory center irradiate to vasomotor center which increases sympathetic activity.
2. Impulses in afferents from vagal stretch receptors in lungs that inhibit the cardio-inhibitory center.
3. During inspiration venous return increases stretching right atria and great veins and mobilizing Bainbridge reflex (given below).

Cardiac Reflexes

Variety of reflexes affect cardiac activity. These reflexes can be classified as:

i. Cardioacceleratory
ii. Cardioinhibitory
iii. Reflexes from other parts of the body.

Cardioacceleratory Reflexes

Venous engorgement of right atria and great veins reflexely increase the heart rate. Afferent fiber arise from the roots of great veins and right atrium, pass along the vagus to cardiac centers.

Venous engorgement stimulates these nerve endings and reflexely inhibit vagal tone and also stimulate sympathetic. Therefore, heart rate increases.

This reflex is called *Bainbridge Reflex* (1915). It is effective if initial heart rate is slow.

Cardioinhibitory Reflex

In resting condition, normally there is inverse relation between blood pressure and heart rate. This was first noted by Marey. Therefore, it is known as Marey's law.

There are stretch receptors in carotid sinus and aortic arch, which are known as baroreceptor: (a) when blood pressure increases these receptors are stimulated more. These afferent impulses reflexly increase the vagus tone – So the heart rate falls, (b) *Conversely* when blood pressure falls, number of afferent impulses going from baroreceptors decrease, therefore the vagal tone is decreased and so the heart rate increases.

Carotid sinus is enlargement at the *root of internal carotid artery.* In the adventitia are many nerve endings. These receptors are stimulated by stretch hence known as baroreceptors. The afferent impulses along these pass up along sinus nerve, which joins glossopharyngeal nerve. Finally, they reach the medullary cardiovascular centers (VMC and CIC of vagus) (Fig. 46.5).

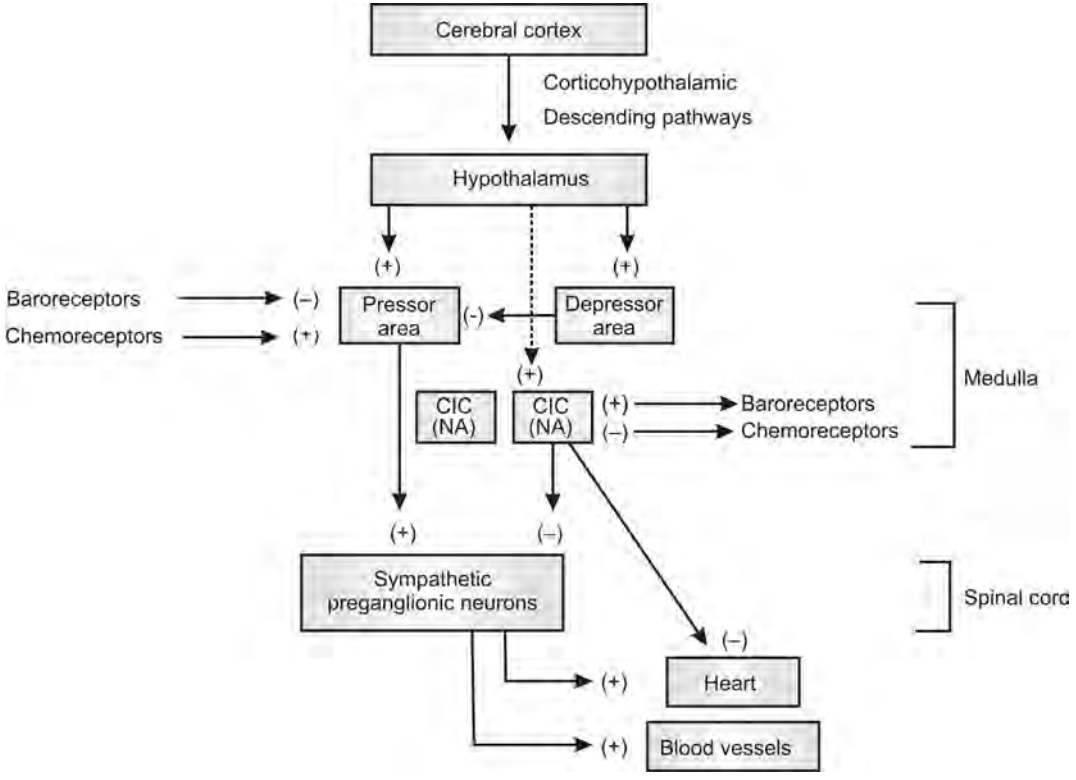


Fig. 46.5: Effect of various afferent discharge on medullary cardiovascular centers – (1) vasomotor center (VMC) and cardioinhibitory center (CIC), i.e. nucleus ambiguous (NA) (+) = Stimulation (-) = inhibition

Aortic arch: Similar stretch receptors are also present in aortic arch. Afferent impulses pass along the aortic nerves, which join the vagi, along which the impulses reach medullary cardiovascular centers.

Sinus and aortic nerves are known as buffer nerves. Effect is best seen when initial blood pressure is normal.

Exceptions to law:

a. Exercise
b. Emotional stimuli, and
c. Hypoxia.

In all of them blood pressure and heart rate both increase.

Reflexes from Other Parts of the Body

For example:

1. Pressure on eyeball results in *slowing* of heart rate.
2. Stimulation of nasal branch of 5th cranial nerve results in *slowing* of heart rate.
3. Stimulation of respiratory passages results in *slowing* of heart rate.
4. Pressure on carotid sinus causes *slowing* of heart rate.
5. Sudden blow on abdomen may *stop* the heart.
6. Moderately painful stimuli *quickens* the heart rate.

Afferents from all parts of the body including heart converge on cardiac centers cardioinhibitory center and cardioacceleratory center and tone of the centers depend on afferent input.

Chemical Control of Heart

1. Adrenal medullary catecholamines: (a) epinephrine and (b) norepinephrine have many actions on heart
   i. Positive inotropic
   ii. Positive chronotropic
   iii. Positive bathmotropic
   iv. Positive dromotropic

   Norepinephrine—causes generalized vasoconstriction therefore blood pressure increase, which will obscure the cardio-acceleratory effect. (because increased blood pressure will reflexly tend to cause bradycardia).
2. Adrenal cortial hormones, angiotensin and serotonine have positive ionotropic effect.
3. Thyroxine has positive chronotropic effect.
4. Hypoxemia, hypercapnia and acidosis – increase the heart rate but decrease the force of contraction.
   i. The chemoreceptors present in carotid body and aortic bodies are stimulated by these changes in blood and the effect is brought about reflexly.
   ii. Also these chemical changes in blood have direct action on SA node.

Circulation is more sensitive to oxygen lack, but respiration is more sensitive to carbon dioxide excess.

1. Increased intracranial pressure–results in:
   i. Hypertension, and
   ii. Bradycardia.

Increased intracranial tension causes compression of blood vessels inside the brain. Therefore, there is accumulation of carbon dioxide in tissue fluid of brain, which stimulate VMC resulting in generalized vasoconstriction. Blood pressure increases and there is reflex bradycardia.

SUMMARY OF FACTORS INFLUENCING HEART RATE

1. Higher centers
2. Respiration – sinus arrhythmia
3. Cardiovascular – reflexes:
   - Cardioinhibitory reflex—Marey's
   - Cardioaccelerator reflex—Bainbridge.

4. Chemoreceptor reflex
    i. Hypoxia
    ii. Excess carbon dioxide.
5. Other reflexes
    i. Pressure on eyeball
    ii. Pressure on carotid sinus.
6. Effect of temperature
    i. Increase in body temperature
    ii. Increases the heart rate.
7. Increased intracranial pressure
8. Endocrine factors
9. Emotions
10. Muscular exercise
11. Metabolic rate
12. Digestion
13. Age
14. Sex – females have higher heart rate than males
15. Surface area
16. Posture
17. Sleep.

CHAPTER

47

Cardiac Output

DEFINITION

At each beat certain amount of blood is pumped out by each ventricle into the circulation, this is called as cardiac output.

Two terms are used:

1. Stroke volume or systolic discharge.
2. Minute volume or minute output
   It must be remembered that cardiac output is the amount of blood pumped by each ventricle not the total amount pumped by both ventricles.

Normal Values

1. 70-80 ml is average stroke volume in adults.
2. 5-6 L is average minute volume in adults. Cardiac output less than 2 L and more than 6 L is definitely abnormal.

CARDIAC INDEX

Output per minute per square meter of body surface is known as cardiac index.

Normal Value

2.4 L/sqm/min to 3.5 L/Sqm/min.

Surface area in normal adult weighing 70 kg is 1.7 Sqm.

Significance of Cardiac Index

Cardiac output changes markedly with body size. Therefore, it is important to find some means by which cardiac output of different sized persons can be compared. So for comparing cardiac output of persons with different sizes, cardiac index is used.

Stroke volume index is stroke volume per square meter of body surface. Its normal value is 47 ml/sq m.

Cardiac output is directly proportional to:

1. Surface area
2. Body weight and
3. Metabolism.

Basic Determinant

Basic determinant of cardiac output is *oxygen requirement by the tissue.*

For example:

Cardiac output is

1. 5 L in lying down position
2. 7.5 L when person is walking slowly
3. 35 L in athlete performing strenuous exercise.

Distribution of Cardiac Output

Under basal conditions approximately out of 5 L:

1. 1.3 L to kidneys
2. 1.0 L to muscles
3. 0.5 L to liver
4. 0.8 L to brain
5 0.2 L to heart.
6. 0.8 L to other viscera and remainder is distributed to skin.

Skeletal muscles even though form 50% of body mass are supplied with 20% of cardiac output at rest, but it increases tremendously in exercise due to redistribution of blood.

Cardiac Reserve

Percent increase in cardiac output that occurs when there is such a need for an increase.

1. In nonathlete cardiac reserve is up to 400%. Four times increase in cardiac output
2. In trained athletic cardiac reserve is up to 500 to 700% (or 5 to 7 times increase in cardiac output).

Cardiac output depends on:

1. Venous return
2. Force of the heartbeat
3. Frequency of heartbeat
4. Peripheral resistance.

VENOUS RETURN

If more blood comes to the heart more is ejected. Hence, anything that increases or diminishes the venous return will alter the cardiac output.

Venous return depends on:

1. Muscular exercise
2. Respiration
3. Pressure difference between capillaries and venules
4. Vasomotor system.

Muscular Exercise

When muscles contract, they squeeze the blood in capillaries and venules towards the heart and help in venous return. This is aided by valves in the veins of lower limbs. The valves are so arranged that the direction of blood flow can be towards heart only. So, anytime the leg is moved certain amount of blood is pumped towards heart. This is known as *muscle pump* or *venous pump.* If the human being stands perfectly still, venous pump does not work. So it is natural habit of human being to shift position constantly, intermittently contracting the muscles of legs.

i. Secondly – to maintain posture there is sustained partial contraction of muscles – which is known as *muscle tone.* It helps in venous return.
ii. Thirdly – above the level of heart gravity aids the venous return.

Respiration

During inspiration the thoracic cage increases in all dimensions, therefore intrathoracic pressure falls. Therefore, the vessels expand and blood is sucked in thoracic veins. This is aided by increase in intra-abdominal pressure due to descent of diaphragm during inspiration and blood is pumped from abdomen towards thorax.

Pressure Difference

From root of aorta there is lowering of pressure. In the arterial end of capillaries the pressure is 32 mm and in venous end it is 12 mm and 0 mm Hg in the right side of the heart. So blood flows from a region of higher pressure to lower pressure and venous blood returns to heart.

Examples:

1. *In congestive heart failure:* Venous return will diminish because pressure in right side of the heart is increased.
2. *In muscular exercise:* Venous return increases because vasodilatation in muscles is associated with general rise of blood pressure.
3. *In shock:* Vasodilatation is associated with fall of blood pressure therefore venous return will fall.

Vasomotor System

Adjusts the lumen of arterioles and venules and thereby alters the venous return. If arterial tone is increased there is less blood flow through the capillaries and so through veins – on the other hand if vasodilatation occurs without general fall of blood pressure venous return increases.

FORCE OF THE HEARTBEAT

This profoundly affects cardiac output. This depends on:

Initial Length of Cardiac Muscle

According to Starling's law of heart, more is the initial length of cardiac muscle, more will be the force of contraction of heart. This is inherent self-regularly mechanism, which permits heart to adjust to changing diastolic volumes. Initial length depends on – degree of filling, which depends on venous return.

b. *Degree of diastolic pause* – filling, rest and recovery take place during diastole. Hence with short diastolic pause, which is inadequate for all these, force of contraction will diminish.

Stroke volume = end diastolic volume – end systolic volume

Normal values ˇ Resting ˇ

End systolic volume = 75 ml

End diastolic volume = 145 ml

145–75 = 70 ml stroke volume

Exercise (severe) ⎫ - End systolic volume = 40 ml ⎭ - End diastolic volume = 180 ml

180 –40 ml = 140 ml = stroke volume

Stroke volume increases in proportion to end diastolic volume upto physiological limit thereafter the volume falls (Fig. 47.1).

So the Starling's Law of Heart States

The force of contraction of ventricular muscle is proportional to its initial length within physiological limits. It represents the intrinsic property of the heart.

Note: It is also known as Frank Starling's law of heart muscle.

Nutrition and Oxygen Supply

Adequate supply of *nutrition,* i.e. glucose, lactates, free fatty acids and *oxygen* supply is essential for *efficient cardiac activity.* This can be supplied by maintaining efficient coronary circulation.

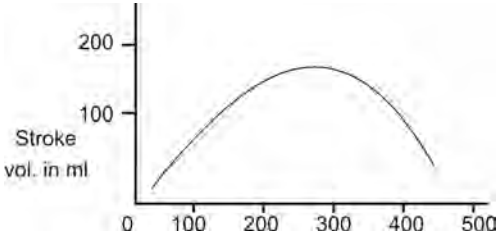


Fig. 47.1: Graph showing relation of end diastole volume and stroke volume (supports Starling's law of heart)

Ion Concentration

Optimum H ion concentration and proper balance of inorganic ions sodium, calcium, potassium and magnesium are required for strong heartbeat.

FREQUENCY OF HEARTBEAT—(HEART RATE)

Heart rate affects both stroke volume and minute volume by altering length of diastole and thereby degree of filling and force of contraction.

1. *Moderate increase* in heart rate will decrease the stroke volume but the minute volume (= stroke volume x heart rate) will increase.
2. If the heart rate *rises too high* the stroke volume is too low so that minute volume also falls. Blood pressure depends on minute volume. So the blood pressure falls and person becomes unconscious. For example, ventricular tachycardia when heart rate may increase to 150-250/min.
3. When heart rate becomes *moderately slow* the diastolic pause increases and therefore, the force of contraction and stroke volume increases and the minute volume may also increase.
4. But when heart rate becomes *very slow* for example in heart block, stroke volume is much more than normal but the minute volume falls.

   Thus, alteration in heart rate on either side will generally raise the minute volume up to a certain extent beyond that minute volume falls.

Numerical examples:

1. Moderate increase in heart rate.
   Heart rate = 100/min and stroke vol. = 60 ml.
   Minute volume = 100 × 60 = 6000 ml or 6 L (i.e. minute volume is increase).
2. Moderate slowing in heart rate
   Heart rate = 60/min and stroke volume = 100 ml minute volume = 60 × 100 = 6000 ml, or 6 L (i.e. minute volume is increased).
3. *In muscular exercise:* The heart rate is increased and venous return also increases. So even with short diastolic pause there is much ventricular filling. So the stroke volume and also the minute volume increases.

   Amount of blood pumped by heart in unit time (= minute volume) depends on heart rate and stroke volume. Heart rate is determined by play of sympathetic and vagal influences on pacemaker (SA node). Stroke volume is the difference between end diastolic volume and end systolic volume.

PERIPHERAL RESISTANCE

If the resistance to blood flow is increased: (a) Blood cannot return with ease from systemic blood vessels, and (b) Blood pressure increases. At first heart fails to expel efficiently but in the next beat the filling becomes more because venous return is added upon residual blood. Consequently, initial length increases and heart contracts with greater force and output is restored. *Optimum blood pressure is essential for adequate cardiac activity.*

CHAPTER

48 Methods of Measuring Cardiac Output and Summary of Factors Influencing Cardiac Output

IN ANIMALS

1. The aorta, pulmonary artery or the great vein entering the heart can be cannulated and the flow is measured by:
   i. Sophisticated flow meters: For example, electromagnetic or ultrasonic flow meters.
   ii. Cardiometers: which are not so sophisticated (Fig. 48.1).
2. Heart lung preparation can be made to measure cardiac output (Fig. 48.2).

Isolated heart lung preparation (Starling's):

i. Was introduced between 1910 and 1914.
ii. Thorax is opened of an anesthetized animal and artificial respiration is instituted.
iii. Arch of aorta is tied beyond the origin of innominate artery and blood from innominate artery is led to artificial peripheral resistance via an elastic chamber. Blood is warmed and led back to right atrium from the reservoir.
iv. Heart is no longer affected by vagi and sympathetic, because the centers controlling these nerves are killed by asphyxia, thus the responses measured are those by denervated heart.
v. The output of the heart can be measured directly by a timed collection of the blood, which has passed through the peripheral resistance or alternately can be registered graphically by enclosing the ventricles in a cardiometer, which is connected to a piston recorder.

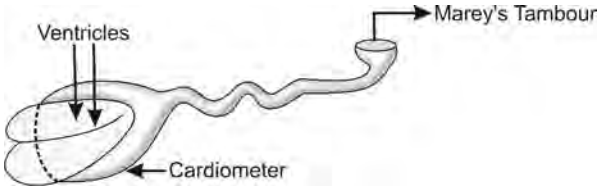


Fig. 48.1: Cardiometer

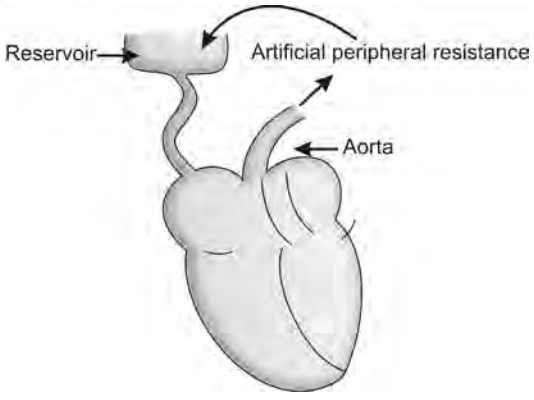


Fig. 48.2: Schematic diagram of heart lung preparation

vi. Venous pressure can be changed by changing the height of the reservoir and arterial pressure can be changed by changing the peripheral resistance and effects of these can be measured.

Cardiac output of dog is 150 ml/kg body weight.

IN MEN

Cardiac output is measured by indirect methods that do not require surgery.

1. By using electromagnetic catheter tip velocity meter—introduced in aorta or pulmonary artery. Volume flow can be known, if cross-sectional area of vessel is known by angiography or echocardiography. Other two methods, which are commonly used are:
2. Oxygen fick method, and
3. Dye dilution method.

MEASUREMENT OF CARDIAC OUTPUT BY DIRECT APPLICATION OF FICK PRINCIPLE

Fick principle: Blood flow through any organ can be determined by finding out amount of substance utilized or given out by the organ/unit time and dividing it by arteriovenous difference of that substance per 100 ml and multiplying the whole by 100.

Pulmonary blood flow =

$$\frac{\text{Oxygen used (taken up) in ml/per min}}{\text{Arteriovenous oxygen difference per 100 ml}} \times 100$$

= Right ventricular output/min

= Cardiac output

1. Arterial blood sample is taken by arterial puncture in man and its oxygen content is determined.
2. Mixed venous blood is withdrawn by intracardiac catheter in right ventricle, because mixed venous blood sample is needed, (as oxygen content of venous blood from different vascular beds differ) and its oxygen content is determined.
3. Ideally oxygen usage is determined simultaneously by closed circuit spirometry.

Example: If arterial blood contains 19 ml oxygen/100 ml and mixed venous blood contains 14 ml oxygen/100 ml

4. The arteriovenous difference is 5 ml/100 ml
5. If the resting oxygen usage is 250 ml/min.

Cardiac output = $\frac{250}{5} \times 100 = 5000$ ml/min = 5 L/min.

Disadvantages

1. Subject may be well alarmed by the ritual which is needed to determine cardiac output and cardiac output may be higher than normal.
2. It is dangerous for a subject to do heavy exercise with indwelling arterial or ventricular catheter, it may precipitate ventricular fibrillation, which is fatal.
3. This method can not be used in congenital heart diseases and shunts.

Dye Dilution Method (Hamilton's)

Principle: A known amount of the dye Evans blue (T_{1824}) is injected into the vein. By its passage through the heart and pulmonary circulation it will be evenly distributed in the bloodstream and its mean concentration during the first passage through an artery can be determined from successive samples of blood taken from artery.

Blood flow in liters per second

$$F = \frac{I}{ct}$$

I = total dye injected

c = mean concentration of the dye
t = duration in seconds of the first passage of the dye.

1. Before the injection of the dye 10 ml of venous blood are withdrawn from the basilic (antecubital vein) through the cannula, which later can be used for injection.
2. This venous sample is divided into the two samples of 5 ml.
3. To one of these is added sufficient dye to give a concentration of 0.5 mg per 100 ml *(standard).*
4. The other sample is used as *blank.*
5. One ml of dye solution containing 5 mg is then injected rapidly into basilic vein and immediately after the injection, the arm is raised to vertical position and gently stroked to further the inflow.
6. Samples of arterial blood are taken at an interval of 0.5-2 sec in a series of tubes.
7. These are later centrifuged together with the blank and standard tube and the concentrations of dye are determined photo colorimetrically.
8. Concentrations of dye in successive samples are plotted on semilogarithmic paper. From the resulting curve the mean concentration of dye can be calculated (Fig. 48.3).

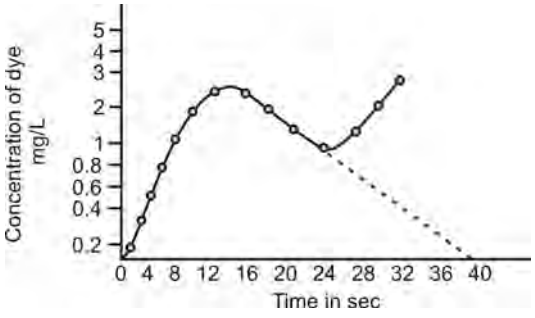


Fig. 48.3: Dye dilution curve

9. Curve shows the dye concentration reaches a peak and then steadily decline only to rise again owing to recirculation of blood containing dye.
10. If the early descent from the initial peak is continued as a straight line to cut the abscissa, the point on the time scale at which this occurs gives the duration of the first passage of the dye through the artery.

In the experiment carried out 5 mg of dye was injected.

Mean concentration of dye during first passage = 1.6 mg/L during the time t of 39 sec.

$$F = \frac{5 \times 60}{1.6 \times 39} = 4.77 \text{ L/min (cardiac output)}$$

Advantages

1. Dye dilution curves can be used in the investigation of congenital and acquired heart diseases.
2. Unlike direct Fick method, catheterization of heart is not required.
3. In heart failure appearance time of the dyes is prolonged, dye concentration in blood climbs slowly to a low peak from which it slowly falls.

Other Methods

Estimation of ventricular output can be made by injection of *radionuclides* and monitoring radioactivity over the heart region during the first passage of the radionucleotide through it.

Ballistocardiographic Method

Based on Newton's third law of motion. Every action has equal and opposite reaction. Ballistocardiogram is a record of the recoil of the body caused by the movement of heart and blood within it in opposite direction.

1. The subject is allowed to lie supine on the Ballistocardiographic table and there are arrangements for taking a photorecord of the vibrations of the whole body imparted to the table and to the recorder (Fig. 48.4).
2. During systole when blood goes to the aorta that is headwards—the body recoils by moving footwards.
3. When blood goes in descending aorta the body recoils by moving headwards (or more convenient method is the recording of the movement of a steel rod kept on stretched legs while lying on fixed table. The movement of the rod can be recorded by suitable sensitive electronic instrument).

Normal Ballistocardiogram shows following distinctive waves HIJKLMN (Fig. 48.5).

H wave is small positive wave—occurs due to headward movement of the body during isometric phase of systole.

I wave is negative wave and is due to footward movement of the body in response to ejection of blood into the aorta during ejection phase.

J wave is large positive wave occurring during headward movement of the body due to rapid flow of blood through *descending aorta.*

1. Stroke volume can be calculated by applying the formula.
2. Stroke volume = 7 x by under root of 2/3 (I + J) AC.
3. I and J are areas of waves.

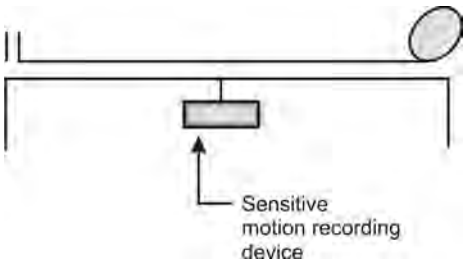


Fig. 48.4: Ballistocardiography table

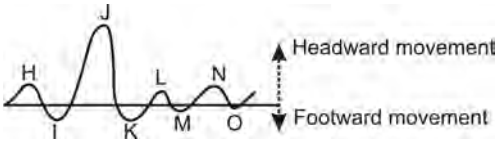


Fig. 48.5: Ballistocardiogram

4. A is diameter of aorta.
5. C is duration of cardiac cycle.
6. Stroke volume × heart rate = minute volume.

Disadvantage

This method is not accurate.

Pulse Pressure Method

Fairly reliable estimation of cardiac output can also be done from recording of pressure pulse contour from the central artery.

1. The basic theory is during diastole no blood flows into artery but it does continue to flow from central arteries into peripheral arteries, thus pressure in central artery falls and greater is the rate of blood flow greater is the drop in pressure.
2. By using empirical formulas the cardiac output can be calculated from the downward slope of pressure during diastole.

Advantage

The beauty of this method is that cardiac output can be measured with each heartbeat and rapid changes in it can be found out.

Disadvantage

Unfortunately the characteristics of pressure pulse curve depend on the distensibility of the arteries as well as the rate of run off of blood through peripheral blood vessels. Therefore, sometimes-serious errors occur.

Echocardiography

Ventricular output can be assessed by echocardiography:

1. It does not require injection or infusion.
2. It involves application of pulses of ultrasonic frequency 2.25 MHz. (megahertz) emitted from the transducer to heart.
3. The reflected waves from various parts of the heart are also received by the same transducer.
4. Record of these echoes displayed against time on oscilloscopic screen displays the movements of ventricular wall, septum and valves during cardiac cycle.
5. Not only cardiac output but also many heart functions can be determined by echocardiography.
6. It requires expertise.

Note: Ultrasound or ultrasonic waves have a frequency higher than highest audible sound (i.e. 20,000 Hz).

In echocardiography 10^6 or 10^7 Hz frequencies are used.

SUMMARY OF FACTORS INFLUENCING CARDIAC OUTPUT

Can be divided into two groups:

1. Physiological
2. Pathological.

Physiological

Age

Cardiac output varies with age. It is lowest in infants and highest in adults, because infants have low surface area. Cardiac index is high in children.

Sex

Because of less surface area in females the cardiac output is slightly less.

Surface Area

Cardiac output per square meter of surface area per minute is 2.4 to 3.5 L/min.

Emotions

Excitement and anger increase cardiac output by 50 to 100%. Grief and shock decrease it.

Digestion

Increases cardiac output, depending on the quantity of food ingested. Therefore, there is pain in cardiac region after meals in persons with coronary insufficiency.

Temperature

If room temperature is above 31°C there is increase in cardiac output. In very cold temperature cardiac output is increased because of shivering.

Posture

Cardiac output is less in erect posture as compared to lying, because in erect posture there is decrease in venous return.

Pregnancy

Placenta decreases the peripheral resistance and allows increased venous return. Therefore, cardiac output increases. In general, cardiac output is increased by 10-30% above normal shortly before term because of:

1. Presence of placenta, and
2. Increased metabolism.

Muscular Exercise

During exercise there is tremendous increase in cardiac output. It may increase 5-7 times or even more in severe exercise.

High Altitude

Due to hypoxia, cardiac output increases temporarily for few days at heights less than 15000 feet. After acclimatization there is no change in cardiac output.

Above 15000 ft, resting pulse rate is more by 15-20 beats/min, therefore, cardiac output increases.

Sleep

Cardiac output is at basal level in deep sleep.

Pathological Conditions

1. In which cardiac output is increased:
   i. Fever
   ii. Anemia
   iii. Hyperthyroidism.
2. In which cardiac output is decreased:
   i. Hypothyroidism
   ii. Hemorrhage
   iii. Congestive cardiac failure
   iv. Shock
   v. Atrial fibrillation
   vi. Heart block.

CHAPTER

49

Physiology of Blood Vessels and Hemodynamics

STRUCTURAL FEATURES OF COMPONENTS OF BLOOD VESSELS (VASCULAR TREE)

All blood vessels except capillaries have walls which have three coats:

1. *Tunica intima:* Inner coat of single layer of endothelial coat.
2. *Tunica media:* Middle coat of smooth muscles.
3. *Tunica adventitia*: Outermost coat of collagen tissue and fibroblasts.

Blood Vessels are Divided into Three Types

1. Arterial vessels
2. Capillaries
3. Veins.

Arterial Vessels

Arterial vessels are of three types:

1. Large elastic blood vessels. For example, aorta and its immediate branches.
2. Large muscular distributing arteries.
3. Small arteries and arterioles. They have diameter of 50-100 microns. Their media is 2-4 cell layer thick and terminal arteriole is less than 5 microns thick (Fig. 49.1).

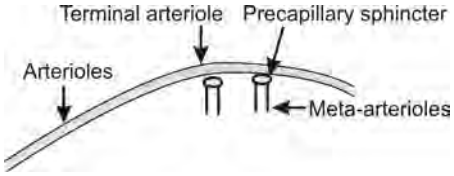


Fig. 49.1: Peripheral blood vessels

1. Side branches from terminal arteriole are known as *metarterioles.*
2. At the junction of terminal arteriole and metarteriole there are concentric smooth muscle cells, which is known as *precapillary sphincter.*

Innervation

Small arteries and arterioles are supplied by *sympathetic* vasoconstrictor nerves. Main density of innervation is in arterioles and precapillary sphincters.

1. *Increased sympathetic discharge results in vasoconstriction.*
2. Normally they are partially vasoconstricted. It is known as tone.

Capillaries

Consist of single layer of noncontractile endothelial cells. They are *not innervated.*

Veins

1. *Smaller veins* or venules are distinguished by their thinner walls in relation to their lumen. Innervation is spares as compared to arterioles.
2. Large veins vary in structure according to their place in the body. Two layers of smooth muscles in media are separated by connective tissue. The inner layer is disposed circularly and outer layer forms a spiral. Only outer layer is innervated.

VASODILATATION

Vasodilatation of parts of vascular system can be achieved by two different ways: (A) Nervous, and (B) Chemical.

Nervous Mechanism of Vasodilatation

1. *Reduction of sympathetic constrictor tone.* For example, exposure to heat causes flushing of skin.
2. Specific activation of vasodilator nerves—such nerves can be divided into:
   i. Sympathetic cholinergic vasodilators.
   ii. Parasympathetic vasodilator nerves.
   iii. Dorsal root vasodilators (axon reflex).

Sympathetic Cholinergic Vasodilators

These supply only skeletal muscle blood vessels, and are much more numerous than the sympathetic noradrenergic vasoconstrictor nerves to blood vessels of muscle which are tonically active (Note—noradrenergic because they release noradrenaline).

1. Vasodilatation of skeletal muscle blood vessels by the cholinergic sympathetic fibers is seen in biological emergencies, where life of wild animal is in danger.
2. In such situations there occurs sudden onset of sympathetic vasodilatation by higher center, which participates in alarm reaction.
3. This converts the animal into head, heart, lung and muscle animal. That is blood is flowing to these organs mainly and the animal can run at the fastest speed for his life (Imagine a deer grazing on the grass suddenly sees a tiger. In this alarm reaction sympathetic vasodilatation of the blood vessels of skeletal muscle takes place and they are supplied with large quantity of blood so that he can run away very fast).
4. Within a few seconds there occurs metabolite (chemical) induced vasodilatation in the muscle, which exceeds the potential of sympathetic vasodilatation.

Parasympathetic Vasodilator Nerves

For example:

1. *Nervi erigents* which supply sexual erectile tissue and contribute to pleasure.
2. *Vasodilator supply of salivary glands*—contribute to biological function

   But they play little part in general overall economy of circulation.

Dorsal Root Vasodilatation (Axon Reflex)

When skin is scratched with pointed object firmly the pain fibers carry the impulse. A branch of this fiber supplies a blood vessel which dilates. Therefore, this reflex is known as axon reflex (Fig. 49.2).

Chemical Vasodilatation

In conditions of increased activity of the tissues, the metabolites act directly on the smooth muscles of peripheral blood vessels and cause dilatation.

Best examples are blood vessels of:

1. Skeletal muscle
2. Heart muscle, and brain.

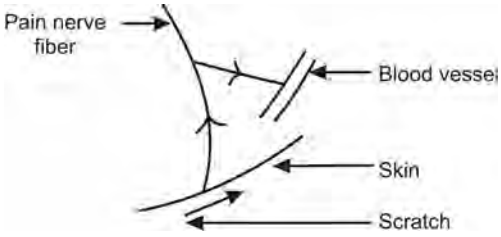


Fig. 49.2: Axon reflex

Functional Characters of Vascular Smooth Muscle

Blood vessels are lined by both:

1. Visceral single unit smooth muscle cells exhibit automatic (inherent) myogenic activity—enhanced by stretch
2. Multiunit smooth muscle cells – no inherent property and dominated by motor nerves.
    i. Large arteries and veins contain muscle cells of second type
    ii. Precapillary sphincters, meta-arterioles and arterioles contain muscle cells of first type.
        a. There are pacemaker cells in arterioles and metarterioles and precapillary sphincters. The activity is propagated from cell to cell and there is rhythmic closure of precapillary sphincters.
        b. Pacemaker activity is:
            i. Increased by – stretch. Mild stretch causes vasoconstriction and hence local control of vascular lumen results (autoregulation).
            ii. Suppressed by—metabolites—which relax the precapillary sphincter and capillary bed opens. When they are washed away the myogenic tone is resumed.
    iii. Activity of nerves is superimposed on myogenic activity
        a. Sympathetic nerve fibers liberate noradrenaline (neurotransmitter). It acts on α-receptors present in smooth muscle lining the blood vessels. Their interaction increases myogenic activity resulting into vasoconstriction.
        b. Circulating noradrenaline or adrenaline also react with α receptors present in smooth muscle lining of blood vessel and cause vasoconstriction.

[*Note:* Sympathetic cholinergic fibers release acetylcholine neurotransmitter at their nerve endings and they cause vasodilatation].

HEMODYNAMICS OR DYNAMICS OF FLOW OF BLOOD

Flow of blood in the vascular tree is governed by certain physical laws. In early 19th century

1. French physicist—Poiseuille
2. Swiss Physicist—Bernoulli
3. English Physicist—Raynolds provided important insight into the physics of blood flow through vascular system.

Flow and Cross-sectional Area Relationship

1. Aorta in man has cross sectional area of about 4 cm^2 and 90 ml of blood will pass through aortic lumen each second at mean velocity 22.5 cm/sec (Table 49.1).
2. As arteries subdivide radius of individual branches decrease but total cross sectional area increases. For example, there are approximately *8000 small arteries* with

Table 49.1: Total cross-sectional area and linear mean velocity of blood flow

		Total cross-sectional area	*Linear mean velocity of blood flow*
1.	Aorta	4 cm^2	22.5 cm/sec
2.	Small arteries (approx no 5000)	63 cm^2 (16 times that of aorta)	1.4 cm/sec
3.	Arterioles	400 cm^2	0.5 mm/sec
4.	Capillaries (at rest when 25% of them are patent)	2800 cm^2 (700 times that of aorta)	0.3 mm/sec
5.	Inferior and superior vena cavae	6 cm^2	7 – 8 cm/sec

internal diameter of 0.5 mm and their total cross sectional area is equal to 63 cm^2.

This value is 16 times that of aorta, hence rate of flow through each of the arteries is = 1.4 cm/sec (= $\frac{22.5}{16}$)

3. Arteries give rise to arterioles. Their total cross sectional area is 400 square cm and velocity of blood flow = 0.5 mm/per sec.
4. There are about 40,000 million capillaries in systemic circuit of a physiological man but only ¼ of these are patent at any time in resting condition.

   The average *capillary* has a radius of 3 µm and length about 750 µm and linear velocity of blood flow through them is *0.3 mm/sec* which is $\frac{1}{700}$ of mean velocity of flow in aorta.

   If all capillaries are patent—the surface for exchange of fluid with tissues is 560 sqm.

   But as normally 25% are patient – 140 sqm surface is available for exchange of fluids and gases and solutes between the blood and the tissues.

   Their cross sectional area is 2800 cm^2 when 25% of them are patent at rest.
5. Progressive confluence of capillaries and venules, etc. lead finally to two *venae cavae.* Cross-sectional area of each vena cava is 50% more than aorta and flow velocity per second through both is less than velocity blood flow in Aorta.

Thus, it is clear that increase in total cross sectional area of blood vessels decrease the linear mean velocity of blood flow.

Flow Pressure Resistance Relationship

The dynamics of blood movements through the vascular system depends on the relationship that exists between:

1. Driving pressure
2. Rate of flow
3. And resistance to flow

Simple relationship is similar to Ohm's law concerning the flow of electric current.

Ohm's law – E = IR
E = voltage
R = Resistance (electrical)
I = current flow

This adapted to movement of fluid in vascular system:

i. $P_1 - P_2 = RF$ (= driving pressure)
ii. P_1 = Point of high pressure
iii. P_2 = Point of low pressure
iv. R = Vascular resistance
v. F = Blood flow preunit time

Movement of fluid through vascular system involves number of additional considerations:

Poiseuille was first to study the flow of fluids through the tubes of capillary diameter using water and large reservoir providing driving pressure.

He was able to show that resistance to flow of fluid was directly related to the length of the tube and viscosity of fluid but inversely related to 4th power of radius.

Thus, Poiseuillie's law:

(a) $R = \frac{8nL}{\pi r^4}$

n = Viscosity of fluid
L = Length of tube
r = Radius of the tube

In words *Poiseuillie s law states that longer the tube or higher the viscosity or smaller the radius then higher is the resistance to flow.*

If value for R is substituted in equation (a)

(b) $F = \frac{\pi}{8} \times \frac{(P_1 - P_2)r^4}{Ln}$

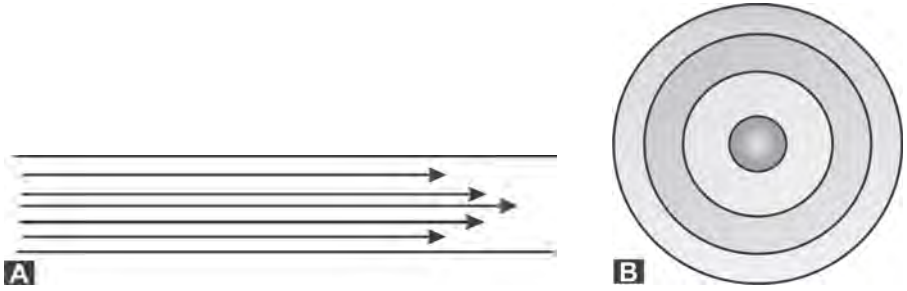
The constant $\frac{\pi}{8}$ is derived from mathematical deduction of volume passing per unit time.

This equation tells us that blood flows from a region of high pressure to a region of low pressure and radius of the vessel determines the resistance to the flow through it.

As normally L (length of blood vessel) does not change in grown up man, n (viscosity of blood) also does not change frequently but r (radius of blood vessel) changes.

In human beings *arterioles* are the terminal blood vessels of arterial system and they are responsible for maximum resistance (or r):

i. They are of small caliber as compared to arteries.
ii. They are the resistance vessels, which control the flow of blood to various tissues.
iii. They are capable of big changes in diameter.
   a. Poiseuillie's equation is satisfactory as long as the fluid flows in a laminar or streamline character (Fluid passing along a tube can be considered as a concentric series of very thin cylinders – the one next to wall is almost motionless, within this is another that moves more rapidly and so on. So the cylindrical elements nearest the center of the tube have highest linear velocity) (Fig. 49.3).
   b. When driving force is high and flow becomes fast (accelerated) the flow no longer remains streamline but the turbulence develops. This



Figs 49.3A and B: (A) Streamline flow, (B) Cross-section of blood vessel showing concentric series of very thin cylinders

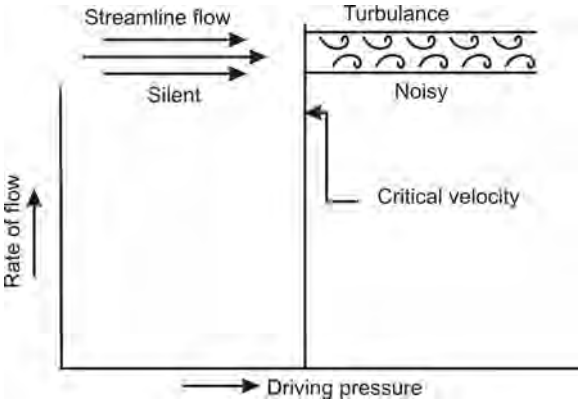


Fig. 49.4: Critical velocity and turbulent flow

happens above a critical flow velocity with this, the flow breaks into vortices and *resistance to flow is tremendously increased (Fig. 49.4).*

This was shown by Raynolds.

Critical velocity varies with viscosity and density of fluid and may be calculated from:

$$V = \frac{Kn}{pr}$$

Where V is critical velocity
K is Raynolds number
n is viscosity
p is density
r is radius of the tube

(Ventricles and aorta are the normal sites of turbulence. None of the small resistance vessels of vascular system show turbulence).

Pressure Flow Relationship

1. Burnoulli pointed out that:
   i. When blood flow is rapid side pressure declines and vice versa, which means when *blood flow is slow side pressure is more and almost equal to perfusion pressure.*
   ii. He also showed that fluid will move from a region of high total energy (P_1) to low total energy (P_2). Perfusion pressure determines the flow of blood to organ (greater the perfusion pressure greater will be flow). By sphygmomanometer we determine lateral pressure and it is a good guide to perfusion pressure as ordinarily velocity of blood flow is not so high and lateral pressure is equal to perfusion pressure.
2. In rigid tubes, there is linear relationship between the pressure and flow of homo-

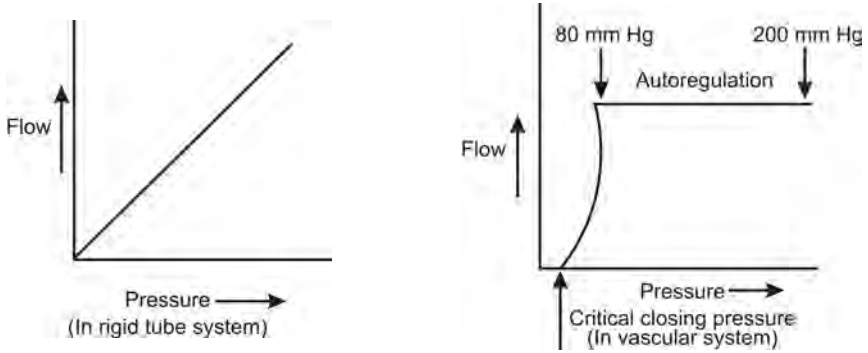


Fig. 49.5: Relation of pressure to flow in a rigid tube system and in vascular system

geneous fluid like water (i.e. as pressure increases flow increases (Fig. 49.5).

i. In blood vessels, this relationship is not linear, but somewhat curved because blood vessels are distensible elastic tubes and show an efficient myogenic control of their own vascular radius. Thus, they serve to stabilize the blood flow over a wide range of pressure. For example 80 – 200 mm Hg, showing *autoregulation (Fig. 49.5).*

3. In small blood vessels when pressure is reduced, a point is reached at which there is no flow of blood even though the pressure is not zero. This is so because:
   i. It takes more pressure to force RBC through capillaries which have diameter less than RBC, and
   ii. Extravascular tissues exert a small but definite pressure on vessel and when the intra luminal pressure falls below this extravascular pressure, the vessel collapses.

   The pressure at which the flow ceases is called the *critical closing pressure* .

LAW OF LAPLACE

Tells the relationship between distending pressure and tension on the wall of hollow viscus to counterbalance (Fig. 49.6).

For hollow viscus it is $P = \frac{T}{R_1} + \frac{T}{R_2}$

P = Pressure (distending pressure)
T = Tension (i.e. wall tension)
R_1 and R_2 = Radii (two principle radii)

For blood vessel it $P = \frac{T}{R}$ (as one radius is infinite in cylinder).

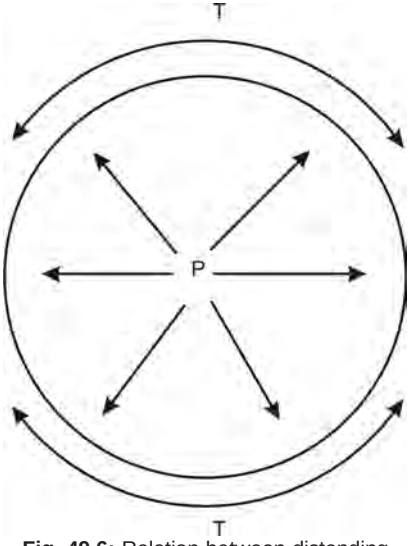


Fig. 49.6: Relation between distending pressure (P) and wall tension (T) in a hollow viscus

Physiological Significance

Smaller the radius of the blood vessel lesser the tension in the wall necessary to balance the distending pressure. This is why the thin walled and delicate capillaries are less prone to rupture.

Blood is Non-Newtonian Fluid

Blood is non-Newtonian fluid – that means its viscosity changes with change in the tube dimension and flow rate, whereas water is Newtonian fluid—that means its viscosity is constant over a wide range of tube dimensions and flow rates.

Poiseuillie

- Used water in his experiments (which is Newtonian fluid).
- Used steady pressure head (In life heart beats rhythmically).
- Used rigid tubes (In life blood vessels are elastic tubes).

So situations in life are far from the condition, which Poiseuillie analyzed.

Summary of Factors Affecting Vascular Flow

1. Pressure head
2. Radius of blood vessel
3. Length of blood vessel
4. Viscosity of blood

$$R = \frac{8nL}{\pi r^4}$$

(These factors are simple in rigid tubes).

But blood vessels are:

1. Elastic therefore radius changes.
2. Stretch causes myogenic activity therefore vasoconstriction takes place.
3. Neurogenic influences are superimposed on myogenic factors.

CHAPTER

50

Peripheral Resistance

It is the resistance which blood has to overcome while flowing through periphery.

Chief factors affecting it:

1. Velocity of blood flow
2. Viscosity of blood
3. Elasticity of arterial walls
4. Lumen of blood vessels
5. Length of blood vessel.

Peripheral resistance is directly proportional to first two factors, and it is inversely proportional to third and fourth factors.

Chief seat of peripheral resistance is arterioles and lesser amount of peripheral resistance is offered by capillaries.

Because

1. Peripheral resistance is inversely proportional to lumen, i.e. narrower the lumen more will be the resistance. The lumen of arterioles is sufficiently narrow as compared to arteries.
2. The total cross-sectional area of arterioles is many times more than that of arteries.
3. Capillaries have even narrower lumen than arterioles but the velocity is much less as compared to arterioles. In arterioles the velocity of blood flow is sufficiently high as compared to capillaries.

Note: As main seat of peripheral resistance is arterioles, greatest pressure drop occurs when blood is passing through arterioles and resistance to flow depends on state of vasoconstriction of arterioles.

VELOCITY OF BLOOD FLOW

1. Higher the velocity more is the frictional resistance. That is why arterioles are chief seat of resistance as the velocity of blood flow is high as compared with capillaries.
2. *Velocity depends on two factors:*
   i. Velocity has inverse relationship with cross-sectional area, i.e. more is the cross-sectional area less will be velocity. For example, total cross-sectional area of arterioles is much more as compared to aorta and so velocity is less in arterioles and more in aorta.
   ii. Velocity has direct relationship with the force with which blood is propelled. More is the force of contraction of heart more will be velocity.

VISCOSITY OF BLOOD

1. This term was used to denote internal friction or lack of slipperiness by Newton.

2. Viscosity of Newtonian fluid like water is constant over a wide ranges of – flow rates and tube dimensions. Whereas, blood is a non-Newtonian fluid, because it is suspension of RBC in plasma. Therefore, viscosity varies with flow rates and tube dimensions. That is why *apparent viscosity* or *anomalous viscosity* is used to denote viscosity of blood.
3. Viscosity of plasma is 1.2 to 1.3 times more than that of water and apparent viscosity of blood is 2.4 times that of plasma.
4. *Viscosity depends on* following factors:
   i. *Number of red cells*: If the number of red cells is increased the viscosity is increased. For example, in polycythemia viscosity is more.
   ii. *Plasma proteins*: Viscosity of plasma is 1.2 to 1.3 times that of water. This is because of plasma proteins present in plasma. Albumin is present in plasma in highest proportion, but it has a compact molecule. Otherwise viscosity of plasma would have been much more.
   iii. *Diameter* of blood vessels through which blood is flowing. When the diameter of blood vessel decreases to a value of 1.5 mm, the viscosity of blood falls and becomes equal to almost that of plasma. This is due to *Fahreus Lindqvist* effect (Fig. 50.1). In narrower tubes there occurs axial separation of red cells, i.e. red cells occupies the fast axial stream and plasma occupies the peripheral slower stream and actual composition of blood changes and number of red cells decrease as compared to plasma, the hematocrit value decreases (normal value is 45% cells and 55% plasma). Therefore, viscosity of blood falls. As the blood reaches the larger vessels the RBCs slow up and there is no longer axial distribution and the viscosity of blood increases.

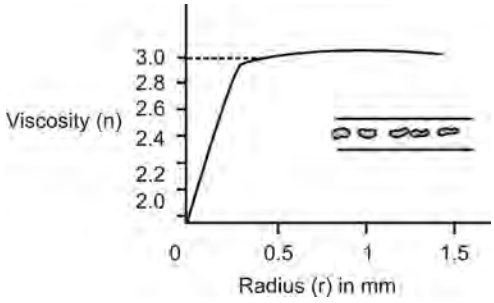


Fig. 50.1: Fahreus Lindqvist effect

   Physiological significance: In smaller blood vessels there is more plasma volume as compared to RBC volume-
      a. This helps to retain fluid in capillaries as it increases colloid osmotic pressure.
      b. Secondly, this helps in exchange of solutes, gases, and fluid.
   iv. *Shear rate:* In laminar flow the velocity of axial stream is highest and slowest in the stream close to vessel wall (Fig. 50.2).

   Therefore, there is friction—between vessel wall and blood, and—between adjacent laminae.

   The rate of change of velocity is known as *shear rate and more is the shear rate more is the friction and more is the viscosity.*
   v. *Temperature*: Viscosity depends on temperature. Higher the temperature lower will be the viscosity.

   Note: Viscosity of blood is measured by viscosimeter.

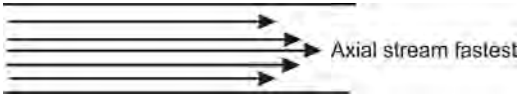


Fig. 50.2: Laminar flow

ELASTICITY OF BLOOD VESSEL

1. Rise of pressure by systolic ejection is limited by elasticity of blood vessels. So if the vessels loose their elasticity the rise of pressure is increased during systole.
2. The resistance offered by rigid vessels is more as compared with elastic vessels. The resistance offered by arterioles and capillaries determines the diastolic pressure. So the diastolic pressure as well as systolic pressure rises when vessels loose elasticity.

   For example, in old age the arterial walls become stiff. So systolic and diastolic pressure rises.

LUMEN OF BLOOD VESSEL

1. Peripheral resistance is inversely proportional to lumen of blood vessels. Smaller the vessel the higher is resistance. The chief seat of peripheral resistance is arterioles; although capillaries have smaller lumen the velocity of flow is very slow in capillaries.
2. Peripheral resistance is inversely proportional to 4th power of radius of the lumen of blood vessel $R \alpha 1/r4$.

EFFECT OF VESSEL LENGTH

As long as the radius of the blood vessel remains constant resistance is directly proportional to length.

In summary peripheral resistance is directly proportional to viscosity and length of the blood vessel and inversely proportional to 4th power of its radius.

$$R \propto \frac{8Ln}{\pi r^4} \text{ (Poiseuille's law)}$$

CONTROL OF PERIPHERAL RESISTANCE

Arteriolar walls are almost entirely muscular. Average arteriole can increase its diameter almost two times by relaxing and constriction of arteriole reduces its diameter. Even normally arterioles offer maximum resistance and they can change their diameter several times, so it can be easily understood that arterioles *vary the total peripheral resistance tremendously,* because resistance offered by a vessel is inversely proportional to 4th power of its radius.

Peripheral resistance is controlled by: (1) Local mechanisms, and (2) Systemic mechanisms which can be divided into: (i) Chemical and (ii) Neural mechanism.

LOCAL MECHANISMS

Vasodilator Metabolites

1. Increased CO_2 tension causes vasodilatation and relaxes precapillary sphincters. The direct dilator action of increased CO_2 is most pronounced in skin and brain.
2. Decreased oxygen tension and decreased pH cause relaxation of arterioles and precapillary sphincters.
3. A rise in temperature exerts direct vasodilator effect. In active tissues temperature rises and cause vasodilatation.
4. Potassium ions accumulated locally has dilator activity.
5. *Histamine:* Liberated due to allergic reactions cause vasodilatation.
6. *Prostaglandins*: Most of them cause vasodilation (some cause vasoconstriction).

(Prostaglandins are widely distributed compounds, almost every tissue contains

prostaglandins. They are synthesized in the body from polyunsaturated fatty acids).

All substances that cause vasodilatation decrease the peripheral resistance.

Local Vasoconstrictors

1. Injured arteries and arterioles constrict strongly, it is partly due to liberation of serotonin from platelets that stick to the vessel wall in the injured area.
2. Some prostaglandins are vasoconstrictors.

Systemic Mechanisms

Chemical Systemic Mechanisms

Kinins: Three related vasodilator peptides called kinins are found in the body (Fig. 50.3).

1. Bradykinin
2. Lysyl-bradykinin
3. Methionyl-lysyl bradykinin
   i. Kinins are small polypeptides that are split away from α 2 globulins (called kininogens) in plasma and tissue fluid, by the action of proteolytic enzymes called Kallikreins.
   ii. Plasma Kallikrein is formed from an inactive precursor pre Kallikrein in presence of active factor XII fragments which are proteolytic and called PreKallikrein activators.

Kinins are converted to inactive peptides by two Kininases – Kininase I and Kininase II (also acts as converting enzyme which converts angiotensin I to angiotensin II) (Fig. 50.4).

Kininase II is found in highest concentration in lungs and lungs are particularly active in removing kinins from circulation.

The action of kinins:

1. The actions of kinins resemble those if histamine. They cause – contraction *of visceral* smooth muscle but they *relax vascular smooth muscle.*
2. They also attract leukocytes, and
3. Cause pain
4. They are potent vasodilators formed during active secretion in sweat glands, salivary glands and exocrine portion of pancreas.
5. They are involved in local vasodilatation in other active tissues.
6. Their role is also suggested in thermoregulatory vascular adjustment.

Circulating Vasoconstrictors

1. Norepinephrine
2. Epinephrine
3. Angiotensin II

are vasoconstrictor agents found in circulation of normal individuals

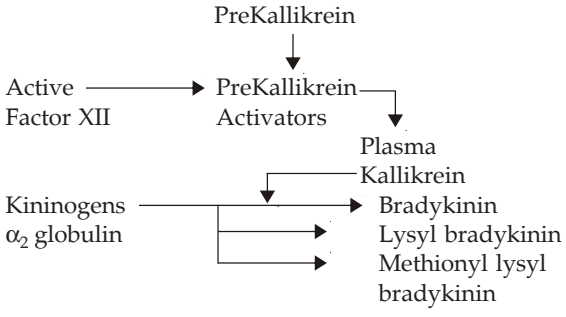


Fig. 50.3: Formation of kinins

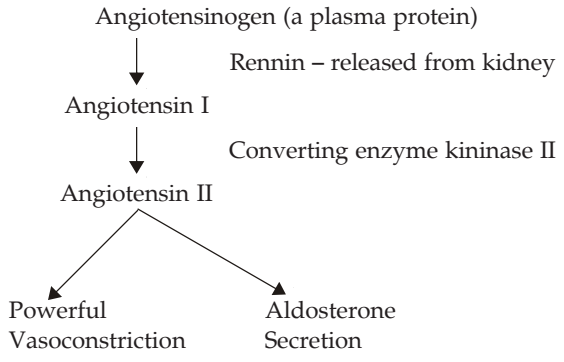


Fig. 50.4: Formation of angiotensin II

4. Vasopressin is not normally secreted in amounts sufficient to produce appreciable vasoconstriction.

Epinephrine and norepinephrine are secreted by adrenal medulla, whenever there is generalized sympathetic stimulation. They circulate through blood and act on blood vessels.

Norepinephrine has generalized vasoconstrictor effect but epinephrine causes dilatation of blood vessels of skeletal muscle and heart.

This action is via the receptors present on the smooth muscles of blood vessels.

They are α and β receptors:
1. α receptors combine with noradrenaline and adrenaline and effect is vasoconstriction.
2. β receptors are divided into β1 and β2.
3. β1 combines with noradrenaline but the affinity is low.
4. β2 combines with adrenaline. They are situated on arterioles of skeletal muscle and heart. When they are stimulated the result is vasodilatation.

Angiotensin II is an octapeptide and has generalized vasoconstrictor action.

Angiotensin II is formed from angiotensin I (by the action of kininase II present in plenty in lungs).

Angiotensin I is formed from angiotensinogen—a plasma protein (by the action of an enzyme rennin released from kidney in response to renal ischemia).

Angiotenin II is (i) a powerful vasoconstrictor, and (ii) it stimulates aldosterone secretion.

Systemic Neural Regularity Mechanisms

All blood vessels except capillaries contain smooth muscle and receive motor nerve fibers from sympathetic division of autonomic nervous system.

1. Arterioles are most densely innervated.
2. Sympathetic noradnergic nerve fibers are vasoconstrictors to all blood vessels except muscular and coronaries.
3. In other words sympathetic stimulation causes vasoconstriction of blood vessels of:
   i. Gastrointestinal tract
   ii. Skin
   iii. Kidneys and
   iv. Other nonmuscular areas.

Only 20% blood flow passes through muscles in resting state.
1. So many time the vasoconstrictor nerves of the body are massively stimulated there is immediate and significant increase in peripheral resistance (Innervation of blood vessels – is dealt with already).
2. There is tonic discharge in vasoconstrictor fibers to most of the vascular beds.

This means that all the time an individual is alive while asleep or awake the impulses are passing from his vasomotor center (which is tonically active) to most blood vessels in the body to cause at least partial vasoconstriction *(which is known as vasomotor tone)* (Fig. 50.5).

Vasodilatation is produced by:
1. Decreasing the rate of tonic discharge in vasoconstrictor nerves.
2. Cholinergic sympathetic vasodilatation.
3. Parasympathetic vasodilator nerves, and
4. Axon reflex.

Tone of the vasomotor center depends on:
1. Input from the periphery.
2. Input from higher centers.
3. Vasomotor center is highly sensitive to oxygen tension and pH of arterial blood.

INPUT FROM THE PERIPHERY

Two types of reflexes are seen known as vasomotor reflexes:

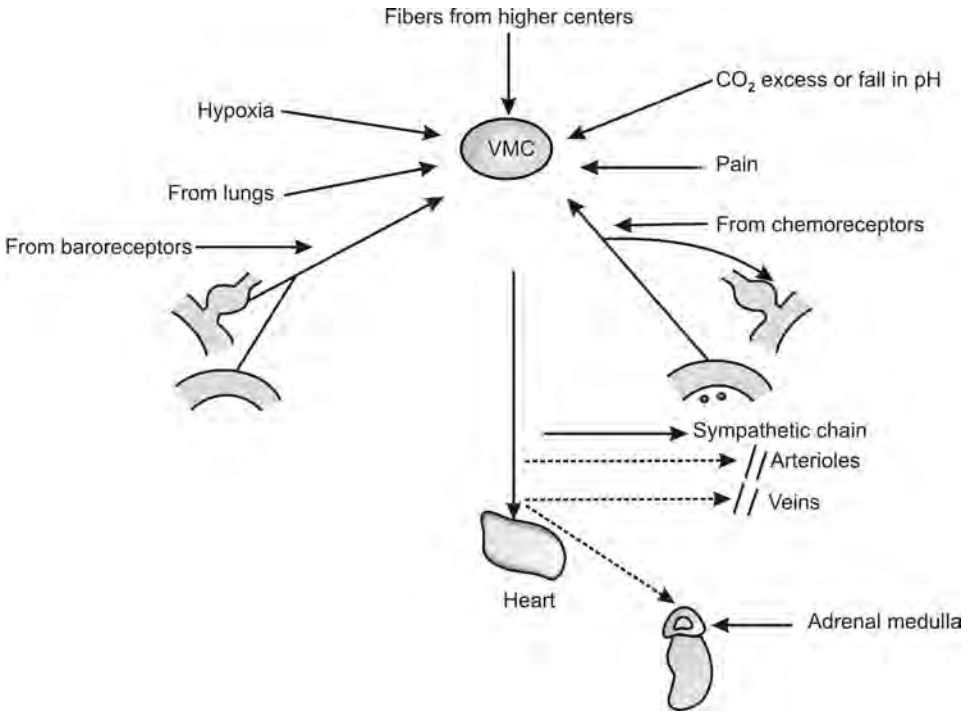


Fig. 50.5: Input to vasomotor center (VMC) and output from it

1. *Depressor reflex:* Decreases peripheral resistance and blood pressure.
2. *Pressor reflex:* Increases peripheral resistance and blood pressure.

Depressor Reflex

When there is increase of blood pressure it stimulates arterial baroreceptors. These afferent impulse are:

1. *Inhibitory to vasomotor center* and the response is decrease in the number of vasoconstrictor impulses from vasomotor center resulting in vasodilatation, and
2. Excitatory to *cardioinhibitory center* (dorsal motor nucleus of vagus, which is part of nucleus ambiguous) and the response is bradycardia.

Pressor Reflex

When there is fall of blood pressure, the stimulation of arterial baroreceptors decreases. So inhibitory impulses to vasomotor center decrease and the vasomotor tone is increased resulting in increased peripheral resistance and blood pressure.

1. Pressure sensitive mechanoreceptors in left ventricle when they are stimulated the reflex response is vasodilatation, fall of blood pressure and bradycardia (Bazold-Jarisch reflex).
2. Atrial receptors, when stimulated cause bradycardia and hypotension due to vasodilatation, especially in renal vascular bed.
3. *Pain:* Usually cause rise of blood pressure due to vasoconstriction.

   i. But if it is prolonged and severe it causes vasodilatation and fall of blood pressure and fainting.
4. Hypoxia and CO_2 excess or fall of pH through peripheral chemoreceptors increase vasomotor tone.

INPUT FROM HIGHER CENTERS

1. When posterior hypothalamus is stimulated impulses reach pressor center of vasomotor center and result is vasodilatation.
   i. When anterior hypothalamus is stimulated for example by heat – vasodilatation results.
   ii. Hypothalamus plays principle role in heat regulation.
2. *From limbic system*: It is center for emotions:

   Emotions like rage and panic increase heart rate and blood pressure due to vasoconstriction and increased cardiac output.

   On stimulation of cingulate gyrus (part of limbic system) – fainting, hypothermia and bradycardia results (This is called playing opossum). Opossum is an animal, which lies listless in dangerous situations. For example, some individuals faint on seeing ghostly scenes.
3. From motor and other areas of cortex fibers may go to vasomotor system. When they are stimulated vasoconstriction results. Some fibers from motor and promotor area may bypass vasomotor center and reach spinal cord. These bypassing fibers cause vasodilatation.
4. Fibers from Prefrontal lobe areas 9, 10, 11, 12 and 13 also reach VMC. These brain areas play powerful role in circulatory regulation in exercise.

CHAPTER

51

Blood Pressure

It is a well known fact that blood escapes from a cut artery under considerable pressure. First attempt to measure pressure was made by Stephen Hales in 1732.

After occluding the artery with a temporary ligature he tied a brass pipe into the femoral artery of a mare and connected it to a glass tube 9′ long. When he loosened the ligature on the artery, the blood rose 8′-3″ = 250 cm above the level of the heart.

IN ANIMALS

Now in animals artery is connected by a tube containing an anti coagulant (3% sodium citrate) to a mercury manometer. Difference in level of two mercury surfaces in the U tube gives pressure, which is expressed in mm Hg (Figs 15.1 and 15.2).

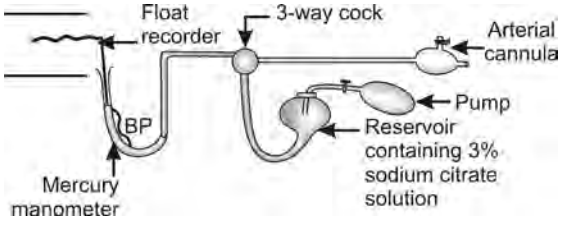


Fig. 51.1: Direct method of measurement of blood pressure in animals

IN MEN

Direct Method

Nowadays accurate and even continuous records of arterial pressure in man can be obtained with strain gauge condenser or tranducer manometers communicating directly with an artery through a small needle. Such record shows oscillation between minimum (diastolic) and maximum (systolic) pressure.

Indirect Method

Direct method is obviously unsuitable for routine clinical use but the blood pressure can be estimated in man indirectly by a method originally invented by Rocci in 1896 by sphygmomanometer.

1. Sphygmomanometer consists of one wide and one narrow limb. The pressure to be measured is applied to the wide limb so that the mercury moves down (Fig. 51.3).

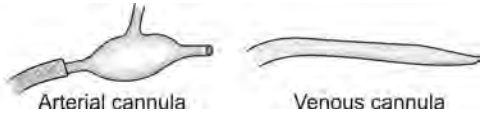


Fig. 51.2: Arterial and venous cannulae used in animal experiments

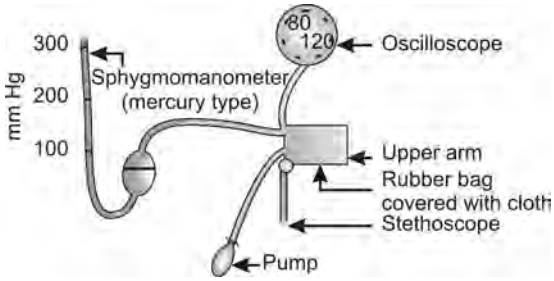


Fig. 51.3: Indirect method of measurement of blood pressure by sphygmomanometer (either mercury type or oscilloscope is used)

2. *How this is done?* A rubber bag of standard size (18 cm × 12 cm for adults) covered with cloth is wrapped round the upper arm, (cubital fossa is kept exposed). The rubber bag is connected to the pump. With this pump the rubber bag is rapidly inflated to above systolic pressure. Then air is allowed to leak a little gradually to allow the pressure in the bag fall gradually. Arterial pressure can be measured in one of the three ways:
   i. The first appearance of pulsation in the arteries distal to cuff may be detected with fingers—which is at systolic pressure. Usually we palpate radial artery and the method is known as *palpatory method.* With this method the diastolic pressure cannot be recorded.
   ii. Pulsations of air in the cuff may be recorded by *oscillometer.*
   When cuff pressure is increased and raised above systolic pressure the oscillations disappear. But on releasing pressure gradually the oscillations become larger and prominent. Pressure at which larger oscillations can be seen is *systolic pressure.* By further release of pressure oscillations become smaller and disappear. Pressure at which they appear smaller or disappear is diastolic pressure.
   This *method* is known as *oscillatory.* It is important method when distinct sounds cannot be heard–for example:
   i. In very young children.
   ii. In conditions of shock in adults.
   Disadvantage – not reliable method.
   iii. More usual method is *auscultatory method.* Bell of the stethoscope is kept lightly on brachial artery at the bend of the elbow. When the pressure is allowed to fall a series of sounds are heard first described by *Korotkoff* in 1905. Therefore, they are known as *Korotkoff s sounds.*

If the pressure in the bag is above systolic pressure the artery is occluded throughout the pulse cycle. When the pressure falls a little below systolic level artery opens momentarily and blood is allowed to escape, which produces a sound. *The cuff pressure at which sounds are first heard is systolic pressure.*

As the cuff pressure is lowered further the sounds become: (i) louder then, (ii) dull and muffled and finally in most individuals they, (iii) disappear.

CAUSE OF THE SOUNDS

Sounds of Korotkoff are produced by turbulent flow in brachial artery. The streamline flow in the unobstructed brachial artery is silent, but when the artery is narrowed the velocity of flow through the constriction exceeds the critical velocity and turbulent flow results.

1. As the cuff pressure is just below systolic pressure, flow through the artery occurs only at peak of systole and the intermittent turbulence produces a *tapping sound*.
2. As long as the pressure in the cuff is above the diastolic pressure in the artery, flow is

interrupted at least during part of diastole and the intermittent sounds have *staccato quality.*

3. When cuff pressure is just below the arterial diastolic pressure the vessel is still constricted but the turbulent flow is still continuous. Continuous flow sounds have a *muffled quality.*

   When the sounds become muffled pressure is equivalent to diastolic pressure.

   Pressures measured are accurate if certain precautions are observed.

Precautions

1. The cuff and manometer must be at the heart level to obtain a pressure that is uninfluenced by gravity.

   Supine, standing and sitting, in all positions cuff and manometer must be at heart level.
2. Blood pressure in thigh can be measured by tying cuff on thigh and placing the stethoscope over popliteal artery, but special cuff must be used. As there is much tissue between artery and cuff and some of the cuff pressure is dissipated hence false high blood pressure is recorded when standard arm cuff is used.

   Same happens in individuals with obese arms, because blanket of fat dissipates some of the cuff pressure.

   In both situations, accurate pressures can be obtained by using a cuff that is *wider than the standard arm cuff.*
3. If the cuff is left inflated for sometime the discomfort may cause generalized reflex vasoconstriction raising the blood pressure.

Definition

Blood pressure is the lateral pressure exerted on the vessel wall by the blood.

1. *Systolic pressure*: Maximum pressure during systole.
2. *Diastolic pressure*: Minimum pressure during diastole.
3. *Pulse pressure*: It is the difference between systolic and diastolic pressures.
4. *Mean pressure* = diastolic pressure + 1/3 of pulse pressure
   OR= arithmatic mean of the two pressures, i.e. systolic and diastolic.

   In any individual arterial pressure is not constant but subject to appreciable variation over short interval of time.
5. The pressure recorded under ordinary conditions of life is called *casual blood pressure.* This figure is higher, sometimes much higher than basal blood pressure.
6. *Basal blood pressure*: Is the blood pressure recorded 10-12 hours after last meal of the previous day and after resting ½ an hour in a warm room (i.e. in postabsorptive phase and in complete mental and physical rest).

Significance of Systolic Pressure

Systolic pressure indicates:

1. Force of contraction of heart
2. Systolic ejection
3. Volume of blood.

   Activity increases systolic pressure.

Significance of Diastolic Pressure

1. It is a measure of peripheral resistance.
2. It remains constant even after day-to-day activity.
3. It is due to tonicity of arterioles.

Diastolic Pressure is More Important than Systolic

Because

1. It does not vary in day-to-day activity.
2. If it is increased then heart has to work against resistance, hence more work is done by heart.

Normal Values

Many attempts have been made to find values between which a subject's blood pressure could be regarded as normal but all such attempts have been for various reasons unsatisfactory:

1. Pressure obtained by sphygmomanometer is affected by the thickness of the arm. Thicker the arm higher is the value
2. Arterial pressure increases with age. In some persons more, in some persons less and no dividing line can be set above which the pressure will increase.
3. Some consider that arterial pressure is also an inherent character like height and in production of high blood pressure at least three factors contribute:
   i. Age
   ii. Heredity, and
   iii. Environment.
4. When subject is supine, the arterial pressure is same (approximately) in the brachial and femoral arteries. In standing position it is more in femoral artery.
5. In 10 percent of the people the systolic recording on the right arm is 20 to 30 mm Hg higher than left.

NORMAL BLOOD PRESSURE

1. In adult *male* systolic blood pressure varies between 110-140 mm Hg with average value of 120 mm Hg.

   The diastolic pressure varies between 70 and 80 mm Hg.
2. In adult *female* systolic blood pressure is less by 5 mm Hg than male of her age, due to female sex hormones.

   Under basal conditions when systolic blood pressure rises above 150 mm Hg and diastolic pressure above 90 mm Hg—the condition is said to be *Hypertension.*

   Under basal conditions systolic blood pressure less than 100 mm Hg and diastolic blood pressure less than 60 mm Hg— it is said to be *hypotension.*

   Arterial blood pressure is conventionally written as 120/80 mm Hg.

FUNCTIONAL SIGNIFICANCE (IMPORTANCE) OF BLOOD PRESSURE

1. It is essential for flow of blood through circulatory tree.
2. It is a motive force for filtration through capillary bed, which is essential for:
   i. Tissue nutrition
   ii. Formation of urine
   iii. Formation of lymph
   iv. Venous return.

PHYSIOLOGICAL VARIATION OF BLOOD PRESSURE

1. *Age:* Blood pressure rises with age:
   i. In newborn baby—60-65 mm Hg
   After fortnight—70-75 mm Hg
   After one month—90 mm Hg
   ii. Then it gradually increases during childhood and adolescence till adult level is reached.
   iii. To obtain rough estimation of normal blood pressure for any adult subject – Age + 100 (i.e. add 100 to his age in years).
   iv. *After 40 years of age*—blood pressure increases and it is very difficult to set a line above which the pressure will be normal or abnormal.
   v. In old age increase in pressure is usually associated with atherosclerosis.
2. *Sex:* In females, blood pressure is lower by 5 mm Hg. Probably due to sex hormones. After menopause the blood pressure level in female reaches male level.

3. *Diarnal variation:* Due to mode of living there is diarnal variation, during day blood pressure increases up to 2 o' clock, then there is a slight fall. In case of night workers the pressure falls in the morning.
4. *Sleep:* In sleep blood pressure falls by 15-20 mm of Hg.
5. *Digestion:* During digestion blood pressure increases depending on type of food. Therefore, patients of hypertension and cardiac disease should not consume rich food and heavy meals.
6. *Posture*: Diastolic blood pressure is slightly higher in standing than recumbent posture.
7. *Exercise:* Systolic blood pressure increases to 160-180 mm Hg.
8. *Emotions:* Anger and excitement increase blood pressure.

   Grief and shock decrease the blood pressure.
9. *Build*: In obese persons the blood pressure is on higher side.
10. Blood pressure varies in right arm and left arm.
11. Blood pressure measured by sphygmomanometer depends on the thickness of the arm.

CHAPTER

52

Factors Determining Arterial Pressure and Regulation of Blood Pressure

FACTORS DETERMINING ARTERIAL PRESSURE

Blood enters the arterial system from left ventricle and leaves through arterioles. The amount entering is determined by cardiac output and amount leaving is determined by the resistance offered by arterioles (peripheral resistance). If more blood enters, i.e. if cardiac output increases or if less blood leaves, i.e. if peripheral resistance increases, the pressure in the arterial system rises.

Conversely, if the cardiac output or peripheral resistance falls the arterial pressure decreases. *Blood pressure is therefore, directly proportional to cardiac output and peripheral resistance* (Blood pressure α cardiac output $\times$ peripheral resistance).

Adjustment of blood pressure according to needs of body may be done by several complex reflexes.

REGULATION OF ARTERIAL BLOOD PRESSURE

Arterial blood pressure is regulated by several related systems that perform specific functions:

1. Rapidly acting (short-term) pressure control mechanisms.
2. Long-term control of pressure mechanisms.

Rapidly acting (short-term) pressure control mechanisms include:

i. Baroreceptor mechanisms
ii. Chemoreceptor mechanism
iii. CNS ischemic response
iv. Hormonal mechanism.

Baroreceptor Mechanisms

There are *stretch receptors or baroreceptors* found in the wall of proximal arterial tree especially in the region of aortic arch and carotid sinuses (Fig. 52.1).

1. When the *arterial pressure rises* there is increased stimulation of these nerve endings and there is increased traffic of impulses up the vagus and glosso-pharyngeal nerves. This leads to:
   i. Reflex slowing of heart rate, and
   ii. Reflex release of vasoconstrictor tone in the peripheral blood vessel (as impulses are inhibitors to vasomotor center).

   The result is: (a) fall in the cardiac: output, and (b) reduction of peripheral resistance which tends to restore blood pressure to normal value.
   ii. *A fall in the arterial pressure decreases* the stimulation of the arterial stretch receptors.

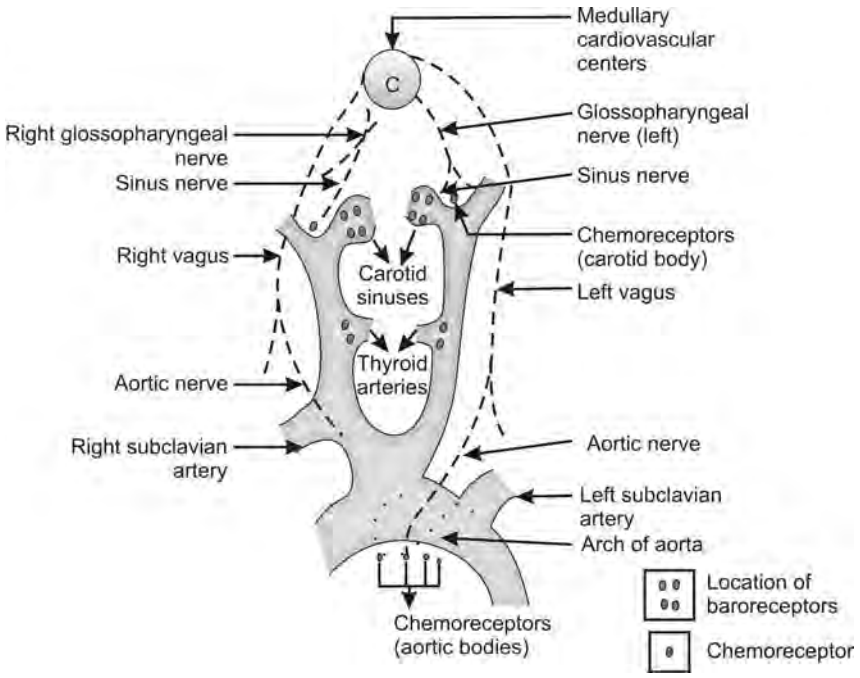


Fig. 52.1: Baroreceptors in the proximal arterial tree and chemoreceptors (carotid body and aortic bodies)

This lead to: (a) reflex tachycardia, and (b) reflex vasoconstriction which tend to raise the blood pressure towards its normal value.

The impulses from carotid sinus are first carried by sinus nerve which joins glossopharyngeal nerve and impulses from aortic arch are first carried by aortic nerves which joins the vagus nerve and vagus and glossopharyngeal nerves take the impulses from baroreceptors to medullary cardiovascular centers:

i. Vasomoter center
ii. Cardiac centers
iii. Vagal centers.

Cardiac and Pulmonary Mechanoreceptors

1. There are receptors in low pressure areas in atria and pulmonary artery which detect the increased pressure in low pressure areas which will occur simultaneously with increased systemic arterial blood pressure.

   When they are stimulated they elicit reflexes parallel to baroreceptor reflexes (i.e. they cause bradycardia and hypotension) and make the total reflex system much more potent for control of arterial pressure.
2. *Other receptors*: Volume receptors are situated in atriocaval and pulmonary veno-atrial region. Increase in atrial pressure stimulates them. It increases the heart rate reflexly (Bainbridge reflex).
3. *Ventricular receptors:* Present in left ventricle, when stimulated they reflexly cause bradycardia and hypotension. (Bezold Jarisch reflex).

   All the baro- and mechanoreceptors in arterial tree, heart and pulmonary vein are vagal receptors except the baroreceptors of carotid sinus which are supplied by glossopharyngeal nerve.

Chemoreceptor Mechanism

Chemoreceptors are present in carotid and aortic bodies. Carotid bodies are found at the bifurcation of carotid artery and aortic bodies are scattered beneath the concavity of aortic arch.

1. Impulses from carotid bodies are carried by sinus and glossopharyngeal nerves and impulses from aortic bodies are carried by aortic and vagus nerves.
2. The nerve endings in both are stimulated by:
    i. Oxygen lack
    ii. Increase in H^+ ion concentration (i.e. decrease in pH)
    iii. Increase in CO_2 tension.
    iv. Asphyxia.

In hemorrhagic, hypotension (oxygen lack, increased in CO_2 tension and decreased pH stimulate them. All will result due to slow circulation), their powerful discharge helps to maintain the systemic blood pressure at higher level. For example, when systolic blood pressure falls to 60 mm Hg, the baroreceptor impulse traffic is sparse, but the chemoreceptors on the other hand are firing vigorously and *combination* of:

1. Withdrawal of baroreceptor restraint on vasomotor center (as impulses from baroreceptors are inhibitory to VMC).
2. Excitatory influence of chemoreceptor discharge on vasomotor center induces a powerful sympathetic vasomotor activity resulting in:
    i. Increased heart rate (which will increase cardiac output).
    ii. Vasoconstriction (which will increase peripheral resistance).

Which Results in Increase of Blood Pressure

This mechanism is called sinuaortic mechanism which includes: (1) baroreceptors in carotid sinus and aortic arch, (2) chemoreceptors present in carotid body and aortic bodies and their, (3) afferent and efferent pathways.

Sinuaortic mechanism plays the chief role in maintaining the blood pressure at constant level from moment-to-moment.

CNS Ischemic Response

Normally, most nervous control of blood pressure is achieved by reflexes originating in baroreceptors and chemoreceptors and low pressure receptors. All of which are located in the peripheral circulation *outside the brain.*

When blood flow to vasomotor center in the lower brainstem becomes decreased enough to cause nutritional deficiency, a condition called ischemia of the neurons in the vasomotor center itself results and the vasomotor center responds directly to the ischemia and become strongly excited and resulting vasoconstriction and acceleration of heart increases systemic arterial pressure. [It is because the slowly flowing blood fail to carry away CO_2 and local concentration of CO_2 increases which has extremely potent effect in stimulating nervous system. Therefore, there is marked stimulation of vasomotor center and elevation of blood pressure].

This arterial pressure elevation in response to cerebral ischemia is known as CNS ischemic response. *It is one of the most powerful activators of sympathetic vasoconstrictors.*

1. It does not become very active till the arterial pressure fall far below (down to 50 mm Hg). Greatest degree of stimulation occurs at a pressure of 15-20 mm Hg.

2. It is an emergency mechanism, which acts extremely rapidly and powerfully.
   In Summary: The first line of defence is by nervous mechanisms.

Hormonal Mechanisms

In addition to a rapidly acting nervous mechanism for control of arterial pressure there are at least three hormonal mechanisms that also provide either rapid or moderately rapid control of arterial pressure.

1. *The norepinephrine*–epinephrine–vasoconstrictor mechanism.
2. *Renin˘angiotensin*–vasoconstrictor mechanism.
3. Vasopressin.
   i. *The norepinephrine˘epinephrine mechanism* – stimulation of sympathetic nervous system causes:
      a. Direct nervous excitation of heart and blood vessels, and
      b. Also causes release of adrenaline and noradrenaline from adrenal medulla. These two hormones circulate to all parts of the body and cause same effects, i.e. they excite heart.
      c. Constrict most of the blood vessels and constrict veins.

   Therefore, different reflexes that regulate arterial blood pressure by exciting sympathetic nervous system cause blood pressure to rise in two ways:
   i. By direct stimulation of heart and blood vessels, and
   ii. By indirect stimulation through release of epinephrine and norepinephrine.

   These two hormones circulate for 1-3 minutes and reach parts that have no sympathetic innervation.

2. *Renin˘angiotensin vasoconstrictor mechanism:* Fall in renal blood flow (which would occur if arterial blood pressure falls) results in the release of the hormone renin from the kidneys. Renin converts the plasma protein–angiotensinogen into angiotensin I which is converted to angiotensin II (by Kininase II). It is a polypeptide which: (a) constricts blood vessels, and (b) release aldosterone from adrenal cortex.

   As a result, salt and water retention takes place (by aldosterone). This together with vasoconstriction produced by angiotensin tend to raise the blood pressure (Fig. 52.2).
3. *Vasopressin:* When arterial blood pressure falls low, hypothalamus and posterior pituitary is stimulated to produce large quantity of vasopressin. It has direct vasoconstrictor effect, which will increase the arterial blood pressure by increasing the peripheral resistance.

Another action of vasopressin—is, it is antidiuretic hormone, so it retains water and urinary excretion of water becomes less and blood volume increases.

Increase in blood volume helps to bring blood pressure to normal.

Two intrinsic (intermediary in action) circulating mechanism for arterial blood pressure regulation.

Capillary Fluid Shift Mechanism

When arterial pressure changes this is associated with changes in capillary pressure, e.g. increased blood pressure causes fluid to move across the capillary membrane into interstitial space. Therefore, blood volume and blood pressure falls. This mechanism is slow in action.

Vascular Stress Relaxation Mechanism

When arterial pressure falls pressure also falls in blood storage areas like liver, spleen, lungs and veins, etc. and when arterial pressure

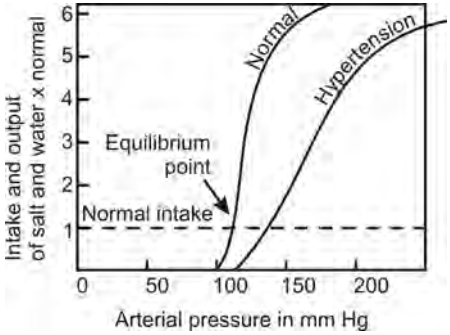


Fig. 52.2: Renal handling of salt and water

increases pressure also increases in blood storage areas.

By pressure change, vessels gradually adapt to a new size, accommodating the amount of blood that is available. It is known as *stress relaxation or reverse stress relaxation.* For example, when massive transfusion is given blood pressure increases at first but later on blood pressure returns to normal in about 10-60 minutes.

Long-term Mechanism for Arterial Pressure Regulation

The nervous regulation of arterial pressure, though active very rapidly and powerfully, generally loose their power to control arterial pressure after a few hours to a few days because *pressure receptors adapt* or, i.e. loose their responsiveness. Therefore, normally nervous mechanism does not play a major role in long-term regulation of arterial pressure.

Long-term regulation of blood pressure is done mainly by *renal˘body fluid pressure control mechanism (Fig. 52.2).*

This mechanism involves: (1) control of blood volume and blood pressure by kidney, and (2) control of kidney function by different hormonal system especially rennin-angiotensin and aldosterone.

Basically it Works as Follows

1. *When arterial pressure falls*: Kidneys retain salt and water and blood volume rises. This in turn will increase the blood pressure.
2. *When arterial pressure rises*: Increased rate at which kidneys excrete both salt and water decreases blood volume and arterial pressure decreases.

How does kidney handle sodium? (Renal sodium handling)

1. Normal kidney plays an important role in maintaining intravascular volume and arterial pressure.
2. It responds to increased pressure by increasing sodium and water excretion – thus reducing arterial pressure to normal levels.
3. Normally sodium intake and output are balanced at a mean perfusion pressure of 100 mm Hg.
4. When higher perfusion pressures are needed to produce loss of salt and water it would facilitate hypertension.
5. A variety of neurohormonal factors: (i) intrinsic, and (ii) extrinsic to kidney can influence the relationship between perfusion pressure and sodium excretion.
   i. Intrinsic factors:
      a. Angiotensin II
      b. Prostaglandins
      c. Kinins
   ii. Extrinsic factors:
      a. Circulating catecholamines
      b. Aldosterone
      c. Sympathetic nervous activity.

In addition, a kidney subjected to elevated pressure over time develops structural changes that limit its ability to excrete sodium and water in response to increased pressure. Then one can understand that hypertension that has developed, is maintained.

CHAPTER

53

Electrocardiogram (ECG)

INTRODUCTION

The activity of the heart muscle is accompanied by electrical phenomenon as when tissue becomes active.

First discovered by *Kolliker and Muller in 1856.* They observed that when the sciatic nerve of frog is placed on beating heart of same or other animal at each systole, muscles innervated by sciatic nerve contract.

Waller was the first to record. In 1903 Einthoven, professor of Physiology in University of Layden *used string galvanometer* for recording action currents of heart and subsequently developed the fundamental theory of electrocardiography.

Lewis, Wiggers, FN Wilson and others contributed to enlarge and consolidate the basic knowledge.

Action current of the heart is transmitted to neighboring structures, therefore, it may be recorded by connecting galvanometer to convenient points of the body surface, without even damaging the skin. When action current is led off directly from the heart the record is called *electrogram* and the term *electrocardiogram* is used when the record is obtained by leads placed on the skin.

Electrocardiography is technique and electrocardiograph is the machine for recording electrocardiogram (Fig. 53.1).

RECORDING APPARATUS

1. Changes in electrical potentials originated by the heart action are of very small magnitude and occur in relatively fast succession. The instrument used for recording them must possess *great sensitivity and rapidity of response.*

   String galvanometer developed by Einthoven in 1903 meets these requirements.

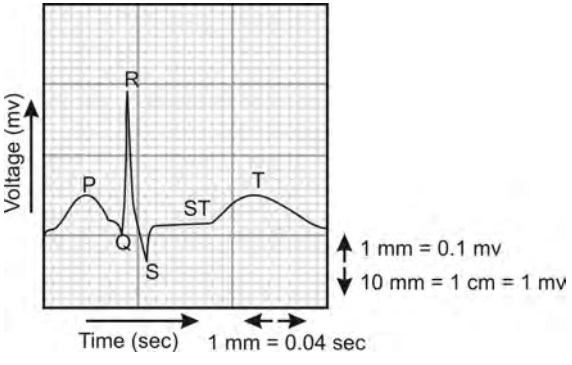


Fig. 53.1: Normal electrocardiogram

2. *The principl*e: On which it is based—when an electric current flows through a conductor placed at right angles to a magnetic field, the conductor moves in a direction at right angle both to: (i) magnetic field, and (ii) the direction of the current.
3. Several models of electrocardiographs are manufactured based on the principle of Einthoven's string galvanometer, from which they differ only in details.
4. In modern electrocardiographs a *stylet* is used, which is warmed so that is leaves a trace on special *plastic coated paper.*

Definition of Electrocardiogram

It is a graphic record of action current of heart led off from body surface.

Electrocardiographic Leads

There are an infinite number of points on body surface from which this current can be led off and recorded. There is general agreement to place the electrodes on *certain conventional places,* which are known as electrocardiographic leads.

The tracing—differs according to the lead used but they all show certain factors in common so that general *description* can be given:

1. Normal electrocardiogram shows at each cardiac cycle, in all usual leads, 3 positive waves or deflections (above the basal line or isoelectric line) and 2 negative waves (below the baseline).
2. They are named with letters as proposed by Einthoven.
   i. The first deflection is positive and corresponds to the spread of excitation in auricles it is named as P wave (denoting presystolic).
   ii. Subsequent 4 deflections are called by letters following P in alphabet so they are named Q R S T and exceptionally there is sixth wave U.
   - P R T are positive waves.
   - Q S are negative waves.

Amplitude of Q and S waves varies considerably and in some leads they may be scarcely marked or completely absent.

Time Intervals

The fine vertical lines are 0.04 sec apart and every fifth line is little thick than others. Interval between two thick lines is 0.20 sec.

Amplification Power of Oscillographs

It has been conventionally decided to adjust the amplification power in oscillographs so that a current of 1 mv causes a deflection of 1 cm (=10 mm) on the record. So the distance between two horizontal lines is 0.1 mv.

Description of Waves

1. P wave is usually low, rounded appearing as wide tracing on the record.
   - Normal duration—0.1 sec
   - Normal height—3 mm.

   Abnormalities in shape, situation, direction and number of P waves give important information on the functioning of the auricles.
   i. Prominent and bifurcate P wave — indicates atrial hypertrophy, as in mitral stenosis.
   ii. In atrial fibrillation P is absent and is replaced by 'f' waves.
   iii. If the cardiac impulse arise in AV node instead of SA node, P is inverted.
2. *QRST (ventricular complex):* These waves are related with ventricular activity. We consider them in two complexes:

   (i) Initial rapid complex (QRS) and (ii) final slow complex (T).

   They are separated by short isoelectric interval ST segment.

U Wave

Seldom appears, when visible it is more prominent in lead II (left arm left leg). It is seen as positive round wave. It is due to repolarization of papillary muscles.

Q Wave

1. It is negative wave.
2. It is never very prominent in normal man.
3. It may be absent without any pathological significance.
4. It is due to activity of muscular part of ventricular septum.
5. It indicates commencement of septal activation.

R Wave

1. It is positive wave.
2. It is highest wave especially in lead II.
3. Amplitude of R depends on direction of the electrical axis of heart during the recording of the particular ventricular complex.
4. In normal subjects it is 7-17 mm (= 0.7 to 1.7 mv).

S Wave

1. It is negative wave.
2. It varies in depth according to subjects and lead, depending on direction of electrical axis of heart.

QRS Complex

In normal subjects is:

1. Thin
2. Straight lines
3. Of uniform width
4. Without any slurring, splintering or notches.

   It's normal duration—0.06 to 0.1 sec (maximum 0.12 sec).

   It is wide in bundle branch block (because one ventricle is stimulated before the other and excitation spreads by abnormal route).

   Therefore, in bundle branch block – QRS is prolonged, and
   - T wave is enlarged and in opposite direction to QRS complex.
5. *T wave:* It is always positive in lead I and II, but sometimes negative in lead III.
   i. It is due to ventricular repolarization.
   ii. It is slow and rounded.
   iii. Its normal duration is 0.16 to 0.22 sec.

Abnormality of T wave depicts myocardial damage, which could be due to—impaired blood supply (leading to hypoxia).

- Infarction.
- Nutritional.
- Toxic.

Total duration of QRST = 0.43 sec which is same as mechanical systole.

Time relation: Certain time relations in the ECG are of great importance.

1. Interval between the beginning P and the beginning of Q (beginning of R when Q is missing) is known as *PR interval*. Its normal duration is 0.12 to 0.18 sec (maximum 0.20 sec). Variations indicate abnormalities or delay in conduction through bundle of His.

   When PR internal is more than 0.2 sec, it denotes a delay in conduction from auricles to ventricles. It is known as 1st degree auriculoventricular block, which may be due to compression or inflammation of the bundle of His or due to vagal stimulation.
2. *ST segment:* It is the interval between the initial and final ventricular complexes.
   i. It is important.
   ii. Normally duration varies with shape and size of T.
   iii. It is always isoelectric, i.e. the record should be at the same level as during diastole (a deviation of 1 mm above or below is allowed).

iv. A greater deviation indicates hypoxia in myocardium as in coronary occlusion or compression of coronary arteries by pericardial effusion.

Note:

1. Electrocardiogram shows the electrical activity of heart which is in the form of wave of depolarization followed by repolarization. The conduction is not linear as in strip because the cardiac fibers are wound like a turban, therefore, direction of conduction is different.
2. ECG is an investigation and has its limitations, sometimes perfectly healthy heart may show abnormality in ECG or grossly damaged heart may show normal ECG.
3. Deflection of electrocardiogram precedes mechanical activity in the heart to which it is connected usually by 0.01 to 0.03 sec.
4. There is no relation whatsoever between the electrical deflection and the mechanical event in the sense that a vigorous systole may be accompanied by a small electrical deflection and *vice versa*.
5. Whenever electrical process is traveling away from the exploring electrode it will record negative wave and when it is traveling towards it, it will record positive wave.

LEADS

Direct Leads

When electrodes are placed directly on the surface of the heart—it is direct lead. This can be done in experiments on animals and during intrathoracic surgery in human beings.

Indirect Leads

The exploring electrodes are kept on body surface: (a) Bipolar leads, and (b) Unipolar leads.

Bipolar Leads

ECG is recorded between two active electrodes.

Einthoven recommended certain leads, which have come into universal usage.

A. *Bipolar limb leads:* Electrodes are placed on the limbs which are acting as conductor material, usually 3 combinations are used:
   i. Lead I - right arm (negative) - left arm (positive)
   ii. Lead II - right arm (negative) - left leg (positive)
   iii. Lead III - left arm (negative) - left leg (positive)
2. *Bipolar chest lead:* Localized analysis of cardiac potentials can be made by placing one electrode on the chest on the precordial area and the other on distant part of the body.

This way is semidirect. Near electrode can capture potentials, which owing to their small magnitude cannot be registered by distal electrodes.

Near electrode can be kept on one of the following six positions:

1. On right sternal margin in 4th intercostal space.
2. On left sternal margin in 4th intercostals space.
3. Midway between left sternal margin (i.e. position and midclavicular line.
4. On the midclavicular line at the level of the apex beat.
5. On the left anterior axillary line at the level of apex beat.
6. On the left midaxillary line at the level of apex beat.

The same six positions are used in unipolar chest leads.

If distal electrode is placed on right arm the precordial lead is called CR , CL—if placed on left arm and CF—if placed on the left leg and the leads can be named CF1…… CF6.

Unipolar Leads

Unipolar chest leads: ECG recorded using active or exploring electrode connected to indifferent electrode at 0 potential (Fig. 53.2).

Wilson's Central Terminal (Fig. 53.3)

Wilson has suggested the use of common terminal connected through 5000 ohms resistance to each one of the right arm, left arm and left leg electrode to counterbalance potentials arising in limbs so that the potential in conductor remains near zero.

So ECG obtained would only register changes produced under exploring electrode placed on one of the 6 chest position. It is a semidirect lead and called V_1…..V_6.

Unipolar limb leads: For study of limb potentials, one terminal is connected to limbs, right arm, left arm or left leg (foot) and other to Wilson's central terminal—this is Wilson's technique and the record is called VR, VL, VF.

Goldberger disconnects from common terminal the limb that is being explored and does not use the usual resistance (Fig. 53.4). Thus, simplifying the technique without altering the results. Letter a meaning augmented precedes the nomenclature. Therefore, record is called aVR, aVL and aVF.

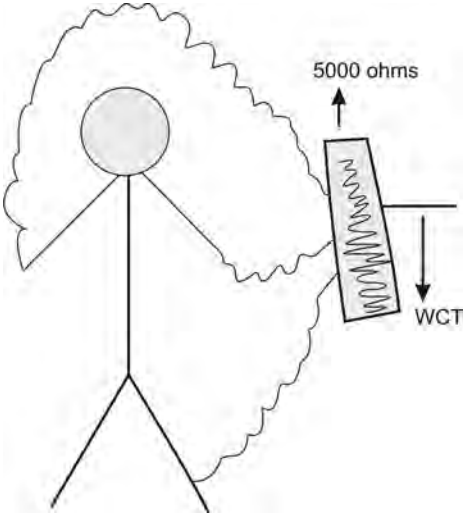


Fig. 53.3: Wilson's central terminal (WCT)

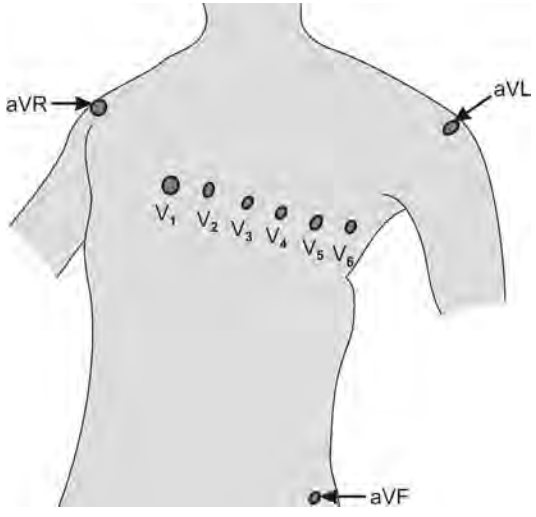


Fig. 53.2: Unipolar ECG leads

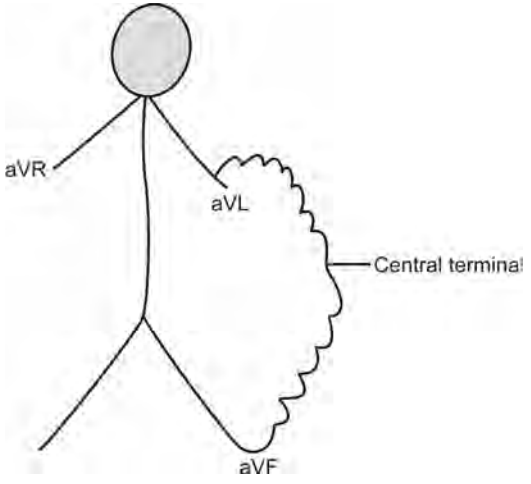


Fig. 53.4: Goldberger technique

Intracardiac Leads

Exploration of cavities by introduction of catheter on which exploratory electrode is mounted and the circuit is completed by Wilson's central terminal. The record thus obtained is *intracardiac electrogram.*

Esophageal Electrode

An esophageal electrode is sometimes used to study atrial activity. The electrode is inserted in a catheter and swallowed and each esophageal lead is identified by letter E followed by the number of centimeters from teeth, for example E 35.

Einthoven's Law

From mathematical analysis of his triangle Einthoven deduced that height of R in lead II should be equivalent to algebraic sum of the height of R in lead I and III (Fig. 53.5).

Normally, ECG is obtained by successive recording of 3 leads and not simultaneous therefore, results are only approximate.

Deflection caused by action current of the heart in each lead will correspond in size to the projection of the arrow on each side of the triangle.

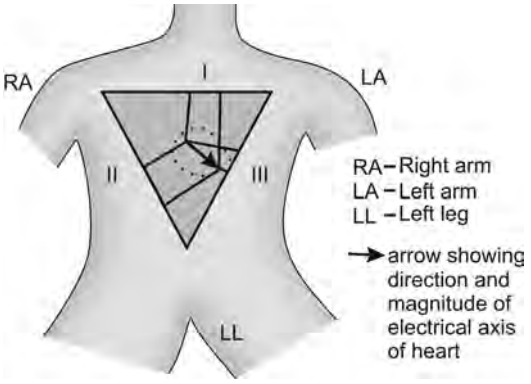


Fig. 53.5: Einthoven triangle and electrical axis of the heart

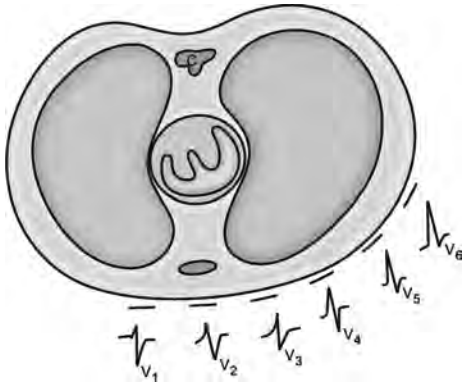


Fig. 53.6: ECG in V_1-V_6 chest leads

Precordial Lead Records in Normal Subjects

When electrode is placed on right side of the precordial area, record shows a *small R* wave, which soon reaches peak, followed by deep S. It is due to the fact that the excitatory state spreading outward reaches surface of the right ventricle before it does that of the left ventricle because of thick muscle.

Leads from left side show tall R with late peak, frequently preceded by small Q and followed by small S (Fig. 53.6).

Leads in the center of precordium is midway.

The ECG gives Information About

1. Spread of excitation process to different chambers of heart.
2. Origin of impulse and spread of impulse along the normal or abnormal path.
3. Correct diagnosis can be established in cases of abnormal rhythm and myocardial damage.

   No information about mechanical vigor of the heart can be obtained from ECG.

CARDIAC VECTOR OR CARDIAC AXIS

Vector is an arrow that points in the direction of the current flow, with the arrow point in

the direction and length of the arrow indicates the magnitude of electromotive force.

Normal direction of mean QRS vector is –30 to + 110 (Fig. 53.7).

Calculation of Cardiac Axis or Vector

1. It is assumed that 3 electrode locations, in standard limb leads, form the points of an equilateral triangle (Einthoven's triangle) and heart lies in the center of the triangle (Fig. 53.8).
2. Then electrical axis of heart or an approximate mean QRS vector can be calculated as follows:
   i. In lead I, if the height of R is + 7 mm and the depth of largest negative is— 2 mm then (+7 –2) +5 mm is the difference.
   ii. Draw a line of 5 mm from the midpoint on the line of the triangle representing lead I towards positive pole.
   iii. Drop a perpendicular from the midpoint of the line and from a point 5 mm away from midpoint towards the center of the triangle.

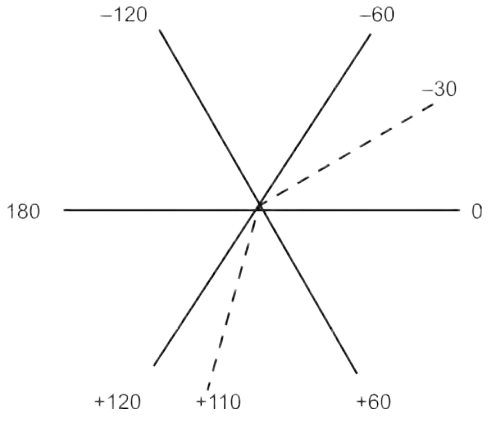


Fig. 53.7: Normal direction of mean QRS vector or electrical axis is –30 to + 110

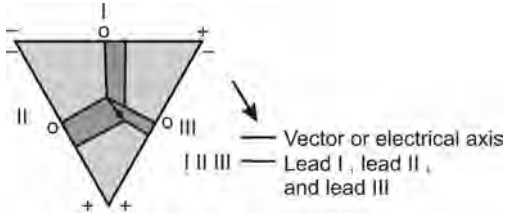


Fig. 53.8: Einthoven triangle and calculation of electrical axis or vector

   iv. Repeat the same procedure for lead II and lead III.
   v. Draw an arrow from the point where perpendiculars from the midpoint intersect to the point where perpendiculars from height of R (minus the depth of largest negative wave) intersect.

This arrow is the vector—showing the direction of electrical axis and magnitude of electromotive force.

Abnormal ECG

Broadly are of four types:
1. Axis deviation
2. Heart block
3. New rhythm centers
4. Myocardial infarction (MI).

Right and Left Axis Deviation (Figs 53.9 and 53.10)

1. Tall R in lead I and deep S in lead III suggest deviation of main electrical axis of heart to the left. It is called *left axis deviation* (Fig. 53.10). For example, in hypertrophy of left ventricle, which may be due to hypertension or aortic incompetence.
2. Deep S in lead I and tall R in lead III suggest *right axis deviation (Fig. 53.9).* For example in hypertrophy of right ventricle which may be due to mitral stenosis or emphysema.

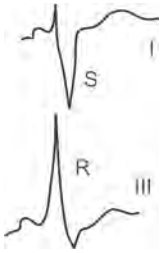


Fig. 53.9: Right axis deviation

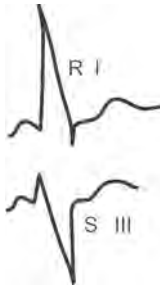


Fig. 53.10: Left axis deviation

HEART BLOCK

Sinoatrial Block

If there is block in substance of node, whole heartbeat is lost. Rarely every alternate beat is lost. Then the heart rate may be 30/min and there is profound slowing of heart rate. This condition is at once unmasked by exercise. Overdosage of digitalis produces this disease as one of the actions of digitalis is stimulant effect on vagus.

AV Block

Partial heart block—conduction is not completely interrupted.

1. *Delayed conduction 1st degree block:* PR interval is increased more than 0.2 sec PR interval may be increased gradually finally one beat is dropped. It is known as Wenckebach's phenomenon.
2. *Dropped beats—2nd degree block:* Two atrial beats followed by one ventricular beat. In ECG 2 P are followed by 1 QRS complex.

   Rarely, there is 3:1, 4:1—block which means 3 Ps are followed by 1 QRS and 4 Ps are followed by 1 QRS complex.

Complete Heart Block

P and QRS complex bear no relationship. Ventricles beat with slow and independent rhythm dictated by a portion of the conducting tissue below the block. Atria and ventricles beat at a different rhythm.

- Rhythm of ventricles is idioventricular rhythm.
- Block may be:
  i. Due to disease of AV node—AV nodal block, or
  ii. Due to block in the conducting system —Infranodal block.
- In AV nodal block, remaining nodal tissue becomes pacemaker and idioventricular rhythm is of about 45/min.
- Whereas in infranodal block the idioventricular rhythm is slower—35/min.
- Cause of the block may be:
  - Excessive vagal stimulation
  - Or digitalis overdose
  - Or asphyxia

  } Block is temporary
  - Coronary occlusion (supplying the bundle of His)—results in permanent block.
  - In some cases, heart rate can be less than, 15/min, which results in cerebral ischemia and fainting—Stokes-Adams syndrome.

Bundle Branch Block

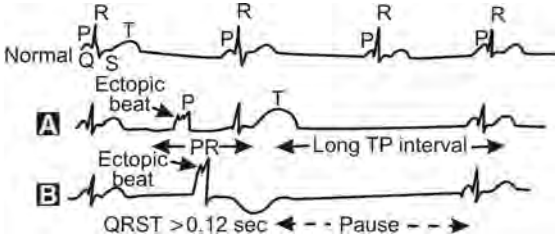
If the block is in one of the branches of bundle of His the excitation process cannot be

propagated directly to one of the ventricles, although it is satisfactorily conducted to other ventricle. The excitation process has to make a detour through ventricular muscle on the affected side to regain bundle tissue below the site of block.

- QRS is prolonged, exceeds 0.12 sec and is abnormal.
- T wave is enlarged and is in opposite direction to QRS.

New Rhythm Centers

1. *Normally SA node acts as pacemaker.* If it is destroyed or cooled *AV* node starts impulses. In such a case atria and ventricles contract simultaneously.
   i. PR interval is reduced.
   ii. P is inverted and buried in R.
2. Occasionally, spontaneous beats arise anywhere in the substance of *atria* or *ventricles.*
   i. These are known as *ectopic beats, premature beats or extrasystoles (Figs 53.11A and B).*
      a. Atrial ectopic beat
         – PR is prolonged
         – P is abnormal
         – And it is followed by a pause.
      b. Ventricular ectopic beat
         – Abnormal ventricular complex
         – Which is not preceded by P and is followed by pause.



Figs 53.11A and B: Extrasystoles: (A) Atrial, (B) Ventricular

Ectopic Rhythm or Tachycardia

Sometimes ectopic focus—initiates heart beat for several seconds, minutes or hours. It is called ectopic rhythm or tachycardia.

1. Abnormal heart action, which appears abruptly and disappears abruptly is known as paroxysmal tachycardia.
2. It is of two types (Fig. 53.12).
   i. Paroxysmal atrial tachycardia, and
   ii. Paroxysmal ventricular tachycardia.
   iii. *In atrial tachycardia* – rate of discharge of atrial impulses is up to 200/min. Atria respond by contraction. All atrial impulses travel to ventricular. All intervals shorten (such as PR, TP).
   iv. *In ventricular tachycardia*—rate of ventricular contraction is up to 200 beats per minute. The QRS complexes are highly polymorphic, resemble ventricular extrasystoles P waves without relation to QRS complexes are seen.

Causes of ectopic beats or rhythm are:

i. Local area of ischemia.
ii. Small calcified plaques.
iii. Toxic irritation of Purkinje system such as by nicotine, caffeine, etc.

Flutter and Fibrillation (Fig. 53.13)

1. *In atrial flutter* (may be paroxysmal) the atrial rate is so rapid (200-350/min), that the atrial repolarization is affected. As a result, each P tends to be followed by T

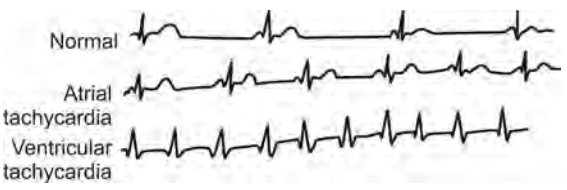


Fig. 53.12: Atrial and ventricular tachycardia

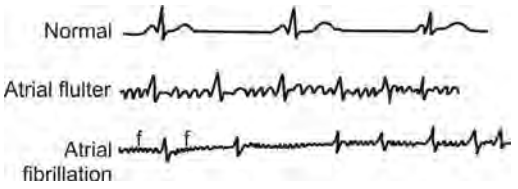


Fig. 53.13: Atrial flutter and fibrillation

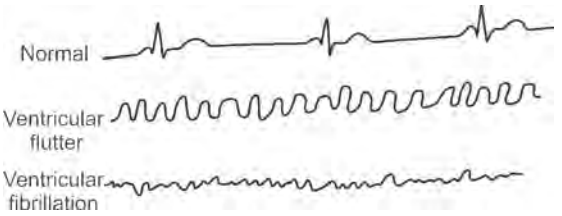


Fig. 53.14: Ventricular flutter and fibrillation

wave pointing in opposite direction giving seesaw appearance in some leads. AV node cannot transmit more than 270 impulses/min. Therefore, there is 2:1 or 3:1 block.

2. *In atrial fibrillation:* There is no coordinated atrial contraction and therefore, no P waves. There is irregular electrical oscillation giving fibrillation waves (f waves), which occur at 300-500/min. The bundle of His cannot conduct impulses at such high frequencies. The QRS complex is irregular in time with a rate of about 150 per min.

   Causes

   Flutter and fibrillation can occur due to:
   i. Mitral stenosis
   ii. Severe hyperthyroidism
   iii. Coronary heart disease.
3. *Ventricular flutter:* Rate of ventricular contractions between 200 and 300/min.
   - ECG shows large oscillations (Hair pin curves) where main and terminal deflections can no longer be differentiated.
4. *Ventricular fibrillation*: Rate of ventricular contractions between 350 to 500 per minute.
   - ECG shows irregular extremely fast small potential fluctuations in rate, rhythm, amplitude and appearance (Fig. 53.14).

     Note: It is fatal condition because fibrillating ventricles cannot pump blood effectively and circulation of blood stops causing sudden death.

Circus Movement

Circus movement—that is formation of circuit around a ring of myocardial fibers by the excitation process.

This results in flutter and fibrillation.

Sites

Where circus movement can develop:
1. The tissues joining the opening of inferior vena cava and superior vena cava.
2. Around the AV valves.

Mechanism of Development of Circus Movement (Fig. 53.15)

There are two mechanism:
1. Depolarization of a ring of cardiac muscle: Normally the impulses spreads in both direction in a ring and the two impulses cancel when they meet on opposite side.
   i. If there is a transient block on one side (due to slowed conduction), the impulse reaching here earlier via a shorter root will find this area refractory and dies off.
   ii. But the impulse, which goes around, i.e. by longer root and reaches here

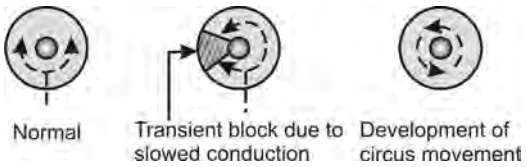


Fig. 53.15: Development of circus movement

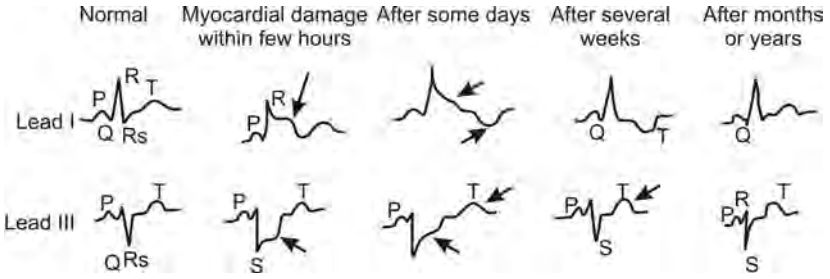


Fig. 53.17: ECG changes following anterior wall MI

late, finds this area no longer refractory. It will pass this area and continue to circle indefinitely producing circus movements.

2. Retrograde conduction due to transient block in bundle of His (Fig. 53.16). Transient block due to slowed conduction in parts of conduction pathways prevents normal conduction and then this area is invaded from below. The area above the block is fully recovered and no longer refractory producing retrograde conduction causing atrial depolarization resulting in atrial beat (atrial echo beat).

Myocardial Infarction

Clinically localized cardiac ischemia may result from the occlusion of coronary vessels by thrombus or embolus. Prolonged ischemia or severe ischemia causes aseptic necrosis of myocardium. It is called myocardial infarction.

These myocardial lesions give rise to distinctive ECG patterns as the myocardial cell membrane becomes leaky as far as potassium and sodium ions are concerned in resting state, i.e. diastole, there is increased K^+ efflux and increased Na^+ influx.

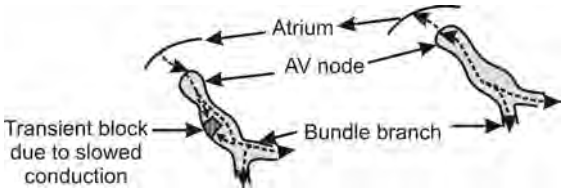


Fig. 53.16: Retrograde conduction in bundle of His

Anterior Myocardial Infarction (Fig. 53.17)

1. Normally, ECG is isoelctric between the end of S and beginning of T wave but shortly after myocardial damage ST is elevated in lead I and ST is depressed in lead III.
2. After some days—deviation of ST decreases and T wave abnormalities appear.
3. After several weeks ST becomes normal and T wave changes remain alone.
4. After months or years they too return to normal.

Posterior Myocardial Infarction

ECG shows:

1. ST elevation in lead III and ST depression in lead I.
2. T is upright in lead I and inverted in lead III.

CHAPTER

54

Coronary Circulation

ANATOMY—RIGHT AND LEFT CORONARY ARTERIES

Right and left coronary arteries supply myocardium (Fig. 54.1). Each arising from the aorta immediately above the semilunar valves. Two coronary arteries encircle the heart as *crown* encircles the head. Therefore, named as *coronary arteries.*

Left Coronary Artery

Divides into:

1. Anterior interventricular branch, which descends in anterior interventricular groove to inferior margin of the heart, then turns round and occupies the posterior interventricular groove.
2. *Circumflex branch:* It descends to the left margin.

Right Coronary Artery

It runs in right part of atrioventricular sulcus to the inferior border. It gives several descending branches.

1. Posterior interventricular branch descends in posterior interventricular groove and meets anterior interventricular branch.
2. *Transverse branch*—runs in atrioventricular sulcus and meets circumflex branch.

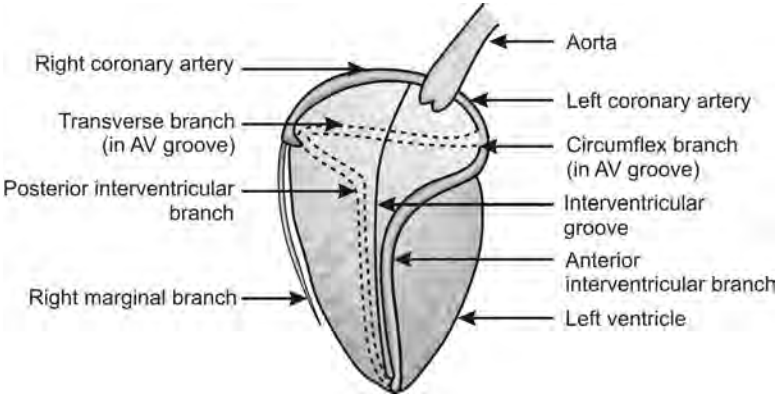


Fig. 54.1: Right and left coronary arteries and its branches

3. *Right marginal branch:* Subdivisions of main artery descends in direc tion of apex to give off myocardial branches which coarse directly into the muscle. Smaller arteries branch perpendicularly to penetrate wall of myocardium and supply entire thickness.

In human heart, the supply is 1 capillary per fiber and roughly there are 750 capillaries sqm in superficial layer and 1100/ capillaries per square meter in deeper layer.

CARDIAC VEINS

Veins accompany arteries in sulci and lie superficial to them.

There are two venous systems:

1. Superficial (beneath epicardium)
2. Deep venous system.

Superficial System of Veins include (Fig. 54.2)

1. *Coronary sinus:* Lies in coronary sulcus at the back of the heart. It opens in right atrium.
2. *Great cardiac vein*: It accompanies left coronary artery and opens in coronary sinus.
3. *Anterior cardiac vein*: Opens directly into right atrium.

Deep Venous System Consist of (Fig. 54.2):

1. Arterioluminal veins—arise from coronary arteries and end in cavities.
2. Arteriosinusoidal veins—arise from coronary arteries and form sinuses.
3. Thebesian veins—arise from capillaries and small veins and empty directly into ventricle.

Eighty percent of left coronary artery drains in coronary sinus. 80-90% of right coronary artery drains via anterior cardiac vein into right atrium.

Important Points

1. Both ventricles receive blood from both coronary arteries.

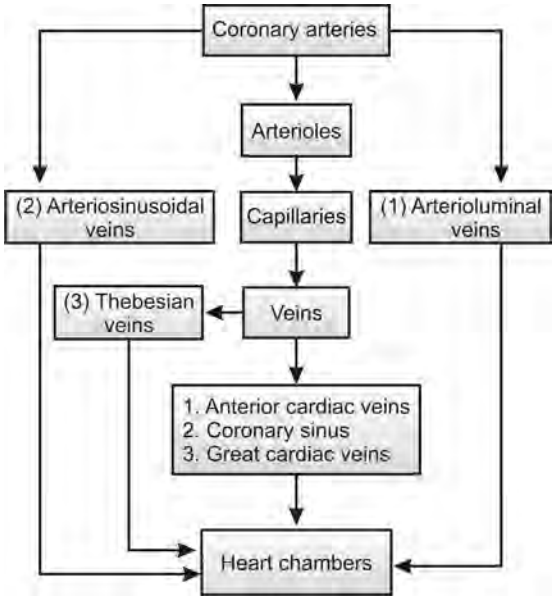


Fig. 54.2: Cardiac veins and their drainage

2. Atria receive blood from corresponding coronary arteries.
3. Left ventricle is supplied maximally because it does maximum work.
4. Fifty percent of hearts have right coronary predominance (in some books 90%).
5. Thirty percent of hearts have balanced supply—These are least vulnerable to cardiovascular disease, and
6. Twenty percent of hearts have left coronary predominance.

Anastomosis and Collateral Circulation

1. *Anastomosis provides byroute:* Through which blood can travel when main branch is occluded.
2. Only a few anastomosis exist between large branches of coronary arteries. This is a fact of life and death importance, but many anastomosis are present in small branches.
3. Collateral channels are blood vessels usually small which allow the blood to flow

from one artery to another if an artery becomes obstructed.
4. Most hearts with occluded coronary artery branch die within a number of hours. If they survive the first few hours, then within 12 hours collateral flow starts, doubles in 2 days and in 3-4 weeks it becomes 40-100%. Therefore, patient recovers from various types of coronary occlusion.
5. Minor anastomosis are present with pericardial and other outside vessels.

Normal Values

1. Normal coronary blood flow in resting human being is 225 ml/min or 4-5% of total cardiac output.
2. Left coronary flow is 70-85 ml/100 gm/min.
3. Coronary artery – coronary sinus – arteriovenous difference is 12 ml (range is 13-14 ml).
4. Myocardial oxygen usage at rest is 7-9 ml/100 gm.

Methods of Measurement of Coronary Blood Flow

In human beings.

By Fick principle using inert gas washout technique-nitrous oxide was used previously (Kety method) (Now hydrogen or helium is used).

Blood flow per minute =

$$\frac{\text{Amount of inert gas taken up in one min}}{\text{Arteriovenous difference of inert gas}} \times 100$$

Nitrous Oxide Method

1. Subject is asked to breathe 15% mixture of Nitrous oxide in air for 10 minutes. Samples of arterial and coronary sinus venous blood are taken (by catheterization of venous system) successively at fixed interval for 10 minutes (equilibrium time).
2. The gas is slowly eliminated by organ under study and washout rate is proportional to blood flow.
3. Nitrous oxide taken up by cardiac muscle per 100 gm = Venous concentration reached × partition coefficient of N_2O after equilibrium.
4. Integrated arteriovenous difference is calculated. Then coronary flow/100 gm/min can be calculated.

   Coronary blood flow/100 gm/min =

$$\frac{100\ V_t + S}{{}_0\int^t (A - V)dt}$$

Where ${}_0\int^t (A - V)dt$ is integrated arteriovenous difference over 10 minutes (dt)

Vt = Coronary sinus venous concentration of N_2O after equilibrium is reached between blood and myocardium in time t.

S = Partition coefficient for N_2O between blood and myocardium in time t

${}_o\int^\tau$ = Integral from zero to t (0 being lower limit and t upper limit).

Radionucleotide Utilization Technique

Radioactive tracers that can be detected with γ scintillation cameras over the chest have been used to study regional blood flow in heart and to detect areas of ischemia and myocardial infarction.

For example:
1. *Thallium 201* (201 TI) is given intravenously for 10 - 15 minutes and 201 TI distribution is proportional directly to myocardial blood flow, and areas of ischaemia can be detected.
2. Radiopharmaceuticals like *technetium Tc 99m stannous pyrophosphate* (99m Tc-PYP) are selectively taken up by infracted areas

and make infarcts stand out as hotspots on scintiscans of the chest.

Coronary Angiography

1. Radiopaque contrast medium is first injected into coronary arteries. X-rays are used to outline their distribution.
2. This can be combined with measurement of 133 Xe washout to provide detailed analysis of coronary blood flow. Angiographic camera is replaced with multiple crystal scintillalion camera and 133 Xe washout is measured.

IN ANIMALS

1. *By electromagnetic flow meters:* It can be implanted round the main left coronary artery or round its circumflex branch—flow per minute of left coronary can be calculated. Another advantage is it gives physical flow of blood also
2. Coronary sinus can be catheterized.

Phasic Flow in Coronary System

Heart is a muscle like skeletal muscle. Therefore, it compresses its blood vessels when it contracts. Throughout the cardiac cycle coronary blood flow undergoes characteristic phasic variation. Flow varies between the systole and the diastole, which reflects balance between driving force or perfusion pressure and impedance to the flow brought about by contraction of the ventricle.

1. During systole inner half (subendocardial) portion of myocardium receives less blood or no blood at all as compared with outer half of myocardium.
2. Left ventricle being thicker the pressure inside left ventricle is greater than aortic pressure *during systole.*
    i. Therefore, flow occurs in subendocardial portion of left ventricle only during diastole and not during systole.
    ii. Therefore, this region is more prone to ischemic damage and is most common site for myocardial infarction.
        a. *In hypertrophied heart*: Bulk of fibers is increased and it is more prone to ischemic necrosis, because intercapillary distance is more and efficiency of oxygen supply is decreased.
        b. *Aortic stenosis:* The pressure in left ventricle must be much greater than aorta to eject blood, therefore coronary vessels are severely compressed during systole. Therefore, such patients are prone to develop myocardial ischemia.
3. *Right ventricle* is less thick, therefore less compression of blood vessels takes place and blood flow is not reduced to a greater extent during systole.
4. The rise in venous pressure in conditions such as congestive heart failure *reduces* coronary flow because it decreases effective coronary perfusion pressure.

Phasic Flow in Left Coronary Artery (Fig. 54.3)

1. *In isometric contraction phase:* Flow in left coronary declines sharply, many times this flow is reversed, because of myocardial tissue pressure rising steeply and aortic pressure head is minimal or lowest.
2. *When ejection phase* of the ventricular systole occurs, improvement of aortic pressure takes place and a sharp peak in flow occurs which quickly subsides, due to throttling effect of high intramural myocardial pressure in contraction period.
3. *In isometric relaxation phase*: Coronary flow increases significantly, peak occurs at early

diastole and then flow declines progressively.

As a whole, greater flow occurs during diastole. At rest systolic component of left coronary artery flow is usually less than 25% of that received during diastole.

Phasic Flow in Right Coronary Artery (Fig. 54.3)

Right ventricular pressure is much lower than left ventricle and intraluminal tensions in right ventricle even during systole never become great enough to shut down the flow. In right coronary artery the pattern of flow roughly resembles the prevailing aortic pressure curve.

Regulation of Coronary Blood Flow

Heart extracts a greater percentage of available oxygen from arterial blood than any other organ. Even at rest about 75% of oxygen is extracted. Heart has little capacity for storing oxygen or acquiring oxygen debt. Therefore, increased demands of oxygen must be met by increasing coronary blood flow.

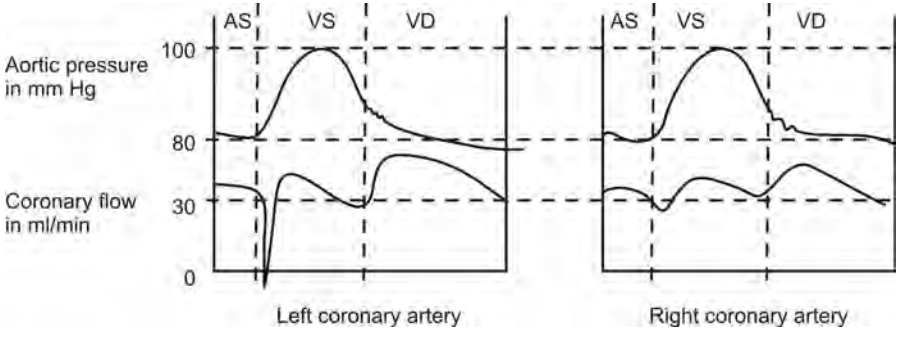
Caliber of coronary artery and consequently the rate of coronary blood flow is influenced by mainly:

1. Pressure changes in aorta
2. Chemical factors
3. Neural factors.

Coronary Circulation shows Considerable Autoregulation

1. *Aortic blood pressure:* Blood pressure in aorta is the driving force for coronary perfusion and it is the major factor for regulation of blood flow through coronaries.
2. *Hypoxia:* Whenever myocardium suffers from hypoxia anaerobic metabolites are produced—most important of them are:
   i. Adenosine nucleotides and adenosine (adenosine diffuses in ECF).
   ii. K^+ ions
   iii. H^+ ions
   iv. Prostaglandins.

   Which acts as vasodilators.
3. *CO_2 excess*— act as feeble vasodilator.
4. *Increased resistance through aorta or pulmonary artery* heart has to work more and produces more metabolites causing vasodilatation.
5. *Heart rate*: When heart rate increases diastole shortens and since peak flow occurs during diastole one might expect the CBF falls, but



(AS = Atrial systole, VS= Ventricular systole and VD = Ventricular diastole)

Fig. 54.3: Blood flow through coronary arteries during different phases of cardiac cycle

in increased heart rate metabolic activity also increases which causes increased formation of metabolites and the coronary blood flow increases (Fig. 54.4).

6. *Neural control:* Stimulation of autonomic nerves affects the coronary blood flow in two ways:

   Directly: Due to direct effect of transmitter substance.

   Indirectly: Due to secondary change in heart activity.

   Stimulation of sympathetic nerves: Increases the coronary blood flow directly as it causes vasodilatation and indirectly as it increases the activity of heart and oxygen consumption.

   Stimulation of vagus: Decreases coronary blood flow according to some physiologists but if it causes cardiac arrest coronary blood flow increases.

7. *Hormones*
   i. Increased secretion of thyroid hormones cause increased myocardial oxygen consumption and increases coronary blood flow.

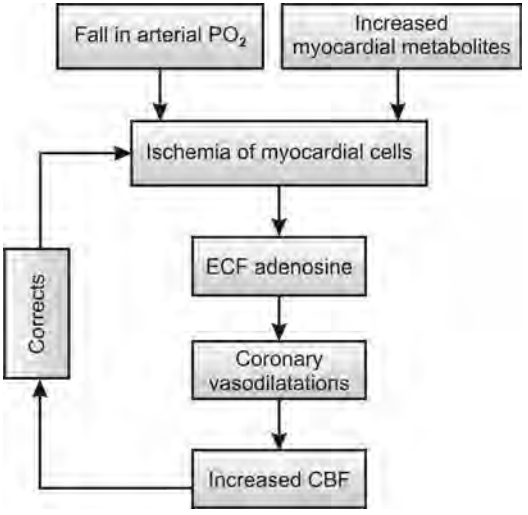


Fig. 54.4: Chemical regulation of CBF (Berne hypothesis)

   ii. Epinephrine and norepinephrine cause considerable vasodilatation. Epinephrine and norepinephrine can either have dilator effect or vasoconstrictor effect depending on presence or absence of specific receptors in blood vessels. Constrictor receptors are called α receptors and dilators receptors are called β. In coronary arteries both α and β receptors are present.

   Normally, β adrenergic responses are predominant. But when β are blocked by some drug and then epinephrine or norepinehrine is given α receptors are stimulated it causes vasoconstriction.

   In occasional animals α receptors predominate and epinephrine and norepinephrine will produce vasoconstriction of coronaries.

   iii. *Acetylcholine:* Infusion of acetylcholine causes considerable vasodilatation, acting on smooth muscles of arteries.

   iv. *Pitressin or angiotensin*: Decreases the coronary blood flow due to increased resistance to flow of blood.

8. *Drugs:* Nitrites, papaverine, aminophylline are coronary dilators and are used in agina pectoris.

   Bradykinin, kallidin and eledosin are most potent naturally occurring coronary vasodilators.

9. *Effect of exercise:* In heavy exercise coronary blood flow is increased four-fold because in exercise:
   i. Cardiac output increases five-fold and
   ii. Increased cardiac metabolic demands occur.

   The coronary blood flow becomes 300-400 ml/100 gm/min.

Coronary Artery Disease

Coronary arteries alone supply the heart which is the pump for circulation. If coronary blood vessels are diseased it produces disturbance in the function of the pump.

Coronary artery disease is one of the leading causes of death in the world.

1. *Angina pectoris:* When oxygen supply of the rhythmically contracting myocardium fails to keep pace with its oxygen requirements, *pain* is aroused.
   i. It is substernal, radiates to left shoulder, inner side of the left arm and to the angle of the jaw.
   ii. The subject knows from experience that this pain can be alleviated by coming to a dead halt, if he has been exercising.
   iii. If it is caused by emotional excitement for example rage, this pain will cut short the outburst promptly.
   iv. *Cause of pain*:
      – Nonmyelinated nerve endings in the adventitia are stimulated by anaerobic metabolites (p factors accumulates).
      – Referred pain.
   v. *Underlying cause:* Narrowing of coronary arteries by atherosclerosis.
   vi. *Vasodilator drugs:* Like glyceryl trinitrite or sodium nitrite provide relief.
2. *Coronary thrombosis:* When a thrombus occludes a branch of coronary artery, the area supplied by this branch undergoes necrosis (myocardial infarction).

It results in intense pain and shock which causes:

- Hypotension
- Nausea
- Vasoconstriction of skin blood vessels
- Sweating.

- If occluded artery is too large—death occurs due to ventricular fibrillation. Such deaths are very rapid.
- If the attack is not fatal—the area of myocardial infarction fibroses.

Diagnosis can be made by:

1. *ECG recording*: Changes in myocardial infarction are discussed in Chapter on ECG.
2. *Enzyme studies*: Damaged myocardial cells leak enzymes and isoenzymes.

Enzyme most commonly measured are:

1. SGOT: Serum glutamic oxaloacetic transaminase.
2. CPK: Creatinine phosphokinase.
3. LDH: Lactic dehydrogenase.

The release of enzymes occur in many other tissues, therefore, the enzyme studies are not specific for myocardial infarction.

CPK and LDH—have isoenzymes—they are present in heart muscle cells in higher concentration than many other organs and measurement of serum concentration of particular isoenzyme helps.

Treatment

Discreet areas of narrowing in the coronary arteries can be detected by coronary angiography and can be removed surgically or bypassed by implantation of grafts – (Coronary bypass surgery).

- *Coronary angioplasty*: It is another procedure where the block in coronary artery branch is removed by inflating a balloon inside the artery (balloon angioplasty).

Myocardial infarction is one of the medical emergencies and many times in spite of every medical effort the balance tilts towards death.

The doctor must learn to face the emergency of death with calm and philosophy. He must be able to impart his calm and philosophy to the dying patient and to his anguished relatives.

Every doctor should respect the gravity of death in whosoever it occurs because:

1. It is the way of all flesh.
2. In due course it is going to touch him and those near and dear to him.
3. It is the illustration of limitation of science.

He can achieve this by developing qualities and requisites, which cannot be ascertained or detected by scientific methods.

CHAPTER

55

Regional Circulation

INTRODUCTION

Circulation through a particular organ is directly proportional to the degree of local activity.

It is adjusted on two lines:

1. By regulating the general circulation.
2. By adjusting the local blood vessels.

Generally, the vasodilatation in an active part is accompanied by vasoconstriction in the other inactive part. In this way blood is shifted from inactive to active region without any fall of general blood pressure. Following are examples of regional circulation:

1. Coronary circulation
2. Cerebral circulation
3. Pulmonary circulation.

CEREBRAL CIRCULATION

Cerebral circulation is very important because arrest of cerebral circulation leads to: (i) unconsciousness within few seconds, and (ii) irreparable damage of brain tissue within few minutes.

Brain cannot acquire oxygen debt like muscle therefore brain must have adequate supply of oxygenated blood all the time.

Anatomical Consideration

- Blood flows into the brain through:
  - i. Two internal carotid arteries, and
  - ii. Two vertebral arteries.

  Supply entire brain. Except for a small contribution from anterior spinal artery to medulla.

  a. Two vertebral arteries combine to form basilar artery of the hindbrain, which divides into two posterior cerebral arteries. In human beings, small fraction of total arterial flow is carried by vertebral arteries.
  b. Each internal carotid artery divides into middle and anterior cerebral arteries.
  c. Intercommunicating arteries unite the six arteries on two sides forming circle of Willis (Fig. 55.1).
  d. From this, various branches arise, which supply various regions of brain.
  e. They anastomose freely with each other and break up into numerous capillaries, which drain into veins.

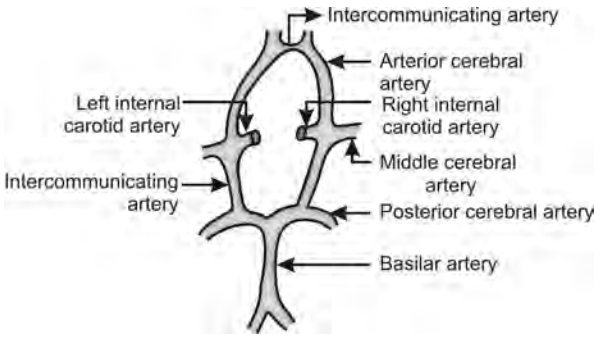


Fig. 55.1: Circle of Willis

f. The veins form internal and external venous plexus and ultimately drain into large cerebral sinuses between the folds of dura, namely-

i. Superior sagittal sinus
ii. Inferior sagittal sinus
iii. Cavernous sinus
iv. Straight sinus

All unite to form two transverse sinuses and they are drained by two internal jugular veins

Part of venous drainage is through paravertebral venous plexus and anastomosing branches with pterygoid and ophthalmic venous plexuses.

Points of Importance

1. Although there is extreme collateral circulation in human brain, it cannot maintain circulation when a large branch is occluded.
2. Gray matter has rich blood supply than white matter because metabolic rate of gray matter is more.
3. Brain being precious is encased in bony cranial cavity, therefore it cannot expand and contain large quantity of blood. Therefore, normal volume of blood contained in brain is constant. This is Monro-Kellie doctrine and arteriolar dilatation is accompanied by reduction in venous content.
4. Cerebral blood vessels have a number of unique features:
   i. Capillaries in brain substance are non-fenestrated.
   ii. There are tight junctions between endothelial cells that do not permit passage of substances, which pass through the junction between endothelial cells in other tissues.
   iii. There are few vesicles in endothelial cytoplasm, therefore there is little vesicular transport.
   iv. The brain capillaries are surrounded by end feet of astrocytes (Fig. 55.2). These end feet are closely applied to basal lamina of the capillaries but they do not cover the entire capillary wall.

Innervation

1. Sympathetic supply comes from cervical sympathetic ganglia, which supply mainly pial arteries and arterioles.
2. Parasympathetic supply comes from facial nerve via great superficial petrosal nerve and vagus.
3. Vessels in brain tissue are innervated by intracerebral noradrenergic neurons that have their cell bodies in brainstem.
4. Myelinated fibers are probably sensory in function since touching or pulling cerebral blood vessels causes pain.

Note: Sympathetic and parasympathetic supply to cerebral blood vessels is not much.

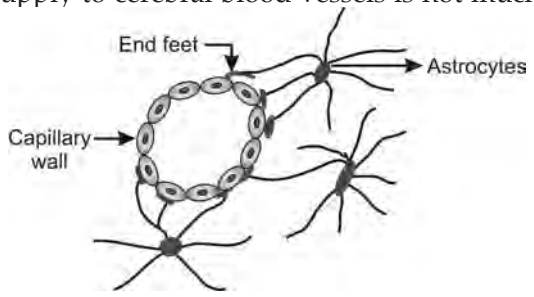


Fig. 55.2: Capillary in brain surrounded by astrocytes

Therefore, whenever there is generalized vasoconstriction cerebral blood flow is not much reduced.

BLOOD-BRAIN BARRIER

60-70 years ago it was first demonstrated that when acidic dyes such as trypan blue are injected into living animals all the tissues are stained except brain and spinal cord. To explain this the existence of blood-brain barrier was postulated, because of which the brain enjoys remarkably *protected* environment.

Penetration of Different Substances in Brain

It was further demonstrated that only water, CO_2 and O_2 cross-cerebral capillaries with ease, but exchange of other substances is low.

In general the rapidity with which the substances penetrate brain tissue is inversely related to their molecular size and directly related to their lipid solubility:

1. Water soluble compounds pass slowly, e.g. *glucose*.
2. There is relatively slow penetration of urea in brain and CSF.
3. *Bile salts* and catecholamines do not enter *adult brain* in more than minute amounts.
4. *Proteins* cross the barrier to a *limited extent*.
5. There is H^+ ion gradient between brain ECF and blood, pH of brain ECF is 7.33 and that of blood is 7.40.

Conclusion

It must be noted that no substance is completely excluded from the brain and the important consideration is the rate of transfer of substance.

Development of Blood-brain Barrier

Cerebral capillaries are much permeable at birth than adulthood. Blood-brain barrier develops during the early years of life. In severely jaundiced infants bile pigments penetrate into nervous system and in presence of asphyxia damage the basal ganglia (Kernicterus), whereas in adult jaundiced patients the nervous system is unstained and not directly affected.

Functions of Blood-brain Barrier

It functions to maintain the constancy of environment of neurons in CNS. These neurons are so dependent upon the ionic composition of the fluid bathing them; that even minor variations have far reaching consequences.

Therefore, additional defence has been evolved to protect them.

Clinical Implication

1. The physicians must know the permeability of blood-brain barrier to drugs. So that they can treat the diseases of nervous system intelligently.
2. Blood-brain barrier breaks down in areas of brain that are irradiated, infected or sites of tumors. The breakdown makes it possible to localize tumors.

Substances like radioactive iodine, labeled albumin penetrate normal brain very slowly but they enter rapidly into tumor tissue making tumors stand out as an island of radioactivity surrounded by normal brain.

DETERMINATION OF CEREBRAL BLOOD FLOW

1. By Fick principle using N_2O (Nitrous oxide). Name of the method is Kety method. Person is asked to inhale mixture of air and 15% N_2O for 10 minutes. During this several samples of blood are collected from internal jugular vein and peripheral artery at frequent interval (Fig. 55.3).

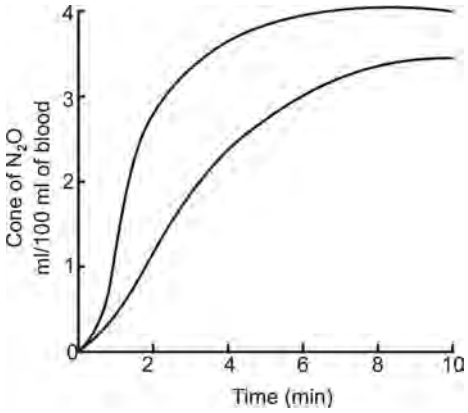


Fig. 55.3: Measurement of cerebral blood flow N_2O technique

N_2O content of arterial and venous blood is determined cerebral blood flow per minute is determined from the arterio-venous difference of N_2O and the partition coefficient for N_2O between blood and brain. Results are recorded in milliliters per 100 gm of brain tissue per minute.

Cerebral blood flow in ml

$$\text{per 100 gm/min} = \frac{100 \times VuS}{\int_{o}^{u} (A \quad V)\,dt}$$

Vu = venous concentration after equilibrium is reached in brain tissue during time u

S = partition coefficient for N_2O between blood and brain tissue.

$\int_{o}^{u} (A \quad V)$ = integrated arteriovenous difference of N_2O during time o to u.

dt = temperature.

Disadvantages

a. This technique can be used in steady state and is not for the measurement of rapidly changing blood flow.
b. It measures average total value of cerebral blood flow during 10 min equilibrium period and gives no information about the relative blood flow in various parts of the brain.
2. It is likely that blood flow is constant but there is regional difference in blood flow in different parts of the brain. Such changes are difficult to detect, but blood flow through cerebral cortex can be measured through intact skull by injecting – γ ray emitter Xe^{133} into internal carotid artery and determining its clearance rate with scintillation counter placed over the skull. With Xe^{133} –
   a. Verbal test increases blood flow in frontal region,
   b. Visual task increases blood flow in parietal and frontal region, and
   c. Reading increased blood flow in post central area and other areas.
3. Glucose is almost the only substrate for cerebral oxidation metabolism. Radioactive glucose cannot be used to determine increased activity of a particular part of brain because it does not remain sufficiently longer to be detected. Therefore, 2 deoxy D [14_c] glucose is used.

Rates of blood flow in various structural components of the brain parallel the local rates of glucose consumption and both rates change in response to local changes in function.

Normal Values

1. Normal cerebral blood flow = 54 ml/100 gm of brain tissue/min (range 50-55 ml)
2. Normal weight of adult brain = 1400 gms (average)
3. Blood flow/min = 750 ml or 15% of cardiac output
4. Oxygen extraction rate = 6.2 ml% (arterial O_2 19 ml% - jugular O_2 12.8 ml%) (Oxygen extraction rate is high (in other tissues it is 4-5% in resting condition).

5. BP in large cerebral artery = 100 mm Hg systolic and 65 mm Hg diastolic; 30-50 mm Hg in capillaries.

Factors which Determine Cerebral Blood Flow

The main factors that determine the cerebral blood flow are:

1. Driving force or perfusion pressure = difference in mean arterial pressure and internal jugular pressure.
2. Cerebrovascular resistance:
   Cerebral blood flow =

$$k \frac{\text{Driving force}}{\text{Cerebrovascular resistance}}$$

Kety has shown correlation between arterial blood pressure and cerebral blood flow – only when BP falls below 70 mm Hg cerebral blood flow will reduce proportional to fall of pressure, above this level cerebral blood flow is governed by vascular tone. Above 70 mm Hg, there is autoregulation blood flow up to 140 mm Hg. Autoregulation is seen when PCO_2 and PO_2 are maintained near normal.

1. CO_2 is powerful factor that affect the cerebral blood flow
   - Increase in PCO_2 causes dilatation of cerebral blood vessels and decrease in PCO_2 causes vasoconstriction of cerebral blood vessels.
   - *For example*, vigorous hyperventilation for 1 minute decrease PCO_2 to 15 mm and (a) dizziness appears because of vasoconstriction of cerebral blood vessels and (b) blurring of vision and narrowing of peripheral field appears because of vasoconstriction of retinal blood vessels.

     Retinal blood vessels are mirror image of cerebral blood vessels.
2. *O_2 lack* - increases cerebral blood flow by vasodilatation
   - Decrease in PO_2 by 75% increases cerebral blood flow by 40%.
   - Hyperbaric oxygen (i.e. O_2 administration under pressure) causes increase in PO_2 and vasoconstriction of cerebral blood vessels.
3. H^+ ion concentration – causes parallel changes like CO_2.
4. Cerebrovascular circuit is relatively unaffected by vasoconstrictor sympathetic nerves.

Maximum cervical sympathetic stimulation – decreases cerebral blood flow by 20%, because cerebral blood vessels are less innervated by sympathetic nerves.

Thus cerebral blood flow is most sensitive to PCO_2, which maintains cerebral blood flow according to the metabolic needs. When metabolism increase, PCO_2 increases and cerebral blood flow will increase to wash out CO_2. For example, in intense cerebral activity (firing of epileptic focus resulting in convulsions) there is increased metabolism and PCO_2 is increased. The cerebral blood flow increases proportionately.

Other Factors which Influence CBF (Cerebral Blood Flow)

1. *Increased intracranial pressure:* Cerebral blood flow is affected by intracranial pressure as well as pressure of cerebrospinal fluid. If any of these increase, it decreases blood flow by compression.
2. *Diet*: As against general belief – studies show that diet has no relation with cerebral blood flow.
3. *Posture*: Tilting head by 20° from horizontal position causes no change in

blood flow, but if tilting is of 90° from horizontal position, there is fall of cerebral blood flow.

4. *Sleep:* Naturally induced sleep causes vasodilatation therefore cerebral blood flow increases.
5. Exercise has no effect on cerebral blood flow.
6. *Age:* Cerebral blood flow is more in younger age group (1st decade of life). After puberty cerebral blood flow decreases. Then in elderly, cerebral blood flow further decreases.
7. *Mental activity*: Cerebral blood flow does not increase with mental activity or anxiety but there may be local increase in blood flow.

CHAPTER

56 Pulmonary Circulation

ANATOMICAL CONSIDERATIONS

1. Quantity of blood flowing through the lungs is equal to that flowing in systemic circulation. The pulmonary artery and its branches have certain peculiarities therefore they can accommodate large stroke output:
   i. Pulmonary artery is thin walled (wall is 1/3 of aorta).
   ii. Pulmonary arterial branches are very short.
   iii. Pulmonary arteries, even the smaller arteries and arterioles have much larger diameter than their counterparts in systemic arteries.
   iv. They are thin and distensible.
   v. Pulmonary veins are also short and distensible.
2. Blood enters lungs through:
   i. Right and left branches of pulmonary artery serve two functions: (a) carries venous blood from right heart for oxygenation and (b) carries nutrition for pulmonary tissue.
   ii. *Bronchial artery:* Arises from aorta and carries oxygenated blood and nutrition for (i) bronchi and bronchiole, and (ii) supporting tissue, connective tissue speta, etc. and then is drained in pulmonary vein. Therefore, output of left ventricle is slightly greater than output of right ventricle.

   Pulmonary arteries break into wide arterioles and network of large capillaries and there are multiple anastomosis. So each alveolus sits in a capillary basket, which surround the alveolus, where gaseous exchange takes place.

   The capillaries join to form venules and veins which form 4 veins. These 4 veins carry oxygenated blood to left atrium. These veins are short but are as distensible as systemic veins.
3. *Lymphatic channels* are more abundant in the lungs than any other organ. They extend in supporting tissues of lungs. They arise in perivascular and peribronchial spaces and extend to hilar region.

   Ultimately they are drained in right lymphatic duct.

   They serve two main functions:
   1. Particulate matter that enters the lungs is carried by them.
   2. Protein is also rapidly removed via these channels from the lung tissue and prevent edema formation.

4. *Vasomotor supply*: Nerves innervate blood vessels of lung profusely.
   i. Sympathetic from upper thoracic segments
   ii. Parasympathetic from vagus—Normally stimulation of vagus causes slight vasodilation.

   Stimulation of sympathetic causes – slight to moderate vasoconstriction. Stimulation of sympathetic in presence of hypoxia causes more vasoconstriction.

Normal Values

1. Volume of blood in pulmonary circuit is 600 ml.
   Heart contains about 400 ml of blood.
   Therefore, there is 1 liter of blood in thorax.
2. Flow per minute
   = Right ventricular output + flow through bronchial artery.
   = 4 - 5L/min at *Rest*.
3. *Blood pressure:* The entire pulmonary system is a distensible and low pressure system.
   i. Pulmonary arterial pressure is 22/8 mm Hg (Fig. 56.1).
   ii. Mean pressure is 13 mm Hg (Range 10-15)
   iii. Pressure in left atrium 2 mm Hg (In some books 5 mm Hg)
   iv. The pressure gradient in pulmonary system is about 11 mm Hg (13 minus 2), as compared with a gradient of about 90 mm Hg in systemic circulation (where mean pressure is 100 mm Hg) (Fig. 56.1).

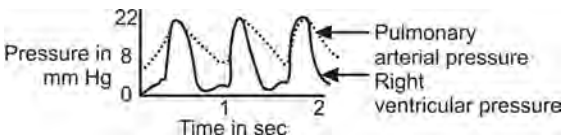


Fig. 56.1: Pressures in pulmonary system

   v. Mean pulmonary capillary pressure is about 8 mm Hg. Whereas colloid osmotic pressure of plasma (exerted by plasma proteins) is 25 mm Hg, which is retaining force for fluid. As the retaining pressure is more therefore fluid is absorbed and pulmonary alveoli are kept dry normally. It is very essential for gaseous exchange.

   When pulmonary capillary pressure is more than 25 mm Hg pulmonary edema results. For example, when there is *backward failure of left ventricle* (i.e. left ventricle fails to pump blood efficiently), because of back pressure, the pressure in pulmonary capillaries increase resulting in pulmonary congestion and pulmonary edema.

   In patients of *mitral stenosis* (mitral valves are glued and opening is narrowed) the pulmonary capillary pressure *progressively rises* and there are fibrotic changes in pulmonary vessels. Pulmonary edema is not a feature of mitral stenosis because fibrosis and constriction of pulmonary arterial vessels protect the capillaries.

Important Points

1. Pulmonary artery is thin and very distensible and offers low resistance to flow. Therefore, work of right heart is less than left and right ventricle is thin walled as compared to left ventricle.
2. Pulmonary interstitial fluid pressure is about –8 mm Hg (minus 8 mm Hg) (a) this pulls alveolar membrane towards capillary membrane, therefore distance between air and blood is reduced and easy gas exchange can take place, (b) Negative pressure pulls fluid out of alveoli and keeps them dry.

FUNCTIONS OF PULMONARY CIRCULATION

1. *Gas exchange*: Mixed deoxygenated blood passes to alveolar capillaries, gaseous exchange takes place between alveolar air and alveolar capillary. Blood gets oxygen and gets rid of CO_2.
2. *Filter:* One of the normal functions of lung is to filter out small blood clots.

   Pulmonary capillaries trap any emboli so that they do not reach heart and brain to block the blood supply.

   The normal function of trapping the small clots of emboli occur without symptoms. But when the emboli block the larger branches of pulmonary artery there is (i) rise of pulmonary arterial pressure, (ii) rapid and shallow respiration (tachypnea).

   Cause is
   1. Reflex sympathetic, vasoconstriction occurs.
   2. Reflex response to activation of vagal pulmonary deflation receptors, close to the vessel wall.
   3. Serotonin or 5 HT (5 hydroxytryptamine) is released from platelet, at the site of embolization and serotonin stimulates or sensitizes these receptors.
3. *Nutrition:* Pulmonary circulation maintains nutrition of lung tissue.
4. *Fluid exchange:* As the pulmonary capillary pressure is low there is absorption of fluid from the alveoli and alveoli are kept dry.
5. *Pulmonary reservoir:* Because of their distensibility pulmonary veins are an important blood reservoir. When a normal individual lies down pulmonary blood volume increases and on standing part of this blood is discharged in the general circulation. Because of this:
   i. Vital capacity is less in lying down position and
   ii. There is occurrence of orthopnea in heart failure.
6. *Synthesis of converting enzyme in endothelial cells which convert angiotensin I in angiotensin I I*

Control of pulmonary circulation

Depends on:

1. *Right ventricle (mechanical factor)* ˇ which depends on:
   i. Force and frequency of right ventricle, and
   ii. Degree of venous return.
2. *Resistance of pulmonary vascular bed*
   This depends on:
   i. *Lumen of blood vessels affected by:*
      a. *Oxygen lack:* Which cause vasoconstriction. Effect is through systemic chemoreceptors and also direct.
         – *CO_2 excess* which cause pulmonary vasoconstriction.

         When a bronchus is obstructed vessels supplying the poor ventilated alveoli constrict and blood is shunted to other areas. The constriction is due to a local effect of the low alveolar oxygen tension on the vessel.

         Accumulation of CO_2 leads to drop in pH and decline in pH also produces vasoconstriction.

         At high altitudes especially in children, the chronic hypoxia leads to increased pulmonary resistance, the pulmonary blood pressure increases leading to right ventricular hypertrophy and ultimately the right heart fails (Brisket's disease).

b. *Hormones:* Pulmonary arterioles are constricted by norepinephrine, epinephrine, agniotensin II and some prostaglandins.
   - They are dilated by acetylcholine.

c. *Pulmonary venules*: are constricted by serotonin, Histamine and *E. coli* endotoxins.

ii. *Conditions of lungs:* Fibrosis, emphysema and pneumonia increase pulmonary vascular resistance.

iii. *Conditions of heart:* Mitral stenosis and left heart failure decrease the venous outflow from lungs and increase pulmonary vascular resistance.

iv. *Respiration:*
   a. During inspiration pulmonary bed enlarges, capillaries get elongated and dilated by negative pressure in the thorax. Therefore, more blood enters lungs.
   b. During expiration reverse changes take place and capillary pressure increase.
   c. Pulmonary resistance increases during maximum inflation and maximum deflation of lungs.

3. *Nervous control:* Pulmonary blood vessels are plentifully supplied by sympathetic vasoconstrictor nerve fibers, and stimulation of sympathetic decreases pulmonary blood flow by 30%. Thus, mobilization of blood takes place from pulmonary reservoir.
4. *Reflex control:* Pulmonary circulation is altered by reflexes originating at baro- and chemoreceptors of sinuaortic mechanism.
   - Stimulation of baroreceptors in carotid sinus and aortic arch cause vasodilatation.
   - Stimulation of chemoreceptors cause vasoconstriction.

Peculiarities of Pulmonary Circulation

1. Pulmonary *artery* carries *deoxygenated* blood and pulmonary *vein* carries *oxygenated* blood.
2. *Filtration of fluid*: *No* filtration of fluid occurs as in systemic capillaries, because colloid osmotic pressure is higher than pulmonary capillary pressure.
3. *Filtration of emboli:* Fine capillaries act as filter and trap the emboli.
4. *Blood enters* lungs from pulmonary and bronchial arteries (two arteries).
5. Pulmonary vascular bed is a *low resistance* circuit whereas systemic vascular bed is high resistance circuit.
6. Pulmonary circulation supplies blood to only *one type* of tissue. Systemic circulation supply blood to different type of tissue.
7. Act as blood reservoir.
8. Pulmonary blood flow *alters* during inspiration and expiration.
9. As pulmonary vascular bed is short and distensible, the blood flow is not fully dependent on neurogenic influences but mechanical factors of right ventricle play more important role.
10. CO_2 excess and oxygen lack cause vasoconstriction of pulmonary blood vessels by direct action, whereas vasodilatation occurs elsewhere.
11. Gravity affects the regional distribution of blood flow through the lungs by altering pulmonary vascular pressure. Lungs are about 30 cm tall and pulmonary

artery enters midway. Thus, blood flowing through apex has to climb 15 cm, so the pressure falls and blood flowing through the base drops 15 cm, so the pressure rises. As the pressure is low *during diastole, the blood flow through the apices of the lungs will cease.* The blood flow through the base is higher because intravascular pressure is higher and *difference* between intravascular pressure and pleural pressure is higher (= higher transmural pressure). This dilates pulmonary blood vessels and *blood flow is higher at the base.*

CHAPTER

57

Capillary Circulation

In capillary the most important function occurs that is, oxygen and nutrients enter the interstitial fluid and carbon dioxide and waste products enter the bloodstream.

This exchange across the capillary wall is essential for the survival of the tissue.

There are about 40,000 million capillaries, which provide about 560 square meter surface area for exchange, in adult human being.

STRUCTURE OF CAPILLARY (FIG. 57.1)

1. Blood from arteriole pass into series of metarterioles, which have a structure midway between that of arteriole and capillary.
2. Some of the metarterioles give rise to thoroughfare channels, which are also called preferential channels. They allow bypass of the capillary bed in some tissues.
3. Other metarterioles give rise to true capillaries. Blood returns by venules to general circulation.
4. Arterioles are highly muscular and their diameter can change many folds. Metarterioles do not have a complete muscle coat, but smooth muscle fibers encircle the intermediate points. Metarterioles lead to capillaries via precapillary sphincter.

Post capillary venules are considerably large than arterioles and have much weaker muscle coat.

Capillary Wall

Capillary wall is composed of unicellular layer of endothelial cells and is surrounded by basement membrane on outside (Fig. 57.2).

1. Diameter of capillary—3 to 8 μm (micrometer) which is about the size of the RBC and barely enough for RBC to pass and other cells to squeeze.

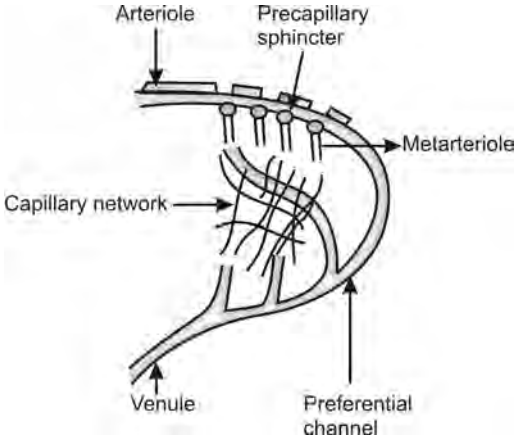


Fig. 57.1: Structure of capillary

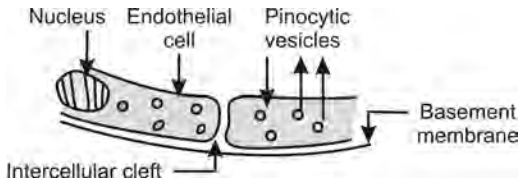


Fig. 57.2: Electron microscope structure of capillary wall

2. There are minute intercellular *clefts* or *pores* in between endothelial cells. Pore size is 2.5 nm (nanometer). Pores are filled by loose reticular fibrillae composed mainly of hyaluronic acid.

   Most of the (a) Water and water soluble ions and molecules pass between interior and exterior of the capillary through their slit pores.
3. In the endothelial cells, there are many pinocytic vesicles. These are formed at one side and move on the other side where they are discharged.

Types

Microscopically there are three types of capillaries:

1. Continuous nonfenestrated, e.g. in brain.
2. Fenestrated capillaries, e.g. in intestinal villi and in renal glomeruli.
3. Discontinuous capillaries or sinusoids, e.g. in liver and bone marrow.

Precapillary region is occupied by small blood vessels that contain some smooth muscle. It includes: (i) arterioles, (ii) metarterioles, and (iii) Precapillary sphincter.

This region:

1. Gives rise to capillaries, and
2. Controls blood flow through capillary bed.

Blood flow in capillaries is called as vasomotion. Blood does not flow in capillaries continuously. Instead the flow is *intermittent.* Metarterioles and precapillary sphincter constrict and relax in alternate cycle 5 to 10 times per minute.

REGULATION OF VASOMOTION

1. Oxygen lack (decrease PO_2) is potent vasodilator especially in skeletal blood vessels. PO_2 affects opening and closing of metarterioles and precapillary sphincters. In presence of oxygen lack intermittent period of blood flow occurs more often and duration of each flow lasts longer.
2. CO_2 excess (increased PCO_2) is potent vasodilator in cerebral circulation.
3. Fall in pH – increases the blood flow.
4. Polypeptides for example bradykinin cause vasodilatation.
5. Histamine cause vasodilatation and increase blood flow.
6. Prostaglandins – some of them increase blood flow.

TRANSCAPILLARY EXCHANGE

Capillary membrane is relatively impermeable to proteins and large molecules.

Three types of transport occur:

1. Diffusion
2. Micropinocytosis
3. Filtration and reabsorption.

DIFFUSION

This is most important means by which substances are transported between the blood and interstitial fluids.

Diffusion of Lipid Soluble Substances

Lipid soluble substances diffuses directly from the blood to interstitial fluids without going through pores and they diffuse through cell wall of capillaries.

a. For example, carbon dioxide and oxygen can pass through all areas of capillary membrane (Fig. 57.3). Therefore, the rate of diffusion is two times that of water.

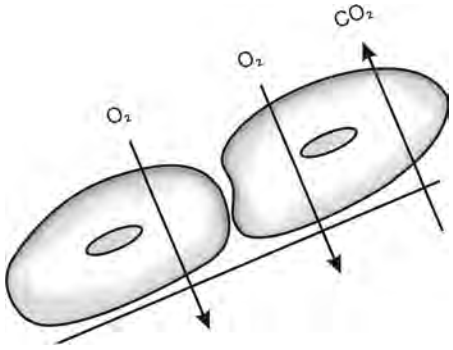


Fig. 57.3: Diffusion of O_2 and CO_2

b. Another example is anesthetic gases and alcohol which are rapidly transferred.

Diffusion of Water Molecules (Fig. 57.4)

Water is next important substance
Diffusion of water molecules occurs in two ways:

1. Directly through endothelial cell – first into the intracellular fluid and then out of the cell on the other side.
2. Through pores. Pores allow bulk flow of water soluble and lipid insoluble substances:

These substances cannot pass through the endothelial cells and they diffuse through pores, which are filled with water. Examples are sodium ions, chloride ions, glucose, etc.

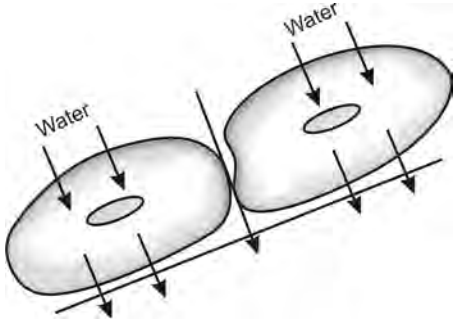


Fig. 57.4: Diffusion of water

Important Points for Diffusion

1. Permeability of capillary pores to different substances will vary according to their molecular size. For example:
   i. Water soluble substances diffuse easily because their size is much less than the pore.
   ii. Protein molecules have a diameter greater than the pore. Therefore, they cannot pass.
   iii. Glucose Na^+ ions, Cl^- ions, urea, etc. have in between diameter.
2. Capillaries in different tissues have extreme difference in their permeability.
3. The rate of diffusion of substance depends on concentration difference. For example, blood has normally higher concentration of oxygen than interstitial fluid. Therefore, large amount of oxygen moves from blood towards tissues. CO_2 concentration is more in tissues than in blood. Therefore, it moves in blood and is carried away.
4. Diffusion occurs in both directions while filtration is the net movement of fluid out of capillaries at the arterial end.

MICROPINOCYTOSIS

Means endothelial cell ingests small amounts of plasma or interstitial fluid (Fig. 57.5). Vesicles, thus formed migrate to other side and open. The movement is slow. Large molecules like proteins, lipoproteins, and polysaccharide diffuse by means of pinocytosis.

- Proteins are returned to blood by lymphatics. (Pinocytosis = cell drinking and phagocytosis = cell eating).

FILTRATION AND REABSORPTION

The rate of filtration at any one point along a capillary depends on Starling forces (Fig. 57.6).

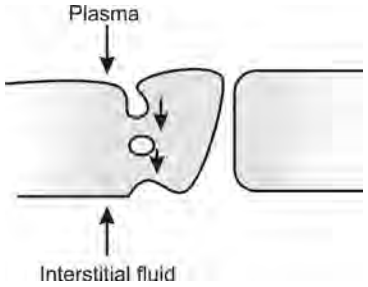
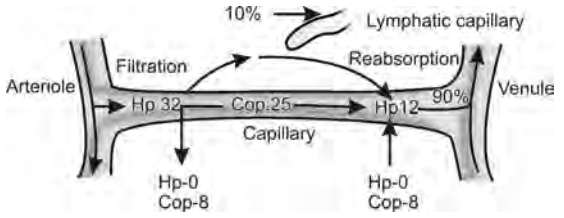


Fig. 57.5: Micropinocytosis



Outward-inward force (32+8) -25 = 15 mm Hg – net force for filtration

Outward-inward force (12+8) –25 = –5 mm Hg – net force for reabsorption

Fig. 57.6: Filtration and reabsorption filtration reabsorption

Forces are named after the physiologist who first described their operational details:

1. Hydrostatic pressure in the capillary. This force is directed outward.
2. Colloid osmotic pressure gradient across the capillary wall (i.e. colloid osmotic pressure of plasma - colloid osmotic pressure of interstitial fluid)
   This force is directed inward.
   - The hydrostatic pressure or capillary pressure considerably differes in different tissues

For example: In resting state

i. The pressure in the glomerular capillary is 70 mm Hg.
ii. In lungs, and liver, it is 8 mm of Hg.
iii. In human finger nail bed the typical values at arterial end 32 mm Hg and at venous end 12 mm of Hg.

Capillary pressure is not constant it depends on state of tone of the resistance vessels.

1. Capillary blood flows slowly, because although capillaries are short but total cross sectional area of capillary bed is large and transit time from arteriolar to venular end of an average sized capillary is 1-2 sec.
2. Fluid moves into interstitial space at arteriolar end of the capillary where filtration pressure across the capillary wall exceeds the colloid osmotic pressure (filtration).
3. Fluid move into capillary at venular end where colloid osmotic pressure exceeds filtration pressure (reabsorption).
4. The amount of fluid that moves across the capillary wall is enormous. It is said that any minute an amount equal to the entire plasma volume enters the tissue from capillaries and an equal amount enters the capillaries and lymphatics.
5. Capillary pressure is higher at arterial end of the capillary than at the venous end; because of this difference fluid is filtered out at their arterial end and then is reabsorbed at their venous end. Thus, a *small amount of fluid actually flow through the tissue from arterial end of the capillary to the venous end.*
6. There is *near equilibrium* but there is slight imbalance of forces at the capillary membrane that cause slightly more filtration of fluid into interstitial spaces.
7. Slight excess of filtration is called *net filtration* and is *balanced by* fluid returned to circulation through *lymphatics.*
8. Normal rate of net filtration in entire body is about 1.7 to 3.5 ml/min, which is returned via lymphatics to circulation. This

keeps interstitial fluid pressure from rising and promote turn over of tissue fluid.

9. Capillary membrane is not completely impermeable to protein (Starling originally thought so). Leakage of proteins important for carrying antibodies and protein bound hormones to the tissues. Rate of leakage depends on size of the pore.

EDEMA

Accumulation of excessive salt and water in interstitial space in the body, usually in dependent parts, which become swollen with fluid.

Edema fluid resembles plasma but has low protein content.

Causes

1. Increase in hydrostatic pressure of veins. For example, in congestive cardiac failure.
2. When colloid osmotic pressure of plasma decreases.

   For example, hypoalbuminemia in:

   i. Protein malnutrition
   ii. Cirrhosis of liver
   iii. Nephrotic syndrome.

In edematous conditions kidneys retain sodium due to aldosterone secretion.

CHAPTER

58

Cutaneous Circulation

Skin weights two kilograms in adult.

Circulation through skin subserves two major functions:

1. Nutrition of the skin tissue
2. Conduction of heat: Heat is carried from internal structure of the body to skin, so that it can be removed from the body.

PHYSIOLOGICAL ANATOMY

To perform these two functions the circulatory apparatus of the skin is characterized by two major types of vessels (Fig. 58.1):

1. Usual nutritive arteries, capillaries and veins.

   Arterioles carrying blood to the skin breaks into metarterioles which in turn give rise to capillaries. The capillaries of the skin run towards its superficial aspect, then make a U turn (bend) to enter deeper parts of the skin. Capillaries join the collecting venules, which joins others to form subpapillary venous plexus. Therefore, color of the skin depends on blood flow through capillaries and subpapillary plexus.
2. Vascular structures concerned with heating the skin.

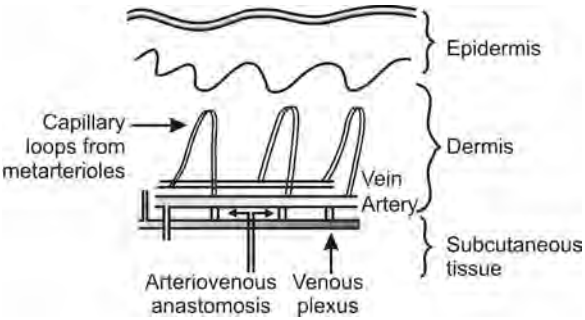


Fig. 58.1: Blood vessel of skin

They consist of:

1. Extensive subcutaneous venous plexus which holds large quantities of blood that can heat the surface of the skin.
2. *Arteriovenous anastomosis*—in some areas communications are present directly between arteries and venous plexuses.
   i. Walls of these anastomotic channels have *strong muscular coats*, innervated by *sympathetic vasoconstrictor nerve fibers*, secreting norepinephrine at their terminal ends.
   ii. When *constricted* they reduce the blood flow into the venous plexus to *almost* nothing.

iii. Or when maximally *dilated* they allow extremely *rapid flow* of warm blood into plexuses.
iv. Arteriovenous anastomosis is *found principally* in the volar surfaces of *hands* and *feet*, *lips*, *nose* and *ears*.

Rate of blood flow through skin varies according to:

1. Metabolic activity of body, and
2. Temperature of surroundings.
   i. Blood flow required for nutrition is slight. At ordinary temperature blood flowing through skin is 10 times its nutritive needs.
   ii. But at very cold temperature blood flow through skin becomes so less that nutrition of skin begins to suffer. For example, in arctic zone finger nails grow more slowly.
   iii. Blood flow through skin in ordinary cool temperature is about 400 ml/min in average adult.
   iv. It can decrease to 50 ml/min in very cold temperature.
   v. It can increase to 3 L/min when skin is heated. Therefore, many persons of borderline cardiac failure develop severe failure in hot weather because of extra load on heart and then revert from failure in cool weather.

REGULATION OF BLOOD FLOW IN THE SKIN

1. *Nervous control:* Hypothalamus regulates blood flow through skin in response to change in temperature by two mechanisms:
   i. Vasoconstrictor mechanisms, and
   ii. Vasodilator mechanism.

   Heating stimulates anterior hypothalamus which causes: (i) vasodilatation especially of skin blood vessel, and (ii) sweating.

   Cooling stimulates posterior hypothalamus, which causes vasoconstriction and cessation of sweating.
2. Skin throughout the body is supplied by sympathetic vasoconstrictor nerves secreting norepinephrine at nerve endings. They are most powerful in feet, hand, lips, nose and ears. These areas are most frequently exposed to cold and large number of arteriovenous anastomosis are present in these areas.
3. At normal body temperature sympathetic vasoconstrictor nerves keep these anastomosis totally closed but when body is overly heated sympathetic input decreases anastomosis dilates and large amounts of warm blood flows in venous plexuses. Thereby promoting loss of heat from the body.
4. In the, skin of arms, legs and trunk almost no arteriovenous anastomosis are there but there are other blood vessels. Therefore, when body is overheated sympathetic impulses decrease and they dilate.
5. When body temperature increases excessively, sweating begins and the blood flow increases two folds in skin of arms, trunk by active vasodilatation (It occurs after sweating begins and does not occur in animals who do not have sweat glands):
   i. Because the sympathetic fibers that supply sweat glands secrete *acetylcholine* which cause vasodilatation, and
   ii. While forming the sweat, the sweat glands secrete an enzyme kallikrein. It acts on globulin *Kininogen* to produce *Bradykinin* which is potent vasodilator.

EFFECT OF COLD ON SKIN CIRCULATION

1. When cold is applied directly to skin—the skin blood vessels constrict (maximum vasoconstriction at 15°C) because of sympathetic stimulation.

2. Then if skin is still further cooled vasodilatation takes place because of paralysis of contractile mechanism of vessel walls due to direct effect of cold on blood vessels.
3. This has got a protective value because it prevents tissues from freezing and is responsible for rubor or redness of skin of face, in severe cold.

Skin Color

It is due to blood in skin capillaries and veins, therefore:

1. When skin is hot and arterial blood is flowing in it, skin is *red*.
2. When skin is cold and blood is flowing extremely slowly, most oxygen is removed from blood before it can leave capillaries. Therefore, capillaries and veins contain large amount of deoxygenated blood and skin has *bluish* hue.
3. Severe constriction of the cutaneous vessels express most of the blood out of the skin into other parts of the circulation. When this occurs the skin takes the color of subcutaneous tissue (mainly collagen fibers) which have wheatish hue and the skin has *ashen white pallor.*

CONDITIONS AFFECTING SKIN BLOOD FLOW

1. Temperature changes in environment
2. Emotions—for example:
   i. Pale with fear
   ii. Blushing—in emotional embarrassment
   iii. Reddening of face in rage.
3. *Cardiovascular shock:* Pallor due to vasoconstriction.

VASCULAR RESPONSES OF SKIN

When skin is stroked firmly with pointed object three local reactions frequently occur, affecting the local skin circulation.

White line

When pointed object is drawn lightly over the skin, the stroke becomes pale this is called white line or white reaction.

Cause

Mechanical stimulation initiates contraction of precapillary sphincter and blood drains out of capillaries in small veins.

This response appears in 15 to 20 secs, maximum in ½ to 1 min, then fades in 3 to 5 min.

Triple Response

When skin is stroked more firmly with pointed instrument, *red line* (or red reaction) appears in 10 sec (range 3 to 15 sec). Peak is reached in ½ to 1 min, then fades gradually.

Cause

Dilatation of precapillary sphincters and active venular dilatation:

1. Due to histamine and polypeptides like bradykinin released from damaged skin.
2. It characteristically outlines the stroke, therefore, known as red line. No nervous mechanism is involved.

This is followed in a few minutes by diffuse or irregular, mottled reddening around the injury. This is known as *flare* (Fig. 58.2).

CAUSES

Dilatation of arterioles, terminal arterioles and precapillary sphincters:

1. Temperature of the skin over this is increased because of increased blood flow.
2. It appears in 15 to 30 secs, spreads for 1 to 10 cm area (usually 2 to 3 cm) around the red line fades soon.
3. This response is *mediated by nerves* but it does not involve the central connections and is due to *axon reflex*. When skin is

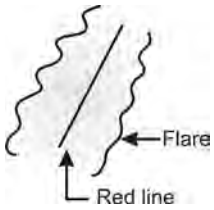


Fig. 58.2: Red line and flare

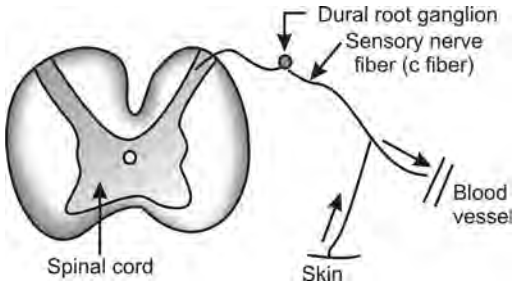


Fig. 58.3: Axon reflex

stimulated impulses travel up one branch of sensory nerve and down the other branch going to blood vessel causing vasodilatation. This reflex is known as axon reflex (Fig. 58.3). It produces long lasting vasodilatation caused due to release of *substance P (Polypeptides) at the nerve endings* supplying the blood vessels.

Wheal

After sometime, blister like swelling develops along the red line. It is raised above the skin about 1 to 2 mm. It appears in 1 to 3 min, becomes maximum in 3 to 5 minutes. In sensitive persons, wheals as high as 1 cm can develop due to excessive sensitivity to *histamine* and other substances released due to injury.

Cause

1. *Increased permeability* of capillaries due to damage
2. Increased capillary pressure due to dilatation of precapillary sphincter.

Fluid in wheal contains considerable proteins. *Example* Lash of whip.

CHAPTER 59

Syncope, Cardiogenic Shock, Causes and Effects of Shock on the Body

SYNCOPE

A transient loss of consciousness, due to inadequate blood flow to the brain. Syncope means *fainting*. It is also called *neurogenic shock*.

Most commonly it is associated with vasodilatation which occurs suddenly. Vasodilatation leads to hypotension and generally is associated with bradycardia. Because of hypotension the blood flow to brain becomes slow and inadequate producing sudden loss of consciousness.

The attacks are short lived and consciousness is restored within few minutes. As the person falls down, the horizontal position of the body improves the cerebral circulation.

Vasovagal Syncope

Syncope resulting from fall of blood pressure due to: (a) *failure of peripheral resistance* (i.e. peripheral vasodilatation). The venous return decreases—the cardiac output falls. Blood pressure falls or (b) it may be due to slowing of the heart.

Vasovagal syncope may be caused due to:

1. Emotional stress
2. Pain
3. Acute blood loss
4. Fear or
5. Assuming an upright position after having been in bed for prolonged period. Fainting is due to pooling of blood in dependent parts of the body on standing (Postural syncope).

Other Causes of Syncope

1. Peripheral circulatory failure
2. Cerebral vascular accident (stroke)
3. Cardiac arrhythmia
4. Transient cardiac standstill (Stokes-Adam's syndrome)
5. Altered blood chemistry as in hyperventilation or hypoglycemia.

Predisposing factors are:

i. Fatigue
ii. Prolonged standing
iii. Nausea
iv. Pain
v. Emotional disturbances
vi. Anemia
vii. Dehydration
viii. Poor ventilation, etc.

First Aid

1. Place the person in horizontal position with head low, so that blood flow to brain is increased.

ii. Clear the airway.
iii. Loosen the clothing.

Fainting is usually of short duration but ascertain the cause of faint.

If person does not recover move the person to hospital.

CARDIOGENIC SHOCK

It is caused when pumping action of the heart is inadequate, therefore, heart fails to pump out all venous return. Therefore, cardiac output decreases.

1. Decrease in cardiac output also reduces circulating blood volume and can therefore lead to shock.
2. Cardiac output may be reduced by:
    i. Disease of the heart (congestive heart failure or arrhythmia) or
    ii. Disease of coronary blood vessels (leading to disease of the heart—myocardial infarction) or
    iii. Pericardial effusion—in this condition, heart cannot expand, therefore, filling is less and it reduces stroke volume.

CAUSES AND EFFECTS OF SHOCK ON BODY

Shock may be either:

1. *Primary:* That is immediately following an injury or
2. *Secondary:* Produced some hours after injury.

The *cardinal feature* of shock is – disparity between:

i. The circulating blood volume, and
ii. The available blood space or the capacity of circulatory system.

Therefore, the *mechanism initiating shock* is that which:

i. Decreases blood volume—e.g. hemorrhage or
ii. Increases the cardiovascular space—e.g. peripheral vasodilatation due to histamine or snake venom.

Whenever such disparity occurs between blood volume and circulatory capacity—certain events follow in a sequential fashion:

1. There is immediate reduction of pressure in the great veins and right atrium.
2. This leads to inadequate filling of the ventricles.
3. Starling's law comes into operation and the stroke volume and consequent the cardiac output is decreased.
4. This decreases arterial pressure and the pulse pressure may fall to extremely low levels (often below 20 mm Hg).

Cardiovascular system tends to correct it by:

1. *Cardiac acceleration,* and
2. *Cutaneous vasoconstriction* characterized by cold skin and blue finger tips and ears.

Increase in heart rate does not help in correcting the situation but in fact it deteriorates the situation by interfering with diastolic filling, and increases the disparity, setting up a *vicious cycle*.

Shock may be Divided into Four Stages

1. *Initial or developing stage* in this the circulatory blood volume is decreased, but the degree is not sufficient to cause serious symptoms.
2. *Compensatory stage* results when blood volume is reduced further. But even at this stage blood pressure is maintained due to vasoconstriction. The blood flow to the skin and the kidney is reduced but the central nervous system and the myocardium still continue to be supplied with enough blood.
3. *Progressive stage*—sets in when the compensatory mechanism is unable to cope up with the situation. There is a steadily

increasing heart rate and vasoconstriction, with last ditch attempt to keep the blood pressure round about 60 to 70 mm Hg.

4. *Irreversible stage* is finally reached when vicious cycle is firmly established and after this treatment is of no value. There is loss of arterial tone, and myocardial depression sets in and arterial blood pressure can no longer be raised even after infusion of whole blood.

Causes of Shock

Any condition that can cause:

i. Decreased blood volume
ii. Inadequate venous return to the heart
iii. Reduction in cardiac output or
iv. Fall in peripheral resistance may initiate shock.

1. More common causes of shock are:
   i. Perforated peptic ulcer
   ii. Ruptured esophageal varices
   iii. Ectopic pregnancy
   iv. Abdominal injuries especially in the area of spleen
   v. Post-traumatic states.
2. Shock also occurs in:
   i. Hemopericardium
   ii. Pulmonary embolism
   iii. Myocardial infarction
   iv. Septicemia
   v. Acidosis
   vi. Hypocalcemia, hyperkalemia
   vii. Decreased pulmonary ventilation.

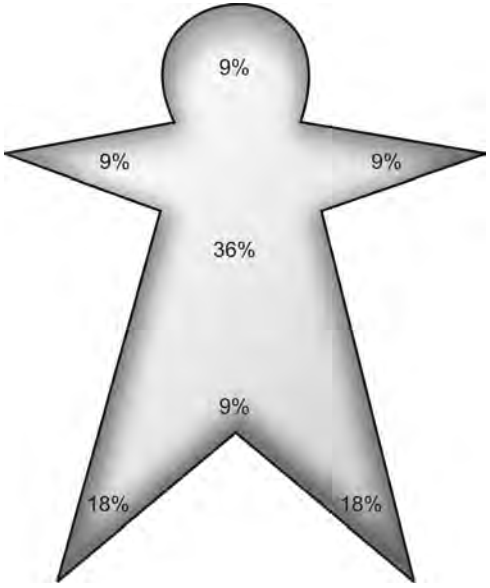


Fig. 59.1: Rule of nine

3. Shock due to *burns, crush syndrome* and *anaphylactic shock* deserve special mention.

Shock in *burns* is due to excessive tissue damage and consequent passage of fluid and plasma into the damaged area. The extent of burn is usually expressed as a percentage of total body surface. A rapid method of estimating the extent, is by the rule of nines, in which the body is divided into multiples of 9% (Fig. 59.1).

Greatest fluid shift occurs during the first 8 hours after a burn and reaches maximum in 48 hours. Hemoconcentration is the characteristic of this phase.

CHAPTER

60 Cardiovascular Adaptations to Various Grades of Exercise

Exercise is a period of increased energy expenditure by skeletal muscle. Enhanced energy is met by increased activity of the normal energy delivery systems, principally the cardiovascular and respiratory systems and just the right increase in the activity of these systems at right time is achieved by the regulatory systems of the body.

Two types of responses are seen:

1. Short-term response to a single bout of occasional exercise
2. Long-term response to regular exercise. Adaptation to regular exercise is known as training.

VARIETIES OF EXERCISE

The term very severe exercise is used for muscular activity which by reason of its severity can only be kept up for *short-time* — example, 100 meters race at top speed. At the end of such exercise the person is completely exhausted.

From physiological point of view characteristic feature of this form of exercise is the inability of the cardiovascular and respiratory systems to supply muscles during the period of exercise with all the oxygen required for their tremendous level of activity. A so-called 'Oxygen debt' is incurred, i.e. a large volume of oxygen has to be absorbed after the exercise is over to dispose off metabolites, which accumulated in the muscles during activity, because of their relative anoxic state.

Moderate exercise is a kind of exercise that can be kept up for long period—example, vigorous walking at 5 km/hour or steady running. Such exercise involve considerable exertion and extensive cardiovascular and respiratory adjustments are necessary.

Its outstanding *physiological feature* is the ability of the body to supply the active muscles, with practically all oxygen they require immediately and to a degree proportional to level of activity.

In practice severity of muscular work is *usually classified* in terms of:

1. The energy expenditure
2. Oxygen intake.
   i. Work including an oxygen consumption of 3 times the basal level is described as *moderate work.*
   ii. While 4 to 7 times the basal oxygen consumption implies *hard (or heavy) work.*

The maximum rate of oxygen consumption during exercise ($VO_{2\ max}$) is useful measurement, which depends on age, sex and state of physical training.

- A likely value:
  - For a 15-year-old boy—46 ml/kg/min
  - For a 15-year-old girl—36 ml/kg/min
  - Value would be higher for young adult but less in old age.
  - Physical training may increase the VO_2 max by as much as 80%.

GRADING OF EXERCISE

WHO in 1978, gave a classification of grading of exercise which is based on energy expenditure or oxygen intake or heart rate increase (Table 60.1).

The adaptation to exercise depends on:

1. Type and severity of work that is performed, and
2. State of training of the individual.

CARDIOVASCULAR ADJUSTMENTS

Skeletal Muscle Blood Flow

1. At rest, skeletal muscles receive about 1 L of blood per min, i.e. 1/5 of cardiac output.
2. With onset of muscular activity the blood flow through active muscles increases dramatically. During maximal exercise skeletal muscle blood flow may exceed 20 L/min.
3. This enormous increase is made possible by arteriolar dilatation and opening up of closed capillaries by relaxation of precapillary sphincters (at rest only 3% of capillaries in skeletal muscle are open).
   - Opening of capillaries helps—increased blood flow and increased surface area is available for exchange.

The increased blood flow is brought about by:

Local Factor

Metabolites of active muscles—which include:

a. Organic molecules – AMP, ADP
b. Inorganic ions – H^+, K^+, $PO4^{3-}$, Mg^{++}, and
c. Low PO_2 and high PCO_2.
   The effect may be due to summation of various factors. All of them cause vasodilatation.

Neural Factors

Stress of exercise causes sympathetic overactivity which cause:

i. **Venoconstriction**—helps to increase venous return, which in turn will increase cardiac output.
ii. Sympathetic cholinergic fibers are *unique* to skeletal muscle, bring about arteriolar dilatation.
iii. Thought of exercise improve muscle blood flow because sympathetic nervous system gets activated via cerebral cortex and hypothalamus.
iv. Impulses from muscles and joints leading to reflex cardiovascular response which include increase in muscle blood flow.

Humoral Factors

Exercise stress—releases adrenaline from adrenal medulla due to sympathetic

Table 60.1: WHO classification of grades of exercise

Grade	*Level*	*Relative load index (RLI)*	*Metabolic energy expenditure tests (METs)*	*Heart rate*
I	Light (mild)	< 25 % of $VO_{2\ max}$	< 3 METs	< 100/min
II	Moderate	25-50 % of $VO_{2\ max}$	3-4.5 METs	100-125/min
III	Heavy	51-75% of $VO_{2\ max}$	4.6-7 METs	125-150/min
IV	Very Heavy (severe)	> 75% of $VO_{2\ max}$	> 7 METs	> 150/min

$VO_{2\ max}$ = Maximum O_2 consumption
METs = Multiples of resting O_2 consumption

stimulation. Adrenaline acts on β receptors and cause vasodilatation in skeletal muscle.

Blood flow through the muscle is also affected by the frequency of contraction of the active muscle fibers. Blood cannot flow freely through capillaries and veins that are compressed by the continuous contraction of neighboring muscle fibers, but intermittently contracting fibers may by their pumping action, actually enhance the blood flow.

Redistribution of Blood Flow

Increase in blood flow through muscles during even moderate exercise is so great that it can be met only by an increase in the cardiac output, but some help is provided by reducing blood flow to:

1. Renal and splanchnic beds
   - This is brought about by: (i) increased sympathetic stimulation, and (ii) release of adrenaline.
   - Renal and splanchnic blood vessels have only sympathetic noradrenergic vasoconstrictor fibers and adrenaline acts on a receptors to cause vasoconstriction.
2. Cutaneous vasoconstriction passes off when body temperature begins to rise and skin blood flow increases to dissipate the heat generated by exercise.

Cardiac Output

Cardiac output rises in direct proportion to increase in oxygen consumption, over a wide range of exercise levels.

The increase in cardiac output during exercise is *due to* increase in both: (a) heart rate, and (b) stroke volume. Physiological *mechanism* that leads to increase in *cardiac stroke volume*:

1. *More complete emptying* by a *more forcible systolic* contraction. This is due to stimulation of sympathetic activity and release of adrenaline, which occurs early in exercise. The heart muscle contracts more strongly with an increase in rate of shortening and relaxation so that duration of *systole is decreased*.
2. *Increased venous return* occurs due to:
   i. Pumping action of contracting muscles
   ii. Sympathetic venoconstriction, and
   iii. Increased respiratory movements — and *Starling mechanism* comes into play causing forceful contraction of ventricles.

Increase in heart rate is brought about by:

1. Reduction of cardioinhibitory action of vagus.
2. Increased activity of sympathetic nerves and release of adrenaline.
3. Release of thyroxine during exercise also contributes to increase in heart rate.
4. Impulses originating in muscles and joints reflexly cause tachycardia.
5. Increased venous return stretches the right atrium, mobilizing Bainbridge reflex.
6. Increased temperature directly increases the rhythmicity of the pacemaker.

Anticipatory Tachycardia

Anticipatory tachycardia, i.e. increased heart rate before the exercise, is mediated by the cortical and limbic influences on medullary cardioinhibitory and cardioaccelerator centers.

Blood Pressure During Exercise

Despite large increase in the cardiac output the arterial blood pressure rises less than might be expected during exercise and diastolic blood pressure may actually fall since the total peripheral resistance is substantially reduced.

Systemic Circulation (Fig. 60.1)

1. *Systolic blood pressure* increases linearly with severity of exercise and it may increase to 200 mm Hg. Increase is more in older subjects, because resting systolic blood pressure in them is more.
   Increase is due to:
   i. Increase in cardiac output
   ii. Vasoconstriction elsewhere (other tissues).
2. *Diastolic blood pressure*
   i. No change or slight fall in mild and moderate exercise because total peripheral resistance falls considerably due to tremendous vasodilatation.
   ii. In severe exercise slight increase in diastolic blood pressure due to vasoconstriction in other tissues.
   iii. *Mean blood pressure* increases from 90 mm Hg to 140 mm Hg in severe exercise.

Pulmonary Circulation (Fig. 60.1)

It is a low resistance circuit, therefore mean blood pressure rises to 15 mm of Hg and it can accommodate large cardiac output without much increase in blood pressure.

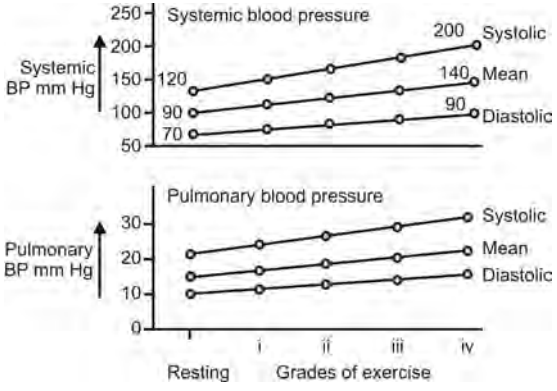


Fig. 60.1: Blood pressure responses in systemic and pulmonary circulation in i to iv grades of exercise

However, in severe exercise pulmonary artery pressure increases markedly.

Coronary Blood Flow

At rest, it is 250 ml/min with 70 to 80% coefficient of O_2 utilization. During maximum exercise it increases by 5 times with 100% coefficient of O_2 utilization.

The increased blood flow is due to:

Coronary vasodilatation by:

i. Catecholamines
ii. Hypoxia
iii. Fall in pH
iv. ATP and ADP (metabolites).

RENAL AND SPLANCHNIC BLOOD FLOW

1. Remains same in mild and moderate exercise.
2. Decreases by 50 to 80% in severe exercise due to stimulation of sympathetic nervous system.

PULMONARY BLOOD FLOW

Pulmonary blood flow—increases linearly with increase in cardiac output in severe exercise.

CEREBRAL BLOOD FLOW

Cerebral blood flow— remains constant in any grade of exercise.

EFFECT OF TRAINING ON CARDIOVASCULAR FUNCTION

Regular exercise has a favorable influence on cardiovascular functions by increasing the reserve capacity for increasing cardiac output.

Heart Rate

Heart rate—in trained sports persons the resting heart rate is less due to increase in resting vagal tone.

During exercise heart rate rises less because he starts with lower resting heart rate. It is beneficial because in untrained person the heart rate increases more and the diastole filling gets reduced.

Stroke Volume

Stroke volume—in trained more of increase in cardiac output is obtained by increasing the stroke volume.

Cardiac Output

Cardiac output—because of above changes trained person can achieve a much larger cardiac output than untrained person during exercise.

SECTION VII: EXCRETORY SYSTEM

CHAPTER

61

Physiological Anatomy

INTRODUCTION

The chief excretory organs are (Fig. 61.1):
1. Kidneys
2. Ureters
3. Bladder, and
4. Urethra.

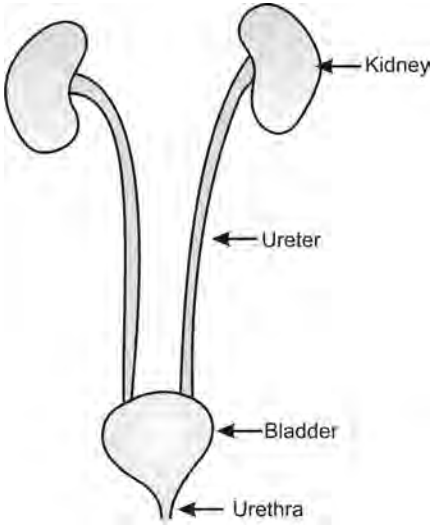


Fig. 61.1: Excretory organs

Kidneys perform important functions like:
1. They excrete waste products of body metabolism.
2. Control the concentrations of most of the body fluids and thus, maintain constancy of internal environment or milieu interieur.
3. Maintain acid base balance.
4. Maintain water balance.
5. Form renin, erythropoietin and kinins. Therefore, kidneys are also endocrine organs.

Briefly, kidneys form urine in following way. Kidneys receive relatively huge blood supply. From it glomerular capillaries filter fluid, which resembles plasma, called glomerular filtrate—180 L/day is formed (approx). Glomerular filtrate is protein free but its crystalloid composition is same as plasma. This filtrate is subjected to extensive absorption by renal tubules.

1. *Water is reabsorbed* so that only about 1.5 L urine is formed/day. They can vary the extent of water reabsorption depending on the need. For example, in dehydration urine output is reduced. But when we drink

excess of water, the urine output is increased.
2. Out of the crystalloid ions filtered nearly all *sodium and chloride are reabsorbed* by the tubules. As these ions are mainly responsible for crystalloid osmotic pressure, the kidneys can maintain normal limits of ionic pattern and crystalloid osmotic pressure by adjusting the relative excretion of water and inorganic ions.
3. *Glucose* is completely reabsorbed by the tubules, provided its plasma level does not exceed 180 mg/100 ml.
4. About 2/3rd of the end product of protein metabolism—urea is allowed to escape in the urine.
5. Kidneys have a specific role in maintaining *acid-base balance*. The normal diet is acid forming and excess of H^+ ions are removed by secretory activity of the kidneys.

   Kidneys also synthesize NH_3 (Ammonia) so that H^+ and NH_3 can combine to form NH_4 radical.
6. Kidneys are the only route for elimination of waste products resulting from metabolism of proteins especially nitrogen and sulfur containing substances.

KIDNEY

The structural and functional unit of kidney is nephron. There are approximately 1.3 million nephrons in each human kidney.

Nephron consist of:

1. *Bowman s capsule and the renal tubule* Bowman's capsule is the terminal cup shaped dilatation of renal tubule.
2. *Glomerulus* is formed by *tuft of capillaries*, which invaginates into cup shaped Bowman's capsule.

Afferent arteriole breaks into glomerular capillaries, which is drained into slightly smaller efferent arteriole. *Glomerular capillaries are lined by endothelium* (Fig. 61.2). Major part of these cells is thin cytoplasm, at nuclear site, cell bulges into the lumen. The thin parts of endothelial cells are riddled with pores → 70 to 90 nm in diameter (seen under electron microscope).

Bowman's Capsule

Bowman's Capsule has visceral and parietal layer. The epithelial cells, which form the visceral layer, are specialized. The cells of the epithelium called *podocytes* have numerous *pseudopodia* (single is pedical) that interdigitate, to *filtration slits* along the capillary wall (Fig. 61.3). The slits are 25 nm wide and each is closed with thin membrane.

Bowman's capsule is separated from capillary endothelium by dense *basement membrane*. This membrane is the only intact membrane in the filtering surface of the glomerulus (Fig. 61.4).

Stellate cells called *mesangial cells* are located between the basement membrane and endothelium. Mesangial cells are common between two neighboring capillaries. Mesangial cells are contractile and play a role in the regulation of glomerular filtration. They also secrete various substances, take up immune complexes and are involved in production of glomerular disease.

The renal tubule consist of:

i. Proximal convoluted tubule
ii. Loop of Henle
iii. Distal convoluted tubule.

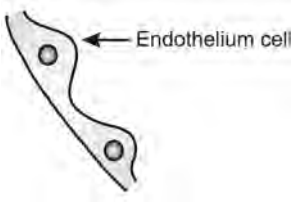


Fig. 61.2: Glomerular capillary wall section

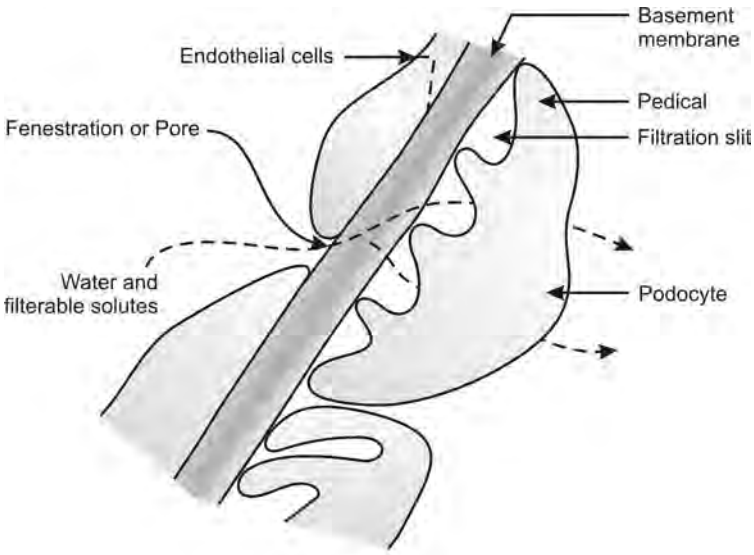


Fig. 61.3: Filtering membrane

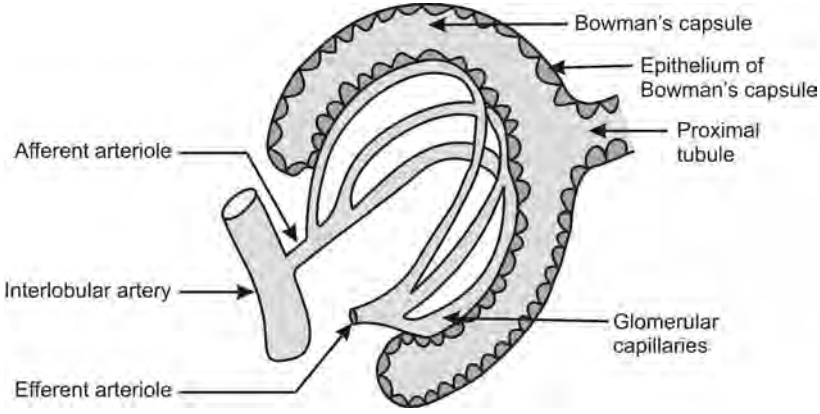


Fig. 61.4: Glomerulus

Proximal convoluted tubule: It is about 15 mm long and 55 µm in diameter. The cells have brush border (microvilli), lateral extracellular space (extension of extracellular space) and apical tight junction.

Loop of Henle: Proximal tubule drains into:

1. *Straight portion* which forms the first part of loop of Henle.
2. It terminates in *thin segment* of the descending limb of the loop of Henle. Thin segment is made up of flat cells.
   i. The nephrons with the glomeruli in the outer portion of the renal cortex have short loops of Henle.
   ii. The nephrons in the juxtamedullary region of the cortex (juxtamedullary nephrons) have long loops extending down in medulla (Fig. 61.5).

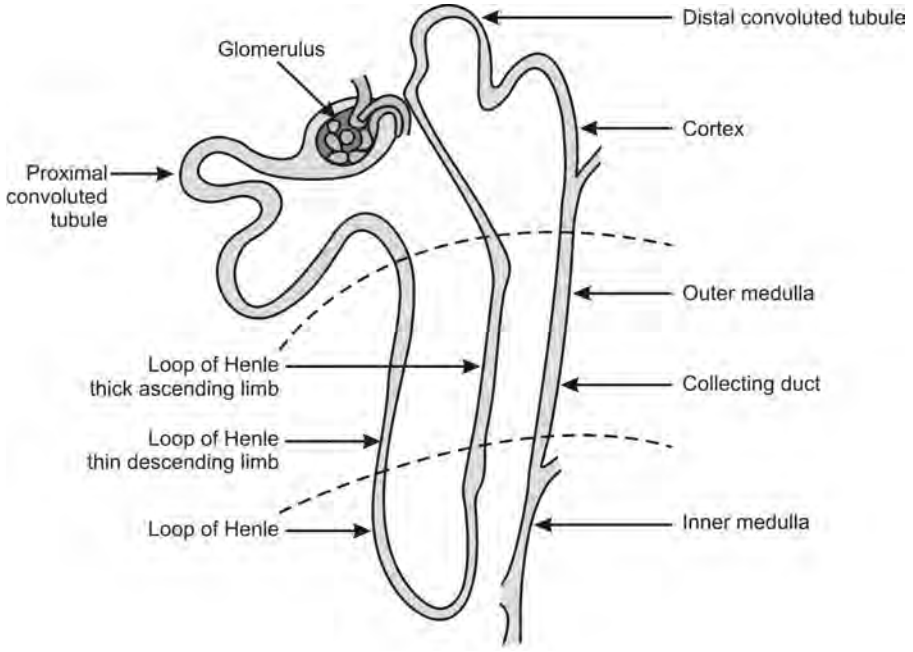


Fig. 61.5: Juxtamedullary nephron

iii. In humans, only 15% of the nephrons have long loops. Therefore, thin segment of loop of Henle varies in length from 2 to 14 mm.

3. Thin segment ends in thick segment of ascending limb of loop of Henle.
   Juxtaglomerular apparatus: The thick ascending loop of Henle reaches the glomerulus of the nephron from which the tubule arose and passes close to its afferent arteriole and efferent arteriole (Figs 61.5 and 61.6).
   i. The walls of the afferent arteriole contain renin secreting *juxtaglomerular cells.* They are swollen and contain dark granules.
   ii. At this point the tubular epithelium is modified to form *macula densa.* The cells become tall and dense.
   iii. There are *lacis cells* near them. The juxtaglomerular cells, the macula densa and the lacis cells near them are

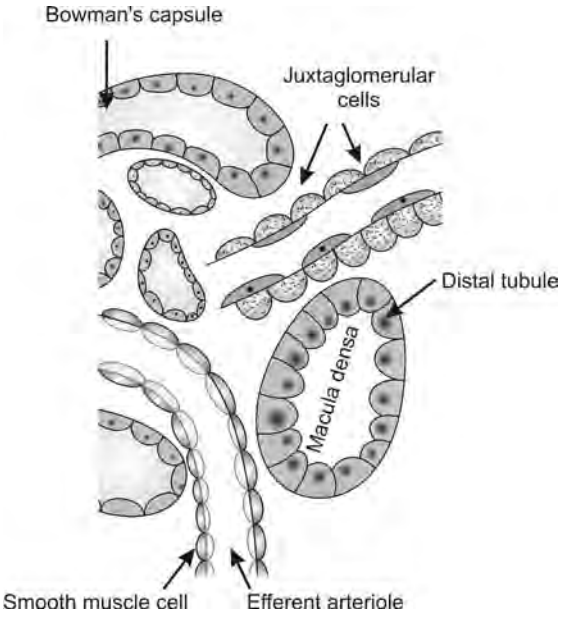


Fig. 61.6: Juxtaglomerular apparatus

known collectively as "the juxta-glomerular apparatus".

Distal Convoluted Tubule

1. It is about 5 mm long.
2. Its cells are lower in height than proximal convoluted tubule cells.
3. There are few microvilli but no distinct brush border.

Collecting Ducts

1. The distal tubules coalesce to form collecting ducts.
2. Collecting ducts are about 20 mm long.
3. They pass through the renal cortex and medulla to empty into the pelvis of the kidney.
4. Epithelium of collecting ducts is made up of:
   Principal cells (P cells) and intercalated cells (I cells)

   Intercalated cell (I cells)
   - i. They are in smaller numbers
   - ii. Also present in distal tubule
   - iii. Have more microvilli, cytoplasmic vesicles and mitochondria
   - iv. They are concerned with:
     a. Acid secretion, and
     b. HCO_3^+ transport

   Principal cells (P cells)

   They are more. Tall with few granules:

   – They are involved in Na^+ reabsorption and vasopressin stimulated water reabsorption.

Total *length* of *nehpron*, including the collecting ducts ranges from *45 to 65 mm.*

Renal Circulation (Fig. 61.7)

Kidneys receive about 1300 ml of blood/min that means 25% of resting cardiac output. It is supplied by *renal arteries.*

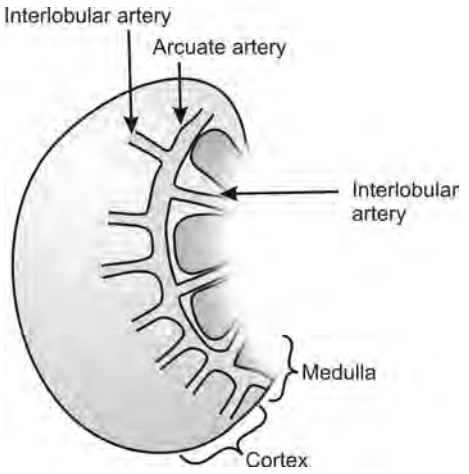


Fig. 61.7: Renal circulation

1. They arise directly from aorta at right angle so that aortic pressure is transmitted through them easily.

   On reaching renal hilus—the renal artery divides into branches—which ascend between pyramids as *interlobular artery.*

   On reaching the corticomedullary junction these divide at right angles into *arcuate arteries.* They in turn give rise to *interlobular arteries.* From interlobular arteries arise afferent arterioles.
2. Afferent arterioles are short and their diameter is larger than efferent arteriole. (i) and (ii) help to maintain high blood pressure in glomeruli.
3. Efferent arteriole again divide into second set of capillaries around renal tubules. This is known as peritubular capillary network.
4. Blood supply of juxtamedullary glomeruli show some difference. Instead of forming peritubular plexus efferent arteriole breaks into straight branches. These are called as vasa recta which go towards apex of pyramids and loop back to corticomedullary junction and empty into arcuate vein. They run alongside the loop of Henle. (1) to (4) are *peculiarities of renal circulation.*

5. Juxtaglomerular apparatus secretes an enzyme—*renin* during renal ischemia or fall of blood pressure.

   The enzyme renin acts on α 2 globulin

   – Angiotensinogen
   ↓
   Angiotensinogen I (decapeptide – inactive) by plasma enzyme
   ↓
   angiotensinogen II (octapeptide – active)
   ↓
   vasoconstriction secretion of aldosterone (hormone which retains sodium chloride and water)

Both factors increase the blood pressure and improve renal circulation so that ischemia is relieved.

URETERS

Sympathetic postganglionic fibers are distributed to: (a) afferent and efferent arterioles mainly, (b) proximal and distal tubule and (c) juxtaglomerular cells, (d) in addition, there is dense sympathetic innervation of thick ascending limb of loop of Henle.

– Pain fibers supplying kidney run parallel to sympathetic fibers and enter spinal cord in the thoracic and upper lumbar roots.

Renal Nerves—Cause

1. Decreased renal blood flow (α1 adrenergic receptors).
2. Increase renin secretion by: (a) direct action of released norepinephrine on β1—adrenergic receptors on *juxtaglomerular cells*, and (b) increases Na^+ reabsorption probably by direct action of norepinephrine on *tubular cells*. The proximal, distal tubule and thick ascending limb of loop of Henle are richly innervated (Fig. 61.8).

Blood Flow

1. When the kidney is perfused at moderate pressures the renal vascular resistance varies with the pressure so that renal blood flow is relatively constant. It is partly due to direct contractile response of smooth muscle of the afferent arteriole to *stretch.* No nervous mechanism may be involved.
2. At low perfusion pressures angiotensin II also plays a role in constricting efferent arterioles. Thus, maintains glomerulus filtrate.

Ureters are smooth muscle tubes that originate in the pelvis of two kidneys and pass downward to enter the bladder.

Urine is propelled through ureters by the peristaltic waves (frequency 1 to 5/min). At lower end, ureter penetrates through trigone obliquely. The ureter courses for several cms under bladder epithelium. So that pressure in

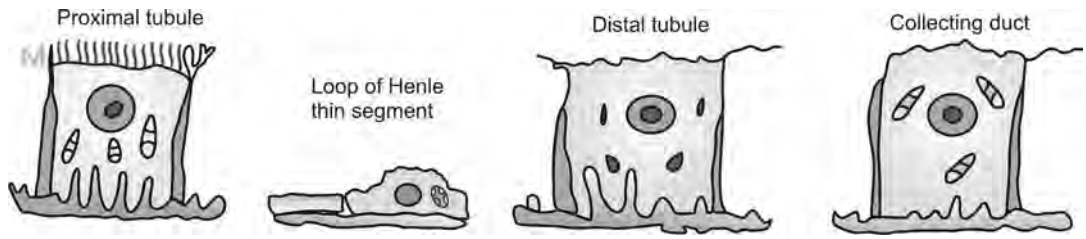


Fig. 61.8: Characteristics of the epithelial cells in different tubular segment

the bladder compresses the ureter thereby preventing backflow of urine.

Ureters are supplied with:

- Sympathetic fibers
- Parasympathetic fibers
- Pain fibers—therefore, if ureter is blocked, for example, by urinary calculi resulting in ureteral dilatation it elicits one of the most severe type of pain that one can experience.

BLADDER

It is a smooth muscle vesicle composed of two principal parts (Fig. 61.9).

1. *Body:* Composed of mainly detrusor muscle.
2. *Trigone:* Small triangular area near the mouth of bladder through which both ureters and urethra pass.

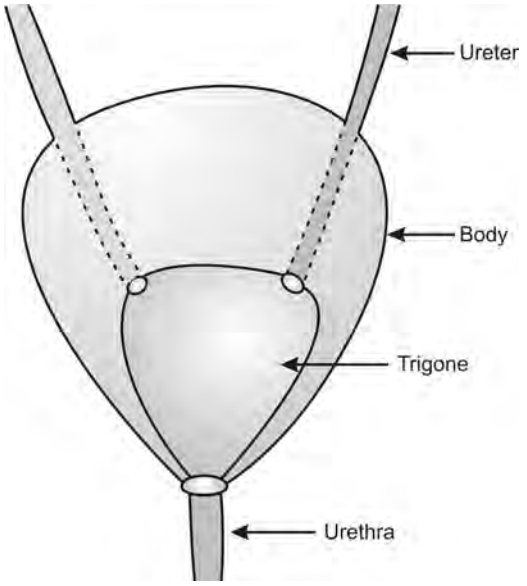


Fig. 61.9: Urinary bladder

Body of bladder has *rugae* on inner surface, which get flattened when filled.

Trigonal muscle is interlaced around the opening of the urethra and maintain tonic closure of urethral opening until the pressure in the bladder rises high enough to overcome the tone of the trigonal muscle. This portion of the smooth muscle is called *internal sphincter*, which can withstand pressure of 18 to 43 cm of water.

About 2 cms beyond the bladder the urethra passes through urogenital diaphragm. This muscle constituents the *external sphincter* of the bladder. This muscle is voluntary or *under control of will.*

With each peristaltic wave of ureter some quantity of urine enters the bladder, when the tension in its wall rises above a threshold value, a nervous reflex called as micturition reflex is elicited. It greatly exacerbates:

i. Pressure in the bladder
ii. Simultaneously causes conscious desire to micturate
iii. It also relaxes the external sphincter allowing micturition.

CHAPTER

62

Glomerular Filtration, Tubular Reabsorption and Secretion

GLOMERULAR FILTRATION

Kidneys receive about 1300 ml blood/minute. 1300 ml of blood contains:

- 700 ml plasma
- 600 ml cells.

1. *Normal values of glomerular filtration rate:* From 700 ml plasma, 125 ml fluid is filtered per minute (which is about 170 L/day) into Bowman's capsule. This is known as glomerular filtrate.
2. *Composition:* The glomerular filtrate has same composition as that of plasma *except.*
   i. No plasma proteins or colloids are present, and
   ii. *Naturally* glomerular filtrate *does not contain any cells.*
3. *Filtration fraction:* The ratio of volume of glomerular filtrate to plasma flow is called filtration fraction 125/700, i.e. 0.16 to 0.20 (normal value).
4. *Mechanism of glomerular filtration:* Glomerular filtrate is the ultrafiltrate of plasma and depends on mainly:
   i. Mean hydrostatic pressure in glomeruli (capillary pressure)
   ii. Colloid osmotic pressure
   iii. Bowman's capsular pressure
   iv. Permeability of the capillaries.

Mean Pressure (Hydrostatic) in Glomeruli

1. Under normal conditions capillary pressure in glomeruli is 60 mm Hg.
2. The pressure in the glomerular capillaries is quite high, that is 60 mm Hg as compared to other capillaries.

Causes

1. Direct origin of renal artery from aorta at right angle.
2. Short length of renal artery.
3. Diameter of afferent artery is more than the efferent artery.

This glomerular capillary pressure of 60 mm Hg is a *filtering force* driving the fluid out of blood vessels into Bowman's capsule. This pressure is autoregulated in spite of variation in general systemic pressure.

But if systemic mean blood pressure is lowered below 60 mm Hg, then blood flow through glomeruli is reduced.

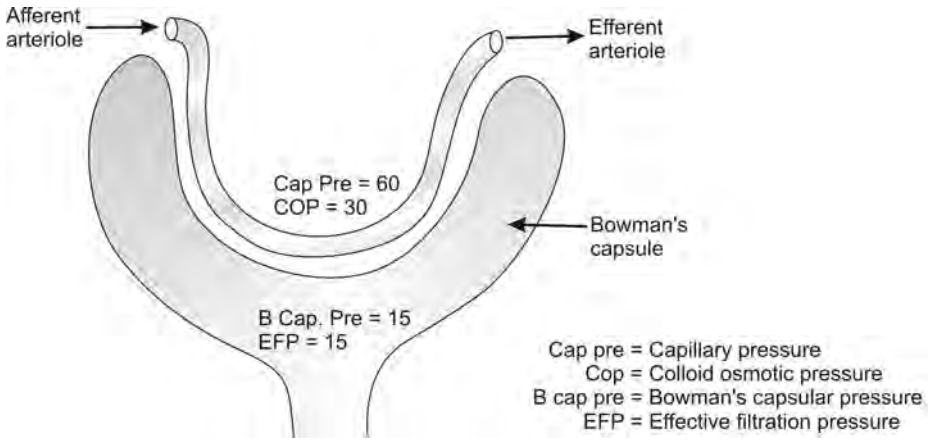


Fig. 62.1: Schematic diagram showing effective filtration pressure

Factors Determining the Effective Filtration Pressure (Fig. 62.1 and Table 62.1)

Table 62.1: Factors determining the effective filtration pressure

Forces favoring filtration	
1. Glomerular capillary pressure hydrostatic	60 mm Hg
	60 mm Hg
Factors opposing filtration	
1. Bowman's capsule pressure	15 mm Hg
2. Colloid osmotic pressure exerted by plasma proteins	30 mm Hg
Total	45 mm Hg
Net effective Filtration pressure	15 mm Hg

Colloid Osmotic Pressure

The colloid osmotic pressure of plasma proteins is 30 mm Hg. This pressure is high in glomerular capillaries because in them the proteins get concentrated through loss of water during the process of filtration.

Colloid osmotic pressure of glomerular capillaries *opposes the filtering force.* That is glomerular capillary pressure tries to drive out the fluid into Bowman's capsule but the colloid osmotic pressure tries to retain fluid in glomerular capillaries.

Bowman's Capsular Pressure

Normally, it is 15 mm Hg. It opposes the filtering force.

When *obstruction* is present in renal tubules the Bowman's capsular pressure increases *much more.*

The net result of opposing forces, or

Effective filtration pressure is = Glomerular Pressure–(Colloid osmotic + Bowman's capsular pressure)

EFP = G Pre – (COP + BCP)
= 60 – (30 + 15)
= 15 mm Hg

Permeability of the Capillaries

Increases in many abnormal conditions, for example—Hypoxia

- Inadequate blood supply
- Action of toxic agents—drugs and poisons
- Many disease processes.

Then *albumin* is the first to appear in urine. With greater damage to nephrons both *white and red blood cells* can pass in glomerular filtrate.

The presence of albumin in urine is called as *albuminuria.* In nephritis the negative charges in the glomerular wall are dissipated and albuminuria can occur without an increase in the size of the pores of the membrane.

Thus, glomerular filtration is governed by physical factors. No vital process is involved.

Evidence

- Oxygen consumption is not increased.
- Heat production is not increased.
- Filtrate collected by micropuncture shows same concentration of: (i) glucose and other solutes (ii) electrolytes and (iii) pH *as that of plasma.*

Therefore, glomerular filtration is *ultrafiltration*, in which, *capillary endothelium* and *visceral layer of Bowman s* capsule act as filtering membrane.

i. Disease process may decrease the permeability of glomerular capillaries by producing a *thickening of the capillary membrane.* In such cases the filtration rate would be reduced.
ii. If the nephron population is reduced by their destruction in the course of a disease, the *total surface area* of the glomerular capillary membrane would be reduced, thereby reducing the filtration rate.

Regulation of Glomerular Filtration Rate

1. Glomerular capillary pressure is the most important determinant of GFR.
   Glomerular capillary pressure can be increased:
   i. By dilatation of afferent arterioles or
   ii. By constriction of efferent arterioles.
   Glomerular capillary pressure can be decreased:
   i. By constriction of afferent arterioles or
   ii. By dilatation of efferent arterioles.
   But in practice it is the *afferent arteriolar* tone which is altered much more frequently.
2. *Renal blood flow* is autoregulated, therefore, glomerular capillary pressure is maintained and consequently GFR is constant in spite of raised blood pressure or fall of blood pressure.
   But autoregulation operates within a limited range of changes in arterial blood pressure.
   When the renal arterial pressure rises above the autoregulatory range the GFR still does not rise. This is achieved mainly by a *decrease in efferent arteriolar resistance (that means efferent arteriole is dilated).*
   But when the renal arterial pressure falls below the autoregulatory range, the GFR falls rapidly.

TUBULAR REABSORPTION AND SECRETION

General Consideration

The glomerular filtrate passes through:

- Proximal tubule
- Loop of Henle
- Distal convoluted tubule
- Collecting tubule
- Pelvis of kidney.

Along this course—it is considerably modified by removal of many substances by reabsorption and addition of some substances by secretion.

Tubular transport, that means tubular reabsorption and secretion are carried by:

1. *Active transport:* Which is carrier mediated and metabolic energy is supplied, e.g. sodium, glucose.

2. Passive transport or diffusion occurs because of: (i) concentration difference or (ii) osmotic gradient (e.g. water) or (iii) electrical gradient across the tubular membrane, for example, negatively charged chloride ions diffuse after active absorption of sodium ions.

   The movement of substances is by way of:
   1. Ion channels
   2. Exchangers
   3. Cotransporters, and
   4. Pumps.

Absorptive Capabilities of Different Segments

1. Proximal tubule—in proximal tubule Large numbers of mitochondria are present and the brush border increases the absorptive area. Therefore, 65% of reabsorption takes place.
2. Thin segment of the loop of Henle plays a specific role in concentrating sodium, in peritubular fluid of medulla.
3. Twelve to fifteen percent reabsorption takes place in distal convoluted tubule and collecting duct.

Reabsorption

An adult man forms on an average 125 ml of glomerular filtrate every minute that comes to 125 × 60 × 24 ml or 180 L. From this only about 1% is lost and rest is reabsorbed.

Apart from water many other substances — like glucose, amino acids and electrolytes are also conserved by the body through reabsorption.

Substances absorbed are:
1. *Threshold* substances, and
2. Nonthreshold substances.

i. *Threshold* substances are transported by an active mechanism, therefore, there is an upper limit to the amount which can be reabsorbed. The upper limit is reached when the carrier mechanism responsible for active transport gets saturated.
ii. *Nonthreshold* substances get reabsorbed by a passive mechanism. Their transport varies directly with the concentration present in the filtrate without any upper limit.

Secretion

1. Hydrogen ion is the only substance, which cannot be got rid of by filtration. It is actively secreted into the tubular lumen. The quantity secreted is such that it is enough for maintaining the internal environment constant in pH.
2. Potassium ions are also secreted passively along an electrical gradient.

Tubular load: All the substances present in the glomerular filtrate constitute a load for the tubule to handle. For example, tubular load for water is 180 L per day (It can fill 10 to 11 medium sized buckets).

Tubular load for other substances is also easily calculated. For example, GFR = 125 ml/min. Concentration of glucose is same in plasma as well as glomerular filtrate. If the blood glucose level is 100 mg/100 ml. that means 125 ml of glomerular filtrate will contain 125 mg of glucose or in other words the tubular load for glucose is 125 mg/minute.

Tubular Transport Maximum

Many of the mechanism for reabsorption and secretion of substances depend on the membrane carrier proteins. Therefore, the maximum amount of a substance that can be

transported (reabsorbed or secreted) depends on the number of carrier molecules available. When all the carrier sites are occupied, the rate of transport cannot be increased any further. Therefore, most substances absorbed by means of a carrier, display a transport maximum (Tm).

The tubular transport maximum for glucose is 320 mg/min, but some glucose appears when tubular glucose load exceeds 220 mg/minute. At this load the plasma glucose level is about 180 mg per 100 ml. Thus, glucose appears in urine when plasma glucose level exceeds 180 mg/100 ml. This level is called threshold plasma concentrations for glucose.

Substances without a Transport Maximum

1. Those substances which are transported by simple diffusion (i.e. without a carrier), e.g. water or urea, do not have a Tm.
2. Many rapidly absorbed substances such as sodium ions, also do not have a Tm although their transport is carrier mediated, because limiting factor for *rate of transport is the rate of diffusion at the brush border* and not the sodium pump at the basolateral membrane.

   Transport of substances, which do not show a Tm depends on the concentration gradient and the time available for transport. Therefore, such transport is called gradient-time transport.

Tubuloglomerular Feedback, and Glomerulotubular Balance

i. Signals from renal tubules feedback to affect glomerular filtration. As the rate of flow through the ascending limb of loop of Henle and first part of the distal tubule increases, glomerular filtration in the same nephron decreases and conversely, decreased flow increases GFR. This process is called *Tubuloglomerular feedback,* and it tends to maintain the constancy of the load delivered to the distal tubule. Sensor probably is macula densa and effect is brought about by constriction or dilatation of the afferent arteriole.

ii. Conversely, an increase in GFR causes an increase in the reabsorption of solutes and of water, primarily in the proximal tubule, so that in general, the percent of solute reabsorbed is held constant. This process is called *Glomerulotubular balance,* and it is particularly prominent for Na^+. The change in Na^+ reabsorption occurs within seconds after a change in filtration.

We have considered general concepts involved in urine formation. Now, we will consider the journey of glomerular filtrate as it passes through the tubules and concentrate, on the way individual substances are handled when body has essentially normal quantities of filtered constituents.

CHAPTER

63

The Proximal Tubule

The proximal tubule is lined with epithelium which has:

1. A brush border on the luminal side, and
2. Sodium pump in the basolateral membrane,

Changes that take place in proximal tubule are:

1. Enormous volume of glomerular filtrate is reduced to 1/3.
2. Quantity of most other substances in filtrate is reduced to 1/3.
3. As a result, concentration of most solutes remains the same as in glomerular filtrate.

   Exceptions are:

   i. Glucose
   ii. Amino acids, and
   iii. Proteins which are absorbed from the filtrate almost completely, and
   iv. Creatinine which is not absorbed at all.
4. Absorption in proximal tubules follow a constant pattern irrespective of:
   i. Fluid and electrolyte status of the body, and
   ii. They are not subject to hormonal control.

   Therefore, absorption in the proximal tubule is called *obligatory.*
5. Fluid leaving proximal tubule is isotonic with plasma as well as with glomerular filtrate.

SODIUM REABSORPTION

1. Reabsorption of sodium and chloride ions plays major role in electrolyte and water metabolism.
2. Reabsorption of sodium is coupled to:
   i. Movement of H^+
   ii. Other electrolytes
   iii. Glucose
   iv. Amino acids
   v. Organic phosphate, and
   vi. Other substances.

   Thus, the mechanism of reabsorption in the proximal tubule and elsewhere in the nephron is designed basically *for reabsorption of sodium.* The other substances are mostly *cotransported:* (i) by a common carrier protein, (ii) or to maintain electrical neutrality, (iii) the movement of water is by *osmosis,* (iv) some substances are transported with water due to *solvent drag.*
3. Sodium ions are absorbed actively by a *Na-K ATPase located in the basolateral membrane.* The pump is driven by the energy released from hydrolysis of ATP. Hydrolysis of ATP

is catalyzed by Na-K ATPase (That means the carrier acts as an enzyme also, which hydrolyzes ATP).

In other words—Na^+ is pumped from the cells into the peritubular fluid, from where it diffuses into capillaries.

4. For each Na^+ transported, a K ion is transported in the opposite direction, i.e. into tubular cell. But the concentration gradient causes diffusion of K^+ back into peritubular fluid (Fig. 63.1).
5. Active transport of sodium in peritubular fluid:
   i. Creates a concentration gradient between glomerular filtrate in the lumen and epithelial cell, and
   ii. It also makes interior of the cell—70 mv negative to outside.

As a result of the concentration and electrical gradients, sodium diffuses from filtrate into the epithelial cell *across the brush border* (Fig. 63.1).

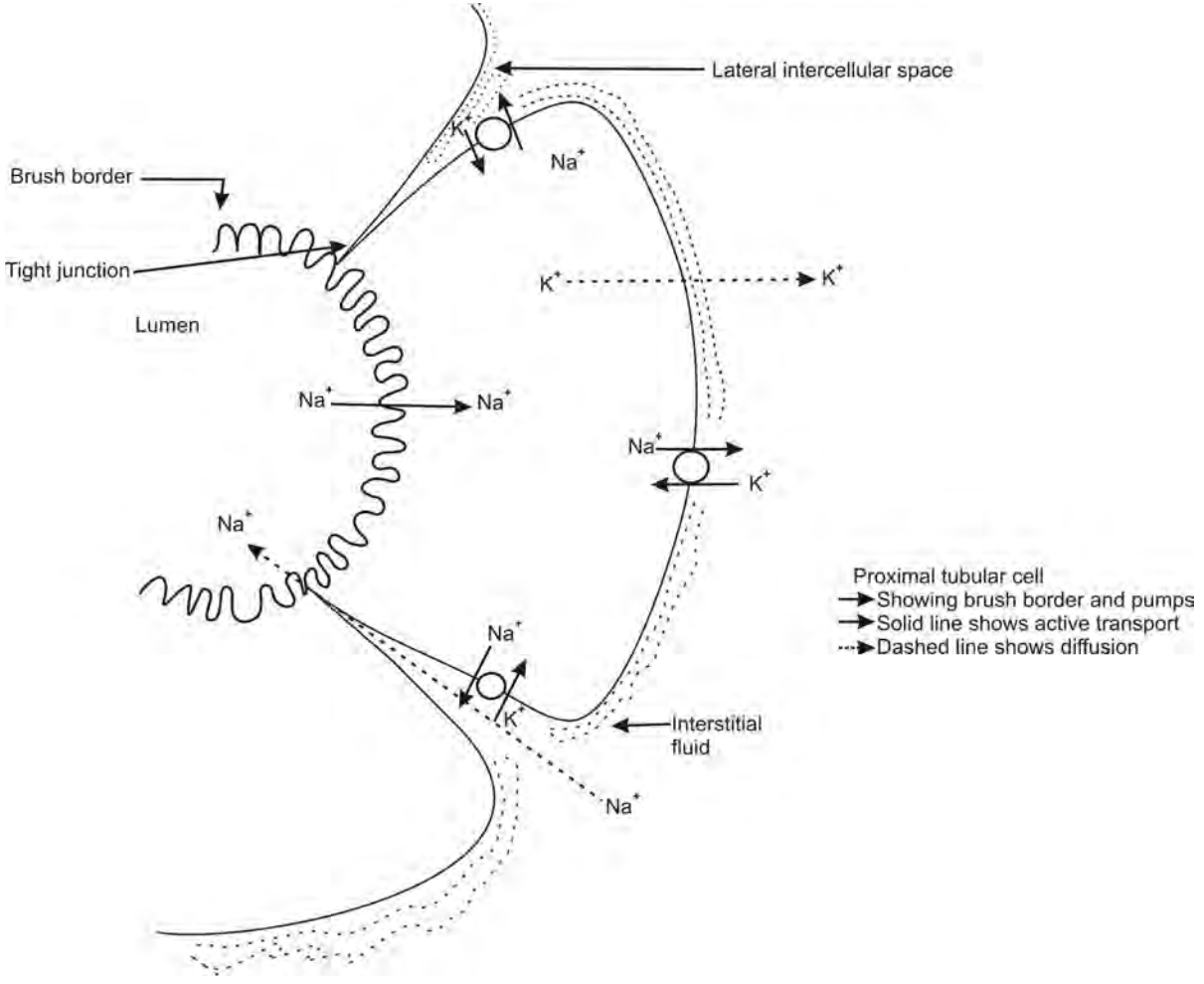


Fig. 63.1: Proximal tubule

6. The *brush border* has a *protein carrier* to facilitate the diffusion.

GLUCOSE TRANSPORT (REABSORPTION)

1. Glucose, amino acids, and bicarbonates — are reabsorbed along with Na^+ in early portion of proximal tubule
2. Farther along the tubule Na^+ is reabsorbed with Cl^-
3. Glucose is typically removed from the glomerular filtrate by secondary active transport.
4. Essentially all of the glucose is reabsorbed. The amount reabsorbed is proportionate to the amount filtered and therefore, to the plasma level of glucose. But when the TmG is exceeded, the amount of glucose in the urine increases. The TmG is about 375 mg /min in men and 300 mg/min in women.

   The renal threshold for glucose is the plasma level at which the glucose first appears in the urine.
5. *Glucose transport mechanism* glucose reabsorption in kidney is similar to glucose reabsorption in the intestine.

   Glucose and Na^+ bind to a common carrier in the luminal membrane and glucose is carried into the cell as Na^+ moves down its electrical and concentration gradient.

   Na^+ is then pumped out into the peritubular spaces and glucose is transported by facilitated diffusion. The energy for this active transport is provided by the Na^+-K^+ ATPase that pumps the sodium out of the cells (Fig. 63.2).

The common carrier specially binds D isomer of glucose and the rate of transport of D-glucose is many times greater than that of L-glucose. Glucose transport in the kidneys is inhibited, as it is in the intestine, by *phlorhizin* (plant glucoside), which complete with D-glucose for binding to this symport.

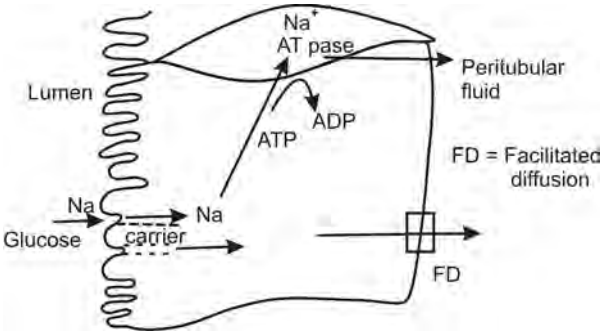


Fig. 63.2: Transport of glucose in proximal tubule

AMINO ACID TRANSPORT

Amino acid transport—like glucose reabsorption, amino acid reabsorption is most marked in early portion of the proximal convoluted tubule. In general, the main carriers in the luminal membrane cotransport Na^+, whereas the carriers in the basolateral membrane are not Na^+ dependent.

When cotransport occurs, Na^+ is pumped out of the cells by Na^+-K^+ ATPase and the amino acids leave by passive or facilitated diffusion to the interstitial fluid.

REABSORPTION OF BICARBONATES (FIG. 63.3)

Reabsorption of bicarbonates in the proximal tubule—about 90% of the filtered bicarbonate is reabsorbed in the proximal tubule.

The mechanism of bicarbonate reabsorption:

1. CO_2 is produced by the metabolism of tubular cell or enters tubular cell from blood or from lumen.
2. CO_2 combines with water with the help of carbonic anhydrase.
3. H_2CO_3 dissociates into H^+ and HCO_3^-.
4. Bicarbonate is reabsorbed in peritubular fluid.
5. H^+ ions are secreted in tubular fluid.

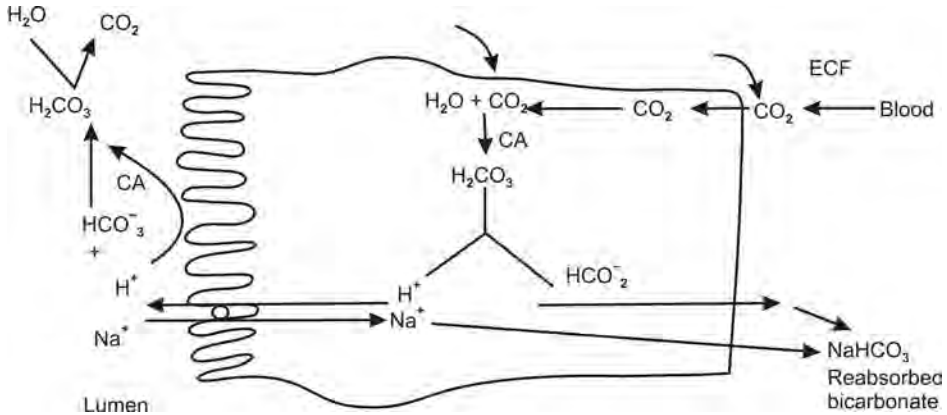


Fig. 63.3: Mechanism of reabsorption of bicarbonate in the proximal tubule, CA = Carbonic anhydrase

6. The secretion of H^+ ions is by secondary active transport, which is coupled with active reabsorption of sodium ions.
7. In the lumen, H^+ reacts with filtered HCO_3 forming H_2CO_3. Carbonic acid dissociates into water and carbon dioxide. This reaction is catalyzed by brush border carbonic anhydrase.

Carbon dioxide may diffuse back into the cells or may enter circulation and eventually eliminated by lungs.

Thus, bicarbonate is reabsorbed indirectly. The bicarbonate absorbed in the blood is not the same as the one, which is filtered possibly because bicarbonate is the large ion and its permeability is not high, but carbon dioxide being a lipid soluble substance can pass through cell membrane with great ease.

Secondly, reabsorption of bicarbonate is associated with secretion of hydrogen ions. However, the secreted H^+ are only recycled and make no change in acid base balance of the body and the ultimate effect of the entire process is simply reabsorption of $NaHCO_3$.

PHOSPHATE REABSORPTION

The phosphate concentration of glomerular filtrate is approximately 1mEq/L. Some 170 mEq of phosphate are filtered daily, of this filtered load about 40 mEq/L is excreted in urine.

Phosphate reabsorption is restricted to proximal tubule that is phosphate reabsorption takes place only in proximal tubule as shown by stop flow technique.

HPO^-_4 or HPO^{2-}_4 are reabsorbed here in the same ratio (4:1) as they exist in plasma and glomerular filtrate, because the pH of the proximal tubular fluid does not change from that of plasma.

Mechanism

Phosphate reabsorption is coupled with reabsorption of sodium in proximal tubule.

CHLORIDE REABSORPTION

Sodium cannot be reabsorbed alone, it must be accompanied by anions. Cl^- is therefore, reabsorbed secondary to sodium and potassium reabsorption.

POTASSIUM REABSORPTION

Filtered K^+ is completely reabsorbed in the proximal tubule. But urine contains some K^+ ions. It means that K^+ is secreted from more distal segments.

WATER REABSORPTION

In proximal tubule 7/8 th of the water which enters the proximal tubule from glomeruli is reabsorbed (Fig. 63.4).

In proximal tubule water moves passively along the osmotic gradient setup by active transport of solutes.

The movement is facilitated by the presence of water channels in the apical membranes of proximal tubule epithelial cells.

The passive reabsorption of water is obligatory or compulsory to maintain isotonicity.

Secretion

Certain substances are secreted from plasma into the proximal tubular fluid actively. For example—para-aminohippuric acid (PAH), penicillin, iodinated dyes (diodrast).

In short, detailed composition of reabsorbed fluid resemble that of filtrate but is not identical because it does not contain creatinine and urea.

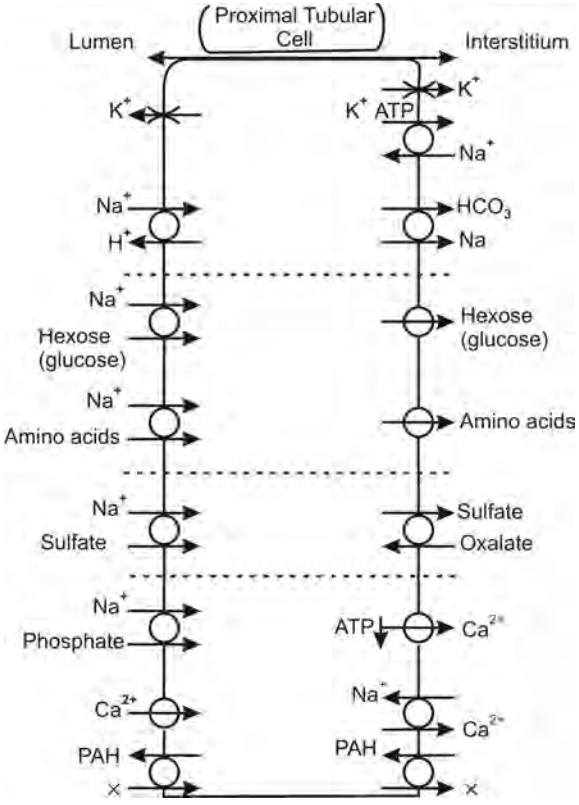


Fig. 63.4: Summary of transport mechanism in proximal tubule

LOOP OF HENLE

The loop of Henle has: (a) a descending, and (b) an ascending limb. The descending limb and a part of ascending limb are lined by thin epithelial cells, (c) while the terminal part of ascending limb is lined with thick epithelial cells.

1. Thin segment, descending limb:
   i. This segment has cells with.
      a. No brush border
      b. Very few mitochondria.
   ii. This segment is highly permeable to water.
   iii. This segment is quite permeable to sodium.
   iv. Transport through thin segment is considerable and passive
   v. Passage through this segment further reduces the volume by 15% without significant change in tonicity.
   vi. This reabsorption is also obligatory.

Reabsorption through proximal tubule and thin segment of descending limb, reduces the glomerular filtrate to one fifth, irrespective to fluid and electrolyte status of the body. Thus, 80% is absorbed back.

2. *Thin segment, ascending limb:* This segment of loop of Henle differs from the descending limb. It is much less permeable to water. This sudden change in permeability plays important role in concentration of urine by countercurrent principle.
3. *Thick segment, ascending limb*
   i. Cells are cuboidal in this segment but the brush border is not well developed.
   ii. Thick segment is almost totally impermeable to water. Again this is important for concentrating urine by countercurrent principle.
   iii. The cells of this segment have pump for active reabsorption of sodium in basolateral membrane.
   iv. Absorption of sodium and other solutes (bicarbonate) without absorption of water leads to dilution of tubular fluid in this segment.

DISTAL TUBULE

1. Distal tubule is that segment of the nephron which begins at the point where the ascending limb of loop of Henle reaches the level of its corresponding glomerulus.
2. It has two functionally district segments:
   i. The early distal tubule
   ii. The late distal tubule.

The early or proximal part of distal tubule is functionally identical to the thick ascending limb of the loop of Henle. Therefore, it dilutes the urine by removing solutes and known as diluting segment.

The late distal tubule following characteristics:

i. It has common transport mechanism for reabsorption of sodium and the secretion of potassium and the activity of this mechanism is regulated by adreno cortical hormone – aldosterone.
ii. Permeability to water is governed by hypothalamic hormone, antidiuretic hormone (ADH).
iii. This segment is otherwise impermeable to water but becomes permeable in presence of ADH.
iv. It can secrete large amounts of hydrogen ions if it is needed to maintain acid base balance.
v. The late distal tubule is impermeable to urea, so urea does not get reabsorbed.

Thus, urea reaching this segment will be excreted.

But reabsorption/excretion of:
- Water
- Sodium
- Potassium, and
- Hydrogen ions depends on requirements of the body to maintain homeostasis.

The cortical collecting duct is functionally identical to late distal tubule.

Reabsorption

1. Sodium absorption is coupled with potassium secretion.
2. Bicarbonate reabsorption in early distal tubule is similar to that of proximal tubule.

   Bicarbonate reabsorption in late distal tubule (10%) is also similar. The difference is absence of carbonic anhydrase in the luminal surface of the cells.
3. *Water:* Normally, 180 L of fluid are filtered through glomeruli each day. Out of which 80% is reabsorbed in proximal tubule and descending limb.

   Reabsorption of remainder of the filtered water can be varied without affecting total solute excretion. When urine is concentrated, water is retained in excess of solute and when it is dilute water is lost from the body in excess of solute. Important for maintaining osmolarity.

   Most of the regulation of water output is exerted by ADH acting on late distal tubule and collecting ducts.

Secretion

1. *Potassium*—ion is both secreted and reabsorbed in the tubule, but potassium balance is maintained by regulating potassium secretion in the distal tubule.

   It depends on— Na^+-K^+ ATPase in the basolateral membrane of the tubular epithelium. K^+ enters the cell, which is partly pumped in lumen and partly it diffuses in lumen (Fig. 63.5).

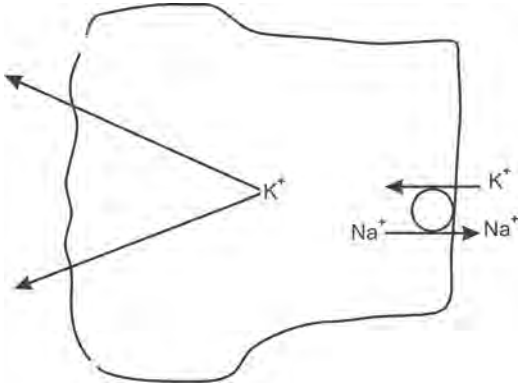


Fig. 63.5: Mechanism of potassium secretion

   Aldosterone increases active secretion of potassium by increasing activity of Na^+-K^+ ATPase and by increasing permeability of the luminal membrane to potassium.
2. *H^+ ions:* Carbon dioxide is generated in the cells or comes from blood stream and not derived from reactions in lumen, is excreted as H^+ and for each H^+ lost one HCO_3^- is absorbed (Fig. 63.6).

The Collecting Duct

This segment retains water and has permeability (sensitive to ADH) and capacity to secrete H^+ ions if necessary.

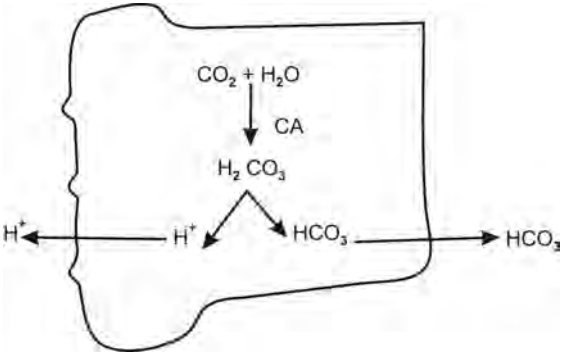


Fig. 63.6: Mechanism of secretion of H^+ ion

Thus, the nephron has four functional segments:

1. *The filtering segment:* Bowman's capsule in which the glomerular capillaries filter the plasma.
2. *The conserving segment:* The proximal tubule which conserves water, electrolytes, glucose, amino acids and proteins by reabsorption.
3. *The concentrating segment:* Consisting of loop of Henle and diluting segment of distal tubule.
4. *Regulating segment*: Late distal tubule and cortical collecting duct and medullary collecting duct. Reabsorption of secretion from this segment is regulated by fluid, electrolytes and acid base status of the body and is under control of aldosterone and ADH.

CHAPTER

64 Concentrating and Diluting Mechanism of the Kidney (Countercurrent Mechanism)

The concentrating mechanism depends upon the maintenance of a gradient of increasing osmolarity along the medullary pyramids. For this purpose anatomically peculiar structures of the nephron namely help:

1. The loop of Henle, and
2. Vasa recta.

The gradient of increasing osmolarity is:

i. Produced by the operation of the loop of Henle as *countercurrent multipliers* (= countercurrent flow results in building up of high vertical osmotic gradient), and

ii. Maintained by operation of vasa recta as countercurrent exchangers (by passive process and depends upon the diffusion of water and solutes in both directions across permeable walls of vasa recta).

DEFINITION

A countercurrent system is a system in which the inflow runs parallel to, counter to and in close proximity to, the outflow for some distance.

This occurs in both, the loops of Henle and the vasa recta.

Loop of Henle

The descending limb in which the tubular fluid flows towards the hairpin bend (downwards) and the ascending limb in which the tubular fluid flows upwards lie close to each other and two such tubes in which fluid flows in opposite directions provide an opportunity for countercurrent multiplication.

Vasa Recta

Vasa recta are capillary vessels which arise from the efferent arteriole, run parallel to loops of Henle and are similar loops; and in them the flow is *countercurrent* (vasa recta are examples of *portal system.* The efferent arteriole is interposed between two sets of capillaries—namely the glomerular capillaries and the peritubular capillaries, vasa recta are part of peritubular capillaries).

Juxtamedullary Nephrons

In juxtamedullary nephrons with longer loops and thin ascending limbs, the osmotic gradient is spread over a greater distance and the osmolarity at the tip is greater. The greater the length of the loop of Henle, the greater the osmolarity that can be reached at the tip of the pyramid.

One-fifth of the total nephrons are juxtamedullary. In kangaroo rat, which lives in desert the loops of Henle are very long some reaching the ureter whereas in rodents, which concentrate their urine to less extent the loops of Henle extend only up to tip of the papilla. Thus, there is some relation between ability to make urine hyperosmotic to plasma and presence of medullary loops of Henle.

CAUSE OF MEDULLARY OSMOTIC GRADIENT

Renal medulla shows an increasing osmotic pressure (osmolarity) with increasing depth. In the cortex osmolarity is 300 mosml/L. It gradually increases in medulla and the osmolarity reaches a level of 1200 m.osm/L at the pelvic tip of the medulla.

Following factors are responsible:

1. Na^+ is actively pumped out of the thick ascending limb of loop of Henle into the medullary interstitial fluid. Along with Na^+ some more substances are absorbed due to secondary active transport.

   Na^+ is followed by Cl^- absorption to maintain electrical neutrality.

   Na^+, Cl^- and other solutes absorbed along with Na^+ by secondary active transport, are absorbed in peritubular fluid and from there they diffuse into descending limb of loop of Henle.
2. The ascending limb is impermeable to water; therefore, water cannot leave it in response to osmotic gradient generated by the expelled Na^+ and other solutes.
3. The medullary region of collecting duct is permeable to urea. Diffusion of urea from these ducts also increases the osmolarity of the interstitium.

Under influence of ADH the permeability of medullary collecting ducts to urea also increases further.

ADH makes collecting ducts also permeable to water, which causes outward diffusion of water. This increases urea concentration within the duct and further diffusion of more urea outward takes place. Urea enters thin limb of loop of Henle and recirculates in distal tubule and collecting duct.

Thus, urea makes an important contribution to the genesis of high osmolarity in the renal medulla and high protein diet increases formation of urea and the ability of kidneys to concentrate the urine.

The *transverse gradient* from ascending limb to peritubular fluid, and from peritubular fluid to the descending limb is *small*, at any level. Therefore, *energy spent on transport is less*.

But because of the *countercurrent flow*, a high vertical osmotic gradient is built up. Therefore, the phenomenon is called the *countercurrent multiplier effect*.

MAINTENANCE OF MEDULLARY OSMOLARITY GRADIENT

Two factors contribute:

1. *Blood flow in medulla is poor:* In cortical nephrons the countercurrent mechanism cannot operate effectively because blood washes away the actively expelled Na^+ and other solutes, as cortical nephrons have rich blood supply (Fig. 64.1).

   In juxtamedullary nephrons the osmotic gradient can be maintained because the blood flow is poor.
2. *The blood vessels (vasa recta) are also U shaped.* The descending limb of *vasa recta* looses water due to osmosis and gains solutes due to diffusion. In ascending limb of vasa recta transport of water and solutes is in opposite direction, by same passive mechanisms and this prevents any significant wash out (Fig. 64.1).

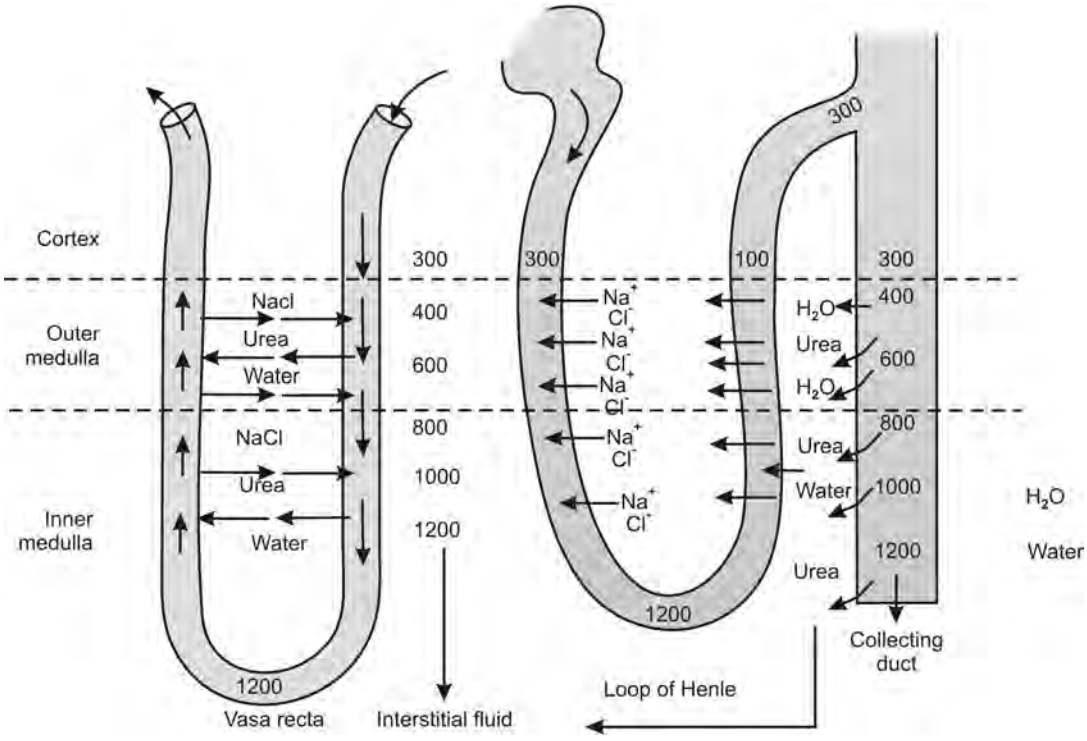


Fig. 64.1: Countercurrent mechanism

Vasa recta also carry away the water reabsorbed from: (a) thin descending limb of loop of Henle and (b) collecting ducts.

Therefore, the volume of blood flowing out of vasa recta is greater than the volume of blood flowing in.

COUNTERCURRENT MULTIPLIER OF LOOP OF HENLE

In countercurrent mechanism, the fluid flows through a long U tube, fluid flowing in one arm of the U and then out in opposite arm.

When fluids in two parallel streams of flow interact appropriately with each other, tremendous concentration of solute is built up at the tip of the loop, e.g. *loop of Henle.*

1. Descending limb is highly permeable to sodium and chloride. Ascending limb has strong active transport mechanism which removes Na^+ which is followed by Cl^- from tubule into the interstitial fluid. Active transport of Na^+ is accompanied by secondary active transport of other substances.
2. Therefore, each time sodium and chloride is transported out of ascending limb it almost immediately diffuses into the descending limb, thus, increasing the concentration of NaCl in tubular fluid—that flows downward toward the tip of the loop.
3. This, NaCl flows on around the loop and is then actively transported again out of ascending limb.
4. In addition, new NaCl is entering the tubular system in glomerular filtrate and

is also transported out of the ascending limb.

5. Thus, by transport again and again of sodium chloride plus constant addition of more and more sodium chloride the concentration of NaCl in the medullary fluid rises very high. This mechanism of loop of Henle is called countercurrent multiplier because a high vertical osmotic gradient is built up.

Countercurrent mechanism in vasa recta: It is another factor which helps to explain very high concentration of sodium chloride in the medulla.

As the blood flows down the descending limb of vasa recta, sodium chloride diffuses into the blood from interstitial fluid and water to interstitial fluid. So, the osmolar concentration rises progressively higher to a maximum concentration of 1200 milliosmols/L at the tips of vasa recta.

Then as the blood flows back, up the loop, all extra NaCl is lost because of *extreme permeability* of *capillary membrane* and because the osmolar concentration of interstitial fluid will become less and less and the water diffuses back in vasa recta.

Therefore, by the time blood finally leaves the medulla its osmolar concentration is only slightly greater than that of the blood that had initially entered vasa recta. As a result, the blood flowing out of vasa recta carries only a minute amount of sodium chloride away from the medulla.

Dilution of tubular fluid in the ascending limb of loop of Henle: The *ascending limb* of loop of Henle is highly impermeable to water and tremendous quantities of NaCl are transported out of ascending limb of loop of Henle into interstitial fluid. Active transport of Na^+ is accompanied by secondary active transport of other substances.

Therefore, the fluid in ascending limb becomes progressively more dilute as it ascends towards cortex and osmolarity decreases to about 100 m. osmols/L before leaving the loop of Henle. Hence, called as diluting segment.

MECHANISM OF EXCRETING DILUTE URINE

Kidney can allow this dilute fluid to empty in renal pelvis. Thus, dilute urine can be formed. So, when body needs to lose more water ADH is absent.

The ascending limb of loop of Henle and diluting segment of the distal tubule are impermeable to water.

The late distal tubule and collecting ducts are also impermeable to water *in the absence of ADH* and no water is reabsorbed in distal tubule and collecting ducts.

But all these segments, ascending limb onwards have a mechanism for active reabsorption of Na^+ and many other solutes except waste products.

Reabsorption of Na^+ and other solutes lead to the formation of dilute urine.

Mechanism for excreting concentrated urine —is exactly opposite.

Large quantities of ADH are secreted. In presence of ADH, the late distal segment and collecting duct are permeable to water and in medullary region the collecting duct is permeable also to urea, which makes osmotic gradient more steep, as a result more water diffuses out of the portion of the nephron which have become permeable to water under influence of ADH.

So, water is reabsorbed by osmosis and there is osmotic equilibrium with that of cortical interstitial fluid that is 300 m.osm/L.

Now, the tubular fluid passes back through the medulla *second time* downward through

collecting tubule and exposed to hyperosmolarity of medullary interstitial fluid. Therefore, large quantities of water are reabsorbed by osmosis into medullary interstitial fluid from collecting duct. The osmolar concentration of fluid in collecting duct increases to 1200 m.osm/L.

All degrees of concentration of urine can occur depending on amount of ADH and composition of urine can be changed from moment-to-moment according to needs of the body. For example, body at times has excess of water therefore, it must excrete dilute urine and when body has deficit water it must excrete minimum water in urine.

Reabsorption of water under the effect of ADH in late distal tubule and collecting duct is known as *facultative reabsorption of water*.

CHAPTER

65

Role of Kidney in Acid-base Balance

One of the most important functions of the kidney is to maintain pH of the body fluids within a very narrow range. Normal pH of ECF is 7.4 and range is 7.38 to 7.42.

Carbon dioxide is an acidic end product of normal energy metabolism and it is constantly produced by the body, CO_2 can be eliminated by lungs.

Besides carbon dioxide other acidic by-products of metabolism are:

1. Sulfuric acid
2. Phosphoric acid
3. Lactic acid
4. Keto acids
5. Hydrochloric acid
6. Uric acid.

Kidneys eliminate acid from the body by *secreting hydrogen ions* into the urinary tubules and thereby help to maintain pH of the body fluids constant.

H^+ SECRETION (FIG. 65.1)

The cells of the proximal and distal tubules secrete H^+ ions like the cells of gastric glands. Collecting ducts also secrete H^+ ions.

In Proximal Tubule

1. H^+ ion secretion occurs due to Na^+-H^+ exchange, which is example of secondary active transport. Na^+ enters the cell in exchange for H^+ secretion in lumen.

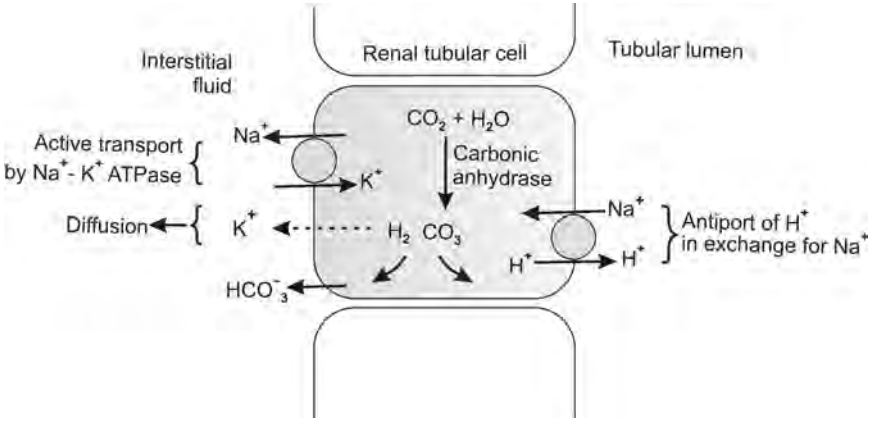


Fig. 65.1: Secreting acid by proximal tubular cells

2. Na^+ is actively transported into interstitium by Na^+- K^+ ATPase. This pump is situated in basolateral membrane of the tubular cell.
3. This lowers intracellular Na^+.
4. Lowering of intracellular Na^+ results in entry of new Na^+ from tubular lumen with coupled extrusion of H^+.
5. H^+ comes from intracellular dissociation of H_2CO_3 and HCO_3^- formed diffuses into interstitial fluid.

   Thus, for each Na^+ ion absorbed one bicarbonate ion enters in the interstitial fluid and one H^+ ion is secreted in tubular lumen and mechanism for H^+ ion secretion is coupled with mechanism of bicarbonate reabsorption.
6. Carbonic anhydrase catalyzes the formation of H_2CO_3. Drugs that inhibit carbonic anhydrase depress H^+ secretion.
7. In proximal tubule, Na^+-H^+ exchange mechanism results in H^+ ion secretion.

In Distal Tubule and Collecting Ducts

H^+ ion secretion is relatively independent of Na^+ in tubular lumen. In this part, H^+ is secreted by an ATP – driven proton pump.

FATE OF H^+ IN THE URINE

The maximal H^+ gradient, against which the transport mechanisms can secrete H^+ ions in lumen, corresponds to tubular fluid pH of about 4.5. At this pH, the H^+ ion concentration in tubular fluid is 1000 times greater *pH 4.5 is thus the limiting pH* (Figs 65.2 to 65.4).

Now, if there were no buffers in tubular fluid, which tie up H^+ in the tubular fluid—this pH would be reached rapidly (as H^+ will bind with Cl^- to form HCl, which is a strong acid) and H^+ secretion would stop.

But three important reactions in the tubular fluid remove free H^+. Therefore, more H^+ ions can be secreted in tubular fluid.

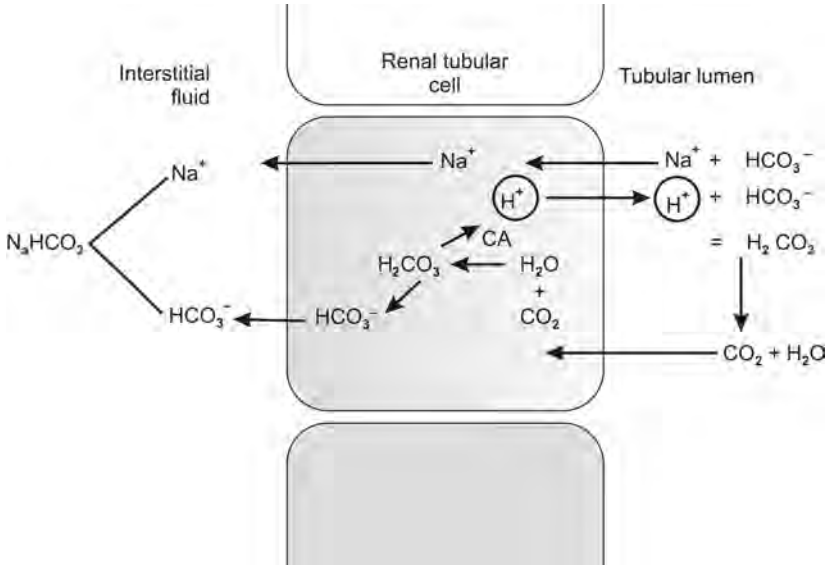


Fig. 65.2: Fate of H^+ secreted into a tubule in exchange for Na^+-reabsorption of filtered bicarbonate

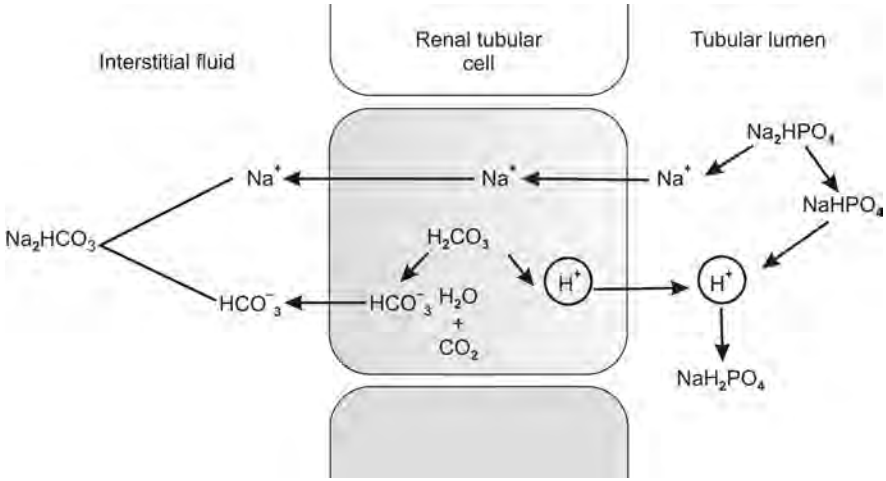


Fig. 65.3: Fate of H^+ secreted into a tubule in exchange for Na^+ formation of monobasic phosphate and reabsorption of bicarbonate

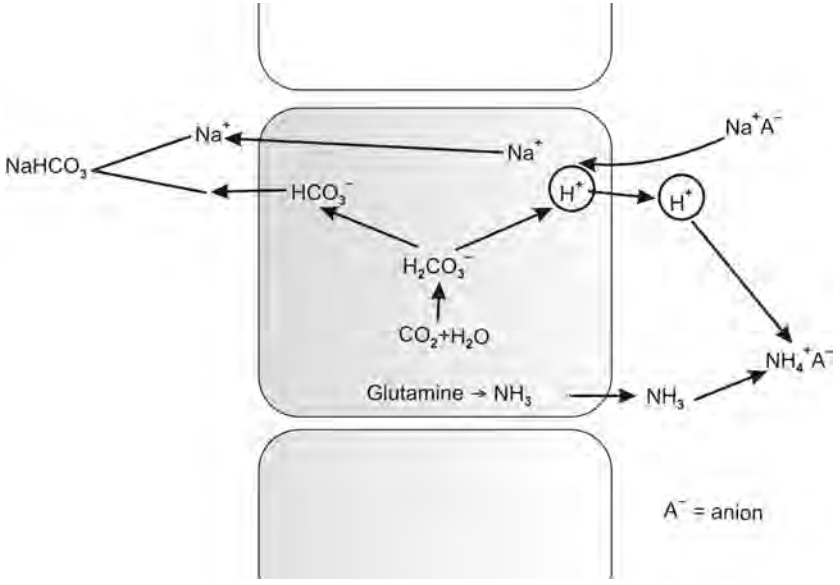


Fig. 65.4: Fate of H^+ secreted into tubule in exchange for Na^+, ammonium formation and reabsorption of bicarbonate

These reactions are:

i. With HCO_3^- to form CO_2 and H_2O.
ii. With HPO_4^{2-} to form $H_2PO_4^-$ and,
iii. With NH_3 to form NH_4^+.

Reaction with Buffers

Concentration of HCO_3^- in plasma is normally 24 mEq/L and therefore concentration of HCO_3^- in glomerular filtrate is also 24 mEq/L.

Concentration of phosphate is only 1.5 mEq/L

1. Therefore, in the *proximal tubule* most of the secreted H^+ reacts with HCO_3^- to form H_2CO_3.
   i. H_2CO_3 breaks down to form CO_2 and H_2O.
   ii. In the proximal tubule, there is carbonic anhydrase in the brush border of the cells. This facilitates formation of CO_2 and H_2O in the tubular fluids. (In distal tubule carbonic anhydrase is not there).
   iii. CO_2 which diffuses readily across all biological membranes, enters the tubular cell where it adds to the pool of CO_2 available for formation of H_2CO_3.
   iv. Since most of the H^+ ions are removed from the tubular fluid, the pH of tubular fluid is changed very little.

   This is the mechanism by which HCO_3^- is reabsorbed. For each mole of HCO_3^- removed from the tubular fluid, 1 mole of HCO_3^- diffuses from the tubular cells into the blood, even though it is not the same mole that disappeared from the tubular fluid.
2. Secreted H^+ also reacts with dibasic phosphate (HPO_4^{2-}) to form monobasic phosphate ($H_2PO_4^-$) (Fig. 65.3).

   This happens to a greatest extent in: (i) *distal tubule* and (ii) *collecting ducts.*

   The reason is that phosphate which has escaped reabsorption in proximal tubule gets concentrated in distal segments of the nephron by reabsorption of water.
3. *Ammonia mechanism:* Secretion of ammo-nia by the tubular cells is another device used by the kidney to dispose of excess of acid radicals from the body fluids (Fig. 65.4).
   i. Ammonia is formed from the amino acid glutamine by the action of the enzyme glutaminase.
   ii. Ammonia is also formed by deamination of glycine, alanined, etc. Ammonia formed in the tubular cells diffuses in tubular lumen, where it binds with hydrogen ions to form ammonium compounds which are excreted.
      a. Thus, secretion of ammonia helps to reduce the acidity of ECF. Synthesis of ammonia depends upon rate of H^+ ion secretion. In acidosis—the secretion of ammonia is increased and excretion of NH_4^+ increases.
      b. Thus, in proximal tubule cells: (a) the NH_4^+ enters the tubular lumen (b) whereas the HCO_3^- enters the inters-titium, helping to buffer the acid load.
      c. NH_4^+ that enters the proximal tubular fluid is reabsorbed in the thick ascending limb of loop of Henle.
      d. This maintains an NH_4^+ gradient by countercurrent multiplication, with a high NH_4^+ concentration in medullary pyramids.
      e. In collecting ducts NH_4^+ enters the tubular fluid and is excreted.
      f. NH_3 is lipid soluble and when formed in the cell it diffuses across the cell

membrane down its concentration gradient into: (i) the interstitial fluid, and (ii) tubular fluid.

In the tubular fluid it reacts with H^+ and the NH_4 formed remains in urine.

The process by which NH_3 is secreted into the urine and then changed to NH_4^+, maintaining the concentration gradient for diffusion of NH_3^+ is called nonionic diffusion.

Factors affecting Acid Secretion (H^+ Ion Secretion)

Acid secretion (H^+ ion secretion) by the kidney is altered by changes in:

1. Intracellular PCO_2.
2. K^+ concentration
3. Carbonic anhydrase level
4. Adrenocortical hormone concentration.

- When intracellular PCO_2 is increased (respiratory acidosis) more intracellular H_2CO_3 is formed and H^+ ion secretion is increased.
- Intracellular K^+ depletion increases H^+ ion secretion because intracellular *K^+ loss causes acidosis* and *K^+ excess inhibits H^+ ion secretion* because the formation of H_2CO_3 is decreased.
- When carbonic anhydrase is inhibited acid secretion is inhibited because the formation of H_2CO_3 is decreased.
  - Aldosterone and other adrenocortical steroids that increase tubular reabsorption of Na^+ also increase the secretion of H^+ and K^+.

The pH of urine in humans varies from 4.5 to 8.0. Excretion of urine, that is at different pH from that of the body fluids has important role for the body's electrolyte and acid base economy. Acids are buffered in plasma and cells, by $NaHCO_3$.→ CO_2 and water are formed. CO_2 is expired and sodium compound of the acid is filtered in glomerular filtrate.

In tubular reabsorption, Na^+ is replaced by H^+ and so Na^+ is conserved in the body.

Also for each H^+ ion excreted with phosphate or NH_4 there is net gain of HCO_3^- ion in the blood, which replenish the supply of this important buffer ion. When base is added to body fluid, OH ions are buffered raising plasma HCO_3^- and extra HCO_3^- is excreted in urine.

Note: Buffer is a substance, which minimizes the impact of the addition of an acid or alkali to the solution on its pH.

CHAPTER

66

Micturition

INTRODUCTION

Micturition is a process by which urinary bladder empties itself, when it becomes filled. Basically:

1. Bladder—progressively fills until the tension in its wall rises above a threshold value.
2. At this time a nervous reflex called micturition reflex is elicited.
3. That greatly exacerbates the pressure in the bladder and simultaneously causes a conscious desire to micturate.
4. Micturition reflex also initiates appropriate signals from nervous system to relax the external sphincter of the bladder thereby allowing micturition.

PHYSIOLOGICAL ANATOMY OF BLADDER AND ITS NERVOUS CONNECTIONS

Urinary bladder is a smooth muscle vesicle composed of two principal parts (Fig. 66.1).

1. *Body:* Composed mainly of detrusor muscle lined by transitional epithelium, which rests on lamina propria (fibroblastic). It has rugae, which get flattened when filled.
2. *Trigone:* Small triangular area near the mouth of the bladder through which both ureters and urethra pass.

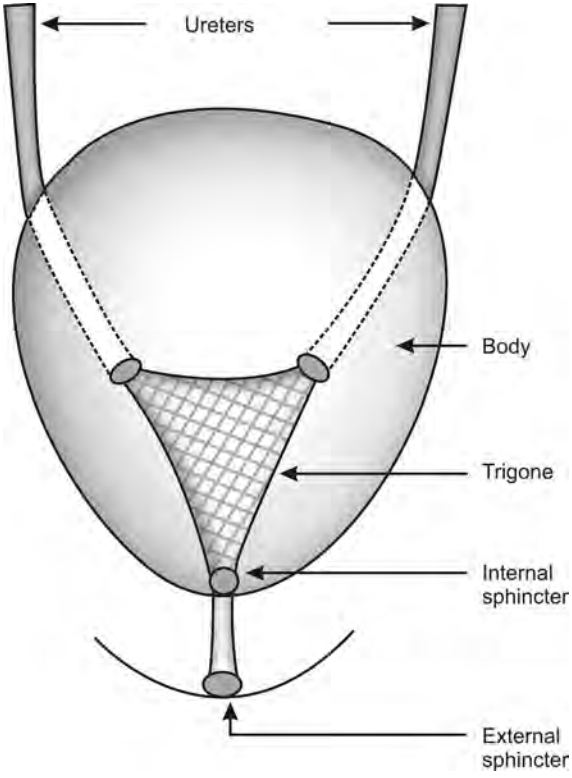


Fig. 66.1: Urinary bladder

During bladder expansion the body of the bladder stretches and during micturition reflex the detrusor muscle contracts to empty the bladder.

Trigonal muscle is interlaced around the opening of the urethra and maintains tonic closure of urethral opening until the pressure in the bladder rises high enough to overcome the tone of the trigonal muscle. This portion of smooth muscle is called *internal sphincter* of the bladder, which can withstand pressure 18-43 cm of water.

About 2 cm beyond the bladder the urethra passes through the urogenital diaphragm. The muscle of which constitutes the *external sphincter* of the bladder. This muscle is voluntary in contrast to other muscles of the bladder, which is entirely involuntary. Normally, this muscle remains tonically contracted, which prevents dribbling of urine.

1. External sphincter is important in forced and sudden increase in intra-abdominal pressure with consequent sudden rise of intravesical pressure to 50 to 80 cm of water.
2. Contraction of levator ani (= muscle of urogenital diaphragm) prevents reflex evacuation of bladder due to sudden rise of intravesical pressure forcing urine into urethra.
3. External sphincter can be reflexly or voluntarily relaxed at the time of micturition.

NERVE SUPPLY OF BLADDER AND URETHRA

Can be divided into two groups: (a) nerve supply of bladder, internal sphincter and proximal urethra, (b) nerve supply of external sphincter and distal urethra (Fig. 66.2).

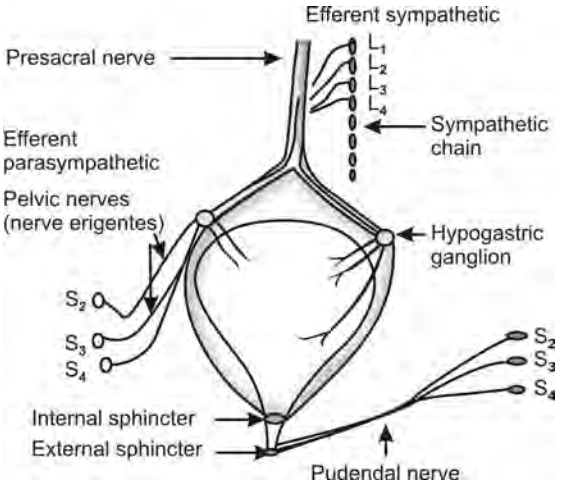


Fig. 66.2: Nerve supply of urinary bladder

Nerve Supply of Bladder, Internal Sphincter and Proximal Urethra

It has both afferent and efferent fibers from both sympathetic and parasympathetic divisions of nervous system.

Afferent sympathetic fibers enter through L_1, L_2 and lower thoracic segments.

Afferent parasympathetic enter through 2nd and 3rd sacred segments.

Efferent parasympathetic arise from L_1-L_4 segments pass through lateral sympathetic chain then through semilunar and inferior mesenteric ganglia and finally through presacral nerve to hypogastric ganglia through two hypogastric nerves and postganglionic fiber are supplied.

Efferent parasympathetic arise from 2nd and 3rd and 4th sacral segments fibers pass through pelvic visceral nerves (nervi erigentes) and end in hypogastric ganglia. Postganglionic fibers arise and supply.

Nerve Supply of External Sphincter and Distal Urethra

Nerve supply of external sphincter and distal urethra—are supplied by pudendal nerves, which arise from sacral segments—S_2, S_3, S_4.

FUNCTIONS OF AFFERENT AND EFFERENT FIBERS

Afferents

Afferents perform two functions:
1. Indicate degree of distension
2. Carry pain sensibility.

Efferents

Efferents perform two functions:
1. Parasympathetic excitation—causes contraction of detrusor muscle and opening of internal sphincter. (External sphincter, which is voluntary, is mainly controlled by pudendal nerves).
2. Stimulation of sympathetic causes bladder to relax.

TRANSPORT OF URINE THROUGH URETERS

Ureters are small smooth muscle tubes that originate in pelvis of two kidneys and pass downward to enter the bladder. Each ureter is innervated by both sympathetic and parasympathetic nerves and each also has an intramural plexus of neurons and nerve fibers that extends along its entire length.

The urine collects in calyces and pelvis of the kidney. Distension of minor calyces due to flow of urine triggers a calyceal contraction which progresses down in the form of peristaltic wave. Wave progresses at a rate of 3 cm/sec along the ureters. The necessary stimulus for contraction is the distention of the successive parts of the urinary tract due to flow of urine. Frequency of peristaltic wave varies. Parasympathetic stimulation increases the frequency and sympathetic stimulation decreases the frequency.

Note: According to some physiologists pacemaker for this automatic contraction may be present at the pelvicalyceal junction and intramural plexus in ureters are partly responsible for peristaltic waves.

At the lower end ureter penetrates through trigone obliquely. The ureter courses for several cm under the bladder epithelium, so that pressure in the bladder compresses the ureter, thereby preventing backflow of urine during micturition.

Ureters are well supplied with pain nerve fibers. Anytime the ureters are blocked (as for example by urinary calculi), intense stretch caused by urethral dilatation elicit, one of the most severe type of pain that one can experience. In addition, pain impulses cause a sympathetic reflex back to respective kidney to constrict the renal arterioles, thereby greatly decreasing urinary output from the kidney. This reflex is called *ureterorenal reflex*. It is obviously important to prevent excessive flow of fluid into the pelvis of a kidney whose ureter is blocked.

MECHANISM OF FILLING OF BLADDER

Normal bladder is completely empty at the end of micturition. The intravesical pressure is equal to the intra-abdominal pressure. As the bladder fills, it adjusts its tone to its capacity, so that minimal alterations of the intravesical pressure occur over a wide range of intravesical volumes.

This phenomenon—called *adaptation,* is an inherent property of the detrusor muscle, solely, not dependent on nervous mechanisms.

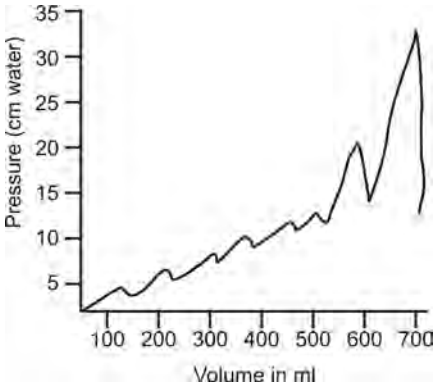


Fig. 66.3: Intravesical pressure in relation to filling (adaptation—initially, later sharp rise of pressure)

It is therefore, present in denervated bladders but not after death. The adaptation is not to a constant pressure but always to a slightly higher pressure than the previous pressure before the addition of urine (Fig. 66.3).

In adult: Direct measurement shows that a pressure of 10 cm of water exists at a filling of approximately 400 ml.

1. First sensation of bladder filling occurs at 150 ml.
2. First desire to void urine occurs at about 250 ml.
3. The physiological capacity of the bladder, that is maximum intravesical volume tolerated without undue discomfort and at which micturition is normally effected ranges between 250 and 450 ml.
4. Filling of bladder beyond capacity is associated with progressive failure of adaptation and intravesical pressure rises much more sharply relative to the intravesical volume. Then despite inhibition from the cerebral cortex, efferent impulses from lower micturition centers reach detrusor causing involuntary contraction of detrusor.

As the filling continues they are associated with sharp rise of pressure and felt consciously as an acute urge to void.

Physiological Capacity of Bladder

The physiological bladder capacity varies greatly with age and psychic factors:

1. At birth, it ranges from 20 to 50 ml.
2. During first year of life, increases 4 times.
3. In adult, it can be as high as 600 ml especially in persons whose occupation make access to lavatory facilities difficult.
4. In all cases the capacity is twice that at which the first desire to void is felt.

The Anatomical Capacity of Bladder

The capacity just before rupture occurs is well above 1 liter and is never approached under physiological condition.

Continence

In addition to accepting urine from the ureters and periodically discharging urine under voluntary control, the bladder must also retain urine. As the bladder fills with urine, continence is maintained by urinary sphincters and proximal 3 cm of urethra, because:

1. The tone of the smooth muscle of this part of urethra is high, and
2. Rich elastic tissue is present surrounding it. Both these keep urethra compressed. Maximum resistance is at the mid urethra.

The external sphincter normally is not necessary for continence and its paralysis does not cause leakage of urine provided the proximal urethra is intact.

In sudden increase in intra-abdominal pressure such as that occurs during coughing, laughing, intravesical pressure may reach 50 to 80 cm of water forcing urine into bladder

neck. Leakage is prevented under these circumstances by reflex contraction of external urethral sphincter and levator ani muscle.

Micturition

Micturition is periodic complete emptying of bladder and is under voluntary control except infancy.

At the end of voiding the bladder is empty and bladder neck is closed and intravesical pressure is close to O. The bladder slowly fills as the ureteral peristalsis jets the urine in bladder and in spite of the increasing intravesical volume its pressure remains low because of phenomenon of adaptation and at no time it exceeds either:

1. Intraureteral pressure at the ureterovesical junction or
2. Urethral resistance provided by closed proximal urethra.

   As bladder radius increases the tension in vesical wall increases—which stimulates proprioceptive end organs in the vesical wall, which send afferent impulses to spinal reflex centers for micturition (S2 - S4), via pelvic nerves.
3. Reflex center for micturition in brain stem, via fasciculus gracilis, and
4. Voluntary center for micturition in the paracentral lobule of cerebral cortex.

The first desire to void is felt at about 250 ml filling. At this stage the spinal reflex center for micturition is inhibited by impulses from the brain stem center via regulatory tracts, preventing efferent impulses from leaving the spinal center.

If micturition is unduly postponed, a feeling of fullness, then discomfort and finally pain results. Pain is transmitted to cerebral cortex via spinothalamic tracts. Under these circumstances voiding is prevented by cortical impulses blocking discharge of spinal center.

When an opportunity is found to empty the bladder—the voluntary restraint placed upon the spinal micturition center is lifted and micturition proceeds automatically—The sequence of events are:

1. The parasympathetic efferent—impulses reach the detrusor muscle and proximal urethra along the pelvic nerves.
2. Voiding contraction of detrusor muscle results generating intravesical pressure of 50 to 150 cm of water.
3. At the same time proximal urethra (or posterior urethra) shortens and widens.
4. The effect is to increase intravesical pressure and decrease:
   i. Urethral resistance, and
   ii. Internal sphincter resistance.
5. And a bolus of urine is forced in proximal (or posterior) urethra. This stimulates parasympathetic visceral afferents from this part of urethra via pelvic nerves to the spinal center.
6. This reflexly relaxes the external sphincter by decreasing the frequency of efferent impulses which normally travel from segments S2-S4, via pudendal nerves to keep the external sphincter in tonic contraction.

In females, the act of micturition ends abruptly. In males, the final passage of urine is, via penile urethra—which is a passive passage. The last drops of urine are removed by contraction of bulbocavernosus muscle.

Certain muscular movements not essential to micturition commonly accompany the act.

1. At the onset of micturition the levator ani and perineal muscles are relaxed—thereby shortening the posterior urethra and decreasing the urethral resistance.
2. At the same time the glottis closes, diaphragm descends and abdominal wall muscles contract. All these accelerate the

flow of urine by increasing the intra-abdominal pressure, which in turn increases intravesical pressure.

3. A voiding contraction once initiated is normally maintained until all the urine has been discharged from urinary bladder, because of facilitatory impulses from brain-stem.
4. The bladder contracts in all direction like a toy balloon deflating through its neck.
5. When the bladder and posterior urethra have emptied, the external urethral sphincter closes, the detrusor relaxes and finally posterior urethra closes gradually.
6. Arrest of voiding stream once initiated is accomplished by a powerful voluntary contraction of external sphincter and perineal muscles.
7. Micturition begins in the 5th intrauterine month with the onset of urinary secretion. It remains a reflex act until 2 ½ years of age, at which time it comes under the control of cerebral cortex. Complete continence is usually achieved at the age of 3 years.
8. Micturition can be started at much less filling of the bladder voluntarily. Under these circumstances the cortical center sends facilitatory impulses to the spinal center and therefore, the spinal center sends efferent impulses to detrusor muscle which begins its voiding contraction and all the events take place successively so that the act of micturition goes to completion.

CHAPTER

67

Renal Function Tests

The function of the kidney is to clean or clear the ECF of the body. Every time a small portion of plasma filters through the glomerular membrane, it passes down the tubule and is reabsorbed leaving behind the unwanted material.

Renal function tests can be classified—into three groups:

1. Tests for renal structural integrity
2. Tests for glomerular functional integrity
3. Tests of tubular functional integrity.

TESTS FOR RENAL STRUCTURAL INTEGRITY

Following methods are used to obtain information about the structure of the kidney:

1. Clinical examination of abdomen—direct palpation of kidney is done in patients—we can find enlarged kidney, e.g. polycystic kidney, tumors of kidney or hydro nephrosis.
2. Straight X-ray of abdomen:
   i. Size of the kidney can be made out
   ii. Presence of kidney stones is revealed.
3. Intravenous pyelography (IVP)—IV substances are injected which contain radiopaque substance, which is filtered through glomeruli and also secreted in tubular fluid by proximal convoluted tubule:

   X-ray pictures are taken at different intervals:
   i. Renal parenchyma is faintly visible: Urinary calyces, pelvis and ureters are visible and demonstrate the size and configuration of pelvis and calyces.
   ii. We come to know about size, shape, position of kidney and unilateral parenchymal disease.
4. *Retrograde pyelography:* Radiopaque substance is introduced in the pelvis after cystoscopy and catheterization. Information about pelvis, calyces and ureter is obtained.
5. *Renal angiography*: Radiopaque substance is injected in abdominal aorta—renal artery and arterial tree becomes marked in X-ray picture.
6. *Renal biopsy*: A piece of renal tissue is removed and examined under microscope (histopathology).

TEST FOR GLOMERULAR FUNCTIONAL INTEGRITY

Kidney receives 1300 ml blood per minute. Out of which 700 ml is plasma flow per minute.

From this 127 ml protein free fluid (which is also free of blood cells) is filtered each minute by the glomerular membrane.

Glomerular integrity can thus be studied by:

1. Measuring glomerular filtration rate (GFR)
2. By examining urine for protein, casts and cells, specific gravity, pH, color, odor, etc.

GFR can be measured with descending order of accuracy by:

1. Inulin clearance
2. Creatinine clearance
3. Urea clearance
4. Plasma concentration of creatinine and urea (or chemical assays).

The concept of renal clearance was defined by *Van Slyke*—as volume of plasma, which would be cleared of a substance by one minute excretion of urine. Take for example, urea clearance, which is 60 ml, it means 60 ml of plasma is cleared of its urea in one minute excretion of urine and according to Van Slyke the term clearance is a convenient way to picture the relationship between urea content of blood and rate of excretion, despite the fact that 40% of urea is reabsorbed in tubule and blood is never completely cleared of that product.

Calculation of Renal Clearance

We take simultaneous samples of blood and urine. Quantity of substance in blood is determined and quantity of substance appearing in urine excreted in one minute is determined. Clearance is calculate by formula:

$$C = UV/P$$

Where C = Clearance value
U = Concentration of substance in urine (mg/100 ml)
V = Volume of urine/minute
P = Plasma concentration of substance (mg/100 ml)

Quotient UV/P is expressed as ml/minute.

Useful hemodynamic measurements can be acquired from clearance methods, for example:

1. If a substance is completely filtered from glomerular plasma into ultrafiltrate at the same concentration as plasma, its clearance will equal GFR. Several substances are suitable in this regard, but the clearance of inulin (a polymer of fructose) is considered ideal for estimation of GFR.
2. Clearance of any substance, which is completely extracted from the plasma with each passage through functional kidney tissue, will measure ERPF (effective renal plasma flow). The clearance of para-amino-hippuric acid (PAH) is taken to represent ERPF.

Methods of Clearance Measurement

1. Exogenous clearance methods
2. Endogenous clearance methods.

Exogenous Type

Clearance is assessed after continuous infusion of the clearance substance. This may:

1. Augment concentration of substance naturally present in the plasma or may
2. Introduce a substance which normally is not present in the plasma, e.g. inulin.

Endogenous Type

Clearance of a substance at plasma concentration, which are naturally occurring in plasma is determined, e.g. urea and creatinine clearance.

Exogenous Clearance Method

In the classic constant infusion method:

1. A substance is infused intravenously at a rate which provides a constant blood level after an initial loading dose and a period

of equilibration in the fluid compartments of the body.
2. Urinary bladder is catheterized for accurate and complete collection of timed urine specimens.
3. Urine flow is increased by IV hydration at 2 ml/min:
   - to minimize error in urine collection
   - to reduce time lag between glomerular filtration and the time of excretion.

Three or more carefully timed collections are made—each of 15 to 30 minutes. At the end of each period the bladder is rinsed and the rinsed fluid is added to the specimens. Blood is collected at accurately measured intervals.

[Several modified methods to reduce error, utilize single intravenous injection of a clearance substance followed by multiple peripheral blood samplings. The decay curve (= falling concentration of the substance) is used to calculate clearance. Urine samples are not used].

1. *Inulin clearance:* GFR can be accurately measured, because it is totally excreted, therefore, the quantity excreted in 1 minute in urine is same as that which is filtered. GFR by inulin clearance is measured for research purposes because it is protracted procedure.

   Endogenous clearance method—for example, urea and creatinine clearance has several advantages over exogenous method =

   i. Concentration of endogenous substance remains fairly constant over 24 hours period even in kidney disease. Therefore, the intervals between the collection of samples may be increased, and
   ii. There is no need of catheterization. Therefore, widely used.
   iii. Relatively simple than exogenous method.

2. C*reatinine clearance:* It is convenient method of obtaining fairly accurate GFR, because creatinine is already present in the body fluids and its plasma concentration is constant in 24 hours. Therefore, only one sample of blood is needed for a 24-hour collection of urine.

   Technique—24 hours collection of urine and one sample of blood during this time are taken. If urine collection starts at 9 am, he is asked to empty bladder and discard this urine. For next 24 hours all samples of urine are collected in one container and ended approximately at same hour when it had begun. Volume of urine is measured and rate of urine flow per minute is calculated.
3. *Urea clearance:* Most widely used test for renal function, because urea clearance is directly related to GFR.

Disadvantages

1. Clearance of urea is less than rate of glomerular filtration.
2. It also varies with urine flow and technical inaccuracies.
3. Serious errors occur if bladder is not emptied completely.
4. Occasionally test is influenced by emotions.

In normal subjects when urine flows at 2 ml/min (minute) the amount reabsorbed is constant and is 2/5 of total quantity which has been filtered and as the urine flow becomes less more urea is absorbed.

In normal subjects when rate of urine flow is 2 ml/min urea clearance is 60% of normal GFR. Such a clearance is called maximum urea clearance.

If urine flow decreases maximum urea is reabsorbed and urea clearance decreases. In normal subejcts if the urea clearance is multiplied by square root of rate of urine flow —a figure is obtained which approximates to

an average of 54 ml/min regardless of rate of urine flow. This mathematical jaggery is called →

$$\text{Standard urea clearance} = \frac{UC}{\sqrt{\text{Rate of urine flow}}} = 54 \text{ ml/min}$$

Procedure

Plasma levels of urea may fluctuate and urea clearance vary with rate of urine formation. Therefore, it is done over a short period.

1. Two glasses full of water is given to increase rate of urine formation, half an hour before.
2. At the beginning—bladder is emptied and urine is discarded.
3. One hour later bladder is emptied again. Urine is saved. Sample of blood is taken.
4. Finally 1 hour later second urine sample is taken.
5. Volume of two successive urine collection is measured and sent to laboratory with blood sample.

Disadvantages

Plasma concentration of urea and creatinine.

Normal value for urea is 20 to 40 mg% and normal value for creatinine is 0.15 to 1.2 mg%.

If GFR falls —their concentration in plasma rises.

Conclusion

In patient, in whom renal disease is suspected, finding of rise of blood urea and creatinine is always good evidence of reduced GFR.

TESTS FOR TUBULAR FUNCTIONAL INTEGRITY

Fluid Deprivation Test

Specific gravity of sample of urine passed on waking should be measured. If 1018 or above, test will not give abnormal value.

Fluid deprivation results in increased concentration of plasma and volume of extracellular fluid shrinks. Both stimulate ADH secretion and urine becomes concentrated.

Test is done over 24 hours. 8 AM to next day 8 AM. Fluid taking is stopped till next day 8 AM—specific gravity of all samples is measured and normally one of the samples should at least have specific gravity 1022 (Range is 1022-1040).

Interpretation of urine concentration test depends on three factors, which concentrate urine.

1. Concentration of ADH circulating—wide variety of factors influence neurohypophysis, e.g.—concentration of ECF—blood volume.
2. Ability of tubules to respond to ADH—depends on integrity of renal tubules—defects may be acquired or congenital, and urine may remain hypotonic even on dehydration.
3. Rate of solute output—increased rate results in osmotic diuresis.

Elimination of Water Load

Early morning in fasting state—bladder is emptied. Patient is asked to drink water 20 ml/kg body weight, in 10 to 20 minutes. Urine is collected every hour for 4 samples. Specific gravity of each sample is measured. A normal person should excrete 75% of the water load and at least one specimen should have specific gravity of 1004. Impaired water elimination indicates renal disease involving renal tubules.

Not a single test gives idea about number of functioning nephrons.

CHAPTER 68

Body Temperature and Heat Balance of the Body

BODY TEMPERATURE

Human being is homeothermic.

That means a human being maintains his body temperature nearly constant in spite of wide variation in environmental temperature. He belongs to 'warm-blooded' category of animals like birds and mammals.

Invertebrates cannot adjust their body temperature and so are at the mercy of the environment. In reptiles, amphibia and fish the mechanism for maintaining body temperature is rudimentary and these species are called "cold-blooded" (poikilothermic) because their body temperature fluctuates over a considerable range.

The body temperature of human being is nearly constant. Body temperature means temperature of deeper structures of the body that is—viscera, liver, brain; and skin has lower temperature.

Deep body temperature = core temperature.

Superficial temperature = shell temperature (skin temperature).

Core Temperature

Most of the heat produced in the body is the result of oxidation. The main sources of heat are the most active tissues – the liver, secretory glands and muscles.

Measurement of Core Temperature

1. Clinically the site used most commonly is the mouth (0.5°C lower than rectal temperature).
2. Axillary temperature record is suitable in children which is about 0.3°C lower than oral temperature.
3. Rectal temperature is highest. It is the best index of core or central body temperature.

Normal Body Temperature

In humans, traditional normal value for oral temperature is 37°C (98.6°F). Range in young adults is 36.3-37.1°C (97.3°-98.8°F).

Following Factors Affect

1. Normal human core temperature undergoes a regular circadian fluctuation of 0.5

to 0.7°C (Circadian rhythm means a rhythm of about 24 hours synchronizing with daily environmental change from light to darkness). In individuals who sleep at night and are awake during the day temperature is lowest at about 6.00 am and highest in the evenings.
2. It is lowest in sleep, is higher slightly in the awake but relaxed state and rises with activity.
3. In women, there is an additional monthly cycle of temperature variation characterized by a rise in basal temperature variation at the time of ovulation.
4. Temperature regulation is less precise in children and they may have about 0.5°C higher level of temperature than adults.
5. During muscular exercise heat produced by muscular contraction accumulates in the body, and the rectal temperature normally rises to 40°C (104°F).
6. Body temperature also rises slightly during emotional excitement, probably owing to unconscious tensing of the muscles.
7. It is elevated by as much as 0.5°C when metabolic rate is high constantly, as in hyperthyroidism. It is lowered, when metabolic rate is low as in hypothyroidism.
8. Some apparently normal adults have a temperature above the normal range (constitutional hyperthermia).

HEAT BALANCE OF THE BODY

Man is evolved as a tropical animal, but most men now live in environmental temperature much lower than 37°C. The relatively accurate control of body temperature is achieved by balancing heat lost from the body against heat gained either by production within the body or by absorption from outside.

Heat balance in man

Heat gain	*Heat loss*
1. Metabolic processes	1. Conduction
- Basal metabolic processes	For example, immersion in water
- Specific dynamic action of food	2. Convection
- Shivering	Air currents
- Nonshivering thermogenesis	3. Radiation—to surroundings
2. Ingestion of hot foods	4. Evaporation
3. Ventilation—in hot climate	Insensible perspiration
4. Radiation	Thermoregulatory sweating
- From sun	Ventilation (Panting in animals)
- From surroundings	
Reduction of heat loss	Reduction of heat gain
1. Vasoconstriction of skin blood vessels and piloerection	1. Behavior
2. Behavior	- Reduction of clothing
- Clothing	- Cooler environment
- Artificial heating	- Increasing radiating surface area
- Reducing surface area	

Heat Gain

The body gains heat: (i) directly when its heat production increases, and (ii) heat is taken up under certain circumstances from environment.

But *reduction of heat loss* from the body may also be considered an indirect form of heat gain.

Heat Production in the Body

1. A proportion of heat produced by the body may be regarded as inevitable or obligatory since it arise from *vital activities* such as respiration, heart beat and circulation, maintenance of muscle tone, secretion and metabolism.
2. The amount of heat produced by a man in temperate climate depends on the kind and amount of *food eaten and metabolized*.

   The metabolic rate increases soon after a meal and remains above the basal level up to 6 hours after the meal. The effect is partly due to:

   i. Digestion and absorption of food and partly due to
   ii. Metabolic pathways involved in the assimilation of the food. It is called *specific dynamic action* of food or *thermic effect of feeding* or *dietary induced thermogenesis.* It is maximum for proteins.
3. *Nonshivering thermogenesis:* The pituitary, thyroid and adrenal medulla are controlled by hypothalamus. Each plays a part in endogenous thermogenesis (Fig. 68.1).

   Stimulation of hypothalamus by cold causes:

   i. Release of thyroid and adrenal medullary hormones. The hormones released by adrenal medulla and thyroid gland increase metabolic rate, and
   ii. Sympathetic stimulation—also increase metabolic rate.

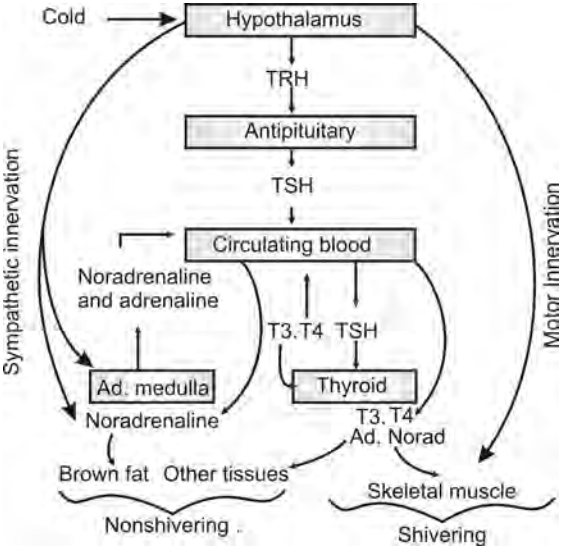
   Neurohormonal mechanism for heat production collectively are called *nonshivering thermogenesis.*
4. *Exercise*: Exercise increases heat production.
5. *Shivering:* Shivering is the result of rapidly alternating contraction and relaxation. This muscular activity does not produce any movement but increase heat production.

   Afferent impulses from skin play a role in producing shivering. For example, in cold, a stream of cold air or water falling on the skin produces shivering within few seconds. The rhythm of cold shivering seems to originate within the areas of motoneuron pool.

Heat Gained form the Environment

The body can take heat from objects hotter than itself:

1. By direct radiation from the sun or heated ground or



Ad. medulla = Adrenal medulla
Ad. Norad = Adrenaline and noradrenaline

Fig. 68.1: Endogenous thermogenesis

2. By reflected radiation from surrounding.

   Amount of heat gained can be reduced by wearing garments, which reflect the radiation (thin white clothes).

   When air temperature exceeds that of the skin, the body surface takes up heat from its surroundings.

   This is a great burden to people living in hot climate.

   Body's thermoregulatory mechanisms produce sweating and heat loss in such conditions.

REDUCTION OF HEAT LOSS

Cutaneous Vasoconstriction

Causes reduction of blood flow to the skin and conserves heat. This is important in cold environment as skin acts as insulator.

Due to vasoconstriction of skin blood vessels its temperature drops and comes closer to temperature of the surroundings. Since, heat loss depends on the difference in the temperature, it is prevented.

Increased Insulation

Animals with fur show erection of hair in cold environment, which insulates the body. Human being achieves the same by wearing clothing, which can trap air in the same way as fur. Air is good insulator and a pocket of air around the body reduces the heat loss.

– Seeking suitable clothing is a type of behavioral response to environmental temperature.

Reduced Air Movement

If air movement is sluggish the warm air surrounding the body will not be replaced by cold air and thus, prevents heat loss. Therefore, when environmental temperature is low, the behavioral response is to stay indoors and keep the doors and windows closed.

Artificial Heating

If environment is warm body looses less heat. Therefore, *behavioral response* to low environmental temperature is to seek warmer surroundings and make the surroundings warm by using fire or heater.

Reduced Surface Area

Loss of heat depends on the surface area exposed for heat loss. Therefore, in low environmental temperature, *behavioral response* is to sit close together, curl up while lying down and cover much of the body with blanket.

HEAT LOSS

Heat produced in the body or gained by the body is lost by dissipation, along with this reduction of heat conservation takes place. It indirectly helps heat loss.

To preserve the balance any surplus heat must be brought to the surface for dissipation. This is achieved by:

1. Circulating blood, which has a *high heat capacity* because of its *large water* content and blood brings heat from deeper structures to the skin.
2. This heat is conducted from the tissues to their body fluids. The rate at which heat is transferred from deep tissue to skin is called *tissue conductance.*

Heat is mainly *lost* at the body surface by skin by: (i) conduction, (ii) convection, (iii) radiation and (iv) evaporation of water.

Conduction

Conduction is heat exchange between objects or substances at different temperatures that are *in contract* with one another.

The amount of heat lost by this method is proportional to temperature difference (temperature gradient) between skin and surrounding atmosphere.

Conduction is aided by *convection,* the movement of molecules away from the area of contact. For example, when fan blows air through the room, it helps heat loss by convection or when person swims through water, heat loss by convection is helped. Coolers help heat loss by increasing temperature difference between body and its surroundings.

Radiation

Radiation is transfer of heat by infrared electromagnetic radiation from one object to another at a different temperature with which it is *not in contact.* For example, when an individual is in a cold environment heat is lost by radiation to cool objects.

Evaporation

Evaporation—the other major process for loss of heat from the body is vaporization of water on the *skin* and mucous membranes of *mouth* and *respiratory passages*.

Vaporization from Skin

There are three types of water loss from the skin:

1. Some water loss goes on continuously at all environmental temperatures and is called insensible perspiration. Its evaporation causes heat loss. *Insensible perspiration* amounts to 50 ml/hour in humans.
2. There is sweating over the palms and soles during moments of emotional stress, also called *cold sweating*.
3. There is sweating all over the body when environmental temperature is high. This is called *thermal sweating.*

This type of sweating is mainly concerned with heat loss. Sweat wets the surface of the body and evaporates. As it evaporates it takes heat form the body. The essential fact to remember is that when:

1 gm of water is converted in water vapor 0.6 Kcal of heat (latent heat of vaporization) is taken up from the body and lost. Therefore, when 1 kg (approximately 1 liter) of water evaporates 600 Kcal are lost from the body.

This is the only means by which heat can be lost, when environmental temperature goes above that of body temperature. It is the evaporation which produces cooling not only sweating. When environmental humidity increases, evaporation becomes difficult and one feels uncomfortable in spite of lot of sweating.

Thermal sweating—is by *eccrine type of sweat glands*—which are: (a) *distributed* on the whole body but are densest on the palms and soles, next dense on head and much less dense on trunk and extremities, (b) they are supplied by *cholinergic sympathetic nerve fibers,* (c) human beings have enormous capacity to sweat, therefore, they can very well withstand heat stress, (d) air movement around the body increases evaporation therefore, heat loss is increased, (e) thermal sweating is increased in physical exercise.

Temperature regulation has priority over the maintenance of water and salt balance. Sweating will continue in spite of severe dehydration and marked salt loss. Heat loss by evaporation varies considerably from 30 to over 900 kcal/hour.

Evaporation from mucous membranes of mouth and respiratory passages:

1. Expired air that leaves the lungs is saturated with water vapor at body temperature. The water vapor is derived from evaporation of water from the moist mucous membrane of the respiratory passages. If the inspired air is dry it takes good deal of water vapor with it during expiration. But if it is saturated with water vapor it takes none at all.
2. Some body heat is lost via the lungs by raising temperature of inspired air to body

temperature. Therefore, increase in pulmonary ventilation increases heat loss.

Therefore, *panting* is also a mechanism of evaporative heat loss. Some animals like dogs lose heat by panting. In panting, breathing is rapid and shallow. This greatly increases the amount of water vaporization in mouth and respiratory passages and therefore, the amount of heat lost. Because the breathing is shallow it produces little changes in the composition of alveolar air.

CHAPTER

69

Thermoregulation, Fever and Hypothermia

THERMOREGULATION

Thermoregulation is good example of homeostasis maintained through feedback mechanisms which operate through: (1) detection of stimuli (2) processing (centers), and (3) responses.

Reflex and Semireflex Thermoregulatory Responses

It includes: (i) autonomic, (ii) somatic, (iii) endocrine, and (iv) behavioral changes. They are under control of hypothalamus.

One group of responses: (a) increases heat loss and (b) decrease heat production.

The other group of responses: (a) decreases heat loss and (b) increases heat production.

Mechanisms Activated by Cold

1. Shivering
2. Hunger
3. Increased voluntary activity
4. Increased secretion of norepinephrine and epinephrine

(1–4: Increase heat production)

5. Cutaneous vasoconstriction
6. Curling up
7. Erection of hairs

(5–7: Decrease heat loss)

Mechanisms Activated by Heat

1. Cutaneous vasodilatation
2. Sweating
3. Increase respiration

(1–3: Increased heat loss)

4. Anorexia
5. Apathy and inertia

(4–5: Decrease heat production)

Detection of Stimuli which Threaten Homeostasis

For detection of stimuli there are thermosensitive cells in:

1. Anterior hypothalamus and preoptic area
2. Cutaneous peripheral receptors
3. Visceral peripheral receptors
4. Thermosensitive neurons in spinal cord, lower brainstem and mid-brain.

Peripheral Receptors

Heat and cold can be felt on the skin and in the upper part of the GI tract.

Detection of Cold

It is mainly due to cold receptors of skin. In skin, there are both cold and warmth receptors but there are more cold receptors than warmth. Therefore, peripheral detection of temperature mainly concerns detecting cold.

Central ThermoSensors

Central thermosensors such as those present in preoptic and anterior hypothalamus detect change in the temperature of the blood.

Central Processors or Centers

1. Lie in hypothalamus:
   i. Connected with thalamus
   ii. Receives all appropriate afferent impulses, and
   iii. Efferent side has access to both autonomic and somatic nervous system.
      a. *Anterior hypothalamus*—initiates heat dissipation mechanism in response to high environmental temperature.
      b. *Posterior hypothalamus*—activates mechanism for heat conservation and heat production.

   Besides hypothalamus thalamocortical circuits also play some role in thermoregulation.

   Cold stimulates posterior hypothalamus—and the reflex responses are shivering and vasoconstriction and the neurohormonal responses to cold—explained in Figure 68.1.

   Warmth or heat stimulates anterior hypothalamus and the responses are vasodilatation and sweating.
2. Lower thermoregulatory centers play subsidiary role.

Synaptic Transmitters

1. *Serotonin:* It is synaptic mediator in the centers controlling the mechanisms activated by cold.
2. *Norepinephrine:* It is synaptic mediator in the centers controlling the mechanisms activated by heat.
3. Peptides may also be involved.

Model of Thermoregulation

1. Various models are proposed
2. Key concepts are common to most models.

They are:

1. Zone of thermal neutrality, and
2. A set point.

Zone of Thermal Neutrality

This means a narrow range of ambient temperature (25-27°C) in which normal body temperature can be maintained solely by physical mechanisms (alteration of cutaneous blood flow is included).

In the zone of thermal neutrality, body has to spend no energy beyond the basal metabolism for thermoregulation because no active energy consuming process such as sweating or shivering is necessary. 25 to 27°C is zone of neutrality only for individual at rest and in postabsorptive state.

Set Point

Posterior hypothalamus (thermostat) is a seat of set point. The thermoregulatory mechanisms bring the core temperature towards the set point.

This set point is reset at higher level in fever.

The Classical Model

Variations in the ambient temperature are:

1. Detected by thermosensors
   – Peripheral (outside the CNS)
   – Central (within CNS).
2. Peripheral thermosensors, those present in skin and viscera convey information about change in ambient temperature via neural pathways to centers.
3. Central thermosensors, those in anterior hypothalamus detect changes in ambient

temperature of the circulating blood through them.
4. Information from all peripheral and central thermosensors is integrated in the centers.
5. Interaction between information from different thermosensors may be additive, multiplicative or a combination of both.
6. The integrated information about ambient temperature is matched with set point.
7. If the matching indicates a tendency of body temperature to fall below the set point, the CNS (mainly posterior hypothalamus) stimulates effector mechanisms for heat production and heat conservation.
8. If there is tendency for the body temperature to rise above the set point, the CNS (mainly anterior hypothalamus) stimulates effector mechanisms for heat dissipation.
9. As a result, the deviation or tendency to deviate is corrected. The initial stimulus is reduced and over compensation is prevented.

Thus, temperature regulation follows the usual principles of negative feedback mechanism.

Temperature regulation is *important in homeostasis.* Therefore, there are many thermosensors, processors or centers and various effector responses, which gives us good reserve and one finds that this particular function is carried out with such accuracy that a change of 25°C in environmental temperature produces a change of only 1°C in the core temperature.

FEVER OR PYREXIA

Fever or pyrexia is abnormal increase in core temperature. Associated with inflammatory response of the body, which may or may not be due to infection.

1. In fever, thermoregulatory mechanism behave as if they were adjusted to new point above 37°C. The temperature receptors then send information that the actual temperature is below the new set point and temperature raising mechanisms are activated. This produces chilly sensations due to cutaneous vasoconstriction and occasionally shivering.
2. The *cause* of fever are substances collectively called as pyrogens released by WBC or macrophages. Interleukin-1 is an example of such a pyrogen.
3. When the disease responsible for fever is cured the hypothalamic thermostat is again reset at the normal level but the person still has fever. Now, core temperature is more as compared to set point, the heat dissipating mechanisms are activated, such as sweating and when body temperature has come down to normal set point, sweating stops.
4. *Antipyretics*—such as *aspirin* resets the hypothalamic set point to normal level and bring down the temperature in fever.
5. The benefit of fever to organism is uncertain.
6. *Very high temperatures are harmful:*
   i. When rectal temperature is over 41°C (106°F) for prolonged periods—*some permanent brain damage* results.
   ii. When it is over 43°C *heat stroke* develops and death is common.

HYPOTHERMIA

In hibernating mammals, body temperature drops to low levels without causing any ill effects that are demonstrable after arousal from hibernation. Therefore, experiments were done on induced hypothermia.

When skin or blood is cooled enough to lower the body temperature in non-hibernating animals and humans, metabolic and physiological processes slow down.

1. Respiration and heart rate are very slow
2. Blood pressure is low, and
3. Consciousness is lost

4. At rectal temperature of about 28°C, the ability to maintain normal temperature is lost but the individual continues to survive and if re-warmed with external heat, returns to a normal state.

Advantages of Hypothermia

1. Humans tolerate body temperature of 21 – 24°C (70-75°F) without permanent ill effects and induced hypothermia has been extensively used in surgery.
2. In hypothermic patients the circulation can be stopped for relatively long periods, because the O_2 needs of the tissues are reduced very much. Blood pressure is low and bleeding is minimal.

Therefore, it is possible under hypothermia:

i. To stop and open the heart
ii. Perform brain operations that would have been impossible without cooling.

SECTION IX: ENDOCRINE SYSTEM

CHAPTER 70

General Considerations

The functions of the body are regulated by two major systems:

1. Nervous system
2. Endocrine system or hormonal system.

Endocrine glands or ductless glands are so called because they secrete physiologically active substances called hormones directly into the bloodstream. The word 'endocrine' is derived from Greek word meaning 'I separate within'.

The word 'hormone' was introduced by Starling (1905) is derived from Greek word meaning 'I excite or I arouse' and was first used in reference to secretin.

DEFINITION

Hormones are substances, which are transported by blood to exert specific effects on cells remote from the site of origin.

The Major Functions, which they Control

1. Different metabolic functions of the body.
2. Rates of chemical reactions in the cell.
3. Transport of substances through the cell membrane.
4. Other aspects of cellular metabolism like growth, secretion.

The most important endocrine glands are:

1. Hypothalamus
2. Anterior pituitary (adenohypophysis)
3. Posterior pituitary (neurohypophysis)
4. Islets of Langerhans in pancreas
5. Adrenal cortex
6. Adrenal medulla
7. Thyroid
8. Parathyroid
9. Ovary
10. Testis
11. Pineal—present in roof of III ventricle of brain. It secretes melatonin.
12. Placenta—secretes estrogen, progesterone, chorionic gonadotropic hormone, somatotropin and relaxin
13. GI tract secretes large number of hormones.
14. Kidney secretes erythrogenin, prostaglandins, 1, 25-dihydroxycholecalciferol.
15. Atrial muscle cells form natriuretic factor or peptide.
16. Skin–vitamin D_3.

METHODS OF STUDY

Functions of endocrine glands have been studied by:

1. Experimental studies.
2. Clinical investigation is patients in whom syndromes resulting from under or over secretion of hormones have been recognized.
3. Studies on isolated organs and cell cultures.

Experimental Studies

1. *Effects of extirpation:* Removal of endocrine gland shows its importance to the body, e.g. removal of thyroid gland produces myxedema.
   i. Removal of parathyroid glands produces tetany.
   ii. Removal of adrenal glands produces death due to adrenocortical deficiency.
2. Use of grafts and extracts—abnormalities, which follow extirpation are corrected by the graft of same gland, e.g. diabetes mellitus—produced by extirpation of pancreas is corrected by giving insulin.
3. By observing the effects of administration of large amount of hormone to normal animals.
4. Development of chemical techniques, which led to isolation identification and in many cases synthesis.

HORMONE ASSAYS

Hormones are present in blood, urine, CSF etc. in extremely minute quantities. Some are as low as millionth of a mg/ml. Therefore, special methods are used for assay.

i. Biological assay: In past, hormone preparations used for therapeutic purposes required biological standardization to ensure constancy of activity. Biological assay of hormone activity is still needed when new synthetic products are being compared with natural hormones, e.g. in case of androgen—we record increase in weight of androgen sensitive tissue such as seminal vesicles in rats.

ii. *Radioimmunoassay* (or competitive radioimmunoassay) developed in 1960s by Berson and Yalow, can be done by using—antibody against hormone or protein with high affinity for hormone.

1. Traces of radiolabelled hormone (•) is incubated with antibody or specific binding protein (O).
2. Little radioactivity remains in free fluid.
3. Addition of unlabelled hormone and incubation increases radioactivity in supernatant fluid.

Principle

The amount of radioactivity in the supernatant is a direct function of the amount of hormone in the specimen (Fig. 70.1).

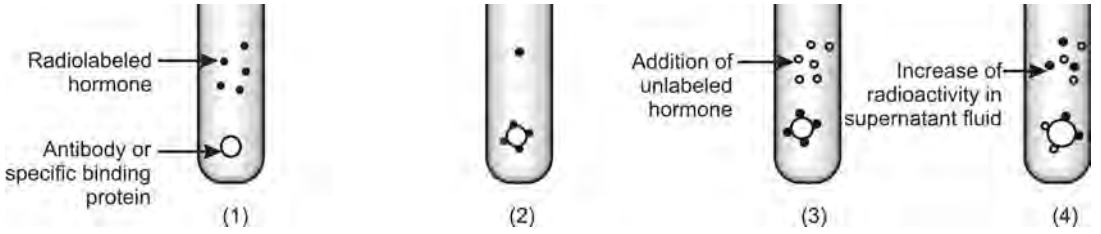


Fig. 70.1: Principle of radioimmunoassay

Advantages

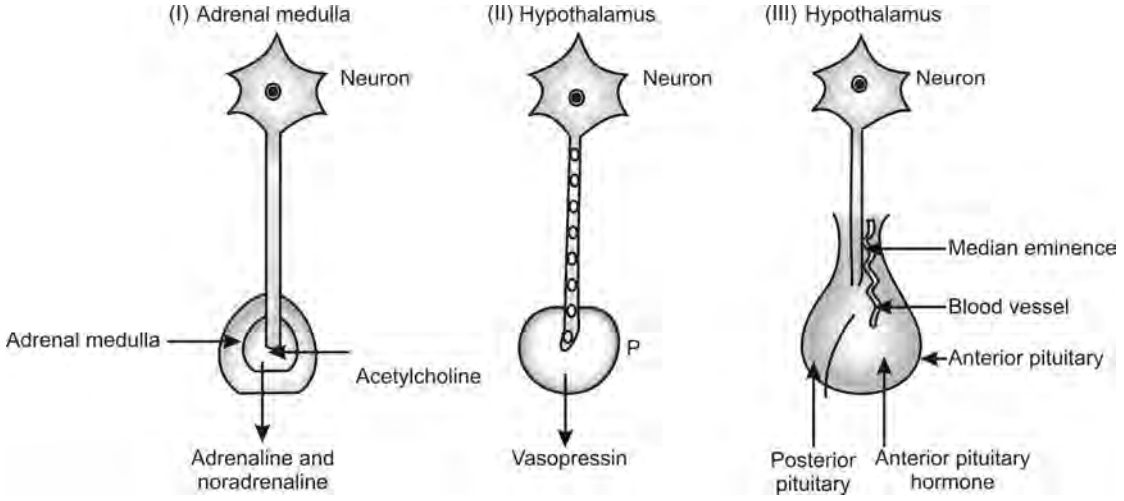
Advantage of competitive radioimmunoassay:

1. High sensitivity
2. High specificity
   But does not relate with biological activity of the hormone.
3. Chemical technique used include:
   i. Fluorescence method for
   ii. Catecholamines, and gas liquid chromatography for steroid hormone.
4. Cytochemical assays, e.g. addition of ACTH as little as 5 attogram (1 attogram = 10^{-18} of gram) causes adrenal steroidogenesis in slices of adrenal gland of pig incubated in ascorbic acid enriched culture medium.

   Disadvantage: too much time consuming and complicated.

REGULATION OF SECRETION OF HORMONE

1. *Direct control*: In few cases secretion is regulated by concentration of substances which are directly controlled by hormone themselves, e.g.:
   i. Insulin secretion from β cells of islets is promoted by a rise in blood glucose, and glucagon secretion from α cells of islets is promoted by a fall in blood glucose level. So blood glucose is maintained normal in spite of variation in carbohydrate intake.
   ii. Ca—fall in plasma calcium promotes secretion of PTH (parathyroid hormone) and rise in plasma calcium increases secretion of calcitonin.
2. *Nervous control of endocrine secretion:* Neurones control endocrines by neurosecretion (Fig. 70.2).
   i. Like neurotransmitters
   ii. Short range hormones.
   iii. Stimulation of sympathetic preganglionic neuron secretes acetylcholine at its nerve ending in adrenal medulla. In response the adrenal medulla secretes adrenaline and noradrenaline.



P = Posterior pituitary gland

Fig. 70.2: Nervous control of endocrine secretion

iv. Hormones of posterior pituitary, e.g. vasopressin are synthesized in hypothalamic neurons and then transported and stored in posterior pituitary, which are secreted from posterior pituitary in response to appropriate signal to hypothalamus.

v. Hypothalamic neurons release short-range hormones in median eminence. From there they are collected by hypothalamo hypophyseal blood vessels and transported to anterior pituitary, where they causes secretion of anterior pituitary hormones.

Hypothalamus receives neuronal connection from many regions of CNS, so it is easy to understand how nervous activity can influence secretion of pituitary hormones.

3. *Feedback effects:* Anterior pituitary hormones are also regulated by the hormones secreted by target endocrine glands—thyroid gland, adrenal gland and gonads.

Hormones of the target gland either act on adenohypophysis or hypothalamus by:

a. Negative feedback that means once the hormone has accomplished the physiological role, it: (i) prevents the same hormone from being secreted or (ii) sometimes the rate of secretion is decreased.

b. Estrogen can exert positive feedback.

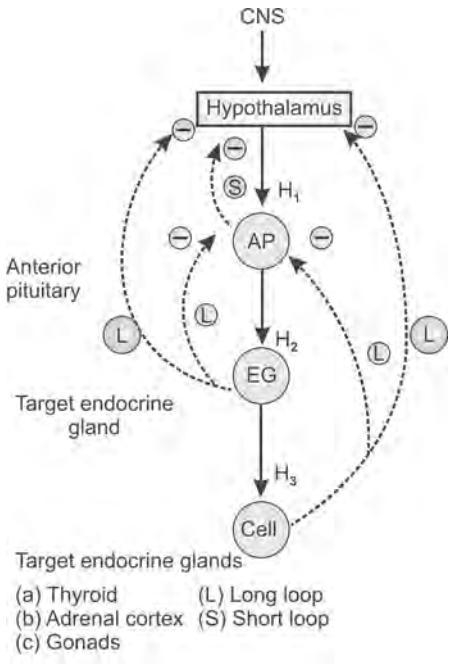
Feedback control is achieved by long loop and short loop (Fig. 70.3).

4. In some cases, many hormones may be concerned in the regulation of the particular activity, e.g. blood glucose is increased by:

i. Glucagon

ii. Glucocorticoid hormone

iii. Growth hormone and adrenaline and blood glucose is decreased by—insulin.



CNS—Central nervous system;
AP—Anterior pituitary;
EG—Endocrine gland
H_1, H_2, H_3—Hormone 1
Hormone 2
Hormone 3

Fig. 70.3: Feedback control

MODES OF ACTION OF HORMONE

Hormones act on cells only after specific combination with receptors either on cell membrane or inside the cell.

Hormones receptors are of two types: (i) mobile, (ii) fixed.

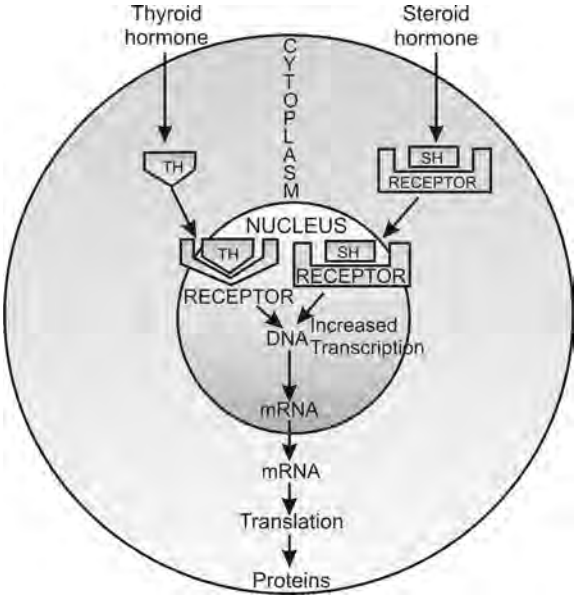
Mobile

i. The hormone, e.g. steroid hormone binds with receptor protein in cytoplasm and then hormone—receptor protein complex or part of it migrates into nucleus (The hormone is lipid soluble and enters the cell. In non-target cells they enter and come out, only in target cells they combine with

receptor) and becomes bound, directly to chromosome, stimulates DNA to increase transcription. So mRNA is produced which in turn causes protein synthesis. Sometimes mobile receptor is in nucleus, e.g. thyroid hormone.

ii. *Another way of action:* A hormone, e.g. estradiol enters lysosomes first and forms estradiol—acid-lysosomal protein complex. This complex passes in nucleus and increases template activity of nuclear chromatin. Thus, lysosomal constituents promote transcriptional and replicative pathways of DNA metabolism [enhancing mRNA and protein synthesis and inducing mitosis].

Both these mechanisms offer an explanation for protein synthesis and hyperplasia which steroid hormones induce in their target organs, e.g. estrogen, testosterone, etc. (Fig. 70.4).



TH—Thyroid hormone
SH—Steroid hormone

Fig. 70.4: Mechanism of action of thyroid and steroid hormone

Fixed

A hormone, e.g. peptide hormone combines with receptor on cell membrane.

The hormone never enters the cell. The binding on outer cell membrane activates enzyme *adenyl cyclase* on inner surface of the membrane and there is formation of 3′- 5′ cyclic AMP from ATP in presence of Mg ions.

Cyclic AMP acts on inactive protein kinases to make them active protein kinases, which phosphorylate many substances.

These reactions are terminated by phosphodiesterase which converts 3′-5′ cyclic AMP into 5′ AMP.

Cyclic AMP system is the basic regulation of the cell metabolism like Krebs cycle.

This accounts for the widespread occurrence of CAMP.

It is found in all cells except mature RBC of mammal.

Cyclic AMP—is the second messenger.

Hormone—is the first messenger.

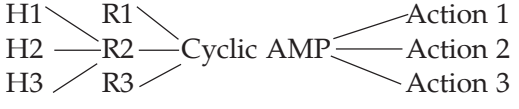
Cyclic AMP was discovered in 1957 by Sutherland who won Nobel Prize for his discovery.

Sequence of events involved in hormonal activation of cyclic AMP.

First step is interaction of hormone and receptor on outer surface of cell membrane. Receptors are different in different cells, e.g. ACTH—activates adenyl cyclase in adrenal cortex leading to secretion of:

1. Adrenocortical hormone
2. No effect on liver cells, glucagon—has effect on liver cells, no effect on adrenal cortex.

This is because each is acting on different receptors



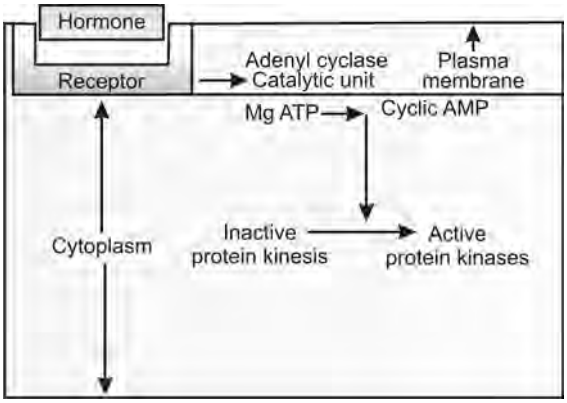


Fig. 70.5: Action of hormone via second messenger

H1, H2 and H3 are three different hormones acting on different receptors R1, R2 and R3 in three different target cells. All leading to formation of cyclic AMP, which causes three different actions in three different target cells.

Thus, there is receptor specificity at hormone receptor interaction site.

Other second messengers exist which help in control of intracellular metabolism (Fig. 70.5):

1. 3′–5′ cyclic GMP (guanosine monophosphate).
2. In many systems, Ca is necessary for hormone action and cyclic AMP itself may only act in presence of calcium.
3. Prostaglandins.

CHAPTER

71 Endocrine Functions of Hypothalamus

Hypothalamus is so-called because it is situated below the thalamus. It is part of brain and it is also connected to pituitary gland. Thus, hypothalamus forms an important link between endocrine system and nervous system (Fig. 71.1).

Pituitary develops from two distinctly different embryological structures.

Anterior pituitary or adenohypophysis develops as an evagination of Rathke's pouch from roof of primitive mouth. Because this evagination is glandular it is called adenohypophysis.

Posterior pituitary or neurohypophysis develops from central areas of hypothalamus called tuber cinereum and median eminence. The median eminence continues as infundibular stem and ends up as infundibular process, which becomes the posterior pituitary or neurohypophysis.

Infundibular stem together with pars tuberalis (a small extension of adenohypophysis surrounding the infundibular stem) forms the hypophyseal stalk.

ENDOCRINE SECRETION OF HYPOTHALAMUS

Secretions of hypothalamus are transported from cell bodies of neurosecretory cells to median eminence.

In median eminence the nerve terminals of other hypothalamic neurons relaying influences from other CNS structures, synapse

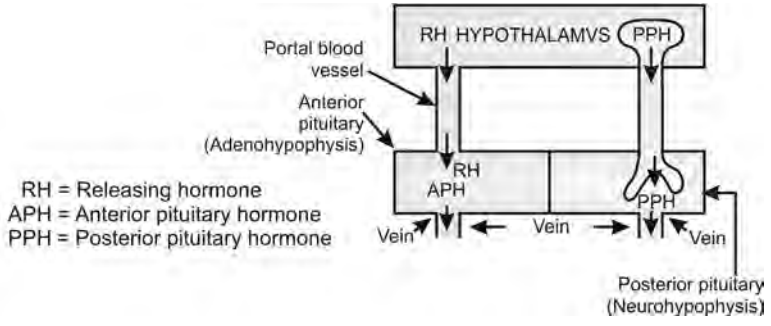


Fig. 71.1: Link between endocrine system and nervous system

with nerve terminals of neurosecretory cells. Through these synapses, various central neural structures influence the release of endocrine secretions of hypothalamus.

The cells of anterior pituitary have receptors for endocrine secretions of hypothalamus, which may be in the form of releasing hormone or release inhibiting hormone.

BLOOD SUPPLY

Superior hypophyseal arteries form a ring round the uppermost part of pituitary stalk, (they are branches of internal carotid artery) and branch to form a network of capillary loops. This network carries the neurohormones and these are transmitted via long portal veins. Long portal veins break into second set of capillaries in the anterior pituitary. Here neurohormones influence the pituitary cells.

A small part of anterior pituitary gets its blood supply via short portal vessels, which originate from network of capillaries formed by the inferior hypophyseal arteries at the lower end of infundibular stem. This network also supplies posterior pituitary.

Portal vessels are blood vessels, which are interposed between two sets of capillaries (Fig. 71.2).

Venous drainage via cavernous sinus to jugular veins.

Pituitary lies outside the blood-brain barrier therefore, can be influenced by general hormones also.

Tancytes—ependymal cells—extend to median eminence.

1. Help—hypothalamus and pituitary hormones in reaching CSF.
2. Bring additional influences of CNS to hypothalamus and pituitary via CSF.

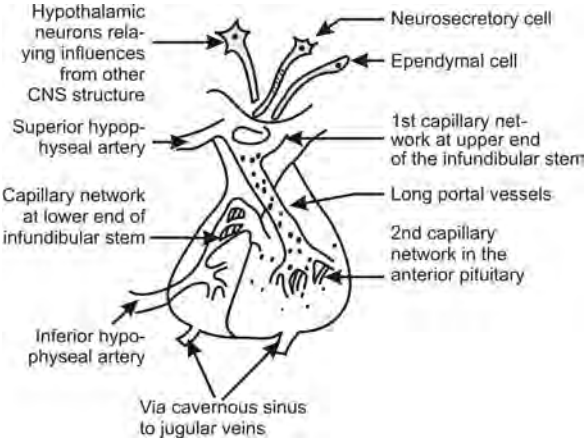


Fig. 71.2: Hypothalamo-hypophyseal blood vessels

Hormones Secreted by Hypothalamus

1. Corticotropin releasing hormone (CRH).
2. Growth hormone releasing hormone (GHRH).
3. Growth hormone release inhibiting hormone (GHRIH) (Somatostatin).
4. Thyrotropin releasing hormone (TRH).
5. Prolactin release inhibiting hormone or factor (PIH or PIF).
6. Prolactin releasing factor or PRF.
7. Gonadotropin releasing hormone (GnRH).

Corticotropin Releasing Hormone (CRH)

1. Polypeptide having 41 amino acids.
2. It stimulates secretion of ACTH or corticotrophin from anterior pituitary, which stimulates glucocorticoid secretion from adrenal cortex.
3. It acts by activation of adenyl cyclase and cyclic AMP.

Control

i. Emotional stress increases CRH.
ii. Glucocorticoids exert negative feedback on CRH secretion.
iii. CRH secretion shows circadian rhythm overridden by demands of stress.

iv. Sleep-activity cycle and dark-light cycle both influence CRH release. During transition from dark to light and sleep to activity the release is at its peak. Air travel across the time zones disrupts circadian rhythm for up to one week leading to impairment of physical and mental performance—jet lag.

Growth Hormone Releasing Hormone (GHRH)

1. Polypeptide having 44 amino acid. It stimulates secretion of growth hormone from anterior pituitary.
2. Acts by activation of guanylate cyclase and cyclic GMP, which stimulates release of growth hormone from anterior pit.

Control

Increases during hypoglycemia:

i. There are glucoreceptor cells in ventromedial nucleus of hypothalamus.
ii. Emotions affect release.
iii. Physical stress like pain, trauma, cold also affect through nervous pathway and growth hormone increases in 2 minutes.
iv. Slow wave phase of sleep increases growth hormone releasing hormone.

Growth Hormone Release Inhibiting Hormone (Somatostatin) (GHRIH)

1. It is polypeptide containing 14 amino acid.
2. It inhibits the secretion and release of growth hormone from anterior pituitary.
3. Acts by activation of adenyl cyclase and formation of cyclic AMP.

Control

It is influenced by:

i. Metabolic substrates, and
ii. Growth hormone concentration.

Somatostatin is also found in:

1. Brain, spinal cord, autonomic ganglia. There it acts as neurotransmitter.
2. Cells of antrum of stomach— where it inhibits the secretion of gastrin.
3. Kidney—it reduces renin secretion.
4. δ cells of pancreatic islets—it inhibits secretion of glucagon and insulin. Therefore, it is favorite molecule of nature for inhibiting the secretion of several hormones.

Thyrotropin Relasing Hormone (TRH)

1. It stimulates secretion of thyrotropin (TSH).
2. It stimulates secretion of prolactin (side effect).
3. Acts by forming cyclic AMP.

Control

1. Cold increases secretion of TRH by inhibiting preoptic area of hypothalamus, which normally inhibits TRH release.
2. Thyroxine weakly inhibits TRH.
3. Circadian rhythm. Peak at about 4 am and lowest at about 6 pm.

Prolactin Inhibiting Factor (PIF)

1. Peptide structure not determined therefore, called factor.
2. Has inhibitory effect on production of prolactin, potent than PRF.
3. Acts by decreasing level of cyclic AMP.

Control

1. Stimulated by circulating prolactin.
2. Changes in plasma substrate affect it.
3. Suckling influences are mediated by nervous pathways.

Prolactin Releasing Factor (PRF)

1. Chemical structure not known.
2. It stimulates secretion and release of prolactin.
3. Its action is insignificant as compared to PIF.

Gonadotropin Releasing Hormone (GnRH)

It is a polypeptide containing 10 amino acid:

- Cells of preoptic area produce it.
- It stimulates secretion and release of LH and FSH.
- GnRH binds to specific receptors in cell membrane of pituitary gonadotrophs and uses Ca, CyAMP and phospholipids as second messenger.

Control

GnRH is under multiple unknown influences:

i. Stress—inhibits.
ii. Olfactory bulb—affects it and secretion in response to phrenomes (which are air, water borne chemicals) is increased.
iii. Retinohypothalamic path mediates the effect of light and dark on gonadotropin secretion.
iv. Dopaminergic nuerons of arcuate nucleus are known for its effect on GnRH.
v. Serotonergic, Noradrenergic, Endorphinergic } inputs affect its secretion.

CHAPTER

72 Pituitary Gland (Hypophysis) and Adenohypophysis (Anterior Pituitary)

PITUITARY GLAND

The pituitary gland together with hypothalamus forms the most influential endocrine system in our body. Pituitary secretes at least nine hormones, some of which are called trophic hormones, that means they cause secretion of other endocrine gland, for example.

i. Thyroid gland
ii. Adrenal cortex
iii. Gonads.

Word pituitary comes from Latin. Pitutia means mucus was introduced by Galen who thought that pituitary secretes mucus into the nasal cavity. The word hypophysis is of Greek origin, which means outgrowth.

The pituitary gland lies in sella turcica of sphenoid bone at the base of the skull. Therefore, it is difficult to access. It is connected with hypothalamus by hypophyseal stalk or pituitary stalk (Fig. 72.1).

Dimension—13 × 11 × 6 mm
- weight in man 0.5 gm

In man, pituitary has two main divisions:

1. Anterior pituitary (adenohypophysis)—75%
2. Posterior pituitary (neurohypophysis)—25%

The third division, pars intermedia is very small and inconspicuous in man but is appreciable in other vertebrates.

Nerve Supply

1. Neurohypophysis is richly innervated.
2. Adenohypophysis receives no significant nerve supply. Few nerve fibers, which are sympathetic nerves, supply blood vessels.

Pituitary gland is under hypothalamic control. Adenohypophysis is influenced by hormones, which come from hypothalamus via portal blood vessels.

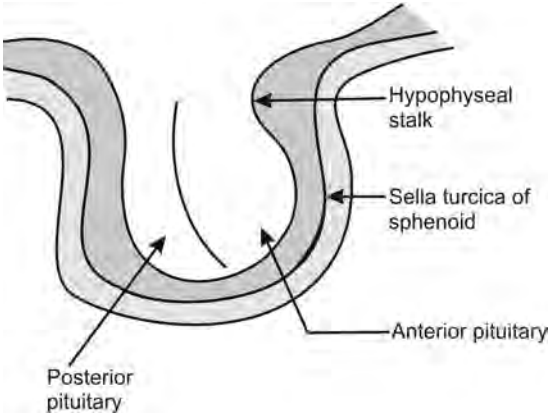


Fig. 72.1: Pituitary gland

Neurohypophysis—by neurons in hypothalamus, which convey hormones from hypothalamus for storage in neurohypophysis.

ADENOHYPOPHYSIS (ANTERIOR PITUITARY)

Secretes hormones, which are peptides or glycoproteins.

1. Growth hormone (GH) or somatotropin or somatotropic hormone.
2. Prolactin or lactogenic hormone or mammotropin
3. Thyroid stimulating hormone (TSH) or Thyrotropic hormone or thyrotropin.
4. Adrenocorticotropic hormone (ACTH) or corticotropin.
5. Gonadotropic hormones or Gonadotropins—they are:
   i. Follicle stimulating hormone or (FSH)
   ii. Leutinizing hormone (LH) or interstitial cell stimulating hormone or ICSH.

Functions of adenohypophysis—numerous:

In general:
- It controls growth of bones
- Muscles
- Viscera.

It influences metabolism of:
- Carbohydrate
- Fat
- Protein.

It controls—growth, development, Structural integrity, Activity of. ┐ Adrenal cortex, Thyroid, Ovary breast, Testis

Cytology of Anterior Pituitary

Cytoplasm of the majority of anterior pituitary cells contain granules, which are granules of peptide hormone or protein hormone surrounded by membrane.

Cells containing granules—chromatophils — 75%.

Cells containing no granules—chromotophobes—25%.

Cell types in anterior pituitary:

1. Growth H cells or Somatotrophs ┐
2. Prolactin cells or Mammotrophs ┘ Acidophil cells
3. TSH cells or Thyrotrophs ┐
4. ACTH cells or Corticotrophs ┘ Basophil cells
5. Gonadotropic cells or gonadotrophs

Hormones are stored in granules for many days, during secretion lipid membrane of the granule fuses with the cell membrane by a Ca dependent process and hormone is released in ECF by exocytosis.

The hypothalamic hormones promote secretion of anterior pituitary hormones, which are brought by hypothalamo-hypophyseal portal blood vessels. This system works as cascade amplifier in quantitative term, e.g. a few nanograms of hypothalamic releasing hormones promote secretion of micrograms of adenohypophyseal tropic hormones and this in turn may release milligrams of hormone from target endocrine gland. The amplification at each stage is at last thousand folds.

Growth Hormone or Somatotropic Hormone or Somatotropin

Chemically—polypeptide contain 190 AA. Its structure varies from species to species. Human growth hormone is now synthesized.

It causes growth of all the tissues of the body that are capable of growing.

Actions of growth hormone:

– It increases the size of cell.
– It increases mitosis therefore, more number of cells are formed.

1. *Skeletal growth:* GH stimulates growth of epiphyseal cartilage. This increases the length of the bone. In adult, after closure of epiphysis GH causes thickening of bone and deposition of calcium. After puberty growth hormone cannot increase the height.

   The effect is indirect—by forming substances—called somatomedin in liver, kidney and muscles, which acts on cartilage and promote their growth.

2. It regulates the growth of muscles and viscera:
   i. Muscles—GH increases mass of skeletal muscle.
   ii. *Viscera:*
   - Liver
   - Kidney

   Especially in these two organs GH is essential for normal development of their cells.

   iii. GH increases the growth of thymus.
   iv. GH increases yield of milk in lactating animals. Weak lactogenic action because GH is similar in structure to prolactin.
   v. GH stimulates erythropoiesis.

   The generalized growth stimulatory effects are due to its overall anabolic effect on intermediary metabolism.

3. *On protein metabolism:* Series of different effects are known:
   i. It enhances transport of amino acid in cells—to increase protein synthesis.
   ii. GH stimulates particular genes to form more mRNA, which diffuses in cell and in ribosomes particular code is translated and a particular protein is synthesized.

   It affects ribosomes also—makes them produce more protein.
   iii. It decreases breakdown of protein.
   iv. It increases mobilization of fat for energy. Therefore, it is protein sparer and carbohydrate sparer.
   v. It increases collagen synthesis.

   It is an anabolic hormone and causes positive N_2 balance.

   Increase in protein synthesis occurs in minutes.

4. *On fat metabolism*
   i. Growth hormone stimulates lipolysis and inhibits lipogenesis. It releases fatty acids from adipose tissue, which are converted to acetyl CoA and utilized for energy.
   ii. GH has ketogenic effect, because if acetyl-Co A is not completely utilized, it is converted into ketone bodies.
   iii. GH in excess—can cause fatty liver by increased deposition fats in liver.

5. *On carbohydrate metabolism*
   i. Under the effect of GH there is decreased utilization of glucose in cell, which rapidly polymerizes to form glycogen.
   ii. GH causes decreased uptake of glucose by the cells. Therefore, blood sugar level increases. This stimulates β cells of islets of Langerhans to secrete more insulin. Prolonged excess of GH causes burn out of β cells by constant stimulation and person develops diabetes mellitus.

6. Calcium absorption from GIT is increased by GH. It also increases retention of water, phosphorus, potassium and chloride, which are utilized in growing tissue.

Thus, growth hormone:

- Increases protein synthesis.
- Uses up fat stores.
- Conserves carbohydrates, and

- Increases growth by increasing protein synthesis and it is anabolic growth promoting hormone.

Regulation of Growth Hormone Secretion

For many years, it was believed that growth hormone was secreted primarily during the period of growth, but disappears at adolescence, but not true. In adults, rate of secretion is same but it is increased or decreased within minutes, e.g. by—stress, starvation, exercise and hypoglycemia.

1. Effect of stressful stimuli, hormones, sleep and amino acids:
   i. Exercise—Stimulate GH secretion, which causes lipolysis—and free fatty acids, provide energy.
   ii. Hypoglycemia causes increase in secretion of GH.
   iii. Certain amino acids—stimulate growth H secretion, arginine is most potent.
   iv. Excitement, exposure to cold, surgical trauma increases growth hormone secretion.
   v. Hormones: (a) estrogen—it is female sex hormone. It increases secretion of GH. Therefore, girls show a spurt of increase in height (at puberty) earlier than boys. But they are shorter because their epiphysis closes earlier, (b) Thyroid hormone—stimulates secretion of GH, (c) Cortisol inhibits production of GH.
   vi. Deep sleep—stimulates secretion of growth hormone.
   vii. Starvation—increases GH. secretion, cause is depletion of proteins.
2. Role of hypothalamus → Hypothalamus secretes:
   - GHRH
   - GHRIH.

GHRH has major control. It is controlled by ventromedial nucleus of hypothalamus, which is sensitive to hypoglycemia.

GHRIH (= somatostatin) is controlled by nearby area.

Therefore,

i. Hypothalamic signals depicting emotions, stress, trauma affect secretion of growth hormone.

ii. Catecholamine, Dopamine, Serotonin } Released by different nuclei in hypothalamus increases in rate of human growth hormone secretion.

Abnormalities of Growth Hormone Secretion

Hyposecretion—Panhypopituitarism

1. It may be congenital—right from birth.
2. Or acquired—at any time of life.
   If cogenital or in childhood it results in Dwarfism or less secretion of GH may be due to destructive lesion of anterior pituitary or failure of hypothalamus to secrete GHRH.

Features of Dwarfism

1. Normal birth weight but there is severe retardation of growth. Features of the body develop in appropriate proportion to each other but rate of development is less therefore, a child of 10 years appears 4-5 years old and 20 year old person appears 7-10 years old.
2. No mental retardation (e.g. dwarfs seen in circus).
3. No deficiency of thyroid hormone and adrenocortical hormone because body is small and requirement of the body are met.
4. Gonadotropic hormones are not sufficient. Therefore, do not develop adult sexual function. In 1/3rd of dwarfs, there is only

deficiency of growth hormone. Gonadotropic hormones are sufficient. They mature sexually and reproduce.

Laron dwarfs—rare. GH secretion is normal but there is deficiency (genetic) of formation of somatomedins in response to growth hormone secretion.

Brissard type of dwarf (fat boy of Dickens): Dwarfs in whom no sign of aging is present. Adult may continue to look like a child.

If Investigations show low level of GH, administration of GH helps if given before puberty.

Panhypopituitarism in Adults

Cause

Tumors of brain like craniopharyngioma, chromophobe cell tumor compress the pituitary or thrombosis of the blood vessel—supplying pituitary, which occasionally occurs during circulatory shock after postpartum hemorrhage (Sheehan's syndrome).

Effects

1. There is hypothyroidism.
2. There is decreased secretion of glucocorticoids.
3. There is decreased secretion of gonadotropic hormone, therefore, sexual functions are lost. Person becomes lethargic, gaining weight because of lack of lipolysis by GH adrenocortical hormones and thyroid hormone.

Treatment: Adrenocortical and thyroid hormone therapy and estrogen in female and testosterone in male.

Hypersecretion—of Growth Hormone Results in

Gigantism

It is characterized clinically by excessive height for age, sex and race.

Cause: Tumor of acidophil cells (acidophil adenoma) or primary disorder of hypothalamus with over secretion of GHRH, therefore, GH secretion increases. If this increased growth hormone secretion occurs before puberty (i.e. before closure of epiphysis) it results in gigantism.

Features

i. Height is increased—8′ - 9′ or 2.5 meters
ii. Initially there is hyperglycemia, which causes increased insulin secretion by stimulating β cells which later degenerate and person develops diabetes mellitus.
iii. If untreated eventually develops panhypopituitarism because tumor grows until whole pituitary is damaged by compression.

Treatment if diagnosed early—by irradiation of pituitary gland or microsurgical removal of tumor.

Acromegaly

If acidophil cell tumor occurs after the closure of epiphysis—person cannot grow taller but soft tissue growth can continue and membranous bones increase in size because their growth does not cease at puberty, e.g. bones of cranium, nose, etc.

The word acromegaly means enlargement of peripheral region.

Features

- Enlargement of bones of hands and feet.
- Bosses on forehead, forehead slants, prominent orbital ridges.
- Nose twice the normal size.
- Lower jaw protrudes.
- Vertebrae increase in size—which results in kyphosis.
- Foot requires 14 number or larger shoe.
- Fingers are thickened.
- Hands are large.

Soft tissue like tongue, liver, kidneys, enlarge. Skin becomes thick, larynx enlarge and voice becomes hoarse.

In general—extremities enlarge, there is drooping shoulder, hands nearly reach knees. movement and gait is awkward, and patient resembles ape.

There is hyperglycemia and glycosuria. BMR is increased.

Thyrotropic Hormone or Thyrotropin or Thyroid Stimulating Hormone (TSH)

Thyroid stimulating hormone (TSH) is glycoprotein and is synthesized in thyrotrophs of anterior pituitary.

Actions

1. It regulates structure and function of thyroid gland.
2. It increases secretion of thyroxine (T4) and triiodothyronine (T3) from thyroid gland.

Effects on Thyroid Gland

1. Increased proteolysis of thyroglobulin and increased release of T3 and T4 in blood.
2. It increases activity of iodide pump and thus, iodine trapping is increased.
3. It increases iodination of thyroxine.
4. It increases size and secretory activity of the thyroid cell. Epithelium becomes columnar from cuboidal.
5. It increases number of thyroid cells.
6. It increases vascularity of the gland.

Control of Secretion (Fig. 72.2)

1. Hypothalamic control - by TRH (Thyrotropin releasing hormone) by hypothalamo-hypophyseal portal blood vessels reaches anterior pituitary. Acts on thyrotrophs.
2. Increased thyroxine level in blood decreases TSH by:
   - Negative feedback acting on anterior pituitary, and
   - Hypothalamus.
3. Rate of cellular metabolism. If too low → increases TSH secretion and vice versa.
4. Cold—exposure to cold cause release of TRH and TSH. Therefore, people moving to arctic region have been known to develop increased BMR.
5. Various emotional stimuli affect output of TSH.

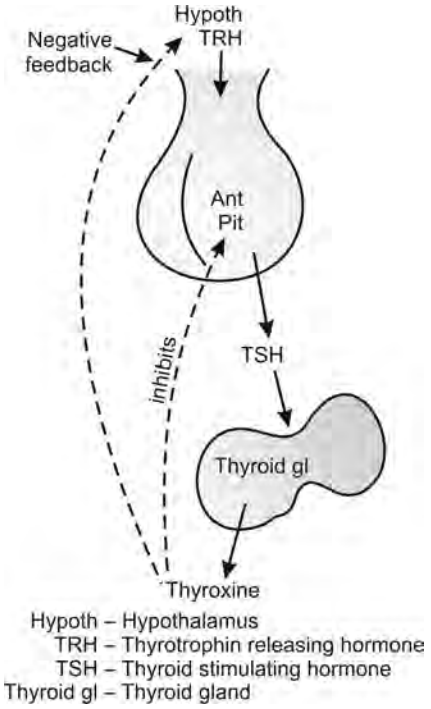


Fig. 72.2: Feedback control thyroid hormone secretion

Mechanism of Action of TSH—Cyclic AMP Mechanism

Adrenocorticotropic Hormone (ACTH) or Corticotropin

Chemistry—polypeptide secreted by corticotrophs of anterior pituitary.

Actions

i. ACTH controls growth of adrenal cortex and structural and functional integrity of most of its cells.
ii. It stimulates secretion of cortisol and adrenal androgens—but does not control secretion of aldosterone from adrenal cortex.

Mechanism of Action—Acts by Cyclic AMP Mechanism

Regulation of Secretion (Fig. 72.3)

1. Hypothalamic control—by release of CRH.
2. Cortisol level—when cortisol is increased it inhibits secretion of ACTH by negative feedback.
3. Stress—physical or emotional increase secretion of ACTH.
4. ACTH secretion shows circadian rhythm.

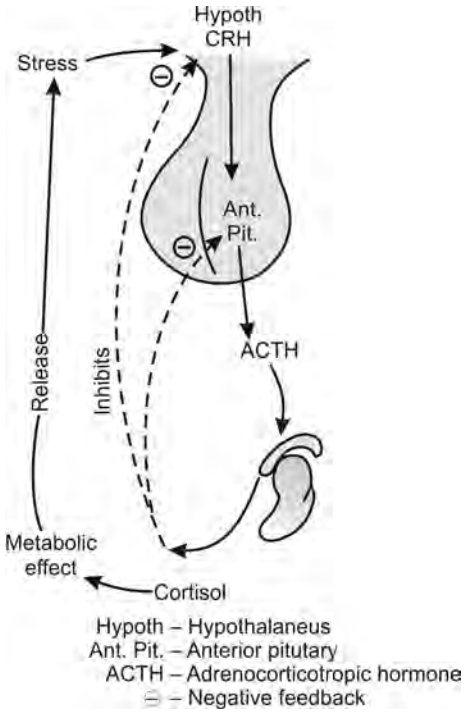


Fig. 72.3: Feedback control of cortisol secretion

Circadian rhythm: A rhythm of about 24 hours which is synchronized with daily environmental shift from darkness to light.

Prolactin—or luteotropic hormone – secreted by luteotrophs of anterior pituitary.

Chemistry

i. Single chain protein
ii. It has structural similarity with growth hormone.

Action

1. Development of breast with several other hormones.
2. Hyperplasia of breast during pregnancy.
3. Synthesis of milk protein.
4. Induces enzymes, which are required for synthesis of milk, sugar, and lactose.
5. PRL—or prolactin blocks synthesis and release of GnRH thereby prevent ovulation.

In males

1. PRL (Prolactin) increases sensitivity of testes to LH.
2. Large doses of prolactin cause decreased libido and impotency.

Both in males and females: It has growth hormone like action on carbohydrate metabolism, i.e. it impairs carbohydrate tolerance.

Mechanism of Action

Prolactin receptors are membrane bound but second messenger is not known.

Number of receptors for prolactin are increased by prolactin itself and estrogen.

Control

i. Prolactin is mainly under inhibitory influence of PIF from hypothalamus. PRH has weak stimulating action.
ii. Suckling—stimulates synthesis and secretion of prolactin. Therefore, more suckling results in more milk output.

Abnormalities: Prolactin deficiency—results in lactation failure.

Prolactin excess: Results in absence of ovulation, infertility and amenorrhea.

Pituitary gonadotropic hormones

- Follicle stimulating hormone (FSH) and Leutinizing hormone (LH) — Regulate gonadal functions

Chemistry and synthesis

- FSH—glycoprotein
- LH—similar structure.

Synthesized by gonadotrophs of anterior pituitary.

Action

1. FSH causes follicle development in ovaries.
2. Spermatogenesis in seminiferous tubules in males.
3. LH - concerned with leutinization of follicle after ovulation.
4. ICSH—In males—stimulates Leydig's cells to secrete testosterone. LH in males is known as ICSH.

Mechanism of Action

Through cyclic AMP.

Control of Secretion

1. Gonadotropin releasing hormone (GNRH) from hypothalamus stimulates the synthesis and release of both FSH and LH.
2. Estrogen and progesterone exert negative feedback effect on FSH and LH through anterior pituitary as well as hypothalamus.
3. A hormone inhibin, which is secreted by the Sertoli cells of testes, inhibits secretion of FSH.
4. 1 or 2 days before ovulation estrogen causes positive feedback and increases secretion of LH and FSH called as surge.

Disorders of Pituitary

1. Dysfunction of acidophil cell

   Hyperactivity:
   i. In young—gigantism.
   ii. In adult—Acromegaly.

   Hypoactivity:
   i. In young — dwarfism.
   ii. In adult–
      a. Sheehan's syndrome.
      b. Acromicria (rare)

Features

i. In later age
ii. Premature senility
iii. Emaciation
iv. Bones of face, hand and feet small.

2. *Dysfunction of basophil cell: Hyperactivity results in Cushing s syndrome,* so named after the name of Harvey Cushing who discovered this in 1932—cause basophill adenoma, which causes increased secretion of ACTH from anterior pituitary which in turn causes increased secretion of cortisol from adrenal cortex. It will be described in detail alongwith dysfunction of adrenocortical secretion.
3. *Dysfunction of chromaphobe cell:* If there is tumor of chromophobe cell, it will press on normal anterior pituitary cells. Therefore, there are signs of both irritation and hypoactivity of anterior pituitary. As tumor grows it affects hypothalamus also.

Results

In Children

Frohlich's syndrome (adiposogenital dystrophy).

Features

1. Stunted growth.
2. Intelligence is less therefore, idiotic look

3. Sexual infantilism (failure of maturation of sex organs and secondary sex characters).
4. Generalized obesity
5. Somnolence
6. Lethargy
7. Voracious appetite

Laurence Moon-Biedl syndrome.

Features

1. Same as Frohlich's syndrome
2. But often runs in families therefore familial
3. Polydactylism
4. Retinitis pigmentosa } may be associated

In Adults

Frohlich's syndrome adult type.

Features

In Males

1. Adiposity—feminine distribution of fat
2. Mental disposition and appearance resemble female.
3. Atrophy of sexual organs.
4. Hands and feet are small and fingers delicate.
5. Skin of body and face is smooth and hairless.
6. BMR—below normal.

In Females

1. Extreme adiposity
2. Atrophy of sexual organs.

CHAPTER

73

Posterior Pituitary (Neurohypophysis)

Composed mainly of glial like cells called pituicytes. Pituicytes do not secrete hormones; they act simply as supporting structure for large number of terminal nerve fibers and nerve endings, which originate mainly in supraoptic and paraventricular nuclei of hypothalamus. These nerve fibers to neurohypophysis from hypothalamus forms hypothalamo-hypophyseal tract.

Nerve endings are bulbous that lie on the surface of capillaries where they secrete two posterior pituitary hormones: (1) ADH or Antidiuretic hormone also known as vasopressin, (2) oxytocin.

These hormones are first synthesized in the cell bodies of supraoptic and paraventricular nuclei and are transported in combination with carrier proteins called neurophysins down to the nerve endings in posterior pituitary gland (Fig. 73.1). There are separate neurophysins for ADH and oxytocin.

Antidiuretic hormone (or vasopressin) is formed primarily in supraoptic nuclei.

Oxytocin is formed primarily in paraventricular nuclei of hypothalamus.

But each of these two nuclei can synthesize approximately 1/6 of 2nd hormone in addition to its primary hormone, e.g. supraoptic nucleus forms ADH plus oxytocin (quantity of 1/6 of ADH).

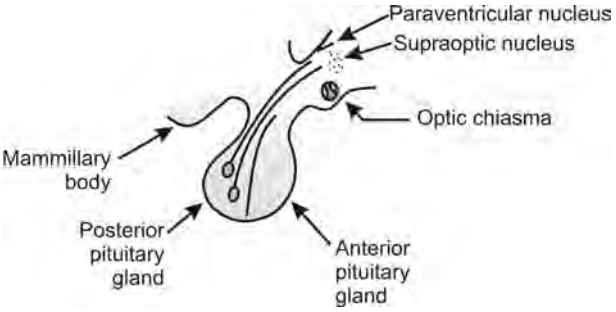


Fig. 73.1: Secretion of posterior pituitary hormones

STORAGE OF ANTIDIURETIC HORMONE

Under resting condition large quantities of ADH and oxytocin accumulate in large secretory granules in these nerve endings, still bound with their respective neurophysins.

But when nerve impulses are transmitted downward along the fibers from supraoptic and paraventricular nuclei the hormones are immediately released from the nerve endings by exocytosis and are absorbed into adjacent capillaries.

Both neurophysin and hormone are secreted together but since they are loosely bound they immediately separate.

FUNCTIONS OF ANTIDIURETIC HORMONE (VASOPRESSIN)

ADH controls excretion of water in urine and therefore, regulates water balance and electrolyte balance. Hence, the name antidiuretic hormone (Fig. 73.2).

Antidiuresis = decreased excretion of water by kidneys.

Mechanism of Action

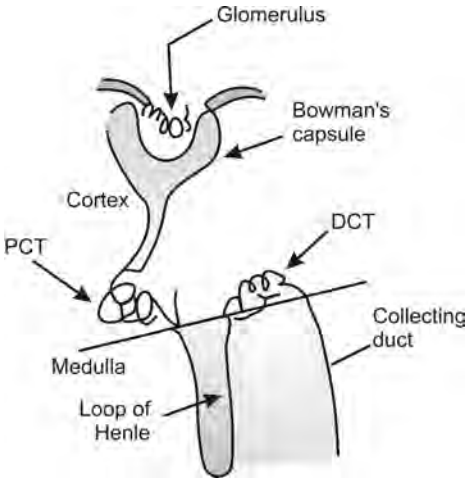
In absence of ADH the collecting ducts, the late distal tubules are almost totally impermeable to water, which prevents reabsorption of water, and the water is lost in urine.

On the other hand, in the presence of ADH the permeability to water of collecting duct and distal convoluted tubule is greatly increased and water is reabsorbed (In simple words ADH opens the water pores of collecting duct and distal convoluted tubules). So that water is reabsorbed by osmosis.

Precise Mechanism—How ADH Acts?

ADH first attaches on receptors present on basal side of collecting duct epithelium. This causes releases of cyclic AMP in cytoplasm of these cells. This in turn open many pores in the cell membrane and water is absorbed by osmosis from tubular lumen to particular fluid.

ADH in large doses causes increase in blood pressure by its action on smooth muscles of arterioles, which causes vasoconstriction. That is why its name is vasopressin.



PCT—Proximal convoluted tubule
DCT—Distal convoluted tubule

Fig. 73.2: Structure of nephron

REGULATION OF ADH—PRODUCTION

1. *Osmotic regulation:* Neurons different from those that secrete ADH are located in hypothalamus, near them, which function as osmoreceptors, which increase or decrease in size in response to degree of concentration of ECF. When ECF is concentrated—osmosis of water out of osmoreceptor—decrease their size and stimulates supraoptic nucleus, impulses are transmitted to posterior pituitary. ADH is secreted—this via blood reaches kidneys → where increased permeability to water takes place→most of the water is reabsorbed from tubular fluid and electrolytes are lost in urine→this dilutes ECF and normal osmotic composition is restored.
   - On the other hand when ECF is dilute, osmosis of water in osmoreceptors increase the size, which inhibit supraoptic nucleus.
2. *Na ion concentration in ECF:* Na ion concentration and osmolarity of ECF is parallel.

   Under normal condition 95% of total osmotic pressure of ECF is determined by Na concentration.

↑ = increase
↓ = decrease

- ↑ In Na concentration - osmolarity increases
- ↓ In Na concentration - osmolarity decreases

Thus, ADH is potent controller of Na ion concentration.

3. Regulation by low blood volume pressor receptors—ADH in moderately high concentration causes constriction of arterioles. Therefore, it can increase blood pressure.

   One of the stimuli for secretion of ADH is severe blood loss which results → in fall of blood volume → fall of pressure in atria of the heart → relaxation of atrial stretch receptors.

   Baroreceptors of carotid and aortic and pulmonary blood vessels also participate in control of ADH secretion.

   Atrial receptors sense the fall of pressure first and baroreceptors sense it later. ADH thus, released causes vasoconstriction and increases blood pressure. Because of this potent vasopressor effect, ADH is called vasopressin.

4. Other factors that affect ADH production
   i. Trauma
   ii. Pain
   iii. Emotional stress.

Substances that inhibit ADH secretion—alcohol.

DIABETES INSIPIDUS

1. Results due to lack of ADH
2. Urine is very dilute
3. Specific gravity 1.002-1.006
4. Urine volume 4-6 liters or more per day
5. There is constant thirst due to water loss.

Cause

Disease of supraoptic—hypophyseal system fails to secrete ADH. When ADH neurons in supraoptic and paraventricular nuclei are damaged or their nerve fibers are damaged by tumors of hypothalamus or hypophysis.

1. Person with diabetes insipidus has a tendency to dehydrate—which is compensated by thirst.
2. But when there is circulatory stress, e.g. hot environment or when water is not available— it can become serious.

Treatment

Injection of vasopressin suspended in oil for slow release.

Excess secretion of ADH—causes **syndrome of inappropriate ADH secretion.**

Occasionally excess ADH is secreted by hypothalamo-hypophyseal system or by certain types of tumors of the body (particularly bronchogenic carcinoma) of lungs.

Characterized by low Na concentration in ECF and water content of body is increased.

OXYTOCIN

Oxys = Swift
Tossos = Labor

An oxytocic substance is one, which causes powerful uterine contraction.

Actions of Oxytocin

1. *Effect on uterus:* Oxytocin hormone powerfully stimulates the pregnant uterus especially towards the end of gestation (= pregnancy). Late in pregnancy the uterus becomes more sensitive to oxytocin. Therefore, oxytocin is at least partially responsible for birth of baby.

   Oxytocin is secreted reflexly during childbirth = (labor). Pressure of the head of the baby on cervix of the uterus stimulates it and nervous signals pass to hypothalamus—which will increase secretion of oxytocin, which causes powerful uterine contraction—which helps in the birth of the baby (Fig. 73.3)*.

*In hypophysectonized animal labor is prolonged.

2. *Effect on milk ejection:* Oxytocin is important in process of lactation. Lactation consists of two processes (Fig. 73.4):
   i. Milk secretion
   ii. Milk ejection.

Oxytocin helps in milk ejection and causes milk to be expressed from the alveoli into the sinuses of breast, from where the baby can obtain it by suckling the nipple.

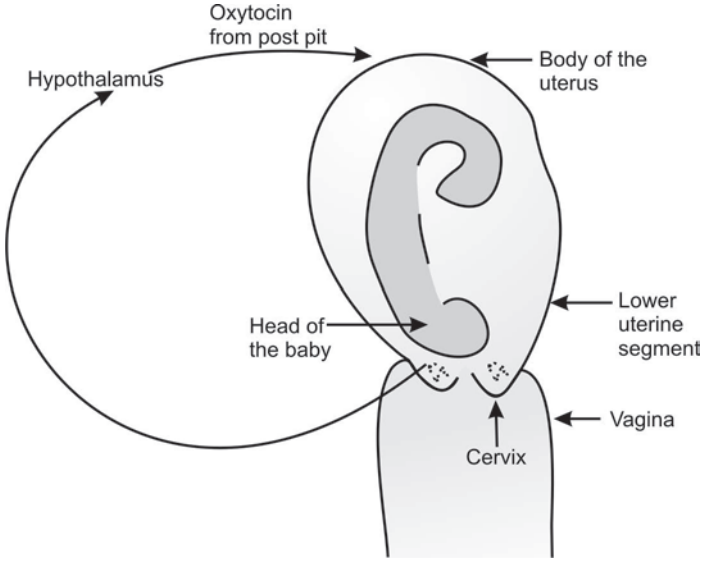


Fig. 73.3: Secretion of oxytocin

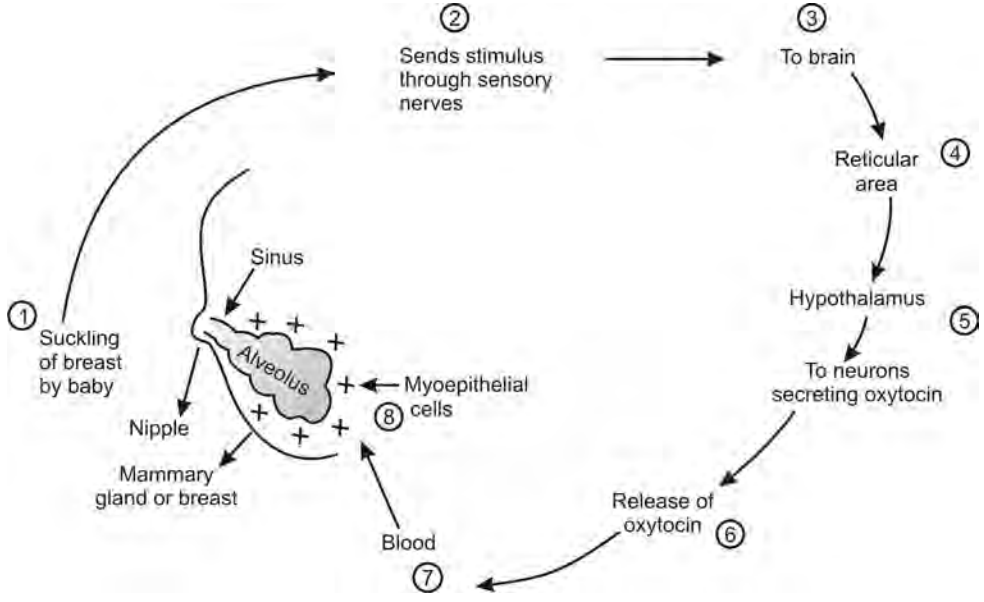


Fig. 73.4: Milk ejection reflex (or suckling reflex)
1 to 8—sequence of events in milk ejection reflex

Myoepithelial cells lie outside alveoli and form lattice work around it. When these cells contract milk is expressed into large sinuses.

3. When baby is suckling the breast the oxytocin released also acts on uterus which contracts and this helps in the process of involution of uterus (i.e. uterus comes back to normal size after the baby is born).
4. Sexual stimulation of female during intercourse increases the secretion of oxytocin—it causes:
   i. Uterine contraction which results in female orgasm.
   ii. This uterine contraction also propels the semen upwards through fallopian tubes.
5. Oxytocin increases contractility of seminal vesicle in male.

Important Points

Posterior pituitary hormones are isolated and identified as octapeptides (= peptides containing 8 amino acids).

1. They are synthesized, also their analogs with increased physiological action like pitocin are synthesized.
2. Neither ADH nor oxytocin are secreted in isolation in response to a stimulus but they appear simultaneously in various proportions, e.g. osmotic stimulus—secretes predominantly ADH and suckling, distention of uterus and coitus—secretes largely oxytocin.

Melanocyte Stimulating Hormone or MSH or Intermedin

It is produced by pars intermedia of the pituitary.

1. It induces darkening of skin of fish and amphibia by expanding of melanophores.
2. Its importance in mammals is not known.
3. Its secretion from pituitary is regulated by two hormones from hypothalamus
   i. MSH releasing hormone (MRH)
   ii. MSH release inhibiting hormone MRIH.
4. Nerve fibers from hypothalamus reach pars intermedia through pituitary stalk. Their endings contain neurosecretory granules, which contain MRH and MRIH.
5. In lower vertebrates—blanching and expansion of melanocytes occurs in response to visual and emotional stimuli.

CHAPTER

74

Thyroid Gland

Word thyroid is derived from Greek—(Thyreos = Shield).

Thyroid gland consist of two lobes—joined by isthmus. It is located immediately below larynx, anterior to trachea, extends on the sides of trachea (Fig. 74.1).

It secretes—Two significant hormones:

1. Thyroxine (T_4)
2. Triiodothyronine (T_3)

   These two hormones have profound effect on metabolic rate of the body.

   It also secretes—a third hormone:
3. *Calcitonin:* It is important for calcium metabolism.

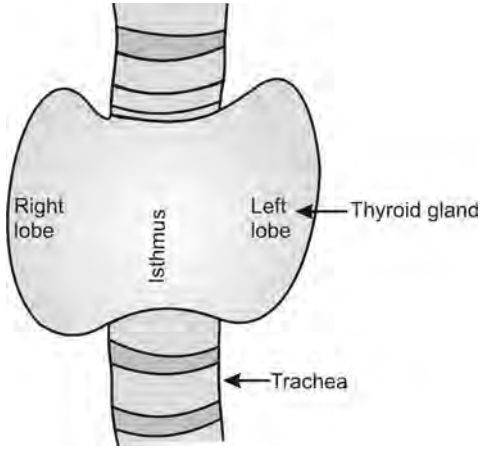


Fig. 74.1: Thyroid gland

Lack of thyroid hormones secretion leads to fall of basal metabolic rate to 40 percent below normal and excess secretion of thyroid hormones results in increased BMR to 60-100 percent above normal.

Thyroid hormone secretion is controlled by thyroid stimulating hormone (TSH, thyrotropin) of the anterior pituitary.

Daily rate of secretion of thyroxine and triiodothyronine: Normally 93 percent of thyroid hormones released from the thyroid gland is thyroxine and only 7 percent is triiodothyronine. But in following few days most of the thyroxine is slowly deiodinated to form additional triiodothyronine. Therefore, the hormone finally delivered to and used by the tissues is triiodothyronine—which amounts to 35 micrograms/day (another 35 micrograms of so called reverse triiodothyronine is formed each day by removal of one of the iodine of thyroxine from the wrong point on the molecule, that is, from near the carboxyl end instead of the hydroxyl end. This reverse triiodothyronine is almost totally inactive and is eventually destroyed).

Functions of both thyroxine and triiodothyronine is same but:

1. Triiodothyronine is 4 times more potent than thyroxine and

2. Triiodothyronine is present in blood in much smaller quantities and persists for much shorter time than thyroxine.

PHYSIOLOGICAL ANATOMY OF THE THYROID GLAND

It consists of closed follicles (100 - 300 micrometers in diameter) filled with secretory substance called colloid.

They are lined with cuboidal epithelium. It secretes into the follicles.

Colloid—mainly consists of a large glycoprotein-thyroglobulin - which contains thyroid hormones within its molecules. Once the secretion has entered the follicles it must be absorbed back through the epithelium into the blood.

Thyroid gland has a rich blood supply.

In between the follicles there are parafollicular cells or C cells, which originate in neural crest and then migrate to ultimobranchial bodies—which fuse with thyroid in mammals. These C cells secrete calcitonin (Fig. 74.2).

FORMATION OF THYROID HORMONES

Iodine: It is essential for formation of thyroid hormones. Requirement of iodine to form normal quantities of thyroid hormones is 1 mg/week. To prevent iodine deficiency, common table salt is iodized with about 1 part sodium iodide to every 100,000 parts sodium chloride.

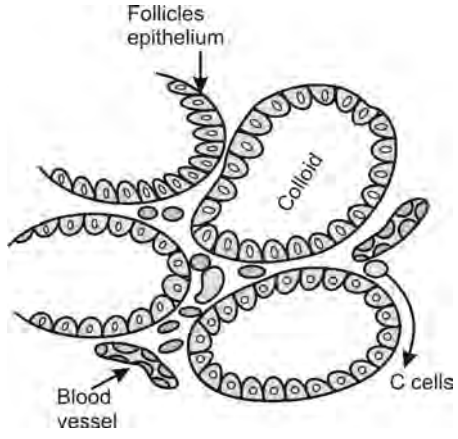


Fig. 74.2: Physiological anatomy of thyroid gland

Fate of ingested iodides: Iodides ingested orally are absorbed from gastrointestinal tract into the blood like chlorides. 1/5 of this is selectively removed from blood by thyroid gland and is used for synthesis of thyroid hormones and the remaining is excreted in the urine.

1. *First stage:* It is transport of iodides from extracellular fluid into thyroid glandular cells and follicles. The basal membrane of the thyroid cell has the specific ability to pump the iodide actively into the interior of the cell. This is called iodide trapping (or Iodide pump) requires ATP. In normal gland the iodide pump concentrates the iodide to about 30 times, its concentration in the blood.

   Thyroid gland cells secrete thyroglobulin. It is a large glycoprotein with a molecular weight of about 335000. Each molecule of thyroglobulin contains 70 tyrosine amino acids. They are the major substrates that combine with iodine to form the thyroid hormones, which are formed within the thyroglobulin molecule. That is they remain a part of thyroglobulin molecule during the process of synthesis of thyroid hormones.
2. *Conversion of iodide to iodine:* This is promoted by peroxidase enzyme and its accompanying hydrogen peroxide molecule.

   Iodide is oxidized to a form of iodine (either nascent iodine I° or I_3^-) that is capable of combining directly with amino acid tyrosine.

   Peroxidase is located either in apical membrane of the cell or attached to it. Thus, iodine is provided at the point where thy-

roglobulin issues from the Golgi complex. When peroxidase system is blocked or it is absent as hereditary disorder, the rate of formation of thyroid hormones falls to zero.

3. *Iodination of tyrosine and formation of thyroid hormones:* Binding of iodine with thyroglobulin molecule is known as organification of thyroglobulin. As soon as thyroglobulin is released from Golgi apparatus, iodine binds with tyrosine of the thyroglobulin.

Oxidized iodine even in molecular form will bind directly but slowly with amino acid tyrosine, but in thyroid cell the oxidized iodine is associated with an iodinase enzyme that causes the process to occur within seconds or minutes.

Successive stages of iodination—Tyrosine is first iodized to monoiodotyrosine and then to diiodotyrosine. Then diiodotyrosine gets coupled with one another, possibly from coupling between two adjacent thyroglobulin molecules (as stored follicular thyroglobulin has a molecular weight of about 670,000). The major product is thyroxine molecule, which remains as part of thyroglobulin molecule OR one molecule of monoiodotyrosine is coupled with one molecule of diiodotyrosine to form *triiodothyronine* (Figs 74.3 and 74.4).

Storage

Each thyroglobulin molecule contains 1 to 3 thyroxine molecules and an average of 1 triiodothyronine molecule for every 14 molecules of thyroxine.

In this form thyroid hormones are stored in the follicles. Total amount stored is sufficient for body's needs for 2-3 months.

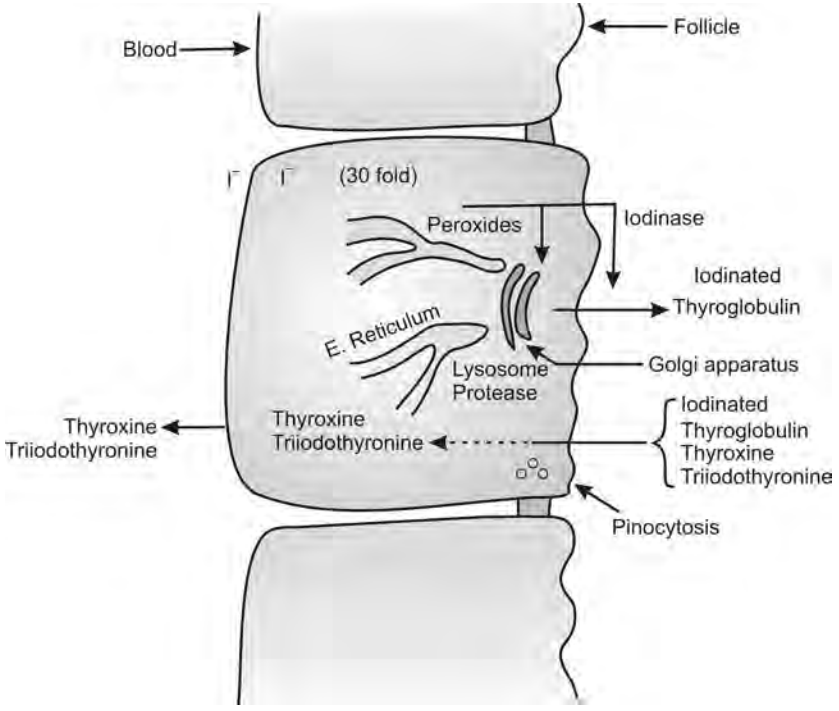


Fig. 74.3: Thyroid cellular iodine mechanism for iodine transport, thyroxine and triiodothyronine formation and release

Therefore, when the synthesis of thyroid hormones ceases entirely the effects of deficiency are not observed for several months.

Release

The apical surface of the thyroid cells sends out the pseudopodia that enclose small portion of the colloid to form pinocytic vesicles. This fuses with the lysosomes to form digestive vesicles, it contains digestive enzymes from lysosomes mixed with colloid. Proteases digest thyroglobulin molecules and release the thyroxine and triiodothyronine. These hormones diffuse through the base of the thyroid cell into the surrounding capillaries (Fig. 74.3).

Three-fourth of iodinated tyrosine in the thyroglobulin never becomes thyroid hormones but remains as monoiodotyrosine and diiodotyrosine. During digestion of thyroglobulin molecule these are also freed. They are not secreted into the blood. Instead iodine is cleaved from them by deiodinase enzyme. So most of the iodine is recycled for formation of thyroid hormones.

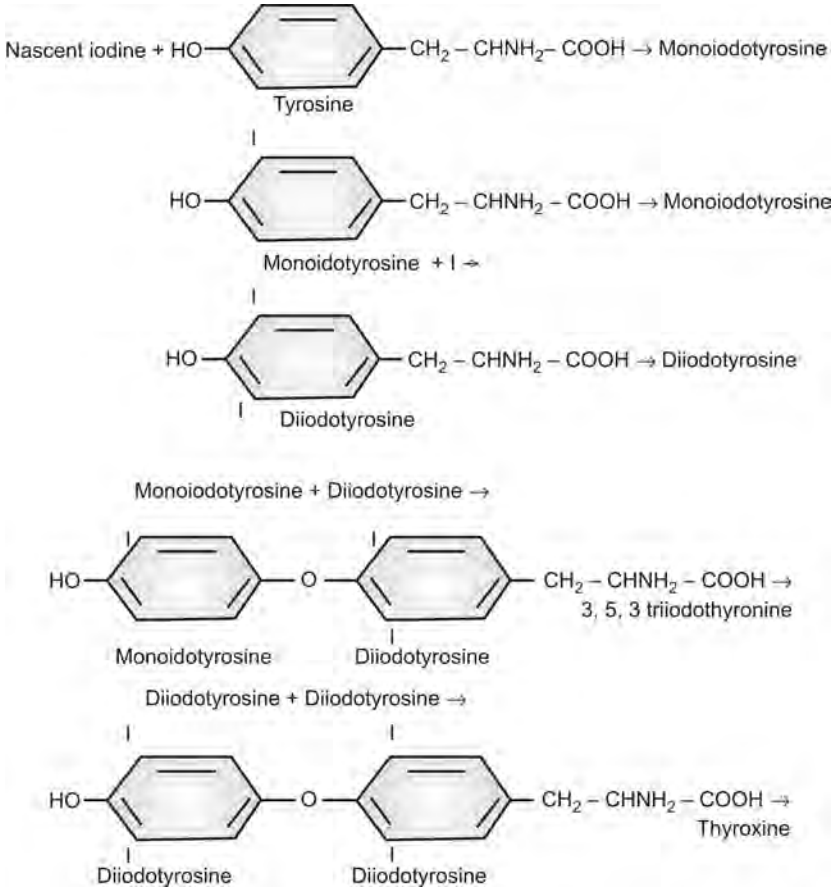


Fig. 74.4: Chemistry of thyroxine and triiodothyronine formation

Transport

The plasma proteins that bind thyroid hormones are:

1. Albumin has largest capacity to bind T_4 but has low affinity.
2. Thyroxine binding prealbumin (TBPA) has moderate capacity and affinity for T_4.
3. Thyroxine binding globulin (TBG)—low capacity for T_4 and high affinity for T_4.

Therefore, most of the circulating T_4 is bound to TBG.

Normally, 99.98 percent of T_4 in plasma is bound, the free T_4 level is only about 2 ng/dl. Normal total plasma T_4 is 8 microgram/dl and plasma T_3 level is approximately 0.15 microgram/dl.

Free thyroid hormones are in equilibrium with protein bound thyroid hormones in plasma and in tissues (Fig. 74.5).

Because of the high affinity of the plasma binding proteins for thyroid hormones, they are released slowly particularly thyroxine. ½ thyroxine is released in 6 days whereas ½ triiodothyronine in 1 day (because of its lower affinity).

On entering the tissue cells both of these hormones again bind with intracellular proteins. Thyroxine once again binding more strongly than triiodothyronine and again stored in target cells themselves and they are used slowly over a period of days or weeks. Therefore, they have long latency.

It is the free thyroid hormones that are physiologically active and that inhibit pituitary secretion.

METABOLISM OF THYROID HORMONES

T_4 and T_3 are deiodinated in liver and kidneys and many other tissues.

In the liver T_4 and T_3 are conjugated to form sulfates and glucuronides, excreted in bile and then in stools.

REGULATION OF THYROID SECRETION

1. *Major regulation is by TSH:*
   i. It is also known as thyrotropin
   ii. Secreted by anterior pituitary
   iii. Molecular weight 28,000
   iv. It is glycoprotein.
2. *Actions of TSH:*
   i. It acts directly on thyroid gland and increases its secretion of thyroid hormones.
   ii. Follicular cells become columnar from cuboidal.
   iii. Hyperplasia of follicular cells
   iv. Reduces the amount of follicular colloid.
   v. It increases vascularity of thyroid gland.

Immediate action of TSH is to release thyroid hormones from colloid.

Later it increases thyroid hormones synthesis by the gland by:

1. Increased iodide trapping
2. Increased iodination of tyrosine
3. Increased coupling reactions.

TSH acts by way of cyclic AMP as second messenger.

TSH binds with receptors on the surface of thyroid cells. This activates adenyl cyclase, which will convert ATP - into cyclic AMP.

HYPOTHALAMIC CONTROL OF TSH

Thyrotropin releasing hormone (TRH) in median eminence is carried by hypothalamo-hypophyseal portal blood vessels to stimulate secretion of TSH (Fig. 74.6).

1. *Negative feedback:* When T_4 and T_3 level is increased in body fluids this decreases further thyroid hormone secretion by decreasing the secretion of TSH:
   i. By direct action on anterior pituitary it blocks stimulant action of TRH.

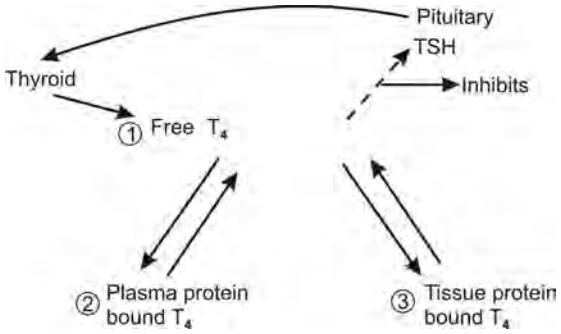


Fig. 74.5: Distribution of T_4 in body (T_3 also is similarly distributed)

ii. Indirect effect through hypothalamus partly caused by changes in temperature of the body. T_3 and T_4 increase heat production. This decreases the secretion of TRH via heat regulating center, which is situated in hypothalamus (Fig. 74.6).

Autoregulation

Autoregulation is essential because dietary iodide may vary greatly and it is found that in normal persons ingestion of large amount of iodine does not affect adversely.

Autoregulation is probably due to an effect of mainly MIT (monoiodotyrosine).

Increase iodide ingestion decreases the sensitivity of thyroid gland to TSH. Apart from this excess MIT depresses iodide transport into the cell, organification and release of T_3 and T_4 from gland.

Apart from this four other factors affect thyroid hormone secretion (Fig. 74.6)

1. *Effect of pregnancy:*
   i. Changes are secondary to increased renal iodide excretion, which produces iodine deficiency.
   ii. Compensated by enlargement of thyroid gland and increased uptake of Iodine.

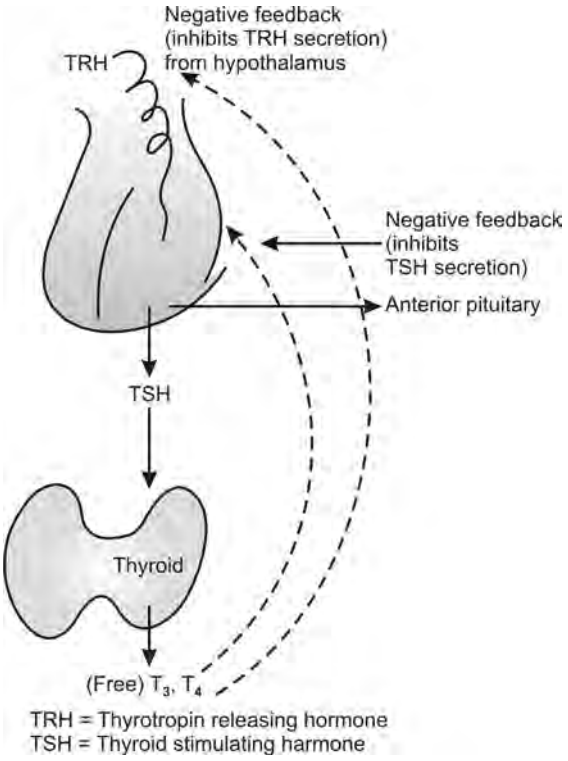


Fig. 74.6: Feedback control of thyroid secretion

iii. Serum TSH is normal in pregnancy.
Thyroid binding globulin (TBG) is increased.
Therefore, total T_4 and T_3 level increases.

2. *Neonatal thyroid hyperactivity:* Immediately after birth, cold stimulate secretion of TSH followed by rise of T_3 and T_4. Within 3-5 days negative feedback brings it back to normal.
   i. *Stress and adrenocortical hormones:* Decrease TSH secretion by inhibiting endogenous release of TRH.
   ii. *Environmental temperature:* Exposure of human beings to cold for several days leads to increase of T_4 and T_3 level. Peak comes after 3 days.

CHAPTER 75

Functions of Thyroid Hormones and Diseases of Thyroid Gland

Thyroid hormones have two major effects on the body:

1. *Metabolic effects*
   i. Calorigenesis
   ii. Regulation of ion and water transport
   iii. Regulation of intermediary metabolism of fat, carbohydrate and protein.
2. *Developmental effects*: Such as control of growth rate in warm blooded animals.

FUNCTIONS OF THYROID HORMONES

In general, effects of *thyroid hormones* are:

Thyroid hormones increase the metabolic activities of almost all tissues of the body:

1. BMR can increase to 60 to 100 percent above normal when large quantities of the hormones are secreted.
2. Rate of utilization of food for energy is increased.
3. Rate of protein synthesis is increased; at the same time the rate of protein breakdown is also increased.
4. The growth rate of young person is accelerated.
5. Mental processes are excited, and
6. Activity of most of the endocrine glands is increased.

Mechanism of Action

1. Thyroid hormones cause *nuclear transcription* of large number of genes. So, mRNA is formed and great number of protein enzymes, structural proteins, transport proteins and other substances are formed.

   In the target cells almost all thyroxine is deiodinated to triiodothyronine. This has high affinity for intracellular thyroid hormone receptors. So, 90 percent of thyroid hormone molecules that bind with receptors are triiodothyronine and only 10 percent is thyroxine.

   The thyroid hormone receptors are attached to DNA strand or are in proximity to them. When receptor, thyroid hormone combination takes place, it initiates transcription process and large number of mRNA is formed. Their translation results in formation of different proteins.
2. Effect of thyroid hormone *on mitochondria:* When thyroxine or triiodothyronine is given to an animal, mitochondria in most cells of the body increase in: (a) size, (b) number, and (c) total membrane surface of the mitochondria.

   Therefore, the principle function of thyroxine is simply to increase the number

and activity of mitochondria and these in turn increase the rate of *ATP formation*, which gives energy for cellular metabolism.

3. Effect of thyroid hormone on *ion transport through* cell membrane:

   Na-K ATPase is an enzyme that is increased in response to thyroid hormones. This enzyme increases the rate of transport of sodium and potassium across the cell membrane. This process utilizes energy in the form of ATP and increases the amount of heat produced.

4. *Calorigenic action or calorigenesis is heat production:* T_3 and T_4 increase the oxygen consumption in almost all metabolically active tissues, exceptions are adult brain, testes, uterus, lymph nodes, spleen and anterior pituitary.

Specific Effects of Thyroid Hormones on the Body

Effects on Growth

1. Thyroid hormones are essential for the metamorphic change in tadpole into the frog. It causes growth, differentiation and maturation in mammals. In human beings this effect is mainly seen in growing children. In hyperthyroid, rate of growth is greatly increased and the child becomes taller for his age. In hypothyroid, the rate of growth is retarded.

   Growth promoting effect of thyroid hormone is based on ability to promote protein synthesis.

2. Important effect of thyroid hormone is to promote growth and development of the brain during fetal life and for the first few years of postnatal life. If the fetus does not secrete enough quantity of thyroid hormone the brain becomes smaller than normal. After birth if thyroid therapy is not started within days or weeks the child will remain mentally retarded.

Effect on Carbohydrate Metabolism

Thyroid hormone causes:

1. Increased rate of absorption of carbohydrates from intestine.
2. It causes rapid uptake of glucose by the cells.
3. Enhanced glycolysis.
4. Enhanced gluconeogenesis.
5. Increased insulin secretion.

Thus, thyroid hormones stimulate all aspects of carbohydrate metabolism.

Effect on Fat Metabolism

Fats are the major source of long-term energy supplies. Therefore, fat stores are depleted. This increases level of free fatty acids in plasma and thyroid hormones increase the oxidation of free fatty acids in the cells.

Thyroid hormone decreases cholesterol, triglycerides and phospholipids in blood because of increased receptors for LDL in the liver, so it is removed from circulation and cholesterol is secreted in bile.

Therefore in hypothyroidism there is increased cholesterol, trigylcerides and phospholipids and prolonged hypothyroidism results in atherosclerosis.

Effect on Vitamin Metabolism

Thyroid hormone increases quantities of many enzymes and because vitamins are essential part of many enzymes or co-enzymes, thyroid hormones cause increased need for vitamins. Thyroid hormone is essential for conversion of β carotene to vitamin A and its conversion into retinene.

Effect on Basal Metabolic Rate

Thyroid hormone increases metabolic rate of almost all the tissues, therefore excess secretion of thyroid hormone can increase BMR to 60-100 percent above normal. In hypothyroidism, BMR falls below normal and may become –30 to –50 percent.

Effect on Body Weight

Increased thyroid hormone secretion always decreases the weight and decreased hormone always increases the weight.

Effect on Cardiovascular System

1. Thyroid hormones increase the number and affinity of β adrenergic receptors in the heart and therefore there is increased sensitivity of heart to catecholamines. So there is increased heart rate and force of contraction of the heart.

   β blockers are used in treatment of severe hyperthyroidism.
2. Action: (i) increases cardiac output therefore systolic blood pressure is increased but the peripheral vasodilatation decreases diastolic blood pressure.
3. Blood flow to tissues is increased because of increased metabolic rate and oxygen consumption by tissues, results in increased metabolic products which cause vasodilatation of peripheral blood vessels.
4. Because of peripheral vasodilatation blood volume is increased.

Effects on Skeletal Muscle

1. *Muscle weakness* occurs in most patients with hyperthyroidism (thyrotoxic myopathy). Partly it is due to increased protein catabolism.

b. Patients with hyperthyroidism show *fine muscle tremors.* It can be observed easily by placing a piece of paper on the extended fingers. Tremor is believed to be caused by increased reactivity of the neuronal synapses in the area of the cord that control muscle tone.

Effects on Nervous System

1. In hypothyroidism, mentation is slow. In hyperthyroidism—rapid mentation, irritability and restlessness.

   O_2 consumption, cerebral blood flow and glucose consumption by brain are normal in adult hypo- and hyperthyroidism.
2. Thyroid hormones enter the brain in adults and are found in gray matter in numerous different locations. In addition, the brain converts T_4 to T_3.
3. Some of the effects of thyroid hormones on brain are probably secondary to increased responsiveness to catecholamines, which results in increased activation of reticular activating system.
4. Thyroid hormones have marked effects on brain development. In hypothyroid infants, synapses develop normally, myelination is defective and mental development is seriously retarded. The mental changes are irreversible if replacement therapy is not begun soon after birth.

Effect on Respiration

Increase rate of metabolism causes increased utilization of oxygen and the formation of carbon dioxide. These effects activate all the mechanisms that increase rate and depth of respiration.

Effect of GIT

1. Thyroid hormone causes increased appetite and food intake.

2. It increases the rate of secretion of the digestive juices.
3. It increases the motility of GI tract often resulting in diarrhea.

Lack of thyroid hormones – cause constipation.

Thyroid hormones also exert effects on *peripheral nervous system.* The reaction time of stretch reflex is shortened in hyperthyroidism and prolonged in hypothyroidism. Therefore, measurement of reaction time of ankle jerk can be used as a clinical test for evaluating thyroid function.

Effect on Sleep

Because of the effect of thyroid hormones on musculature and CNS the hyperthyroid person always feels tired but he has difficulty in falling asleep because of: (a) activation of reticular activating system, and (b) excitatory effects on synapse.

Extreme somnolence is feature of hypothyroidism.

Effect on Other Endocrine Glands

Thyroid hormones when secreted in increased amount increases secretion from most of the other endocrine glands but it also increases the need of the tissue for these hormones.

Effect on Sexual Function

For normal sexual function, thyroid secretion needs to be approximately normal.

1. In men:
   i. Lack of thyroid hormone is likely to cause loss of libido.
   ii. Excess of thyroid hormone causes impotence.
2. In women:
   i. Lack of thyroid hormone often causes menorrhagia and polymenorrhea which means respectively excessive and frequent menstrual bleeding.
   ii. In other women it may cause amenorrhea and irregular periods.
   iii. In hypothyroid women lack of thyroid hormone decreases libido.
3. In women *hyperthyroidism* may result in oligomenorrhea which means reduced bleeding and occasionally amenorrhea.

DISEASES OF THYROID GLANDS

Iodine in sufficient quantity is essential to prevent hypothyroid state, which may be caused by: (i) iodine deficiency in blood or by, (ii) presence of goitrogenous substances in diet.

Vegetables of Brassicaceae family particularly cabbage and turnip contain progoitrin and a substance that converts this compound into goitrin. Goitrin is an active antithyroid agent.

Progoitrin activator is heat labile and is destroyed by cooking but there are activators in intestine (bacterial origin) which will form goitrin even after vegetable is cooked. Goitrin prevents utilization of iodine and interfere with synthesis of thyroxine.

This will result in decreased blood thyroxine level, which will result in increased secretion of TSH. Under the effect of TSH, the gland hypertrophies and compensate for iodine deficiency and signs of hypothyroidism do not appear.

But in: (a) pregnancy, (b) puberty, and (c) infection the body's need for iodine is increased. Such conditions may lead to hypothyroidism.

Hypothyroid mother gives birth to *cretin* because faetus requires adequate thyroid hormone during later stages of pregnancy. In parts of the world where there is iodine deficiency in soil, the foodstuffs contain less iodine. Mother in such areas gives birth to

cretin, resulting in *endemic cretinism*. To prevent, additional iodine is given in later half of pregnancy.

In iodine deficiency hormone pattern of the gland also changes and gland produces more T_3.

In areas where iodine intake is less than 60 micrograms/day goiter is common. (Thyroid gland enlarges due to increased TSH). This increases the ability of the gland to trap iodides and synthesize sufficient hormone to maintain *euthyroid state.*

In areas where intake is less than 20 micrograms/day, very large glands are common and compensation is incomplete.

Hypothyroidism (in Adults known as Myxedema)

Results when circulating levels of T_4 and T_3 are less. In 1885, George Murray successfully treated myxedema with sheep's thyroid extract, first demonstration of replacement endocrine therapy.

Cause

1. Simple goiter due to iodine deficiency (common cause).
2. Autoimmune thyroid disease.
3. Abnormality of enzyme system required for formation of thyroid hormones.
4. Presence of goitrogenous substances in diet.
5. TSH deficiency due to hypothalamus pituitary disease.

Whatever may be the cause it results in deficiency of circulating T_3 and T_4 in adults:

Signs and symptoms are:

1. Intolerance to cold (cause –decreased thermogenesis).
2. Extreme somnolence sleeping 14-16 hours/day.
3. Slow heart rate.
4. Decreased cardiac output.
5. Decreased blood volume.
6. Increased weight (cause – low metabolic rate and lack of lipolysis).
7. Constipation.
8. Mental sluggishness, which means slowness of thought, speech and action.
9. Poor memory, intellectual deterioration.
10. Depressed growth of hair, loss of hair scaliness of skin and puffiness of face.
11. Hoarseness of voice (Husky voice).
12. In extreme cases edematous appearance throughout the body.
13. Lastly myxedema coma.

Myxedema: Develops in patients with almost total lack of thyroid function. In this condition for reasons not explained, greatly increased quantities of hyaluronic acid and chondroitin sulfate bound with protein form excessive tissue gel in the interstitial spaces. This causes the total quantity of interstitial fluid to increase. Because of the gel nature of the excess fluid it is relatively immobile and edema is *non-pitting* type.

Atherosclerosis: Results because of increased lipid levels especially serum cholesterol, depending on which blood vessels are affected there is deafness, peripheral vascular disease, coronary insufficiency, etc.

Investigations

1. Free thyroxine and triiodothyronine level in plasma is low. Determined by a technique known as radioimmunoassay (RIA).
2. Concentration of TSH in plasma is measured by (RIA) is high except in pituitary failure.
3. Previously protein bound iodine (PBI) was measured – as an index of circulating level of thyroid hormones. It is less than 2 microgram/dl.

4. Basal metabolic rate (BMR) ranges between –30 to –50 percent below normal (– means minus).

Treatment

Oral ingestion of tablet containing thyroxine daily. The hormone normally has duration of action of more than one month. Daily oral dose of thyroxine can maintain a steady level of the hormone.

Cretinism

Caused by extreme hypothyroidism in fetal life, infancy and childhood.

This condition is characterized by failure of growth and mental retardation.

Cause

1. Congenital lack of thyroid gland (Congenital cretinism).
2. Failure of thyroid gland to produce thyroid hormones because of a genetic defect in the gland.
3. Iodine lack in the diet (endemic cretinism).

Newborn child without thyroid gland may appear normal and functions normal because it has been supplied with some (but usually not enough) thyroid hormones by the mother while in uterus. But few weeks after birth his movements become sluggish and both his physical and mental growth is greatly retarded and cretinism manifests. Treatment any time will cause normal return of physical growth but unless a cretin is treated within a few weeks after birth its mental growth is permanently retarded—because of retardation of *growth, branching* and *myelination* of neuronal cells of the CNS at this critical time which is important in the normal development of mental powers.

Chief Features of Cretinism

1. Obese stocky short child whose soft tissue growth is depressed but bone growth is more depressed.
2. Milestones of development are delayed.
3. Stunted growth, club like fingers, deformed bones and teeth.
4. Rough, thick dry and wrinkled skin.
5. Hairs scanty.
6. Face—bloated, idiotic look.
7. Thick and parted lips.
8. Large protruding tongue, with dribbling saliva.
9. Broad nose.
10. Abdomen – Potbelly.
11. Sexual characters underdeveloped.
12. Mental growth is retarded.
13. GIT—appetite is less.
14. Constipation present.
15. Child is susceptible to cold.

Investigations

1. BMR is decreased.
2. Serum cholesterol is increased.
3. T_3 and T_4 plasma level is low.
4. TSH level is increased (not so in pituitary deficiency).
5. PBI is less.

Treatment

A tablet containing thyroxine given orally daily in sufficient dose. If not treated early the mental derangement persists.

Hyperthyroidism OR Thyrotoxicosis OR Graves' Disease OR Exophthalmic Goiter OR Toxic Goiter

Causes

1. Increased moderate enlargement of the gland due to tremendous hyperplasia, so

that the number of cells is increased several times and there is infolding of follicular membrane. Each cell secretes thyroid hormones several times.

Cause of such enlargement is thyroid-stimulating immunoglobulins (TSIs), which bind with TSH receptors on the membrane. They induce activation of cyclic AMP in thyroid cells resulting in hyperthyroidism. They have prolonged stimulating effect on thyroid gland lasting as long as 12 hours (TSH effect lasts for little over one hour). High level of thyroid hormones secretion by TSI in turn suppress TSH formation from pituitary.

These antibodies that cause hyperthyroidism develop as result of autoimmunity that has developed against thyroid tissues.

2. *Thyroid adenoma:* Hyperthyroidism occasionally result from localized adenoma (tumor) that develops in the thyroid tissue and secretes large quantities of thyroid hormone. Because adenoma secretes large quantities of thyroid hormones the function of the remainder of the gland is almost totally inhibited as TSH secretion from pituitary is suppressed.
3. *Increased TSH secretion:* Rare cause of hyperthyroidism.

Symptoms of Hyperthyroidism

Skin

1. Intolerance to heat.
2. Increased sweating.

Muscles

1. Mild to extreme weight loss.
2. Muscular weakness – due to loss of muscle mass and specific thyrotoxic myopathy.
3. Extreme fatigue.
4. Tremors of hands (fine).

CNS

1. Nervousness or irritability.
2. Inability to sleep.

CVS

1. Pulse rate is increased, sleeping pulse rate may be 100-160/minute.
2. Atrial fibrillation may be present.

Eye

Exophthalmos: Most hyperthyroid persons develop protrusion of eyeball called exophthalmos. It is symmetrical. This is different than just staring appearance, which is also produced in hyperthyroidism because of retraction of eyelids due to sympathetic overactivity.

It is due to swelling of the extraocular muscles and to a lesser extent swelling of connective tissue within the rigid bony walls of the orbits. This pushes the eyeball forward. The cause of exophthalmos is autoimmune attack on extraocular muscles and orbital connective tissue by cytotoxic antibodies. The antibodies are formed to antigens common to the (a) eye muscles, (b) thyroid, and (c) some other tissues.

The condition sometimes becomes severe to cause stretching of optic nerve and damage vision. More often eyes are damaged because the eyelids do not close completely, when the person blinks or sleeps, as a result the epithelial surfaces of the eyes become dry and irritated and often infected, resulting in ulceration of the cornea.

Diagnostic Tests of Hyperthyroidism

1. Most accurate measurement of free thyroxine and triiodothyronine in patients plasma by proper radioimmunoassay technique (RIA).
2. BMR is increased to + 40 to + 100 percent.

3. Concentration of TSH in the plasma by RIA—in usual type of hyperthyroidism TSH suppression is complete and there is almost no TSH in plasma.
4. Concentration TSI is measured by RIA— it is high in usual type of hyperthyroidism but low in thyroid adenoma.
5. Protein bound iodine (PBI) was previously used as an index of plasma concentration of thyroid hormones. It's normal value is 4-8 microgram/dl. It is increased in hyperthyroidism sometimes up to 16-20 microgram/dl.
6. Blood sugar level is increased.
7. Serum cholesterol level is reduced to 100 mg percent or less.
8. Sleeping pulse rate is increased.
9. Uptake of Radioactive iodine—with gamma ray counter is increased.

Treatment

1. Surgical removal of most of the thyroid gland. To prepare for surgery propylthiouracil is administered for several weeks till BMR becomes normal. Then high concentrations of iodides, for 1-2 weeks, immediately before operation causes gland to recede in size, and its blood supply to diminish.
2. *Radioactive iodine:* 80-90 percent of radioactive iodine is absorbed by hyperplastic toxic gland within a day after injection. It destroys secretory cells of thyroid gland. Usual dose is 5 millicurie.

   Several weeks later if still hyperthyroid state exists, additional doses are given till person is normal.
3. *Antithyroid drugs:* All stages of thyroid hormone synthesis and release can be depressed by these drugs.

   For example, Thiocarbamides–inhibit organic binding of iodine and block coupling reaction.

Clinically used drugs in this group are: (i) propylthiouracil, and (ii) methimazole.

Thiocyanates—inhibits iodide trapping.

Iodides—in large doses cause transient inhibition of organic binding.

The position of iodides in thyroid physiology is unique. Some iodide is needed for normal thyroid function, but too little iodide or too much, both (cause abnormal thyroid function).

CHAPTER

76

Parathyroid Glands and Calcitonin

PARATHYROID GLANDS

So named because of their location along side the thyroid gland. In humans, there are usually 4 parathyroid glands, 2 embedded in superior poles and 2 in its inferior poles. The locations of parathyroid gland and their number can vary considerably.

Each parathyroid gland is a richly vascularized disk measuring 6 × 3 × 2 mm. They are small reddish or yellowish brown bodies. Total weight is about 120 mg. In man, parathyroid glands lie always outside the capsule of the thyroid gland (Fig. 76.1).

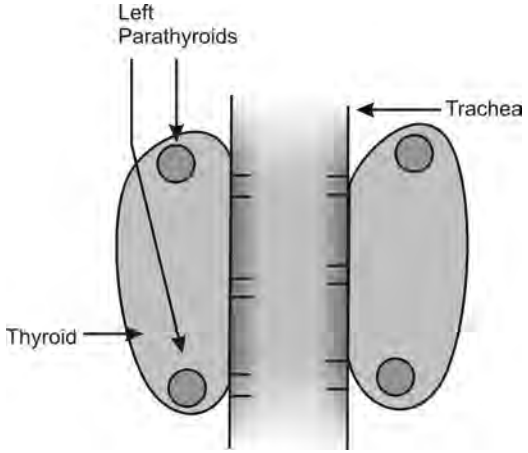


Fig. 76.1: Parathyroid glands

Histology

It contains two distinct types of cells (Fig. 76.2):

1. Chief cells
   - i. Abundant
   - ii. Contain prominent Golgi apparatus and endoplasmic reticulum
   - iii. Contain secretory granules
   - iv. They synthesize and secrete parathyroid hormone.
2. Oxyphil cells
   - i. Less abundant
   - ii. Large
   - iii. Contain oxyphil granules and large number of mitochondria
   - iv. In human few are seen before puberty afterwards they increase with age.

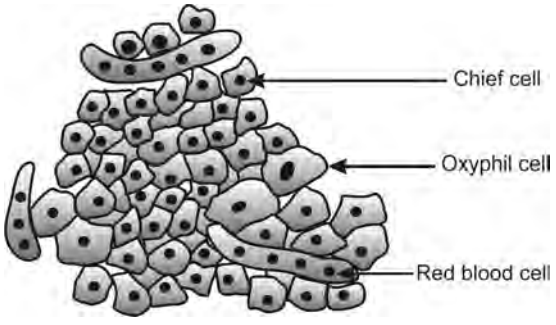


Fig. 76.2: Histology of parathyroid gland

Possibly they are degenerated chief cells. Among these two cells are wide vascular channels.

Function

Parathyroid glands are essential for life, their removal can cause death from asphyxia resulting from spasm of—laryngeal muscle, thoracic muscles and diaphragm.

The hormone secreted by parathyroid gland is called parathyroid hormone or parathormone, which keeps constant the concentration of calcium in intracellular and extracellular fluids, in spite of wide variation in calcium intake and calcium excretion.

Other hormones are also important in:

Calcium Homeostasis

1. 1,25-dihydroxycholecalciferol
2. Calcitonin
3. Thyroid hormone
4. Adrenal glucocorticoids
5. Gonadal hormones
6. Growth hormones

(All hormones beginning with g)

But most important hormone is parathyroid hormone for calcium homeostasis.

Chemistry

In man, it is a polypeptide, containing 84 amino acids and has molecular weight of 9500. In parathyroid gland – proparathyroid hormone with higher molecular weight is found.

The normal plasma level of parathyroid hormone (PTH) is 10 - 55 pg/ml. The half-life of PTH is less than 20 minutes and it is rapidly cleared by the Kuffer cells in the liver into two polypeptides: (i) C terminal, and (ii) N terminal fragments, out of which N terminal fragment is biologically active.

Control of Secretion

Secretion of parathyroid hormone is controlled by: (1) concentration of Ca in blood, which perfuses the parathyroid gland:

1. The slightest decrease in calcium ion concentration in the extracellular fluid causes the parathyroid glands to increase their secretion within minutes.

   If the decreased calcium concentration persists, the glands will hypertrophy. For example, parathyroid glands are greatly enlarged in: (a) rickets, (b) pregnancy, and (c) during lactation.
2. Conditions that increase the calcium ion concentration above normal cause decreased activity and reduced size of the parathyroid glands. For example,
   (a) excess quantities of calcium in diet, (b) increased vitamin D in diet, (c) Bone resorption, by other causes, e.g. bone absorption caused by disuse.
   (2) level of 1,25-dihydroxycholecalciferol in plasma – active form of vitamin D which absorbs Ca^{2+} from gut.

Actions of Parathyroid Hormone

The main organs on which it acts are:

1. Bone
2. Kidney, and
3. Intestine.

Mechanism of Action

PTH on *bone* and *kidney* involve activation of adenyl cyclase by way of a membrane receptor and G8. Therefore, cyclic AMP formation is increased. Cyclic AMP is a second messenger. Within few minutes after administration of parathormone the concentration of cAMP increases in: (i) osteocytes, (ii) osteoblasts, and (iii) other target cells. This cyclic AMP is probably responsible for: (a) osteoclastic

secretion of enzymes and acids to cause bone reabsorption, (b) formation of 1,25-dihydroxycholecalciferol in the kidneys.

There are other effects of parathormone that function independently of the second messenger mechanism.

Action on Bone

Parathyroid hormone has two phases of action. That means parathormone mobilizes calcium from the bones into the extracellular fluid in two phases:

1. Early or rapid phase
   i. Begins in minutes
   ii. There is movement of calcium from deeper aspects of the bones to the surface.
   iii. Results from activation of already existing bone cells mainly osteoclasts and osteocytes, which results in calcium and phosphate reabsorption.
2. Late or slow phase
   i. Requires several days or weeks
      a. There is increased transcription of DNA and translation of mRNA and subsequent increase in the synthesis of lysosomal enzymes.
      Lysosomal enzymes cause hydrolysis of protein matrix of the bone.
      b. There is multiplication of the osteoprogenitor cells, which become converted into bone dissolving osteoclasts.
      c. Demineralization of bone by parathormone secondarily stimulates formation of osteoblasts, which leads to fresh bone formation.
      d. Constant turnover of this type helps in remodeling of bone throughout life in response to mechanical and other stresses.
      e. Increased turnover of collagen increases the level of hydroxyproline in the urine.
      f. With sustained increases in PTH, bone resorption always exceeds bone formation.

Summary of Actions

Parathyroid hormone acts *directly* on bone and causes bone resorption and mobilization of calcium.

1. Plasma calcium is increased.
2. Plasma phosphate level is decreased.
3. It also increases urinary excretion of phosphate. Phosphaturia is due to decreased absorption of phosphate in the proximal tubules.
4. PTH also causes reabsorption of calcium from distal tubules.
5. Increased urinary excretion of hydroxyproline.
6. PTH increases conversion of 25-hydroxycholecalciferol into 1,25-dihydroxycholecalciferol in kidney.
7. PTH after several hours promotes calcium absorption from the gastrointestinal tract. This effect is *indirect*. Parathyroid hormone causes conversion of 25-hydroxycholecalciferol into 1,25-dihydroxycholecalciferol in kidney and this causes absorption of more calcium from gastrointestinal tract.

1,25-dihydroxycholecalciferol (DHCC) is the physiologically active metabolite of vitamin D.

Vitamin D

Plays important role in calcium metabolism. Vitamin D deficiency causes poorly calcified bones resulting in *Rickets* in children and *osteomalacia* in adults.

Vitamin D is formed in skin by the action of sunlight. Vitamin D includes D_2 and D_3.

1. 7-dihydrocholesterol occurs normally in skin, when exposed to sunlight (ultraviolet rays), it is converted to D_3. D_3 is cholecalciferol.
2. D_2 is obtained from plant sterol known as ergosterol. Irradiation by ultraviolet rays (Sunlight) converts it into D_2. D_2 is ergocalciferol.

Fish oil, milk, egg yolk are good sources of D_3. Vitamin D_3 (cholecalciferol) is formed in the skin by the action of sunlight but because of clothing this reaction is prevented and therefore we are dependent on diet, for vitamin D.

Vit D_3 either formed in the skin or ingested in diet is inactive. It requires biochemical alteration, first in liver, where it is converted into 25-hydroxycholecalciferol then in kidney, where it is converted into 1,25-dihydroxy-cholecalciferol by the action of parathyroid hormone.

Thus, when plasma calcium falls, increased secretion of PTH follows which increases formation of 1,25-DHCC and 1,25-DHCC causes increased absorption of calcium from the gut (Fig. 76.3).

Mechanism of Action

1,25-dihydroxycholecalciferol is a steroid. It acts via a receptor. When it binds with the receptor transcription of DNA to form some mRNA takes place. This mRNA forms calcium binding proteins and these proteins facilitate Ca^{2+} movement across the intestinal epithelium.

1,25 DHCC is a *hormone* as it is produced in the body, transported by bloodstream to act at a distant site and vitamin D_3 and 25-hydroxycholecalciferol are hormone precursors.

Plasma calcium level is normally about – 10 mg/dl.

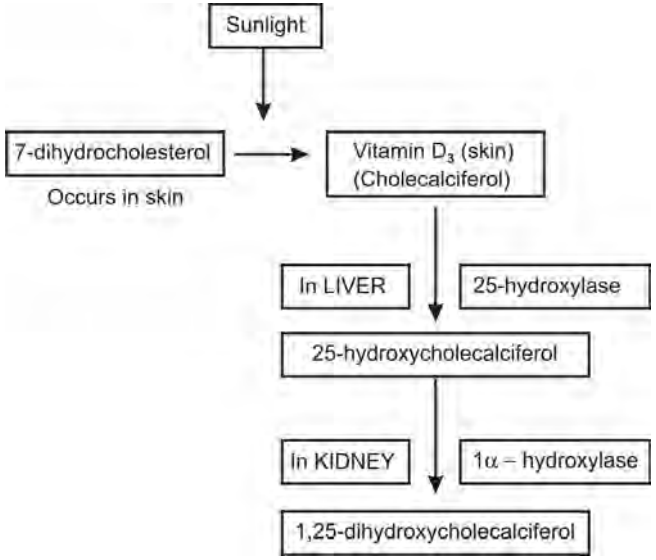


Fig. 76.3: Formation and hydroxylation of vitamin D_3

It includes:

1. Protein bound calcium 45 percent (bound to albumin and globulin).
2. Complexed calcium 5 percent (combined with citrate HCO_3, etc.).
3. Ionized calcium – 50 percent. It is diffusible and is physiologically active.

Level of ionized calcium in plasma depends on:

1. Calcium absorption from gut (therefore on 1,25 DHCC formation, and
2. Level of secretion of parathyroid hormone.

Hypoparathyroidism or Tetany

Parathyroid hormone (PTH) is essential for life. Most common cause of hypoparathyroidism is removal of, or damage to, the parathyroid gland during partial thyroidectomy or extensive operation for laryngeal or esophageal carcinoma.

There is a steady decline in the plasma calcium level. Signs of neuromuscular hyperexcitability appear followed by full-blown hypocalcemic tetany. Plasma phosphate levels usually rise as plasma calcium level falls.

Clinical Features of Hypoparathyroidism or Tetany

1. Tingling and numbness of extremities.
2. Feeling of stiffness in hands and feet.
3. Cramps in extremities.
4. Carpopedal spasm (Trousseau's sign).
5. Laryngeal stridor (Laryngismus stridulus).
6. Facial irritability (Chvostek's sign).
7. Generalized convulsions.
8. Visceral manifestations.

Carpopedal spasm: May occur spontaneously or it may be brought on by compression of a limb by blood pressure cuff for few minutes. This occludes circulation.

1. In the upper limb, the metacarpophalangeal joints are flexed, the fingers are extended, the thumb is flexed on the palm and the wrist and elbow are flexed.
2. In the lower limb the toes are planter flexed and feet are drawn up:

Laryngeal stridor: It is due to sudden spasm of laryngeal muscles. The glottis is closed, no air can enter and progressive cyanosis develops. After a variable period the spasm relaxes and air enters with a crowing sound.

Facial Irritability (Chvostek's Sign)

A quick contraction of the ipsilateral facial muscles elicited by tapping over the facial nerve after its exit from stylomastoid foramen (in front of ear). This sign is produced because of increased excitability of nerves to mechanical pressure.

Visceral Manifestations

1. Intestinal colic
2. Biliary colic
3. Bronchospasm
4. Profuse sweating.

All are due to increased excitability of autonomic ganglia.

Investigations

1. Total calcium level falls to 6-7 mg/dl.
2. Ionized calcium level falls to 3 mg/dl.
3. RIA shows low or undetectable parathyroid hormone.

Treatment

In most patients:

1. Vitamin D is administered in high quantities, as high as 100,000 units per day together with.

2. Intake of 1 to 2 gm of calcium per day. This will keep calcium ion concentration in normal range.
3. At times 1,25 DHCC is administered instead of nonactive form of vitamin D because it is more potent and much more rapid in action.

Causes of Clinical Tetany

Tetany can occur due to: (i) hypocalcemia or (ii) alkalosis.

Hypocalcemia: Tetany from hypocalcemia can occur after parathyroidectomy, in rickets, in osteomalacia and in renal failure with phosphate retention. It is the fall in ionized plasma calcium, which affects the neuromuscular tissue; alteration of protein bound calcium has no effect.

Alkalosis: Produces tetany, although total plasma calcium level is unaltered. For example: (a) hyperventilation, (b) profuse vomiting or (c) excessive ingestion of sodium bicarbonate may cause alkalimic tetany. In these alkalimic states there is increased plasma protein ionization. Protein ions 'mop up' ionized calcium. Therefore, plasma level of ionized calcium falls.

Hyperparathyroidism

Cause

The gland may undergo: (i) hyperplastic change or (ii) tumor formation – with excessive secretion of parathormone (common in women) results in a clinical condition known as ostitis fibrosa cystica.

Characterized by:

1. Raised serum calcium because of excessive osteoclastic activity in bones (12 - 15 mg/dl or more).
2. Diminished blood phosphate level.
3. Excessive excretion of calcium and phosphate.
4. Formation of renal stones.
5. Bone resorption takes place with increased. susceptibility to fractures occasionally large cystic areas in bone develop.
6. Serum alkaline phosphatase level increases.
7. Impairment of renal function.
8. In extreme cases, calcium phosphate crystals deposit in lungs, renal tubules, stomach mucosa and thyroid gland.

Signs and Symptoms

1. Muscular weakness (cause depression of central and peripheral nervous system).
2. Constipation.
3. Abdominal pain.
4. Loss of appetite.
5. Multiple fractures may result due to slight trauma especially when cysts develop.
6. Depressed relaxation of the heart during diastole.

All characteristics, signs and symptoms are due to increased plasma calcium and increased resorption of bones.

CALCITONIN

Calcitonin in mammals is secreted by parafollicular cells or C cells present in thyroid gland in between thyroid follicles.

In lower animals like fish, amphibia, reptile and birds it is secreted by ultimobranchial bodies (glands) and plays important role in control of blood calcium level, when these animals change their habitat from fresh water to sea water. In human beings, ultimobranchial glands do not exist as such but are incorporated in thyroid gland.

1. Chemically polypeptide having 32 amino acids.
2. Molecular weight 3400.

3. Hormone is stored in parafollicular cells in the form of granules.
4. When calcium level increases above normal calcitonin is secreted. Its secretion is parallel to increase in plasma calcium level.

Physiological Effects

It lowers the calcium ion concentration in plasma rapidly beginning within minutes after injection of calcitonin. It acts directly on bone:

1. Immediate effect is to decrease activity of osteoclasts. This effect is especially important in children because it favor deposition of calcium.
2. More prolonged effect is to decrease formation of new osteoclasts. Decreased osteoclasts are followed by decreased osteoblasts. Therefore, over a long period the net result is reduced osteoclastic and osteoblastic activity and the effect on plasma calcium is transient lasting for a few hours to a few days.

In adults – calcitonin has a very weak effect on plasma calcium.

So to regulate calcium concentration two mechanisms are available: (1) Calcitonin and (2) parathormone, but there are two major differences:

i. Calcitonin mechanism operates more rapidly reaching a peak activity in less than 1 hour in contrast to 3 to 4 hours required for peak activity to be attained following parathyroid secretion.
ii. Calcitonin mechanism mainly acts as a short-term regulator of calcium ion concentration, because parathyroid control mechanism overrides it, also receptors for calcitonin on osteoclasts are down-regulated.

Therefore, for long-term regulation of calcium ions in ECF, parathyroid hormone is important. Yet for short period, for example, an hour after calcium meal, calcitonin seems to play significant role.

CHAPTER

77

Adrenal Glands—Adrenal Cortex

Adrenal or suprarenal glands are two in number and are situated on the top of each kidney.

There are two endocrine organs in the adrenal gland:

1. Adrenal medulla (inner) secretes catecholamines, and
2. Adrenal cortex (outer) secretes steroid hormones.

They differ in their: (a) development, (b) histological structure, and (c) function.

ADRENAL CORTEX

Adrenal cortex is essential for life: Whenever we suffer from stress, its hormones get us through it. Its chief hormones are:

1. Cortisol
2. Corticosterone, and
3. Aldosterone.

Through these hormones the adrenal cortex regulates the metabolism of:

1. Carbohydrate
2. Protein
3. Fat
4. Water, and
5. Electrolyte.

Embryology: Adrenal cortex is developed from urogenital ridge.

Histological structure: Cells of adrenal cortex are arranged in three zones (Fig. 77.1).

1. Zona glomerulosa: In this, the cells lie with their long axis parallel to its surface.
2. Zona fasciculata: In this, columns of cells lie vertical to the surface.
3. Zona reticularis: In this, the cells are arranged irregularly.

In man, zona glomerulosa act as one unit producing mainly aldosterone and zona fasciculata and reticularis act as single unit—its function is to form cortisol, corticosterone, androgen and estrogen.

The *cells* of adrenal cortex contain: (i) High cholesterol in ester form. This is precursor of adrenocortical hormones, and (ii) Ascorbic acid.

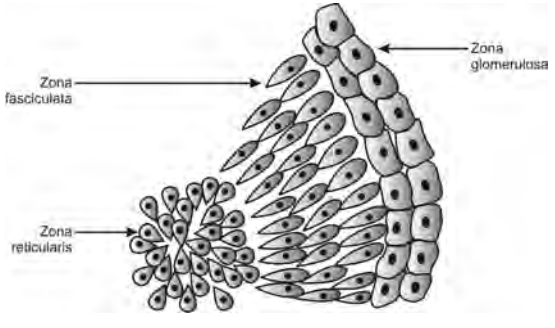


Fig. 77.1: Histological structure of adrenal cortex

Adrenal cortex has *no nerve supply*.

Adrenocortical hormones: They are steroid in nature. Important hormones can be grouped as:

1. Glucocorticoids (so named because they have a striking effect on glucose formation) (i) Cortisol – average amount secreted 10 mg/day, (ii) Corticosterone—3 mg/day (both C_{21} steroids).
2. *Mineralocorticoids* (so named because they promote Na retention and K excretion) (i) Aldosterone—0.15 mg/day, (ii) 11-deoxycorticosterone 0.2 mg/day (Both C_{21} steriods)
3. Androgen (C_{19} steroid)
   i. Dehydroepiandrosterone– 20 mg/day having mild masculinizing action
4. Progestins
   Progesterone— 0.6 mg / day
5. Estrogen
   Estradiol – traces.

Sex Hormones

SYNTHESIS

Adrenal cortex can manufacture cortisol and corticosterone from *cholesterol.*

↓

Intermediaries are pregnenolone and progesterone

↓

Another pathway

Aldosterone

In progesterone hydroxylases introduce hydroxyl group at carbon 17, 11 and 21 position, in that order to produce cortisol.

REGULATION OF CORTISOL SECRETION

1. By ACTH from anterior pituitary. It binds to high affinity receptors on plasma membrane of adrenocortical cells. This activates adenyl cyclase which increases cyclic AMP. This second messenger brings about changes necessary for synthesis of cortisol (Fig. 77.2).

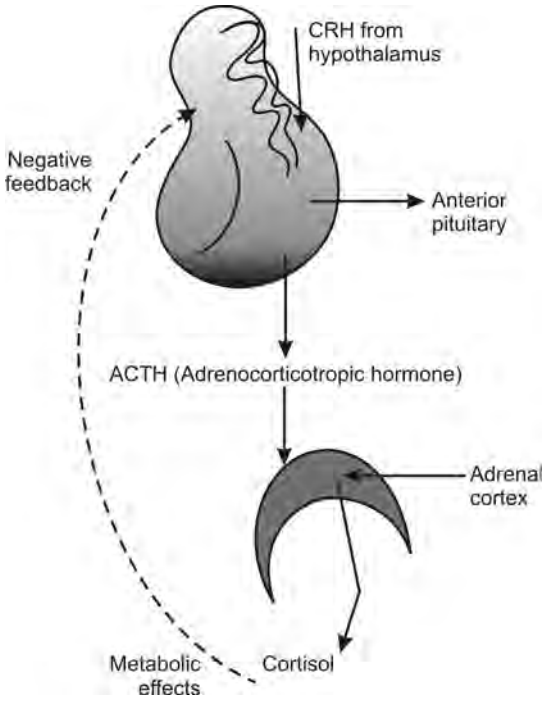


Fig. 77.2: Regulation of cortisol secretion

During fetal life, the human adrenal is large and under pituitary control, but the 3 zones of permanent cortex represent only 20% of the gland. The remaining 80% is the large *fetal adrenal cortex*, which undergoes rapid degeneration at the time of birth. A major function of this fetal adrenal is secretion of sulfate conjugate of androgens that are converted in the placenta to *estrogens.*

TRANSPORT IN THE BLOODSTREAM

Cortisol in plasma is bound to a globulin called transcortin or corticosteroid binding globulin (CBG). There is also a minor degree of binding to albumin. Transcortin is synthesized in liver. half-life of cortisol is about 60-90 minutes, because it is bound to protein.

Aldosterone: It is bound chiefly with albumin to only a slight extent. Therefore, its half-life is 20 min.

Plasma cortisol level–in man shows a marked circadian variation. It is due to circadian rhythm in the secretion of ACTH. Mean plasma cortisol level between 6 to 8 am is 150 microgram/dl. It falls steadily during the day to reach 30 microgram/dl between midnight and 3 am.

Cortisol is not stored in adrenal gland. Therefore, rapid activation of synthetic machinery is needed when there is sudden need of enhanced secretion.

-17 ketosteroid a metabolite of steroid hormone is excreted in urine.

ACTIONS OF ADRENOCORTICAL HORMONES

Glucocorticoids mainly act in the formation of glucose and mineralocorticoids mainly cause sodium retention and potassium excretion. But this functional separation is not complete. The mineralocorticoids also form some glucose and because glucocorticoids are secreted in far more quantity its action on sodium and potassium is important.

Action of glucocorticoids: Cortisol in humans is the main glucocorticoid, corticosterone being present in much smaller amounts.

Mechanism of action: Multiple effects of glucocorticoids are initiated by binding to glucocorticoid receptors, which promote the transcription of certain segments of DNA. This in turn, via appropriate mRNA, leads to synthesis of enzymes that alter cell function.

Actions on Carbohydrate Metabolism

1. Cortisol is necessary for normal carbohydrate metabolism: (a) *cortisol deficiency* leads to *hypoglycemia* and decreased liver glycogen, cause- increased sensitivity to insulin, (b) *cortisol excess* lead to *hyperglycemia*, glycosuria and increased liver glycogen because of increased *resistance* to insulin.
2. Cortisol accelerates neoglucogenesis in liver from amino acids formed from protein breakdown (muscle).
3. Cortisol increases glucose formation from pyruvates.
   Thus, increased glucose is formed from protein source that is nitrogenous substance as well as non-nitrogenous substance.
4. Cortisol inhibits glucose uptake by peripheral tissue. *Adrenal diabetes* – gluconeogenesis and decreased uptake of glucose by peripheral tissue cause blood sugar to rise.

Action of Protein Metabolism

Cortisol promotes catabolism of protein. Normally breakdown of protein is counter-balanced by anabolic processes.

But if cortisol is in excess it causes:

1. Negative nitrogen balance
2. Retardation of growth
3. Wasting of muscles
4. Thinning of skin
5. Reduction of lymphoid tissue
6. Cortisol mobilizes amino acid from the nonhepatic tissues.

This results in increased concentration of amino acids in plasma plus cortisol enhances transport of amino acids into the hepatic cells. These amino acids in lever are then converted to: (1) glucose, (2) plasma proteins, (3) other proteins, etc.

Action on Lipid Metabolism

Cortisol mobilizes fats from the extremities and deposits on trunk. Thus, there is redistribution of fat.

Concentration of free fatty acids is increased. They are utilized for energy.

In starvation or other stresses, cells utilize fatty acids for energy instead of glucose and glucose is conserved.

Electrolyte and Water Metabolism

Cortisol promotes retention of sodium and chloride and excretion of potassium by the kidney. Cortisol is much less potent than aldosterone for this action.

In adrenal deficiency: There is deficient diuretic response to water drinking and excess water load is not disposed for 12 weeks. Cortisol counter acts this tendency, maintains extracellular fluid volume, provides adequate glomerular filtration rate and allows diuresis to occur.

Cortisol excess: Cause excessive sodium retention; water retention leading to edema and hypertension. Potassium excretion is increased leading to potassium deficiency, muscular weakness and ECG changes.

Action on Muscle Power

Muscular weakness is a feature of *adrenocortical insufficiency*. It is more efficiently relieved by cortisol.

In *excess secretion,* cortisol causes muscular weakness by breakdown of muscle protein and loss of creatinine from muscles with edema and fibrosis (steroid myopathy).

Action on Blood

Adrenocortical insufficiency is associated with
1. Eosinophilia
2. Lymphocytosis
3. Neutropenia and
4. Anemia.

All are counteracted by cortisol.

Excess cortisol is associated with:
1. Eosinopenia – because of: (a) destruction in circulating blood, and (b) sequestration of eosinophils in lungs and spleen.
2. Lymphopenia
   Excess cortisol causes lysis of fixed lymphoid tissues of thymus, spleen, lymph nodes, etc.
3. Neutrophilia.
4. Polycythemia.
5. Cortisol increases platelet count and shortens blood-clotting time.

Action of CVS

Because of maintenance role of cortisol on ECF composition, blood volume is maintained.

In excess secretion – Cortisol increases blood pressure.

In adrenocortical insufficiency hypotension. Cortisol can overcome hypotension associated with adrenocortical insufficiency because:
1. It restores Na
2. It restores circulating blood volume
3. It overcomes myocardial weakness
   In deficiency vascular smooth muscle is non-responsive to norepinephrine and epinephrine and increased permeability leads to vascular collapse. Cortisol restores its responsiveness. This action is known as permissive action.
4. In cortisol excess there is increased blood lipids and serum cholesterol leading to atherosclerosis.

Action on CNS

Symptoms due to abnormal activity with CNS are seen in adrenocortical insufficiency and cortisol excess.

In cortisol excess (Cushing s syndrome)
1. There is euphoria
2. Person is restless and excitable

3. Fits occur in epileptic subject

In adrenocortical insufficiency (Addison s disease)

1. There is restlessness
2. Insomnia
3. Inability to concentrate
4. Slowing of EEG waves than normal α rhythm.

Gastrointestinal Tract

1. Cortisol increases gastric acidity and pepsin production. Therefore, it can produce peptic ulcer.
2. It promotes absorption of fat from intestine.

Bone Metabolism

Excess Cortisol

1. Causes
2. Decreased growth of cartilage
3. Thinning of epiphyseal plate in children
4. Defect in synthesis of protein matrix
5. Decreased absorption of calcium from the gut and decreased deposition in bone
6. Cortisol antagonises vitamin D and there is increased loss of calcium in urine.

All these effects lead to osteoporosis especially of vertebra. This is important hazard of treatment with cortisol.

Infection Inflammation and Trauma

Inflammation is tissue reaction to injury:

1. Vascular dilatation
2. Increased capillary permeability
3. Movement of WBC to site of injury.
    i. Cortisol reduces all of the above reactions. Therefore, swelling and congestion becomes less and patient feels better.
    Therefore, it is *anti-inflammatory.*
    ii. Similarly cortisol stabilizes lysosomes, checking the release of hydrolytic enzymes from lysosomes. This again is an *anti-inflammatory effect.*
    iii. Cortisol decreases collagen formation and proliferation of fibroblasts. Therefore, scar formation does not take place.

Healing by scar formation is not always desirable in places like eye, joint, skin. Therefore, cortisol is used.

Inflammation is a normal and desirable response of the body to injury. However, ferocious inflammatory response can cause irreparable tissue damage. Therefore, cortisol is used to suppress inflammation.

But cortisol does not remove the cause of inflammation and may affect adversely by immunosuppression and inhibition of scar formation.

When cortisol is given externally—endogenous production stops because of negative feedback. Now if you stop giving cortisol to the patient, the capacity to secrete cortisol is gradually resumed. Therefore, always withdraw cortisol in tapering doses.

Steroids hide the smoke while smouldering continues.

Cortisol Secretion in Stress

Any type of stress, physical or mental will cause marked increase in ACTH secretion by anterior pituitary gland and within minutes cortisol secretion increases.

Different types of stress that increase cortisol secretion are:

1. Trauma
2. Infection
3. Intense heat or cold
4. Injection of norepinephrine and other sympathomimetic drugs
5. Surgery
6. Injection of necrotizing substances beneath the skin

7. Restraining the animal from movement
8. Any debilitating disease
9. Pain.

How cortisol secreted relieves stress?

i. Probably by making available amino acids and fats to cells for energy and for glucose synthesis which is needed by the tissues.

ii. Amino acids can also be used for synthesis of purines, pyrimidines and creatine phosphate, which are necessary for maintaining cellular life and reproduction.

Amino acids are mobilized from labile protein stores of all other tissues except muscles and neurons. They will be utilized when all proteins are mobilized.

CHAPTER

78

Mineralocorticoids and Disorders of Adrenocortical Function

MINERALOCORTICOIDS OR SALT RETAINING HORMONES

Aldosterone is the chief mineralocorticoid secreted by adrenal cortex. It was first isolated by Simpson and Tait in 1952 at Middlesex Hospital and Medical School at London, as crystalline substance. It was named aldosterone because of the aldehyde group present in it at C-18. It is a steroid hormone.

Its main function is to cause retention of Na^+ and increased excretion of K^+ and main *site of action* is distal convoluted tubules (DCTs) and collecting tubules (CTs) of kidney, where it promotes absorption of Na^+ in exchange of K^+ and H^+.

Loss of adrenocortical secretion causes death within 3 days to 2 weeks – cause is without mineralocorticoids, in the ECF concentration of potassium rises markedly and concentration of Na^+ and Cl^- decreases. Total ECF volume and blood volume decreases greatly. Person's cardiac output falls leading to shock and death.

The sequence can be prevented by administration of aldosterone or some other mineralocorticoid. Therefore, mineralocorticoids are said to be life saving portion of adrenocortical hormones. While glucocorticoids are equally necessary to allow the person to resist the destructive effects of life's intermittent stresses. Aldosterone exerts nearly 90 percent of the mineralocorticoid activity of adrenocortical secretion.

Actions

Renal Effects of Aldosterone

1. Effect on tubular reabsorption of sodium and tubular secretion of potassium—The basic action of aldosterone is to increase absorption of Na in DCT and CT (To a lesser extent in DCT and mainly in CT). Therefore, sodium concentration in ECF increases and that of K falls. When sodium is absorbed through tubular epithelium because of electrical gradient chloride follows, as osmotic gradient is also created from tubules towards peritubular fluid, water follows sodium absorption. If enough water does not follow Na^+ concentration in ECF increases and this will stimulate: (i) secretion of antidiuretic hormone, and (ii) thirst mechanism.

   These two together will bring the ECF concentration and volume back to normal. Therefore, sodium concentration is maintained.

When aldosterone *concentration increases* it causes excessive loss of potassium, this is known as hypokalemia. When K^+ ion concentration falls below half normal, muscle paralysis or severe muscle weakness develops. This is caused by alteration of the electrical excitability of the nerve and muscle fiber membranes, which prevents transmission of normal action potentials.

On the other hand when *aldosterone is deficient* in the ECF, K concentration rises far above normal, when it becomes 60-100 percent above normal, serious cardiac toxicity including weakness of contraction and arrhythmia becomes evident and still higher concentrations lead to heart failure.

2. *Effect on ECF volume:* Aldosterone increases sodium absorption, water follows it and therefore, ECF volume increases. In absence of aldosterone ECF volume decreases. Therefore, ECF tends to change in proportion to rate of aldosterone secretion.

   Increase in fluid volume lasting more than 1 to 2 days leads to an increase in arterial pressure, which cause excretion of water and salt through kidney. This is called pressure diuresis. The secondary increase in salt and water excretion by the kidneys as a result of pressure diuresis is called as *aldosterone escape*. Another factor responsible for it is atrial natriuretic peptide (ANP).
3. *Effect on H ion secretion:* Although mainly K ions are secreted into tubules in exchange for Na^+ absorption, to a much lesser extent it causes secretion of H^+ ion in exchange for sodium, leading to mild alkalosis.

Effect of Aldosterone on Circulation

In *absence of aldosterone* ECF vol decreases, circulatory shock develops rapidly and death follows.

In hypersecretion of aldosterone ECF increases, blood volume increase, therefore cardiac output increase, aldosterone escape occurs and cardiac output is not above by 5 to 10 percent but prolonged hypersecretion leads to hypertension.

Effect of Aldosterone on Sweat Gland, Salivary Gland and Intestinal Absorption

Sodium chloride is reabsorbed from excretory ducts of these glands by action of aldosterone while K and bicarbonate ions are secreted. This effect is important in hot environment when lot of sweating takes place and when excessive saliva is lost.

Aldosterone also greatly enhances sodium absorption by intestine, which prevents loss of sodium and chloride in stools.

Mechanism of Action

1. Aldosterone is lipid soluble, therefore easily diffuses in the inside of the cell.
2. In cytoplasm, there are specific receptor proteins.
3. Aldosterone receptor complex diffuses into nucleus where it undergoes alterations, finally it induces DNA to form different mRNA.
4. mRNA diffuse in cytoplasm and with ribosome's help, form different proteins: (a) mostly enzymes, and (b) membrane transport proteins.

These are required for transport of Na^+, K^+ and H^+ transport through the cell membrane of renal tubule.

Enzymes include Na-K ATPase – important for Na-K pump, for exchange of Na^+ and K^+. Membrane protein include –channel protein inserted in the luminal membrane. So, sodium rapidly enters in the cell and then pumped by Na-K pump located in basolateral membrane. Remember the site of action is cells of collecting duct and distal convoluted tubules of kidney.

In *physiological amount:*

1. Aldosterone has marked action on sodium and potassium distribution in the body, but.
2. Has very *little* action on carbohydrate, fat and protein metabolism.
3. It has no anti-inflammatory action and
4. It *does not* inhibit secretion of ACTH from anterior pituitary.

Some synthetic steroid like *spironolactone* acts as aldosterone antagonist and blocks Na and K exchange in CT and DCT by competitive enzyme inhibition.

11-deoxycorticosterone has 3 percent activity of aldosterone. Its synthetic form deoxycorticosterone acetate (DOCA) is cheaper and readily available than aldosterone hence used.

Regulation of Aldosterone Secretion

Five factors play essential role in the regulation of aldosterone.

1. Increased potassium ion concentration in the extracellular fluid greatly increases aldosterone secretion.
2. Activation of renin – angiotensin system in response to diminished blood flow to the kidneys. Angiotensin is powerful stimulant of aldosterone secretion. Aldosterone thus secreted will: (a) absorb Na^+ and excrete excess potassium, and (b) increase blood volume and arterial pressure thus returning renin – angiotensin system also back to normal.
3. Increased sodium ion concentration in ECF – very slightly decreases aldosterone secretion.
4. ACTH from anterior pituitary gland is necessary for aldosterone secretion but has little effect in controlling the rate of secretion.
5. Decreased sodium ion concentration increases aldosterone secretion.

Adrenocortical Sex Hormones

Androgens are the hormones that exert masculinizing effects and they promote protein anabolism and growth.

At puberty in both sexes – adrenal androgens secretion increases and contributes to:

1. Increase in muscle mass
2. Growth of sexual hair
3. Seborrhea.

But adrenal androgens are weak androgens.

DISORDERS OF ADRENOCORTICAL FUNCTION

Can be of two types: (1) due to lack of secretion or (2) due to excess secretion.

There are three main types of hormones:

1. Cortisol
2. Aldosterone
3. Sex hormones.

So, clinical syndromes are corresponding to under or over secretion or are mixed syndromes.

Adrenal Cortex Insufficiency

Can arise in following ways:

1. Destruction of adrenal cortex by disease will decrease secretion of all the hormones.
2. Anterior pituitary failure—produces atrophy of two inner zones of adrenal cortex leaving aldosterone secretion almost unaffected.
3. Congenital defect in formation of cortisol.
4. Destruction of adrenal cortex by disease → Two important deficiency syndromes occur–
   i. Acute adrenal insufficiency (adrenal crisis) – due to failure of cortisol secretion.
   ii. Chronic adrenal insufficiency (Addison's disease) – in which secretion of both cortisol and aldosterone is less.

Acute Adrenal Insufficiency

Occurs when patients with adrenal cortex capable of secreting only basal amounts of cortisol, are exposed to a sudden stress.

Clinically there is:
1. Profound shock
2. Fall of BP
3. Muscular weakness
4. Oliguria
5. Urea retention
6. Rise of plasma K^+
7. Initial fever then hypothermia
8. Vomiting and dehydration.

All changes are reversed by administration of cortisol.

Addison's Disease

It results because of chronic insufficiency of both cortisol and aldosterone. Most common cause – adrenal glands are destroyed because of tuberculosis – bilateral.

Other causes:
1. Atrophy of adrenal cortices because of autoimmunity against the cortices.
2. Invasion of glands by cancer.

Outstanding clinical features:
i. Muscular weakness
ii. Ready fatiguability
iii. Pigmentation of skin and buccal mucosa
iv. Anorexia
v. Loss of weight
vi Nausea, vomiting, diarrhea
vii Dehydration
viii. Hypotension
ix. Symptoms of hypoglycemia
x. Decreased growth of body hair
xi Inability to withstand trauma, infection hemorrhage and other stresses.

3. Electrolyte and water imbalance—defects are due to loss of sodium by the kidney along-with chloride. That is salt is lost and potassium is retained.
   i. Therefore, plasma level of sodium and chloride is less and plasma potassium rises.
   ii. Dehydration is there
   iii. Hence, fall of blood pressure
   iv. Hypotension leads to renal failure.
4. Muscle weakness is because of salt loss.
5. Hypoglycemia is because of cortisol deficiency.
6. Reduced capacity to withstand stress is because of cortisol deficiency.
7. Loss of weight is because of loss of water and anorexia.
8. Pigmentation is because of increased secretion of ACTH, which partly acts as melanocyte stimulating hormone as ACTH and MSH are similar.

Investigations will show:
1. Morning level of plasma cortisol is reduced to zero.
2. Administration of ACTH fails to produce adequate rise of cortisol.
3. In urine – 17 ketosteroid excretion is almost absent.

Treatment

Persons with Addison's disease can live for years if small quantities of mineralocorticoides and glucocorticoids are administered daily.

Addisonian Crisis

In Addison's disease the output of glucocorticoids does not increase during stress. So when they are exposed to stress, e.g. surgery, 10 times the normal need of glucocorticoids are needed.

Severe deficiency in times of stress is called as Addisonian crisis.

Anterior Pituitary Failure

It results because of decreased secretion of ACTH leading to decreased secretion of cortisol. Aldosterone is normal.

Clinical features are similar
Except
1. Electrolyte balance is normal.
2. Skin pigmentation is not there.
3. Evidence of decreased function of other glands such as thyroid gland is present.

Congenital Adrenal Hyperplasia—Virilism

It occurs due to congenital deficiency of enzymes responsible for hydroxylation.

Lack of 21 hydroxylase Progesterone fails to get hydroxylated and it gets converted into androgen. Because cortisol is absent, therefore there is increased secretion of ACTH. This ACTH causes hyperplasia of adrenal cortex, which produces *only androgens.*

Clinical Feature

Virilism and excessive growth.

In Boys

1. Precocious sexual development.
2. Premature growth of body hair.
3. Stocky, prematurely virile person called as infant Hercules.

In Girls

Masculanization takes place (pseudohermaphrodite= female child with male sexual characters).

If block is beyond the formation of *deoxycorticosterone* (due to lack of 11 hydroxylase) – there is rise of blood pressure with virilism.

Treatment

In both types, administration of physiological amount of cortisol will inhibit secretion of ACTH, decrease the hyperplasia and reduce androgen secretion to normal. All signs and symptoms disappear and if treatment is started early, normal sexual development can take place.

Overactivity of Adrenal Cortex

Three main clinical syndromes result:
1. *Cushing syndrome:* Because of excessive secretion of cortisol.
2. *Hyperaldosteronism:* Because of excessive secretion of aldosterone.
3. *Acquired adrenogenital syndrome:* Because of excessive secretion of androgens and estrogens.

Cushing's Syndrome

It occurs because of prolonged and excessive secretion of cortisol (Fig. 78.1).

Cause

1. *Adrenal tumor:* Producing excessive amount of cortisol. Remaining adrenal cortex and contralateral adrenal cortex are atrophic because of lack of ACTH.
2. *Adrenal hyperplasia:* Occurs because of tumor of anterior pituitary (Basophil adenoma), which secretes excessive amounts of ACTH.

Signs and Symptoms

1. Wasting and weakness of muscles because of breakdown of muscle proteins.
2. Centripetal distribution of fat with wasting of extremities – so there is moon like face
3. Slit eyes.
4. Fish like mouth (pouting lips).
5. Pads in supracondylar region (buffalo hump).
6. Pendulous abdomen.

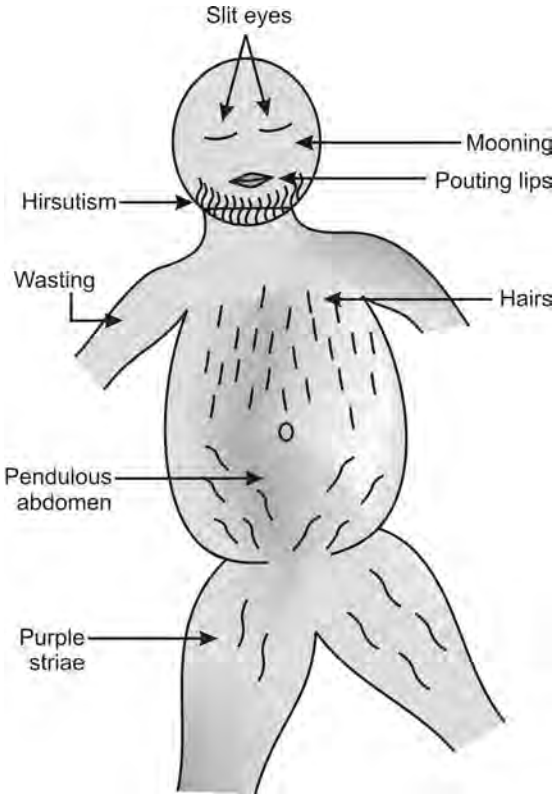


Fig. 78.1: Cushing's syndrome

1. Hirsutism
2. Pendulous abdomen
3. Pouting-lips
4. Wasting
5. Purple striae
6. Slit eyes
7. Hairs
8. Mooning

7. Skin is of fine texture, paper like underlying blood vessels show through.
8. Purple striae-over abdomen, thighs and upper arm.
9. Abnormal hairiness of face, chest and abdomen (Hirsutism)
10. Thinning of bone (osteoporosis) because of loss of protein and excessive withdrawal of calcium, therefore fractures occur with trivial trauma
11. Signs of diabetes mellitus– hyperglycemia and glycosuria.
12. Sexual changes – in male – impotency, in female amenorrhea.
13. Atherosclerosis—resulting in increased blood pressure.

Investigations Show

1. Plasma sodium level is increased.
2. Plasma potassium level is lowered. alkalosis is present.
3. Eosinopenia, lymphocytopenia and polycythemia
4. Plasma, cortisol level is elevated.
5. Increased excretion of urinary 17 ketosteroids.

Adrenogenital Syndrome

In Adults

Cause: Adrenal tumor producing, sex hormones. There is tendency of conversion of sexual characters to opposite sex (changes of sex).

In Females

1. There is change of voice (hoarseness).
2. Enlargement of clitoris
3. Growth of body hair (masculine distribution)
4. Increased muscular growth.

Investigations Show

1. High level of androgens in plasma, daily secretion of androgens increase to 30-50 mg /day.
2. Increased excretion of 17 ketosteroids in urine.

Rarely

In Male

1. Feminization takes place because of estrogen secreting adrenal tumor.
2. Enlargement of breasts
3. Atrophy of testes.
4. There is decreased interest in women.

Hyperaldosteronism

1. Occurs due to overproduction of aldosterone.
   Two types of hyperaldosteronism occur.
   i. *Primary*: Results due to adrenal adenoma of zona glomerulosa (Conn's syndrome).
   ii. *Secondary:* Increased secretion of aldosterone occurs due to *extra* adrenal *causes,* that is due to conditions arising out of adrenal cortex for example—edemation states.

In primary hyperaldosteronism:

1. Blood pressure is high
2. Hypernatremia
3. *Hypokalemia* – prolonged loss of potassium causes hypokalemic nephropathy which results in polyurea and polydipsia.
4. Alkalosis
5. Muscular weakness
6. *No* edema.

In secondary hyperaldosteronism: Edema is present.

Cause of edema may be—c*ongestive cardiac failure:*

1. Nephrosis
2. Toxemia of pregnancy
3. Cirrhosis of liver with ascites

In edematous state there is increased formation of angiotensin II, which increases aldosterone secretion.

Cause: In edema there is fall of blood volume causing fall of blood pressure, which results in renin formation.

Treatment: Drugs that antagonize aldosterone for example, spironolactone.

CHAPTER

79

Adrenal Medulla

Adrenal medullary secretions contribute to fight and flight reactions.

1. The *cells* of adrenal medulla are large, ovoid and columnar, grouped in clumps around blood vessels. Many cells contain fine granules, stained brown with chrome salts therefore called *chromaffin tissue* (Fig. 79.1)
2. Chromaffin tissue is also present (i) in *infants* along the aorta near the origin of inferior mesenteric artery. This is known as organ of Zuckerkandl, (ii) human *skin* surrounding *blood vessels* and *nerves*, (iii) in gut – here it is known as *enterochromaffin* cells, (iv) in *ganglion cells* of sympathetic nervous system.
3. The adrenal medulla is in effect a *sympathetic ganglion* in which the postganglionic neurons have lost their axons and become secretory cells.

   Adrenal medulla and ganglion cells of sympathetic have common origin – primitive neuroectoderm.
4. *The active principles – called – catecholamines* are:
   i. Epinephrine (adrenaline)
   ii. Norepinephrine (noradrenaline)
5. *Two cells types* can be distinguished morphologically:
   i. Epinephrine secreting has larger less dense granules, and
   ii. Norepinephrine secreting has smaller very dense granules-that fail to fill the vescicles.
      a. 80 percent cells are epinephrine-secreting type
      b. 20 percent cells are norepinephrine-secreting type.
6. Adrenal medulla is richly supplied by nerves they are preganglionic nerve ending of sympathetic nervous system. They secrete acetylcholine – neurotransmitter.
7. Different stimuli cause either predominantly secretion of Epinephrine or norepinephrine reflexly. For example:
   i. Asphyxia mainly secretes norepinephrine
   ii. Hypoglycemia mainly secretes epinephrine.

Therefore, it is believed that there are two types of nerve endings supplying adrenal medullary cells –one type supplying the cells secreting epinephrine and other type supplying the cells secreting norepinephrine.

FORMATION OF CATECHOLAMINES

There are two sites for formation of catecholamines:

1. In adrenal medulla, and
2. Noradrenergic nerve endings (or sympathetic nerve endings).

Catecholamines are formed from an essential amino acid – *Tyrosine*, which can be formed from another essential amino acid Phenylalanine.

Phenylalanine
↓ Hydroxylation
L Tyrosine
↓ Hydroxylation
L DOPA (Dihydrophenylalanine)
↓ Decorboxylation
Dopamine
↓ Hydroxylation
Norepinephrine
↓ Methylation
Epinephrine

Some chromaffin cells form norepinephrine only, while in others norepinephrine undergoes methylation to form epinephrine.

Epinephrine and norepinephrine thus formed is stored in granules in adrenal medullary cells and norepinephrine also in sympathetic nerve endings.

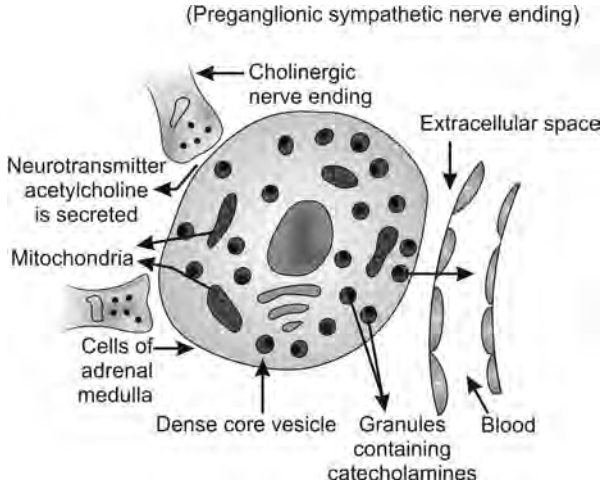


Fig. 79.1: Norepinephrine secreting adrenal medullary cell

Regulation of Secretion

In physiological conditions the secretion of catecholamines from adrenal medulla is entirely controlled by splanchnic nerves, which are preganglionic sympathetic fibers. These fibers end round the cells of medulla and release acetylcholine. Acetylcholine stimulates the cells and promotes inward movement of calcium ions. This causes chromaffin granules to discharge catecholamines in the intercellular space by a process of exocytosis. From there it is absorbed in venous blood (Fig. 79.1).

Plasma Level

1. In recumbent humans the normal plasma level of – free norepinephrine is about 300 pg/ml. There is 50 to 100 percent increase upon standing.
2. Free epinephrine level normally is about 30 pg/ml.

In plasma, 70 percent of norepinephrine and epinephrine are conjugated to sulfate. Sulfate conjugate are inactive.

Removal and inactivation of catecholamines after release.

Catecholamines have a half-life of about 2 minutes in circulation.

They are removed by different processes:

1. Uptake 1 (neuronal) – free norepinephrine is taken up into presynaptic adrenergic nerve terminals by process known as uptake 1 which involve active transport into the neuronal cytoplasm. This accounts for 85 percent of released norepinephrine. It is acted upon by enzyme Monoamine oxidase (MAO) present in mitochondria.
2. Uptake 2 (Extraneuronal) is mediated by postsynaptic cells such as those of heart and smooth muscle cell. This is followed by intracellular inactivation by enzymes. This accounts for 15 percent of released norepinephrine (Fig. 79.2).

3. MAO and COMT (Catechol – O-methyl transferase) both are present in liver. They inactivate circulating catecholamines formed in adrenal medulla.

   Norepinephrine $\xrightarrow{\text{MAO}}$ 3, 4 dihydroxymandelic acid

   Norepinephrine $\xrightarrow{\text{COMT}}$ Normetanephrine

   Epinephrine is similarly metabolized to metanephrine

   End product of epinephrine and norepinephrine metabolism by combined action of MAO and COMT is 4 hydroxy – 3 methoxymandelic acid Vanillylmandelic acid (VMA)
4. Normally 2-3 percent of released catecholamines escape enzymic destruction and are excreted in urine.

30 microgram of norepinephrine and 6 microgram of epinephrine are excreted in urine as free hormones and rest is excreted as metabolic product, for example, VMA and free or conjugated metanephrine and normetanephrine.

ACTIONS OF CATECHOLAMINES

Stimulation of adrenal medulla release hormones that have almost the same effects throughout the body as sympathetic stimulation except that the:

1. Effects are greatly prolonged
2. Epinephrine secreted by adrenal medulla increases rate of metabolism and cardiac output to a greater extent than that caused by direct sympathetic stimulation only.

Stimulation of sympathetic usually involves stimulation of entire sympathetic system including adrenal medulla. So, epinephrine and norepinephrine are released at the same time. Therefore, organs are stimulated dually or in two ways by: (a) sympathetic stimulation and by, (b) epinephrine and norepinephrine through circulation.

Another important value of adrenal medulla is capability of epinephrine and norepinephrine to stimulate structures that are not innervated by direct sympathetic fibers. For example, the metabolic rate of every cell of the body is increased although a small proportion of cells are innervated by sympathetic fibers.

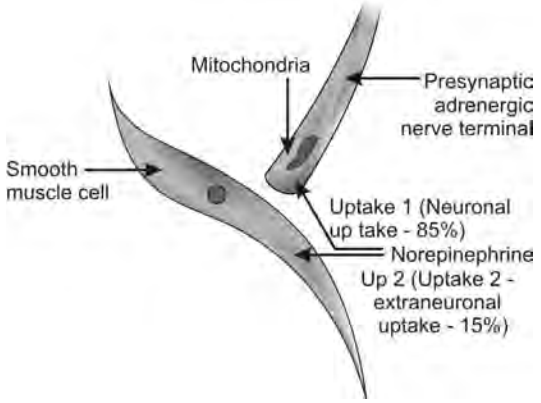


Fig. 79.2: Uptake of norepinephrine

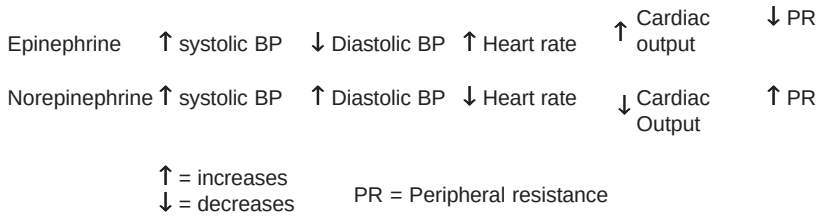
On Circulation

1. There is difference in the actions of adrenaline and noradrenaline (epinephrine and norepinephrine) on circulation.

   There is difference in the actions of epinephrine and norepinephrine because – (explanation).

   i. Epinephrine increases blood flow in skeletal muscle and liver via β_2 receptors. Noradrenaline (norepinephrine) produces vasoconstriction in most organs via α_1 receptors.

      Therefore, epinephrine decreases total peripheral resistance and is net vasodilator. Norepinephrine increases total peripheral resistance and is net vasoconstrictor.



Therefore, diastolic blood pressure falls with epinephrine and it increases with norepinephrine.

ii. Epinephrine causes increase in systolic blood pressure and decrease in diastolic BP. The mean pressure is unaltered and baroreceptor stimulation is insufficient and its direct effect on heart causes increase in heart rate (Reflex bradycardia does not take place as mean blood pressure does not increase).

Norepinephrine increases systolic blood pressure and diastolic blood pressure also. Therefore, mean blood pressure is increased which stimulates carotid and aortic baroreceptors producing reflex bradycardia that overrides direct action, of norepinephrine which is cardioacceleratory. When blood pressure increases – heart rate decreases – Marey's law.

iii. Epinephrine – increases cardiac output because: (a) it increases force of contraction of heart, and (b) it increases heart rate (β_1 receptor).

Norepinephrine (a) increases force of contraction (β_1 receptors) but (b) it decreases heart rate.

Therefore, cardiac output is decreased.

2. *On coronary arteries*: Both epinephrine and norepinephrine increase coronary blood flow.

Cause: (i) direct vasodilator action which is receptor action (β_2 receptors predominate), (ii) Increased heart action produce increased metabolites, which cause vasodilatation.

Therefore, in patients with angina pectoris, increased secretion of adrenaline produces heart attack, as more pain producing metabolites are formed which are produced due to increased activity of the heart.

3. *Blood vessels of skin and mucous membrane:* Both epinephrine and norepinephrine constrict blood vessels of skin and mucous membrane (α_1 and α_2 receptors). Epinephrine produces more pallor.

With larges doses of epinephrine and norepinephrine difference between two compounds are lost – both raise systolic and diastolic blood pressure, increase heart rate, cause ectopic ventricular beats and may lead to ventricular fibrillation. Both increase force and rate of contraction, these responses are mediated via β_1 receptors

4. *Action on veins*: Noradrenaline increases tone of veins, therefore it increases venous return.

On Respiration

1. In anesthetized *animals* large doses of adrenaline may induce apnea (adrenaline apnea).

Cause: Increased blood pressure stimulate inhibitor afferents in carotid sinus and aortic arch and inhibitory impulses are irradiated to respiratory centers.

2. *In man:* Infusion at physiological doses of both epinephrine and norepinephrine.
   Cause: Increase in rate and depth of breathing.
   i. Increased pulmonary ventilation
   ii. Decreased alveolar CO_2
   iii. Epinephrine increases O_2 consumption by 30 percent
   iv. Norepinephrine has no effect on O_2 consumption.
   Cause: For all of the above is stimulation of respiratory center.
3. Adrenaline (epinephrine) causes relaxation of bronchiolar muscle (β_2 receptors) and cause dilatation of bronchi. Therefore, asthmatic patients who have difficulty in breathing because of bronchoplasms are benefited by epinephrine. Secondly, epinephrine also causes vasoconstriction of blood vessels of mucous membrane. This causes shrinkage of mucosa and reduces the secretion of mucus. This also helps them.

   Norepinephrine is much less bronchodilator than epinephrine.

Action on Smooth Muscle

1. *Eye:* (i) Epinephrine causes dilatation of pupil because of contraction of dilator pupillae muscle (α_1 receptors), (ii) It also causes retraction of eyelids by stimulating their smooth muscles.
2. *GIT:* Adrenaline (epinephrine) causes relaxation of general musculature of the gut but causes contraction of pyloric and ileocolic sphincter (α_1 receptors).
3. It causes contraction of capsule of the spleen in cat but not in man.
4. Epinephrine causes contraction of wall of gallbladder (β_2 receptors).
5. Urinary bladder – epinephrine relaxes the detrusor muscle (β_2 receptors) and contracts sphincter and trigone (α_1 receptors).
6. *Uterus:* Response to epinephrine depends on state of the uterus, whether pregnant or not and effect is variable.
   Epinephrine – inhibits contraction of uterus
   i. In late pregnancy
   ii. Labor
   iii. Puerperium.

   Norepinephrine – stimulates contraction.

Action on Skeletal Muscles

Epinephrine increases blood flow and causes increased force of contraction of normal and fatigued muscles.

Metabolic Actions

1. *Blood sugar*: Epinephrine increases blood sugar by glycogenolysis and causes glycosuria (α1, β2 receptors). Norepinephrine also causes similar response but it is 1/5th potent in this respect.
2. *Blood lactate:* Increases because of rapid glycogenolysis in skeletal muscles. Increased blood lactate is used up by heart for energy.
3. *Calorigenic action:* Physiological dose of epinephrine increases oxygen consumption by 30 percent, (norepinephrine has no such effect)

   Epinephrine and norepinephrine cause prompt increase in metabolic rate: (i) cutaneous vasoconstriction leads to rise of body temperature by preventing heat loss, (ii) increased metabolism of lactate, and (iii) increased work of heart and muscles of respiration.

4. *Adipose tissue:* Epinephrine acts on fatty issue to cause lipolysis (β_1, β_3 receptors) and release of free fatty acid.

Action on Blood

1. Blood coagulation time is decreased.
2. Increases red cell count and also packed cell value.
3. Hemoglobin percent is increased.
4. Plasma protein concentration is increased Cause is: (i) mobilization of cells from depots, (ii) fluid moves out of blood vessels.

Action on Skin

Because of constriction of blood vessels of skin (a) Pallor (α_1,α_2 receptors), (b) because of contraction of arrectores pili muscles – *erection of hair*. (α_1 receptors), (c) because of stimulation of apocrine glands by circulating epinephrine – sweating.

CNS

1. Catecholamines increase *alertness.* Epinephrine and norepinephrine both are equally potent in this respect.
2. In humans epinephrine usually evokes more anxiety and fear
3. Stimulation of breathing
4. Tremors of extremities.

For above actions norepinephrine is less potent.

Site of Action

There are specialized receptors – located either in (i) cell membrane (for example, intestinal smooth muscles) OR (ii) intracellularly (for example, liver cells).

There are different types of receptors which account for: (a) excitatory, (b) inhibitory or (c) metabolic action.

Note

1. In 1948 Ahlquist – postulated existence of α and β adrenergic receptors.
2. Subdivision of receptors - α receptors are divided into: (i) α_1 and (ii) α_2. β receptors are divided into: (i) β_1, (ii) β_2 and (iii) β_3.
3. Stimulation of some α receptor give excitation while stimulation of others give inhibition and stimulation of some β receptors give excitation while other give inhibitory response (heart muscle is example where β1 stimulation is excitatory).
4. Norepinephrine mainly excites α receptors but also β receptors slightly. Epinephrine excites both equally.
5. In skeletal blood vessels and coronary blood vessels epinephrine acts on β receptors to cause vasodilatation, whereas norepinephrine acts on α receptors to cause vasoconstriction.
   (*Note:* In coronary blood vessels normally β receptors are more than α receptors).

Regulation of Secretion

Physiological stimuli effect medullary secretion through nervous system.

Increased adrenal medullary secretion is part of the diffuse sympathetic discharge provoked in emergency situation. This brings about various circulatory and metabolic adjustments such as increased mobilization of carbohydrates, rise of blood pressure and increased oxygen consumption. All these help in fight, flight or fright reactions.

Cannon called this as the 'emergency function of the sympathoadrenal system'.

Stressful situations in which secretion of catecholamines is increased:

1. Physical exertion and certain emotional stress.
2. Exposure to cold.

3. Fall of arterial blood pressure.
4. Asphyxia.
5. Anesthetic drugs.
6. Hypoglycemia.
7. Stimulation of afferent nerves, e.g. pain fibers.

Norepinephrine secretion is increased by emotional stresses with which the individual is familiar, whereas epinephrine secretion rises in situations in which the individual does not know what to expect.

CHAPTER

80

Pancreatic Hormones

PANCREATIC FUNCTIONS

Pancreas has two functions:

1. *Exocrine:* Pancreas secretes pancreatic juice which has digestive function.
2. *Endocrine:* Pancreas secretes important hormones,
   i. Insulin
   ii. Glucagon
   iii. Somatostatin
   iv. Pancreatic polypeptides.

These four peptide hormones are secreted by islets of Langerhans in the pancreas.

Physiological Anatomy of Pancreas

Pancreas is composed by two major types of tissues (Fig. 80.1):

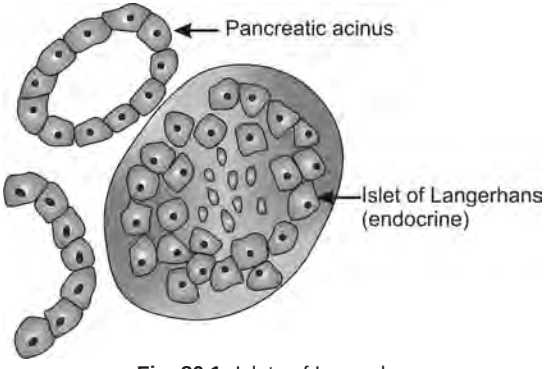


Fig. 80.1: Islets of Langerhans

1. Acini – which secrete digestive juice and
2. Islets of Langerhans secrete four peptide hormones insulin, glucagon, somatostatin and pancreatic polypeptide.

Islets of Langerhans in human being consist of four distinct cell types:

i. A - α - secrete glucagon
ii. B - β - secrete insulin
iii. D - δ - secrete somatostatin
iv. F - secrete pancreatic polypeptide

The hormones are stored in granules.

Structure and Synthesis of Insulin

Insulin is a *polypeptide* containing 2 chains of amino acids linked by disulfide bridges. Some categorize insulin as small protein.

Insulin is synthesized in endoplasmic reticulum of B-cells, then transported to the Golgi apparatus, where it is packaged in membrane bound granules. These granules move to the cell wall and their membrane fuse with membrane of the cell, expelling the insulin to the exterior by exocytosis. Insulin then enters a neighboring capillary to reach blood stream.

First insulin preprohormone is formed in endoplasmic reticulum. This has molecular weight of about 11500 but then it is cleaved to form a proinsulin with molecular weight of

about 9000. This is further cleaved in Golgi apparatus to form insulin before being packaged in the secretory granules. When finally secreted some of it still is in the form of proinsulin. Proinsulin has no insulin activity.

Mechanism of Action

Insulin acts by combining specific receptors located in cell membranes. The receptor is a glycoprotein and this activated receptor causes subsequent effects in the target cells. In insulin deficiency receptors are upregulated.

Degradation

The half-life of insulin in circulation is about five minutes in humans. Insulin binds with receptor and is internalized. 80 percent of secreted insulin is normally degraded in liver and kidneys.

Insulin was first isolated by **Banting and Best** from pancreas (Nobel Prize in 1923). From that time the picture of diabetes mellitus changed overnight.

Regulation of Secretion

1. The major control of insulin secretion is exerted by a feedback effect of plasma glucose directly on the B cells of pancreas. When blood glucose level increases, insulin secretion increases. First preformed insulin is released – giving rise to first peak. Then more insulin is formed and released – the 2nd peak in 2 to 3 hours. Then over a period of one week rate of insulin secretion increases causing hypertrophy of B-cells.

   Other Factors

2. *Amino acids*: Increase insulin secretion. Arginine and lysine are most potent.

   Purpose is to increase protein synthesis when amino acids are available, as insulin helps in transport of amino acids in the cell.

3. *Gastrointestinal hormones*: Gastrin, secretin, cholecystokinin, gastric inhibitory peptide (GIP) are secreted from gut after person takes food.

   They cause moderate increase in insulin secretion. This is an anticipatory increase in blood insulin for glucose and amino acids to be absorbed from the meal.

4. *Other hormones*: Either (i) directly increase insulin secretion or (ii) potentiate glucose stimulus for insulin secretion are:
   i. Glucagon
   ii. Growth hormone
   iii. Cortisol
   iv. Estrogen and progesterone to some extent.

Prolonged stimulation of any of these in large quantities can lead to exhaustion of the Beta cells of islets of Langerhans and cause diabetes mellitus. Therefore, diabetes develops in person on high pharmacological dose of cortisol or in gigantism and acromegaly.

METABOLIC EFFECTS

On Carbohydrate Metabolism

Immediately after a high carbohydrate meal – glucose that is absorbed in blood causes release of insulin.

Glucose enters all cells by facilitated diffusion, but in muscles, fat and variety of other tissues, insulin facilitates glucose entry into the cells by increasing the number of glucose transporters in the cell membrane.

In muscles—resting muscle membrane is only slightly permeable to glucose except when it is stimulated by insulin. Therefore, during much of the day muscle tissue depends for energy on fatty acid.

Under two conditions muscles do utilize large amount of glucose.

1. During periods of moderate-to-heavy exercise, exercising muscle fibers become

highly permeable to glucose even in absence of insulin because of the contraction process itself.

2. Muscles utilize glucose after meals for few hours. During this time glucose concentration is high, also pancreas is secreting large quantities of insulin and this insulin causes rapid transport of glucose in muscle cells.

   If the muscle is not exercising during period following a meal and glucose is transported into the muscle cells in abundance, then most of the glucose is stored in the form of glycogen in muscles. This glycogen can later be used by the muscles for energy.

   The first step after the entry of glucose in muscle cell is phosphorylation of glucose during storage as glycogen.

   Muscle glycogen is different from liver glycogen, as it cannot be reconverted to glucose because there is no glucose phosphatase.

In Liver

1. Insulin also increases the entry of glucose into liver cells, but it does not exert this effect by increasing the transporters in the cell membrane instead it induces hexokinase and this increase the phosphorylation of glucose. So that intracellular glucose concentration stays low, facilitating entry of glucose in the cell.
2. It induces enzymes that help storage of glucose as glycogen but inhibits the enzymes that cause liver glycogen to split into glucose.

   The net effect is to increase the amount of glycogen in the liver.

In Brain

In brain it is quite different from most other tissues of the body in that the insulin has no effect (or little effect) on uptake of or use of glucose. Brain cells are permeable to glucose without insulin.

Brain cells normally use only glucose for their energy. Therefore, it is essential that blood glucose level be maintained always above a critical level. When the blood glucose falls too low (below 50 mg/dl) symptoms of hypoglycemic shock develop, characterized by fainting convulsions and coma.

Effects on Fat Metabolism

Effects of insulin on fat metabolism are not as dramatic as on carbohydrate metabolism but they are important in the long run.

Long-term effects of lack of insulin are – Atherosclerosis often leading to, heart attack, or cerebral strokes or other vascular accidents.

The different actions are:

1. Insulin stimulates adipose tissue lipoprotein lipase in the capillary endothelium. This releases free fatty acids from circulating triglycerides by lypolysis. Glucose is also converted to fatty acid by insulin.
2. Free fatty acids enter the fat cell where they are converted to triglycerides after esterification with α-glycerophosphate, which is derived from glucose entering fat cell in response to insulin action.

   In short, insulin makes free fatty acid and alpha glycerophosphate in the fat cell, which combine to form triglycerides.
3. Insulin inhibits adipose tissue lipase and reduced breakdown of triglycerides in fat cell. This reduces supply of free fatty acids to liver and their breakdown to keto acids. Insulin also stimulates peripheral utilization of keto acids. Therefore, insulin is *antiketogenic.*
4. In liver, insulin stimulates synthesis of free fatty acids from glucose and acetyl Co-A like adipose tissue.

Effects on Protein Metabolism

The effect of insulin on protein metabolism are important for growth.

1. Insulin stimulates entry of amino acids into muscles and stimulates synthesis of proteins from these amino acids by stimulating transcription and translation processes.
2. Insulin inhibits proteolysis and oxidation of amino acids—anticatabolic action.
3. Insulin exerts similar action on protein metabolism of bone, adipose tissue and liver.

Other Actions

1. Insulin stimulates cellular uptake of potassium, magnesium, and phosphates.
2. Insulin acts on selected areas of brain to:
   i. Influence food intake,
   ii. Gastric secretion, and
   iii. Autonomic activity.

Effect of Insulin on Growth

As insulin is essential for protein synthesis, therefore it is essential for growth along with growth hormone. Both the hormones work synergistically.

GLUCAGON

It is secreted by α cells of islets of Langerhans of pancreas. Its function is opposite to that of insulin and most important function is to increase blood sugar level.

Chemically – It is a linear polypeptide.

i. Molecular weight 3485
ii. It contains 29 amino acids.

Actions

1. Glucagon is glycogenolytic, therefore it increases blood sugar level causing hyperglycemia, therefore it is known as hyperglycemic factor.

   Glucagon stimulates glucose formation but prevents its utilization leading to rise of blood sugar. Precise mechanism of action:

   i. It binds with receptors on liver cells; it acts via G8 to activate adenyl cyclase and increase of cyclic AMP intracellulary. Cyclic AMP activates protein kinase, which in turn will activate phosphorylase. Phosphorylase acts on glycogen.
   ii. It binds with other receptors also present on liver cells to activate phosphorylase C which results in increase of cytoplasmic Ca^{2+} stimulating glycogenolysis.
   iii. It inhibits resynthesis of glycogen by inhibiting glycogen synthatase.
2. Glucagon does not cause glycogenolysis in muscles.
3. It increases gluconeogenesis from available amino acids in the liver and increases its metabolic rate, (due to increased hepatic deamination of amino acids).
4. It increases ketone body formation in the liver.
5. It is lipolytic, which in turn leads to increased ketogenesis.
6. Glucagon activates adenylate cyclase in myocardium. This causes increased force of contraction. Therefore, it is used in refractory heart failure, as it does not cause increase in excitability of heart.

Regulation of Glucagon Secretion

1. Level of glucose in the blood is most important factor in regulation of glucagon secretion. Low levels of glucose stimulate A cells to secrete it.

2. Free fatty acids—inhibit secretion of glucagon.
3. Glucagon secretion is increased by stimulation of the sympathetic nerves to pancreas.
4. Exercise—when there is increased utilization of glucose, glucagon level increases.

SOMATOSTATIN

Somatostatin is secreted by D-cells of pancreas and also from hypothalamus.

Actions of Pancreatic Somatostatin

1. It inhibits secretion of insulin and glucagon from islets of Langerhans. It also inhibits secretion of exocrine pancreas.
2. Somatostatin inhibits the secretion of GI hormones gastrin and secretin.
3. Therefore, it reduces secretion of hydrochloric acid, pepsin and pancreatic secretion.

A, B and D cells have gap junctions, therefore secretion of one cell can modify secretion of other cell and coordinate their secretory functions.

DIABETES MELLITUS

Diabetes is derived from a Greek word and mellitus has its origin in the Latin meaning honey or sugar. It is common disorder. In this lack of insulin causes prolonged hyperglycemia and further complications related to it and others. In severe cases, complication is sometimes acidosis and coma.

Cause of clinical diabetes mellitus is always *deficiency of the effects of insulin* at the tissue level, but the deficiency may be due to varieties of abnormalities.

There are two *common forms of diabetes:*

1. Insulin dependent diabetes mellitus (IDDM) or Type I diabetes. Also called as juvenile diabetes.
2. Non-insulin dependent diabetes mellitus (NIDDM) or Type II diabetes. Also called as maturity onset diabetes.

Juvenile diabetes develops early in life, before the age of 40 years and maturity onset diabetes develops after 40 years (that is later in life). Both types run in families and heredity plays important role.

Deficiency of insulin may be:

1. Absolute deficiency due to B cells destruction or
2. Relative deficiency due to: (a) excess growth hormone, (b) or excess glucagon or (c) presence of insulin antibodies.

All of the above, causes diabetes mellitus usually called just diabetes.

Pathophysiology of Diabetes

1. Normal physiological function of insulin is to promote glucose utilization. Therefore, insulin deficiency reduces glucose utilization leading to: (i) accumulation of glucose in the bloodstream and blood glucose may rise above 180 mg/100 ml.
2. Increased mobilization of fats from storage areas.
3. Depletion of proteins from body tissue.
4. Loss of glucose in urine – when blood glucose increases above 180 mg/100 ml, so much glucose is filtered by glomeruli, that it cannot be completely absorbed by the renal tubules. Therefore, glucose is lost in urine causing *glycosuria.*
5. Presence of glucose is renal tubules exert osmotic effect which reduces reabsorption

of water by the tubules. Therefore, excess urine is formed and large volumes of urine are passed more frequently. This is called *Polyuria.*

6. Loss of large volume of water from the body stimulates thirst mechanism and the person drinks too much water. This is called *Polydipsia*.
7. Blood glucose level is high but utilization by cells is low and less utilization of glucose by feeding centers stimulates hunger and the patient eats more. This is called *Polyphagia.*
8. He eats more, his blood glucose is high but as the utilization is poor he loses weight and becomes weak. This is known as *Asthenia*.
9. Since, glucose cannot be utilized so body obtains energy from fat. Excess utilization of fat in impaired carbohydrate utilization, leads to production of excess ketone bodies– leading to ketosis.

Metabolic profile of diabetes thus resembles starvation. Therefore, diabetes is called a condition of starvation amidst plenty.

Symptoms of diabetes are:

1. Polyurea – excessive loss of urine
2. Polydipsia – excessive water drinking
3. Polyphagia – excessive eating
4. Asthenia – lack of energy
5. Loss of weight.

Diagnosis

1. Urine is examined for sugar. It shows presence of sugar: There are certain other conditions in which sugar is present in urine without diabetes mellitus. Most common is renal glycosuria in which sugar appears in urine because of lowered renal permeability to glucose.
2. *Blood glucose*: Normal fasting blood glucose is 80 to 90 mg /dl and 110 mg/dl is generally considered to be upper limit of normal. In diabetes mellitus, it is higher than 110 mg%.
3. *Glucose tolerance test (GTT):* When a normal fasting person ingests glucose 1 gm/kg body weight, the normal blood glucose rises from 90 mg% to 120 to 140 mg% and then falls below normal in 2 hours.

   In diabetes mellitus, fasting blood glucose is about 110 mg% and GTT is always abnormal. After ingestion of glucose these persons have much greater rise and glucose level falls to control value only after 5 to 6 hours and it fails to fall below control level. Failure to fall below control shows that normal increase in insulin secretion does not occur in diabetic person.

   Diagnosis is definitely established by GTT (Fig. 80.2).
4. *Acetone breathe:* In severe diabetes, some acetoacetic acid can be converted to acetone, which is volatile and is vaporized into the expired air. Therefore, one can make a diagnosis of diabetes by smelling acetone in patient's breath.

   Ketoacids can be detected by chemical tests in urine and their quantitative estimation helps in determining the severity of diabetes.

Treatment

There are three basic elements in the treatment of diabetes:

1. Diet
2. Insulin, and
3. Exercise.

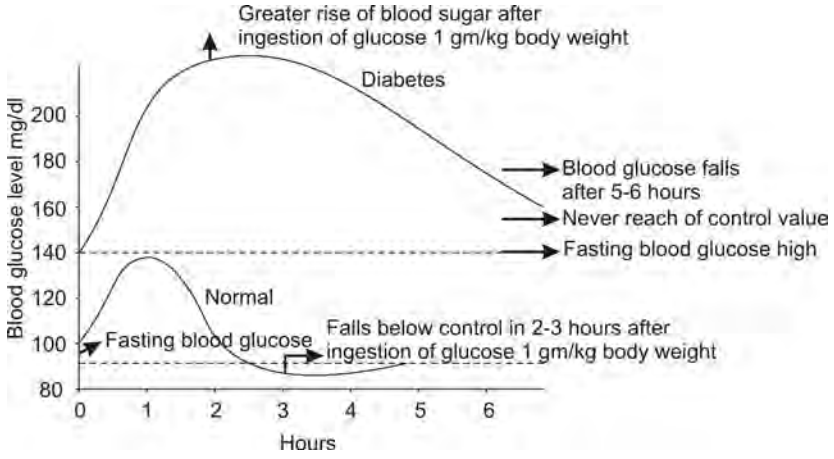


Fig. 80.2: Glucose tolerance curve in a normal and diabetic person

Diet is altered in such a fashion that post meal hyperglycemia is reduced and carbohydrate tolerance is improved. Complexed carbohydrate and fiber in daily diet is sufficient, so that carbohydrate tolerance is improved possibly by upregulation of insulin receptors.

Insulin: May be considered replacement therapy for diabetes mellitus. But it has to be given by injection as being a protein it is broken down during digestion, if given by oral route.

Hypoglycemic drugs: In most patients of diabetes considerable pancreatic function is still intact. In them, insulin secretion can be increased by stimulating B-cells by hypoglycemic drugs.

Some hypoglycemic drugs improve oxidation of glucose in tissues.

Exercise

Exercise acts by upregulating insulin receptors. Therefore, mild diabetics can be treated with exercise and if diabetes is not so mild, it reduces requirement of insulin of the patient.

Some complications of longstanding diabetes require mention:

1. Proliferative scarring of the retina (diabetic retinopathy).
2. Renal disease (diabetic nephropathy).
3. Loss of nerve function, particularly in autonomic nervous system (diabetic neuropathy).
4. Accelerated atherosclerosis:
   i. Ieads to circulatory insufficiency in legs with chronic ulceration and gangrene, and
   ii. To increased incidence of stroke and myocardial infarction.

CHAPTER 81

Female Reproductive Organs and Ovarian Cycle

All living beings reproduce. Reproduction is a process by which organisms make more organisms like themselves. It is essential to keep a species alive.

FEMALE REPRODUCTIVE ORGANS

Organs are located in pelvis (Fig. 81.1).

1. *Uterus:* It is shaped like upside down pear, with thick muscular wall (9 cm x 6.5 cm x 3.5 cm). It is divided anatomically and functionally into body and cervix. Fundus lies above the insertion of fallopian tubes and is part of the body of the uterus. The cavity of the uterus communicates with that of fallopian tubes.

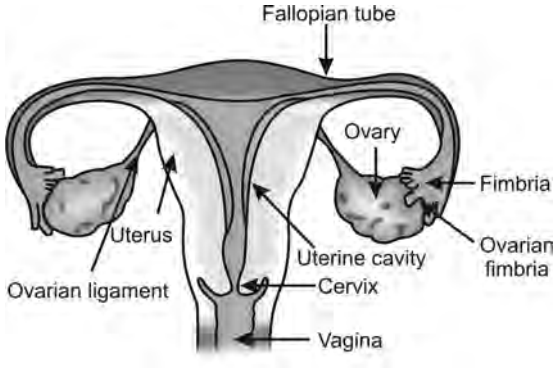


Fig. 81.1: Female reproductive organs

Body of uterus lead to cervix (=neck) with strong and thick walls, cervix opens in vagina and opening is very small.

Wall of uterus consists of three layers:

i. The peritoneal covering called perimetrium.
ii. The muscle layer or myometrium and
iii. The mucous membrane or endometrium.

The muscle fibers in myometrium are arranged in criss cross fashion.

2. *Vagina:* Cervix projects in vagina, which is muscular, hollow tube, which extends from uterus to the outer opening of vagina at the vulva. The outer opening is covered with a membrane (=hymen) in unmarried girls. Length is about 8 to 12 cm, where posterior vaginal wall is longer than anterior. Thus, vagina is obliquely placed. Upper end is attached to cervix.

Vagina is covered over by mucous membrane, which keeps it protected and moist.

3. *Fallopian tubes:* Each fallopian tube is attached to the cornu of the uterus and lie in upper edge of the two folds of broad ligament. Each tube is about 4" long (or 10 cm) and has tiny passageway. The outer end is wide, funnel-shaped and is fimbriated and opens in peritoneal cavity. Fimbria are motile. One fimbria – the ovarian fimbria is larger and longer than others and is attached to the region of the ovary.

   Ovaries: Two in number, lie one on each side of the uterus. They are the female gonads. Size 35 mm × 25 mm × 18 mm (3.5 × 2.5 × 1.8 cm). They produce the female gametes or germ cells or ova (singular = ovum). When ovum is released from the ovary it enters the fallopian tube. The tiny hairs inside the fallopian tubes help its passage into the uterus.

   The ovum is produced by the ovary and discharged at regular interval of about 28 days.

OVARIAN CYCLE

In non-pregnant woman of reproductive age one ovum is discharged from one of the two ovaries once in 4 weeks. The discharging of ovum is called *ovulation.*

The cycle in which one ovarian follicle (called Graafian follicle) matures, ovum is discharged and corpus luteum is formed from ruptured follicle which finally degenerates, is called ovarian cycle.

Ovarian cycle coordinates tightly with uterine cycle.

Uterine Cycle or Menstrual Cycle

From few days before ovulation, the endometrium starts to prepare itself for embedding of fertilized ovum. But when fertilization does not occur the endometrium breaks down. The desquamated endometrium and blood are shed off via the vagina. This is called *menstruation.* Thus, menstruation also occurs cyclically at interval of about 4 weeks and the cycle is called menstrual cycle – during which growth of the endometrium and subsequent breakdown occurs.

Reproductive cycle: Includes both ovarian cycle and menstrual cycle.

Menarche: The appearance of first menstrual flow in the life of a girl is called menarche. The age at which menarche occurs is normally between 11 to 14 years.

Menopause: The permanent disappearance of menstrual cycles in the life of a woman is called menopause. The age at which menopause occurs varies normally between 45 to 50 years. Menopause is also known as the climacteric.

Puberty

Puberty is a slow process involving several years during which the secondary sexual characters develop, sexual organs develop to maturity and menstruation is established.

Puberty take about 3-5 years.

Until puberty the hypothalamus and the anterior pituitary gland are under some inhibitory influence of a higher brain center. At puberty this inhibition is gradually withdrawn and the hypothalamus starts secreting GnRH (Gonadotropin releasing hormone) in a pulsatile manner initially during sleep, and later throughout 24 hours. Under the stimulus of GnRH the anterior pituitary gland releases FSH and later LH as well as, growth promoting hormone.

The effects—Growth promoting hormone causes a spurt of growth.

1. The ovaries respond by developing Graafian follicles and secreting estrogen.

2. *Estrogen is responsible for:
   i. breast development
   ii. Female fat distribution which is responsible for female shape of the body.
   iii. Vaginal and uterine growth.
   *Estrogen is also spelt as of estrogen.
3. Adrenal androgen causes pubic and axillary hair growth at the time of puberty.
4. Estrogen causes proliferation of endometrium and brings about menstruation.

The initial cycles may be irregular and anovulatory due to inadequate follicular maturation. Later, the cycles become regular and ovulatory.

Psychic changes: Girls become more emotional, shy, introvert, protective and are attracted towards males.

Changes During Ovarian Cycle and its Hormonal Control

In ovarian cycle – there is:

1. Follicular phase during which ovarian or Graafian follicles grow, followed by
2. Ovulation, followed by
3. Luteal phase – during which corpus luteum is formed and it degenerates subsequently.

Follicular Phase

The development of a primordial follicle into a graafian follicle is under control of follicle stimulating hormone (FSH) secreted by anterior pituitary gland.

Structure of Graafian Follicle

After puberty its size measures 12 to 16 mm in diameter. Mature graafian follicle is spheroidal or ovoid in shape and contains pent up secretion liquor folliculi. The lining consists of two layers. *Theca interna* layer lies on outer side – important for production of estrogen and progesterone. On inner side of theca interna lies a layer of granulosa cells. Its cells are large; nuclei stain deeply and contain little cytoplasm. *Theca externa* lies on outer side of theca interna.

In one-area granulosa cells are collected together to form projection into the cavity of graafian follicle – called *cumulus oophorus.* Ovum lies in this heap of cells. The granulosa cells, which are immediately adjacent to ovum have radial arrangement and form *corona radiata.* The corona radiata remains attached to ovum after its discharge into peritoneal cavity (Fig. 81.2).

Several follicles commence to develop in each cycle. Of the several follicles, one grows faster than the other and produces more FSH receptors and estrogen. The rising estrogen level causes a negative feedback to the anterior pituitary gland. The fall in the level of FSH withdraws gonadotropic support to the other lesser-developed follicles, which atrophy.

Ovulation

Ovulation is estimated to occur 14 days before the first day of the next cycle (i.e. 1st day of next menstruation). This interval is more or less fixed. In cases of irregular cycles, the follicular phase varies and luteal phase remains constant.

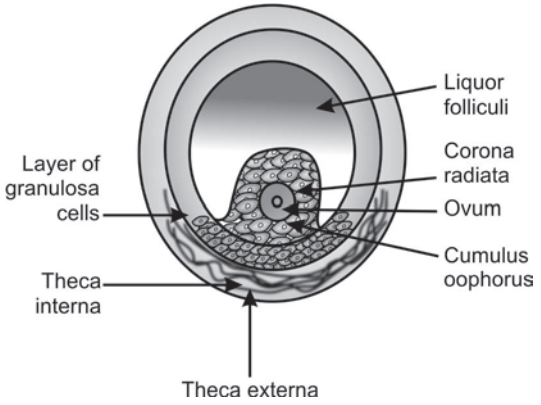


Fig. 81.2: Graafian follicle

When ovulation occurs – the ovum surrounded by corona radiata, escapes out of the graafian follicle. It is quickly picked up by tubal fimbria, which hugs the ovary at ovulation.

The rupture of graafian follicle occurs because of contraction of micromuscle present over theca externa. The contractions are brought by prostaglandin secreted under the influence of LH.

When estrogen level is very high and prolonged, estrogen exerts positive feedback action and indirectly causes vigorous secretion of LH. Phenomenon is called LH surge, which is very essential for ovulation (Fig. 81.3).

The aperture through which an ovum escapes from the ovary is called the stigma.

Unless fertilized, the ovum does not survive for more than 24 hours, but degenerates in fallopian tube without leaving any trace of it.

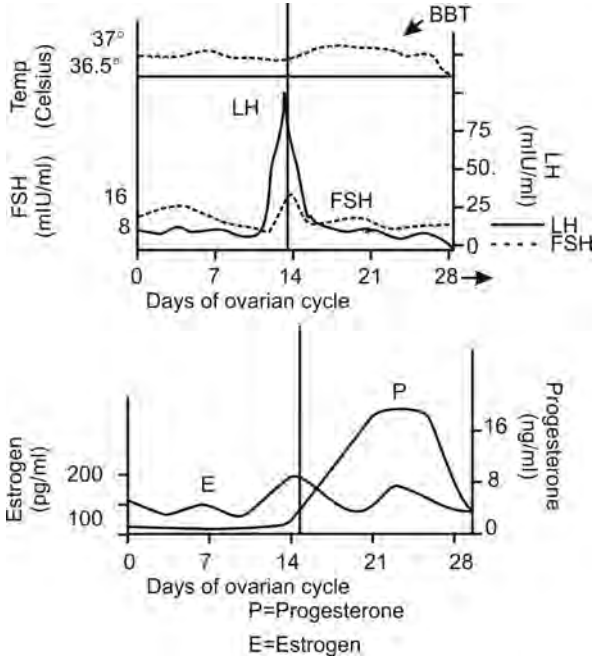


Fig. 81.3: Pituitary and ovarian hormone levels in reproductive cycle (ovarian cycle)

Luteal Phase

After extrusion of the ovum, what remains of the graafian follicle is called corpus luteum (=yellow).

During growth of graafian follicle, LH receptors begin to appear on the granulosa and theca cells as the follicle grows due to FSH activity. These granulosa cells become lutein cells and the target cells of LH are the lutein cells.

LH causes formation and maintenance of the corpus luteum. It also causes formation of progesterone in the corpus luteum from the lutein cells, which is secreted.

Under the effect of LH corpus luteum grows, its cells proliferate and bloat up. The corpus luteum reaches maximum size (2 cm) by the 22nd day of normal cycle.

1. If the pregnancy fails to occur, by 8th postovulatory day, the corpus luteum starts degenerating and hyalinization sets in. During last week of the cycle, vascularity of corpus luteum diminishes, deposition of hyaline tissue takes place and this hyaline body is called corpus albicans.
   As the granulosa cells, which have become lutein cells under the effect of LH, secrete more and more of progesterone, this eventually causes negative feedback to anterior pituitary and secretion of LH falls. Under low concentration of LH, corpus luteum and its secretory activity cannot be maintained and corpus luteum begins to degenerate.
2. If ovum is fertilized, the corpus luteum continues to grow and forms the corpus luteum of pregnancy. This corpus luteum is more larger and more cystic than the corpus luteum of menstruation and may attain the size of 2.5 cm. Individual granulosa cell is also large. The secretion also increases. The corpus luteum of pregnancy is functionally active up to

fourteenth week. Thereafter, the placenta takes over the secretory function and carries pregnancy to term.

For maintenance of corpus luteum of pregnancy a hormone known as human chorionic gonadotropin hCG is necessary, which is secreted by placental tissue. hCG begins to be secreted before the completion of first week of gestation. The actions of hCG are like that of LH, hence corpus luteum is maintained.

Detection of ovulation: Various methods are utilized by the clinicians.

1. Basal body temperature (BBT): In post ovulatory phase or luteal phase the BBT shows 0.5°C rise. BBT is recorded before the subject leaves her bed in the morning and even before she opens her mouth to speak. Rise of BBT is associated with the rise of progesterone in the body. As all cases do not necessarily show the rise of BBT in their postovulatory phase, it is not very dependable procedure.
2. Estimation of progesterone levels in postovulatory phase.
3. A piece of endometrium is removed in 2nd half of the cycle and characteristic histological appearance of secretory phase in endometrium under the effect of progesterone, ensures presence of progesterone, which in turn is indicative of ovulation. The procedure is called endometrial biopsy.
4. Serial vaginal cytology
5. Serial cervical mucus study

Both show definite changes if ovulation has taken place

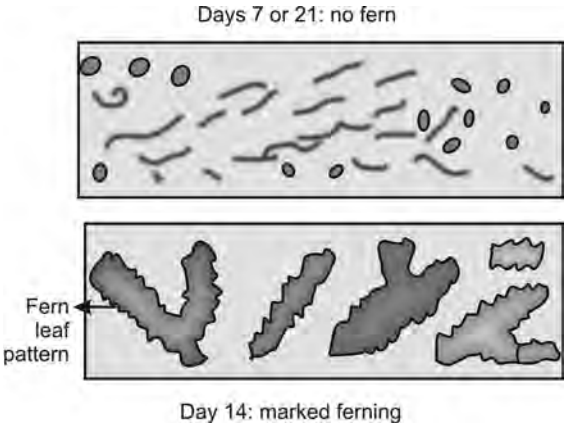


Fig. 81.4: Fern leaf pattern of cervical mucus on a glass slide

Cervical mucus: Becomes much thicker in postovulatory phase.

Fern test: A drop of cervical mucus pressed between two glass slides gives a typical fern-leaf pattern when the mucus is thin. Repeated at short intervals the appearance of marked ferning and then its disappearance would indicate that ovulation has taken place. It disappears under progesterone influence (Fig. 81.4).

CHAPTER

82

Menstrual Cycle and Its Hormonal Control

Coinciding with the cyclical changes in ovary, cyclical changes take place in the uterus, which we call as menstrual cycle. First day, of the cycle is denoted by 1st day of menstrual bleeding.

Duration of cycle on an average 28 days or 30 ± 3 days. In some women the cycle is prolonged of 45 days or so and in some it may be short of 21 days or so.

DIFFERENT PHASES OF MENSTRUAL CYCLE

1. Proliferative phase or postmenstrual phase.
2. Secretory phase or premenstrual phase.
3. Menstrual phase

1. *Proliferative phase:* The phase of menstrual cycle which starts when regeneration of menstruating endometrium is complete and lasts until the fourteenth day of a 28 day cycle is referred to as *proliferative or estrogen phase.*

   From day 1 FSH slowly begins to rise and under its effect large number of theca cells are formed in growing graafian follicle, which secrete large amounts of estrogen.

   Going into circulation estrogen reaches the uterus and exerts profound influence on uterine endometrium, stimulating its proliferation. The endometrium, which is about 0.5 mm thick, to begins with, reaches about 3.5 mm by fourteenth day. During proliferative phase, the *glands,* which are simple tubular become slightly sinuous and their columnar epithelium become taller than before.

   The *stroma* becomes extremely edematous with wide separation of individual cells.

   The *arteries* become coiled and spiraled.

   Proliferative phase will last for 14 days in a 28 days cycle.

2. *Secretory phase or premenstrual phase:* The secretory phase begins on 15th day and persists until the onset of menstruation.

   After ovulation the ruptured graafian follicle becomes corpus luteum and begins to secrete progesterone while continuing the production of some estrogen as well. As soon as progesterone appears on the scene a change becomes evident in the endometrium. The tubular *endometrial glands,* already well developed under the proliferative action of estrogen now start secreting copiously (uterine milk) and become tortuous or cork screw. *Glycogen* content of endometrium increases.

The coiled *arteries* become more *spiral* and form perpendicular columns in the mucosa. *Stroma* remains edematous. The stroma cells become swollen (=hypertrophy). The endometrium becomes 8-10 mm in thickness in secretory phase. The secretory phase reaches its peak by the twenty-second day of the cycle. The endometrium now is ideal for the implantation of the fertilized ovum.

If the discharged ovum is *not fertilized*, around 26th day or 2-3 days just before the end of the cycle a significant change occurs. The progesterone level in blood, which was high now begins to exert a negative feedback on LH secretion (and positive feedback of estrogen on LH is also falling as corpus luteum is primarily progesterone producer). As a result LH secretion drops. Corpus luteum begins to atrophy due to absence of adequate LH support. At this period of the menstrual cycle all the hormones – FSH, LH, estrogen and progesterone – are at the lowest.

3. *Menstrual phase:* On day 28 endometrium also begins to degenerate, due to withdrawal of hormonal support, due to sudden atrophy of corpus luteum in the ovary, the estrogen and progesterone fall so low that the markedly thickened endometrium disintegrates and is expelled in the form of vaginal bleeding. Menstrual bleeding indicates end of one cycle and beginning of next cycle (Fig. 82.1).

MECHANISM OF MENSTRUAL BLEEDING

As the progesterone level falls the spiral of coiled arteries of the endometrium go into spasm, depriving a part of the endometrium of its blood supply. This part undergoes ischemic necrosis (= becomes dead because of lack of blood supply). The arterial wall itself finally becomes weak and ruptures. Bleeding occurs along with it the dead part of endometrium is washed away. After few hours the same process occurs in another spiral artery. Bleeding is in bouts, not continuous. This process continues for 3 to 5 days.

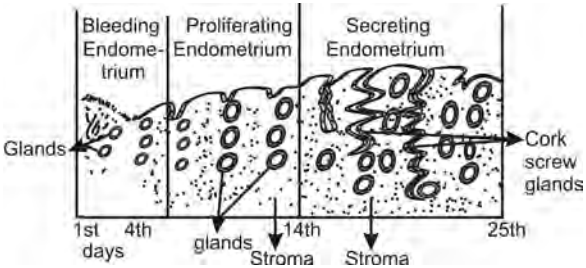


Fig. 82.1: Endometrium in menstrual cycle

Normally about 30 to 50 ml blood is lost in one cycle. Menstrual blood does not clot because it is already clotted and liquified within the uterus.

Loss of blood in menstruation is physiological, but excess loss of blood causes anemia in women.

Regeneration

Regeneration of denuded epithelium is already in progress before menstrual bleeding has stopped. Regeneration is complete in 48 hours after the end of menstruation.

Repair is brought about by the glandular epithelium growing over the bare stroma.

FSH level begins to rise and another graafian follicle begins to grow secreting estrogen in the beginning. Under its effect the endometrium starts proliferating.

Note: Basal part of endometrium (stratum basale) is always preserved and starts regeneration. This part has independent blood supply from the straight basal arteries.

Other Changes during the Menstrual Cycle

1. *Fallopian tube:* It undergoes receptive relaxation following ovulation followed by increased motility and finally returns to normal.
2. *Uterine cervix and vagina*: Estrogen makes the cervical mucus thin so as to allow passage of sperms.

   Progesterone makes the mucus thick and tenacious to seal uterus from harmful external agents.

   Vaginal epithelium becomes more and more keratinized as the estrogen level rises.
3. *Mammary glands:* Fullness and tenderness of breasts is felt by many women towards the end of the cycle. This is due to action of estrogen and progesterone on the breast tissue.
4. *Premenstrual weight gain:* Due to estrogen and progesterone there is some water retention in premenstrual phase and feeling of heaviness in some women.
5. *Behavior*: Evidence is not conclusive about general behavior or sexual responsiveness in women has any correlation with the menstrual cycle.

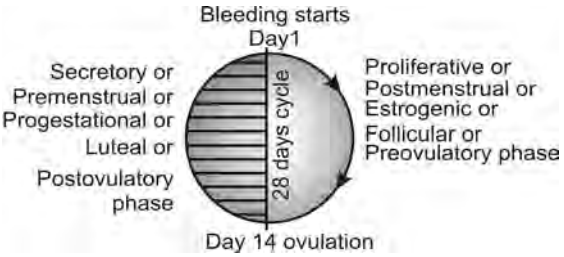


Fig. 82.2: Phases of menstrual cycle

Menstrual cycle is a continuous process and one cycle merges into the next, but for practical purposes we divide it into two parts or phases as shown in Figure 82.2.

ANOVULAR MENSTRUAL CYCLE

Its occurrence is common for a few cycles after menarche and just prior to the onset of menopause. In such cycles no ovulation occurs and therefore no formation of corpus luteum. Menstrual flow is withdrawal bleeding, i.e. it is due to lowering of the level of estrogen only.

Note: Some cases of infertility is due to anovular menstrual cycle. As no ovum is liberated the woman is infertile.

CHAPTER

83

Ovarian Function and Female Sex Hormones

OVARIAN FUNCTION

1. Ovaries produce an ovum monthly, and
2. Ovaries produce hormones responsible for
   i. Maturation of graafian follicle
   ii. Ovulation
   iii. Menstruation
   iv. Maintenance of pregnancy in early weeks of gestation

FEMALE SEX HORMONES

1. The steroidal hormones are: Estrogen and Progesterone

   Estrogen is mainly secreted by the graafian follicle in the follicular phase or preovulatory phase.

   A *small* amount is secreted by the corpus luteum in the premenstrual phase.

   Progesterone is secreted by corpus luteum.
2. Nonsteroidal hormone: *Inhibin* is present in graafian follicle. It is a protein hormone that stimulates LH secretion and inhibits FSH.
3. Other hormones produced by ovary in small amounts are testosterone and androstenedione.

Estrogen

Estrogens are group of substances which produces estrus in female animals. They are mainly estradiol, estrone and estriol.

Natural oestrogens are C18 steroids, which are produced by (a) granulosa cells of graafian follicles and corpus luteum, (b) Adrenal cortex is a secondary source. Estrogen is secreted as estradiol.

Estrogen is inactivated in liver and excreted as some estradiol, estriol and conjugates of esterone.

Peak level is reached approximately 2 days before ovulation or 24 hours before LH surge. Peak level is up to 350 pg/ml thereafter, its concentration falls but a small rise is seen again in mid luteal phase.

Synthetic estrogens are readily available in market, which are used clinically.

Transport

Most of the estrogen in blood is bound to albumin and specific steroid binding globulin. Only about 3 percent of circulating estrogen is in free state.

After menopause, when ovarian function ceases, estrogen levels naturally fall very low.

Biosynthesis mainly from cholesterol.

Testosterone can be converted in body into estradiol.

Mechanism of Action

Estrogen combines with receptors in the cytoplasm of target cells and then is carried to nucleus where it activates transcription of DNA. New mRNA is formed as a result of which specific proteins are synthesized.

This can result into hyperplasia and hypertrophy of target organs like myometrium, endometrium, breast.

Stimulation of DNA also causes mitosis. So more cells in target organs are formed (= hyperplasia).

Actions of Estrogens

1. *Feminization and secondary sex characteristics:* The texture of female skin and shape of female form are considerably influenced by estrogen. Female pattern of fat deposition occurs.
2. *Specific actions on genital tract:*

   Vulva and vagina

   i. Development of vulva.
   ii. Vascular stimulation of vulva and vagina.
   iii. Epithelial stimulation of vulva and vagina. Cornification of superficial layers of vagina occurs.
   iv. Deposition and metabolism of intracellular glycogen in vaginal epithelium.

   Uterus

   i. Causes myohyperplasia of the myometrium and cervix.
   ii. Increases uterine vascularity.
   iii. Regenerates the endometrium after menstruation and is responsible for proliferative hyperplasia of the endometrium.
   iv. Stimulant effect on the glands of the endocervix and their mucus secretion.

   Fallopian tubes

   Estrogen stimulates the tubal musculature.
3. *Breasts:* Growth of breasts by—Hypertrophy of parenchyma, especially ducts of the breast, increased vascularity and areolar pigmentation.
4. *Action on other endocrine glands*: Estrogen inhibits FSH secretion, prolactin and TSH.

   It stimulates LH secretion and helps corpus luteum formation and to a lesser extent ACTH secretion.
5. *Skeletal system:* It influences calcification of bone. It causes closure of epiphysis in adolescent girls.

   In postmenopausal women, decalcification of bone due to estrogen deficiency causes osteoporosis, which leads to kyphosis.
6. *Water and sodium metabolism:* Estrogen tends to cause water and sodium retention.
7. *Blood cholesterol:* Estrogen lowers blood cholesterol and thereby provides natural protection to women against atherosclerosis (lipid deposition in the arterial wall).

Progesterone

It is C_{21} steroid hormone.

Source

1. Corpus luteum is the *main* source of progesterone.
2. Progesterone is also an intermediary product of synthesis of adrenal corticosteroids. But this progesterone has little biological activity.

It is metabolized in liver and excreted in urine as pregnandiol.

3. During pregnancy it is secreted by placenta in large amounts.

Plasma level rises after ovulation and reaches a peak level of 15 ng/ml at mid luteal phase. With degeneration of the corpus luteum, its level falls and this brings about menstruation.

If pregnancy occurs, the corpus luteum persists and enlarges and continues to secrete progesterone. This high level of hormone prevents menstruation and leads to amenorrhea of pregnancy (Amenorrhea = absence of menstruation).

Biosynthesis: Progesterone is synthesized from cholesterol.

Actions of Progesterone

Endometrium: Progesterone cause secretory hypertrophy of endometrium and prepares it for implantation of fertilized ovum. But it acts only on estrogen-primed tissue. Its sudden withdrawal results in menstrual bleeding.

Progesterone helps in implantation of the ovum and formation of placenta.

Uterus: Progesterone causes myohyperplasia of uterus.

Pregnancy

1. Most important role of progesterone is during pregnancy. It inhibits the excitability and contractility of the myometrium.

   During pregnancy distention of the uterus by growing fetus might cause reflex contraction of uterus. But this is prevented by progesterone, which suppresses excitability of uterine musculature and abortion is prevented.
2. Production of large amounts of progesterone initially by corpus luteum and later by placenta prevents menstrual bleeding during pregnancy.
3. Progesterone inhibits ovulation during pregnancy by feedback suppression of LH.

Fallopian Tube

Progesterone causes hyperplasia of the muscular lining of fallopian tube and makes peristaltic contractions more powerful and tubal glands secretion increases.

Cervix: Progesterone causes its hypertrophy and makes cervical mucus more viscous. It makes internal os competent (i.e. keeps it closed) and holds pregnancy to term.

Vagina: During early pregnancy vagina becomes violet colored due to venous congestion.

Breasts: Progesterone stimulates development of mammary glands, particularly the lobules and acini of mammary gland during puberty. This action is more marked during pregnancy when the placenta secretes it in large amounts.

Fluid retention: Progesterone causes water and sodium retention and is contributory factor in premenstrual tension and weight gain.

Smooth muscle: Progesterone relaxes smooth muscle—uterine muscle therefore relaxes in pregnancy. Ureter dilates under its effect.

Thermogenic: Progesterone raises the body temperature by 0.5 ° C during the second half of the menstrual cycle. Basal body temperature (BBT) is based on its thermogenic effect, in a menstrual cycle.

Anabolic effect: Progesterone exerts an anabolic effect and this partly accounts for some weight gain, which may follow their administration.

Virilization: While part of progesterone administered is metabolized to estrogen, it is also partly metabolized to testosterone and

therefore if administered to a patient during pregnancy can have virilizing effect on a female fetus.

Control of Ovarian Function

Different phases of the menstrual cycle are dependent upon changes occurring in the ovary, they are in turn dependent on the anterior pituitary which is under control of hypothalamus.

How pituitary hormones control ovarian hormone secretion is already discussed.

Hypothalamus is in intimate relationship with the other cortical areas, especially areas concerned with emotion (like limbic system). In women the menstrual cycles may be abnormal under emotional stress. They may be completely suppressed under conditions of emotional tension. For example, a girl after puberty leaves her home for the first time to reside in hostel may be facing emotional stress and it may cause menstrual irregularity or suppression of menstrual cycle.

Ovarian Hormone Feedback

Ovarian hormones exert their feedback both at the level of the hypothalamus as well as the anterior pituitary. Estrogen and progesterone modify the frequency of GnRH (Gonadotropin releasing hormone) secretion and therefore anterior pituitary hormones are accordingly secreted.

Other hormones secreted by ovary are:

1. *Relaxin:* It relaxes the connective tissue and is probably secreted by ovary.

   Relaxin is water-soluble protein and nonsteroid. It causes relaxation of pelvic girdle. Therefore, it has a role in pregnancy.
2. *Inhibin:* This is water soluble nonsteroid protein (peptide) secreted by graafian follicle. It is named inhibin because it is known to suppress pituitary FSH. In normal ovarian cycle—FSH and LH initiate secretion of estrogen in the graafian follicle, estrogen causes secretion of inhibin which in turn suppresses FSH secretion but stimulates LH secretion (remember LH surge).
3. *Ovarian androgens:* They are testosterone, dehydroepiandrosterone (DHA) and androstenedione. They are intermediaries of estradiol biosynthetic pathway. Some of these androgens escape in the blood.

After menopause the increased ovarian stroma is responsible for the rise in these hormones and development of facial hair (hirsutism) in some postmenopausal women.

CHAPTER

84

Physiology of Pregnancy and Maternal Changes during Pregnancy

PHYSIOLOGY OF PREGNANCY

Normal duration of pregnancy is 280 days or 9 calendar months and 10 days or 40 weeks or 10 lunar months.

For convenience the period of gestation is always counted from the date of last menstrual period (LMP). This is followed by continuous amenorrhea.

Fertilization and Implantation

Ovum is released from mature graafian follicle at the time of ovulation. Ovum is immediately received into the funnel shaped fimbrial end of the fallopian tube.

Fertilization generally occurs in the mid portion of the tube. Sperms swim up from uterine mouth after coitus. The fastest sperms reach this portion of tube in 5 to 45 minutes. Therefore, sperm motility is normal requirement for fertility.

After coitus sperms remain alive in female genital tract for 2 to 3 days and are released into uterus in batches, by cervical mucus.

Only one sperm out of thousand sperms may succeed in crossing the mucus barrier. Therefore, abnormal sperms lag behind due to poor motility.

If fertilization does not occur the ovum dies in 24 hours. Sperms survive up to 3 days in female genital tract.

Zona pellucida: It is a clear tenacious membrane surrounding the ovum – recognizes the sperm of same species (because sperms of other species are rejected) and it ensures that only one sperm enters the ovum. Proteolytic enzymes present in the acrosomal cap on the sperm, helps in penetrating the zona pellucida (Fig. 84.1). Enzyme hyaluronidase released in the process, remove the cells of cumulus oophorus, which cover the ovum.

Once the sperm enters the ovum, the fusion of 2 gamete pronuclei takes place and zygote now regains the normal complement of *46 chromosomes.* Zygote begins to divide and soon becomes blastocyst. The blastocyst has an outer layer of syncytiotrophoblast and inner layer of cytotrophoblast.

Zygote is slowly propelled forward by: (a) gentle movement of cilia of fallopian tube, (b) peristaltic contraction of the tube and flow of tubular secretion.

Nearly 4 days after fertilization the ovum reaches uterine cavity and by this time endometrium is well prepared for its reception. The syncytiotrophoblast attaches itself to the

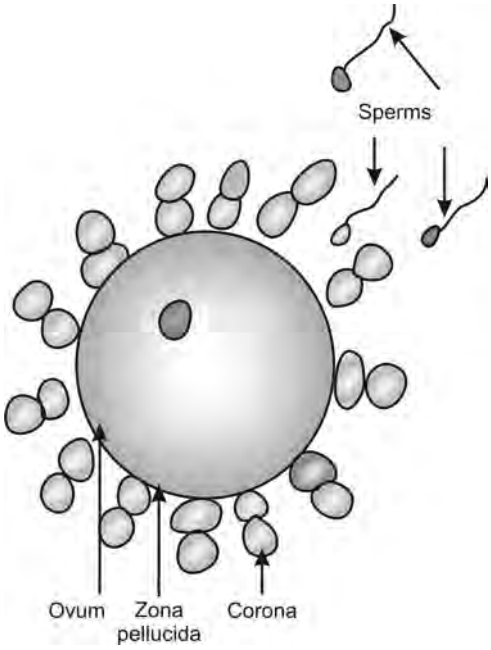


Fig. 84.1: Ovum

endometrial surface and 7 days old blastocyst slowly implants itself into the endometrium.

The syncytiotrophoblast start secretion LH like hormone human chorionic gonadotropin (hCG) which diffuses into mother and prevents the corpus luteum in the ovary from regressing. Progesterone continues to be secreted by the corpus luteum and no menstrual bleeding occurs. hCG is like LH in action. hCG can be detected in the mother's urine as early as 10 days after conception, i.e. 4 to 5 days before the next menstrual period is due.

Pregnancy Tests

The pregnancy test routinely performed today is based on presence of hCG in pregnant woman's urine. Method of detection of hCG is immunological.

In principle it is extremely simple. Pre-prepared antibodies against human B-hCG molecule are mixed with woman's urine. Antigen-antibody reaction occurs and the complex settles down as precipitate. In order to make the precipitate easily visible to naked eye, the antibodies are coated on white latex particles, so the precipitate increases.

The immunological test is not foolproof; proteinuria may give a false positive test.

Note: Now 'do it yourself' kits are available.

During pregnancy, the whole physiology of the mother is geared to meet the demands of this state. The cardiac output, BMR and ESR are increased. So also the activity of endocrine glands is increased. An extraendocrine gland, namely the placenta forms whose secretions alter the maternal physiology.

The ovary is essential for pregnancy to continue in early weeks, but after few weeks the placenta is able to form the hormones required for the continuation of pregnancy.

Functions of Placenta

Both mother and the zygote contribute to the formation of the placenta. Basic structure of placenta is such that a large pool of maternal blood is formed in which the finger like chorionic villi of the zygote float and it can take in variety of substances from maternal blood and it can pump out substances in maternal blood, as the need arises. Large highly vascular and fully functional placenta develops at the end of third month.

Three groups of functions are performed by the placenta:

1. Production of hormones.
2. Transport of substances between the mother and fetus.
3. Protection of fetus.

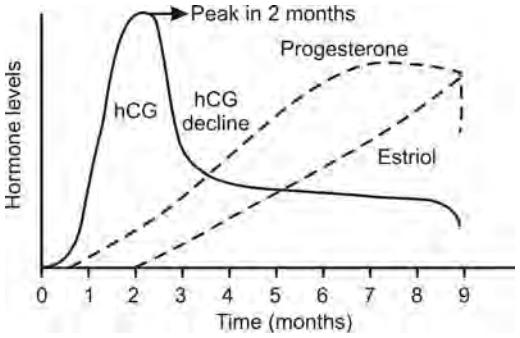


Fig. 84.2: Pattern of changes in the blood levels of various hormones during normal pregnancy

Production of Hormones

Placenta is the largest endocrine gland and is the only one, which can produce both protein and steroid hormones (Fig. 84.2).

i. *Human chorionic gonadotropin (hCG):* The syncytiotrophoblast cells start producing hCG within 7 days of fertilization. It enters the maternal blood. hCG has LH like activity, therefore production of progesterone from corpus luteum continues, so that no withdrawal bleeding occurs. Progesterone is helpful in maintaining pregnancy as it decreases excitability of uterus to stretch or distention.

hCG level in maternal blood and urine reaches peak around 2 months after the LMP. After the 3rd month it begins to decline. By now the placenta is fully formed and it starts producing its own progesterone.

Note: The corpus luteum, which is continued in pregnancy – is known as corpus luteum of pregnancy.

ii. *Progesterone and estrogen:* Placenta produces large amounts of estrogen and progesterone.

Estrogen is the main hormone responsible for the: (a) spectacular growth of uterus in pregnancy. The myometrium grows both by hyperplasia and hypertrophy. Endometrium, stroma cells (= decidua) also show prolific growth, (b) Breasts also grow in pregnancy due to high estrogen.

Progesterone s main function appears to: (a) keep the myometrium in a quiet state that is it opposes any uterine contraction. (b) Secretory changes occur in breast but no secretion takes place. Progesterone acts on tissues, which are primed by estrogen.

Placenta is not fully equipped for steroid synthesis (i.e. steroid hormones like estrogen and progesterone) because deficiency of enzymes 17-hydroxylase and 17-20 desmolase. Fetal and maternal adrenals therefore cooperate with the placenta in the synthesis of steroid hormones.

Progesterone is directly synthesized from cholesterol or acetate, but for estrogen production, intermediary metabolites are exchanged, between adrenals and placenta.

iii. *Human placental lactogen (hPL) or human chorionic somatomammotropin (hCS)*: They are protein hormones. They have action similar to two hormones of pituitary – growth hormone and prolactin.

iv. *Other hormones and enzymes*: Secreted by placenta are—Relaxin which relaxes the pelvic ligaments for childbirth. Renin, TSH, ACTH – activity is present in placental extract. Enzymes like – oxytocinase, histaminase, alkaline phosphatase are produced by placenta. Oxytocinase concentration increases during pregnancy. Neurotransmitter – like acetylcholine is also produced by placenta.

Transport of Substances

i. It acts like lungs and exchanges oxygen and carbon dioxide by diffusion through it. Oxygen coming from maternal blood and carbon dioxide diffusing out from the fetus.
ii. Through placenta waste products of the fetus also go out into the maternal circulation, and hence placenta acts like kidney or has excretory function.
iii. Many immunoglobulin molecules from maternal circulation cross the placental barrier to confer a passive immunity in the fetus.
iv. All nourishment of fetus are received from placenta from maternal blood like water, glucose, amino acids, minerals, vitamins, etc.
v. Many drugs can also cross placental barrier, e.g. anesthetics if used during labor, these drugs can cause damage to the fetus.

Protection of the Fetus

Placenta acts as a barrier, which prevents the entry of harmful substances into fetal circulation. The placental membrane or barrier separating mother's blood from fetal blood is 25 microns thick. But in last few months of pregnancy the cellular layers degenerate. Placental membrane is reduced to just 2 microns and barrier weakens. Viruses and many drugs now can cross the barrier and may produce harmful effects.

MATERNAL CHANGES DURING PREGNANCY

Weight gain in mother during pregnancy can be attributed to:

1. Baby—3.0 kg.
2. Placenta and amniotic fluid—1.5 kg.
3. Enlargement of uterus and breasts—1.0 kg.
4. Increase in blood volume—1.5 kg.
5. Fat deposition—4 kg.

Thus, total weight gain is 10 to 12 kg during pregnancy. Some edema is common, particularly in lower limbs, partly is due to fluid retention and partly due to pressure of uterus on abdominal veins.

Blood: Erythropoiesis increases during pregnancy at the same time blood volume also increases, due to: (a) water retention, and (b) hemodilution. Therefore, hemoglobin concentration decreases. Therefore, 10.5 gm% Hb – is normal in pregnant woman.

Iron supplementation is needed in late pregnancy as fetus draws considerable amount of iron from mother for his own erythropoiesis.

Blood has higher concentration of factors VII, VIII and IX during pregnancy. Blood coagulates more easily. May be a precaution against blood loss during childbirth. But it increases the tendency of thrombosis.

Endocrine Organs

Anterior pituitary remains suppressed because of high levels of estrogen and progesterone during pregnancy. Very little FSH, LH and GH are secreted.

Thyroid – increases in size.

Electrolyte balance: There is sodium retention. Therefore, water retention and possibility of edema. Sodium and water retention is there due to combined effect of estrogen and aldosterone.

Cardiovascular System

In pregnancy:

1. Resting heart rate – increases.
2. Cardiac output increases by about 30 percent.

3. Blood pressure – particularly diastole blood pressure falls. Systolic BP may remain unchanged.

Note

1. A combination of edema, albuminuria and rising blood pressure may mean onset of pre-eclampsia. Therefore, resting BP over 120 mm Hg after about 30 weeks of pregnancy is a cause of concern.
2. Thus, during pregnancy regular check up of weight, Hb%, looking for edema, albuminuria and measurement of blood pressure are necessary to assess the health of the mother.

Respiration

Oxygen consumption increases by 20 percent during pregnancy. Therefore, respiratory rate and tidal volume is increased.

Kidneys

Pregnant woman's post meal urine may test positive for glucose although she may not be diabetic. This is partly because the glomerular filtration rate is increased and therefore tubular load of glucose exceeds the tubular maximum for glucose reabsorption.

Skeletal System

There is lumber lordosis and change of posture with waddling gait in late pregnancy.

Ligaments of pelvic joints relax, which help in childbirth.

Sex of the Fetus

It is determined at the time of fertilization human beings have 46 (=23 pairs) of chromosomes. Of which 44 are autosomes and rest two are sex chromosomes. These two sex chromosomes in female are XX, whereas in case of the male they are XY.

Therefore, female chromosomal pattern is 44 + XX and male chromosomal pattern is 44 + XY.

Owing to the reduction cell division (meiosis) a gamete (which means a spermatozoon or an unfertilized ovum) will contain 22 autosomes + 1 sex chromosome (total 23).

In case of ovum it will be always 22 + X

In case of spermatozoon it may be (i) 22 + X or (ii) 22 + Y

When fertilization occurs, zygote's chromosomal pattern can be 44 + XX $\rightarrow$ genetic sex of zygote will be female or

44 + XY $\rightarrow$ genetic sex of zygote will be male, which will grow into female and male child respectively. Thus, the spermatozoon (not the ovum) is the sex determining factor.

Amniotic Fluid

Amniotic fluid baths the fetus. It is derived from plasma in very early pregnancy and later receives its major contribution from fetus as ECF equilibrates across the fetal skin. After 20 weeks amniotic fluid is formed increasingly from fetal urine and lung fluid.

Maximum volume is about 1 liter.

Functions of Amniotic Fluid

1. Protection of fetus – cushions external trauma.
2. It provides even temperature cushion and helps in thermoregulation of fetus.
3. It maintains the fetus in weightless condition.
4. Allows freedom of movements and breathing movements necessary for normal development.

CHAPTER

85

Labor, Lactation and Methods of Family Planning

LABOR OR PARTURITION OR DELIVERY OR CHILDBIRTH

The process by which baby is born is known as labor or parturition or delivery or childbirth.

Onset of Labor

It is due to—Hormonal changes and neural factors.

These two group of factors, trigger the uterus to contract and expel the fetus at the end of about 9 months of gestation.

From 14th week of pregnancy onwards the uterus contracts, these contractions are painless weak, a-rhythmic and infrequent, until the last month or so of pregnancy. Then their strength and frequency increase. From 30th to 34th week onwards the contractions become stronger and more frequent – Braxton Hicks contractions.

The increasing uterine activity after 36th week is accompanied by increasing sensitivity to oxytocin.

Hormonal Changes

Let us now consider the hormonal changes that lead to increased sensitivity of uterus to oxytocin.

1. *Estrogen and progesterone ratio*: The uterine muscle is kept in quiescent state by progesterone where as increase in contractility of muscle fibers as pregnancy progresses, is due to the action of estrogen and also to stretching. Towards the end of the term progesterone level falls and several other factors release the uterus from inhibition and strong uterine contractions begin.
2. Oxytocin is the posterior pituitary hormone, which stimulates powerful uterine contractions. But no appreciable rise of oxytocin in serum has been found at term. Therefore, it is the sensitivity of uterus to circulating oxytocin, which increases as the pregnancy approaches full term. Estrogen stimulates and progesterone inhibits the formation of oxytocin receptors.
3. *Prostaglandin:* Increase in estrogen/progesterone ratio or withdrawal of progesterone stimulates the synthesis of prostaglandin and uterine contraction. Oxytocin stimulates the release of prostaglandin particularly when estrogen level is high and progesterone level is low.
4. The normal placenta produces an enzyme oxytocinase, which destroys oxytocin. The

ageing placenta (or the placenta which has reached term) may not produce this enzyme and so concentration of oxytocin may increase.

Neural Factors

1. As the pregnancy advances, distention of the uterus and cervix by the growing fetus reflexly stimulate uterine contractions.

   In twin pregnancy the duration of pregnancy is shorter and labor occurs about 15-20 days earlier as the stretch is more in these cases.
2. As the pregnancy advances there is less liquor amnii in proportion to fetal mass and so the fetal parts directly stimulate uterus to contract.
3. Rupture of amniotic membrane and dilatation of the cervix are seen at the onset of labor. Pressure in the region of cervix stimulates contraction of the uterine muscle at the fundus by a local reflex effect.

Stimuli from cervix also bring about release of oxytocin. So initially a few contractions will dilate the cervix which in turn bring about further contractions thus a positive feedback mechanism is set in motion.

In *summary* the mechanism of onset of labor is not due to any one factor but is due to interplay of various hormonal factors and neural factors also help in onset of labor.

Let us explain why Braxton Hicks contractions do not lead to labor—The contractibility of uterus must reach a certain stage, when next uterine contraction must be stronger than the first. Various hormonal factors as discussed above and the uterine stretch increase the contractility of uterus so that positive feedback mechanism is established.

In most labors head of the fetus is the presenting part. This acts as a wedge and causes pressure on cervix when the uterine fundus contracts. Pressure on cervix initiates local reflex to uterine body and next contraction is stronger. Secondly, the pressure on cervix causes reflex secretion of oxytocin from posterior pituitary, which help in causing strong uterine contraction and contractions are coordinate so that fundus contraction is stronger than lower part of uterus.

Until such time that uterine contractility has not reached this stage, when the subsequent contraction is not stronger than the first, it will not lead to labor, therefore Braxton-Hicks contractions do not lead to onset of labor.

Note: In recent years data is collecting which shows fetus initiates its own delivery.

A hormone *relaxin* relaxes pelvic joints and soften cervix, thus it helps in childbirth.

LABOR

Three stages of labor are described:

First Stage

Which begins with onset of strong uterine contractions, which are painful. This stage lasts for several hours and bring about full dilatation of cervix. It denotes the end of the first stage. Usually membrane ruptures at this point.

Second Stage

Which lasts for short time, in which uterine contractions become much more strong and push the baby out through the birth canal. Birth of baby denotes the end of 2nd stage.

During birth of the baby strong abdominal contractions (voluntary) help the uterine action.

Third Stage

Placenta is separated and expelled. This is associated with small amount of blood loss. Contraction of uterus prevents blood loss.

The whole process of labor is akin to a moderately heavy muscular work and blood lactate concentration rises.

LACTATION

Milk is the natural food of the newborn in mammals and the process by which milk is secreted by the mammary gland is known as lactation.

Development of the Breast

Before puberty, the breasts are rudimentary. Breast development in girls begins at pubertal age. During each menstrual cycle the breasts grow to some extent till it reaches the adult size at about 19 years. During pregnancy its full development occurs and lactation occurs after the birth of the baby. During pregnancy few drops can be squeezed out in advanced pregnancy. Hormones that cause these changes are

1. Estrogens are needed for the pubertal growth of breasts and it mainly produces proliferation of the duct system. The action continues over the menstrual cycles and is greatly enhanced during pregnancy because of placental estrogens.
2. Progesterone induces proliferation of milk secreting acini and lobules. Thus estrogen and progesterone together are responsible for full development of mammary gland (Fig. 85.1).

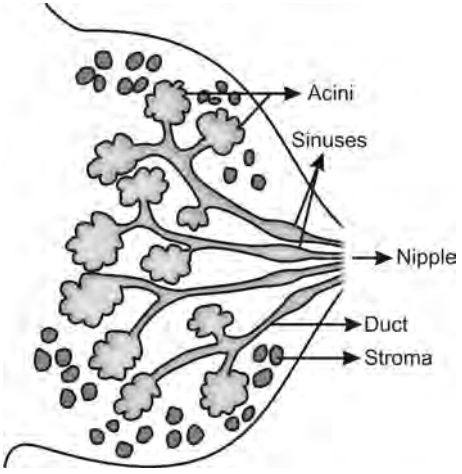


Fig. 85.1: The female breast

Formation of Milk

During lactation: Breasts are metabolically active. Formation of milk needs considerable energy. Hence, lactating mother needs 500 additional calories per day. Raw material to synthesis milk should be supplied from mothers diet.

Hormones Required for Formation of Milk

1. Prolactin is the hormone mainly responsible for milk production. It synthesizes milk by the acini.
2. Growth hormone, insulin, thyroxine and cortisol help milk secretion. They stimulate cellular metabolism in general.

Note: Synthesis of milk is known as Lactogenesis and Initiation of milk secretion is known as galactopoiesis.

Average quantity of milk produced in women is about 500 to 850 ml/day, but much higher quantities are also recorded. Frequent emptying of the breast is a powerful stimulus for further milk secretion.

There is no milk production during pregnancy but expulsion of uterine content (labor) somehow triggers milk secretion; and milk secretion starts within a day or two of delivery. Explanation is high level of estrogen coming from placenta keeps lactation inhibited. Thus, small amounts of estrogen are

required for the growth and function of mammary gland but high levels are inhibitory. This fact is used clinically and large does of estrogen are given for 3-7 days if the baby dies and lactation is suppressed.

Estrogen acts at two levels: (i) directly on mammary gland blocking the action of prolactin, and (ii) indirectly by suppressing prolactin release by anterior pituitary.

Milk Expulsion

Expulsion of milk from the mammary gland is effected by a reflex mechanism. When the baby suckles the nipple this reflex is set in known as suckling reflex (Fig. 85.2). The nipple and areola are richly supplied by nerve fibers. When baby suckles the nipple the afferent impulses pass to hypothalamus, which sends impulses to posterior pituitary to release oxytocin. This hormone causes powerful contraction of the myoepithelial cells surrounding the acini and expresses milk. This is often aided by positive pressure applied by the baby by making an airtight connection around the nipple and areola and then blowing its cheeks and milk is poured in the mouth of the baby. Simultaneously the secretion of prolactin from the anterior pituitary is increased to replace the milk.

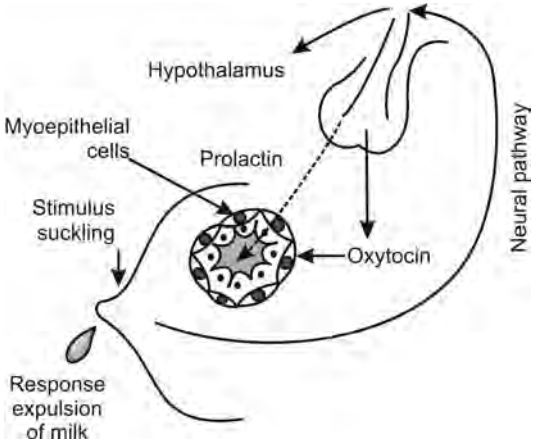


Fig. 85.2: The suckling reflex

This reflex is also elicited, by hearing the cry of the baby, by the mother or cuddling the baby, as these actions can also induce oxytocin release reflex.

This reflex can be inhibited by number of factors – e.g. emotional upset and secretion of adrenaline, which is secreted by fear, anger, etc.

During the Period of Lactation

Contraception

After the birth of the baby ovulation and menstruation do not generally start for months together if mother continues to feed the baby. (lactational amenorrhea). This is nature's way of spacing the births.

Cause: It is due to high prolactin level which keeps the FSH and LH suppressed.

Duration: Three months to 3 years and may not last for the full duration of breast-feeding in every case.

Involution of Uterus

Oxytocin released at every session of breastfeeding also acts on uterus and it returns to normal size in about 2 months.

Emotional Bonding

Mother child bonding takes place during breastfeeding and mother gets psychological satisfaction.

Breastfeeding is now being advocated all over the world because of following advantages

1. Breast milk is sterile.
2. It is easily available and convenient to give.
3. It is at right temperature.
4. It is inexpensive.
5. It is neither too concentrated nor too dilute.
6. It is easily digestible by the baby.
7. It rarely produces allergy in baby.
8. It's composition automatically changes according to the needs of the baby.

9. It gives immunity to baby as antibodies from mother are secreted in breast milk.

METHODS OF FAMILY PLANNING

Contraceptions are necessary to control world population.

In Females

Mechanical Devices

1. A rubber cap fitting closely around cervix prevents sperms from travelling up.
2. It can be used with spermicidal jelly to increase its efficacy.

Both are not very much acceptable and not 100 percent reliable.

Intrauterine Contraceptive Devices (IUCD)

Presence of intrauterine inert foreign body in uterus prevents pregnancy.

Mechanisms of action: Leukocytes, which accummulate in uterine fluid in response to foreign body make the endometrium unsuitable for implantation of fertilized ovum.

Variety of IUCDs are available – and are extensively used. They are:

i. Lippe's loop-simple plastic wire
ii. Copper T-copper bearing
iii. Progesterone T-progesterone bearing.

Advantages

1. Easy to insert
2. Long lasting contraception
3. Fertility is restored soon after the device is pulled out.

Safe Period Method

Also known as calendar or rhythm method. Using two physiological facts: (i) ovulation occurs 14 days prior to onset of next menstruation and (ii) ovum has a short life of 1-2 days; the coitus or intercourse is *avoided* 4-5 days before and 4-5 days after the day of ovulation (i.e. week in the middle of which ovulation is supposed to take place). All the other days of the cycle are safe.

Disadvantage: Method is not very reliable.

Advantage: Natural method.

Oral Pill

Oral contraceptive pill

They are used all over the world.

Principle

Estrogen and progesterone in combination given orally to woman for 21 days from the start of the cycle would prevent ovulation while preserving her menstrual bleeding. Powerful synthetic estrogen (like ethinyl oestradiol) and progestins (like norethisterone) allows very small amounts of the hormones to be effective after oral administration. Several types of pills are there:

1. *Estrogen only Pill* – not suitable because of danger of complications when estrogen is given alone over long periods. Danger of cancer is also there.
2. Progesterone only Pill – (minipill) taken continuously throughout the month. Ovulation occurs but conception does not take place. This action is perhaps related to changes in cervical mucus.
   Disadvantages Reliability uncertain-Irregular bleeding may occur.
3. *Sequential Estrogen + Progesterone Pill*— Estrogen for first 14 days and progesterone for next 7 days to simulate normal menstrual cycle. Withdrawal bleeding occurs after a few days.

Discredited—because of risk of endometrial cancer.

4. *Combined estrogen plus progesterone Pill:* Highly effective and most widely used today, estrogen content is very low in some brands.

Main action is on ovulation (= Prevention of ovulation) other actions also help in contraception.

Like

1. Disturbance of the delicate balance of estrogen-progesterone may make cervical mucus impermeable to sperms.
2. Endometrium unfavorable for implantation.
3. And may disturb the normal motility of Fallopian tubes.

Side effects: (Related mainly to estrogen)

1. Risk of thromboembolism
2. Hypertension
3. Diabetes
4. Obesity
5. Breast engorgement.

New non-hormonal contraceptive pill for woman – now marketed under the trade name 'Saheli'. It contains a synthetic compound 'centchroman' which seems to suppress corpus luteum function.

Injectables and Implants

These drug delivery systems are being tried which will release the hormones within the body, slowly, over a period of months.

Examples

1. Norplant – silastic capsules implanted under the skin.
2. Depo injections – (provera, Noristerat) They contain progestins only.

Surgical Methods

Tubectomy (= sterilization). Fallopian tubes are ligated and cut.

Note: Laparoscopic occlusion of the tubes is done with silicone rubber bands, which are slipped over a loop.

Methods of Family Planning (Contraception) in Males

Mechanical-condoms

Which prevent the seminal fluid from being deposited in the vagina. They are used since long and widely.

Advantages

(a) They are cheap, (b) Simple to use, (c) free from side effects, (d) highly reliable.

Surgical Method

Sterilization in the male is vasectomy. Vas deference is ligated and cut. So, that permanent contraception results.

New Methods in Males

Methods are being tried for inhibiting spermatogenesis but danger of testes losing its endocrine function and loss of libido are serious limitations.

Similarly drugs (antiandrogens) are being tried so as to make sperms non motile. But simultaneous loss of libido and secondary sex characters make it difficult for use.

New Methods in Females

1. Pregnancy vaccines are being developed, which is a specific antibody against B-subunit of hCG, to be taken in non-pregnant state, but booster doses will have to be taken repeatedly.
2. Pregnancy vaccines are being tried against zona pellucida proteins – they will destroy ovum. Again booster doses will be required.

CHAPTER

86

Male Reproductive System

The male reproductive organs are both inside and outside the pelvis (Fig. 86.1).
The male reproductive organs include:

1. The testes or testicles (pair).
2. The duct system, which is made up of epididymis and vas deferens.
3. The accessory glands, which include the seminal vesicles and prostrate gland.
4. The Penis.

Note: Singular – Testis and pleural – testes.

Testis: Each testis weights about 25 gm in the adult. Testes have two major functions:

1. Spermatogenesis
2. Production of male hormones.

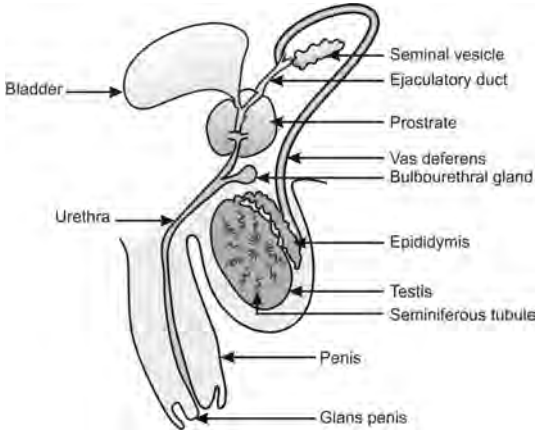


Fig. 86.1: Male reproductive system

Each testis: It is oval in shape (5 cm × 3 cm). It is divided into several compartments. In each compartment there are several seminiferous tubules (usually 2 or 3). Each seminiferous tubule is about 70 cm long and produces the spermatozoa or sperms. Between the seminiferous tubules there are masses of cells, called interstitial cells or Leydig cells (Fig. 86.2). These cells secrete male hormone testosterone.

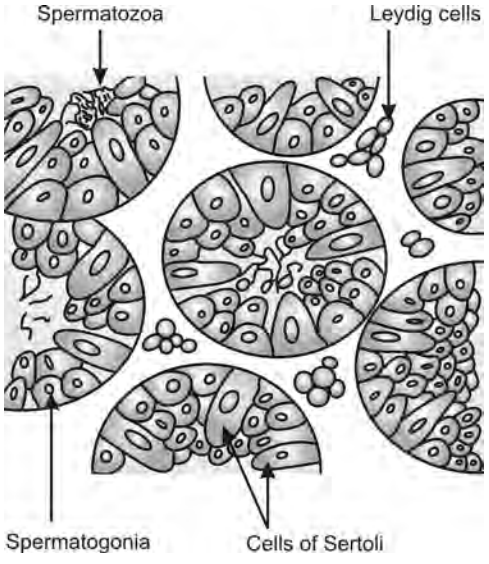


Fig. 86.2: Histology of testes

The basement membranes of the seminiferous tubules are lined by highly specialized type of cells called spermatogonia. The spermatozoa occupy the central part of the lumen. Between spermatogonia and spermatozoa lie several layers of cells.

Another kind of cells called cells of Sertoli are attached with the basement membrane. Precursors of spermatozoa are attached with the cells of Sertoli.

The seminiferous tubules open into a structure called rete testis, from this about a dozen efferent ducts arise which open in the epididymis. Epididymis is highly coiled structure. The spermatozoa are stored here.

Vas deferens is a long muscular tube which carries the spermatozoa forward, i.e. towards penis. It passes along side the testes and is connected with epididymis.

The epididymis and the testes hang in scrotum outside the pelvis. Scrotum is a bag of skin, which helps to regulate the temperature of testes, which needs to be cooler than the body temperature to produce sperms. The scrotum changes size to maintain right temperature.

1. When the body is cold – scrotum shrinks and becomes tighter to hold in body heat.
2. When it is warm – the scrotum becomes larger to get rid of extra heat.
3. These changes occur subconsciously.

THE ACCESSORY GLANDS

1. *Seminal vesicles:* Are sac like structures, one on either side, attached to the vas deferens at the side of the bladder. From each seminal vesicle, arises one duct, which joins the vas and the combined duct is called ejaculatory duct, which opens in prostatic part of urethra. There are thus 2 ejaculatory ducts.

   Seminal vesicles form seminal fluid which forms the bulk of the semen.

   Seminal fluid is rich in
   i. Citrate, ii. Fructose } are utilized as fuel by sperms in vagina
   iii. Hyaluronidase – can split mucopolysaccharide, so that the mucus plug within the cervical canal can be penetrated by the spermatozoa.
   iv. *Prostaglandin:* May cause contraction of uterus during coitus which exerts a suction like action on sperms and sperms are drawn inside the uterus.
2. *Prostrate gland*: It is a fibromusculoglandular structure. It produces some part of the semen, surrounds the ejaculatory ducts at the base of the urethra, just below the bladder. It provides fluid that lubricates the duct system and nourishes the sperms.
   i. *Urethra* is the channel that carries the semen to the outside of the body through the penis.

The penis is made up of two parts: (a) shaft and (b) glans. Shaft is the main part and glans is tip of penis. Sometimes called head. At the end of the glans there is a small opening through which the semen and urine exit the body through urethra.

The inside of the penis is made up of a spongy tissue that can expand and contract. Glans penis is covered by foreskin.

Male reproductive system also produces sex hormones (mainly testosterone by Leydig cells), which help a body to develop into a sexually mature man during *puberty.* When puberty begins usually between the ages 10 and 14 the pituitary gland secretes hormones that stimulate the testes to produce *testosterone.*

Testosterone brings about many physical changes. The stages of puberty generally follow a set sequence.

1. During the first stage of puberty the scrotum and testes grow larger.
2. Next the penis becomes larger and seminal vesicles and prostrate gland grow.
3. Hair begins to appear in the pubic area and later it grows on the face and under arms.
4. During this time male voice also deepens and becomes hoarse.
5. Boys also undergo a growth spurt during puberty as they reach their adult height and weight.

Once the male has reached puberty, he will produce millions of sperms everyday. The process of formation of sperms is known as spermatogenesis.

SPERMATOGENESIS

sperm formation begins during early adolescence and declines gradually in old age. A single ejaculate of 2 to 5 ml may contain 150 to 300 million sperms.

Spermatogenesis Involves Four Stages

1. Cell multiplication
2. Maturation
3. Transformation or spermiogenesis
4. Capacitation.

From spermatogonia to fully formed sperms takes about 74 days in man. Capacitation or ripening of sperms in epididymis requires about 2 weeks.

Cell Multiplication

Spermatogonia undergo rapid Proliferation. On division they separate into two types. Type A and Type B. Type A preserve the spermatogonial cell pool. Type B provide the next generation of germ cells, i.e. primary spermatocytes.

Maturation

Primay spermatocytes divide to produce two secondary spermatocytes. This division is meiotic. Number of chromosomes gets reduced from 46 to 23. Secondary spermatocyte is short lived and rapidly divide to produce two spermatids.

Transformation

Spermatids do not divide any more. They gradually transform themselves into spermatozoa by getting rid of extracytoplasm. The oval head contains haploid number of chromosomes and minimum of essential enzymes. A long tail develops (Fig. 86.3). The developing spermatids remain safely anchored in deep recesses on Sertoli cells. As soon as they are fully formed they are released (process is called spermiation).

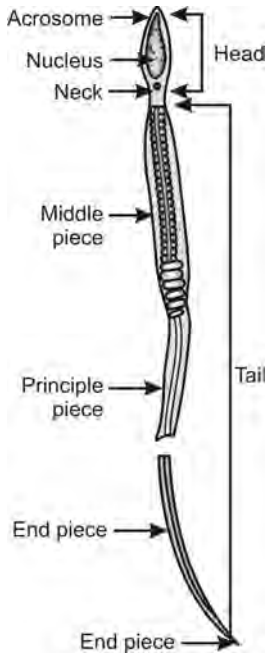


Fig. 86.3: Spermatozoon

Then they are carried through rete testis and efferent ducts to reach the head of the epididymis. Secretions of the tubule help this process.

Capacitation

The newly formed sperms look perfect in shape but are not able to fertilize the ovum. They need to ripen for some days. The process is called capacitation. Following facts are known about capacitation:

1. Capacitation occurs mainly in the epididymis but completed only in the female genital tract (uterus and fallopian tubes).
2. During capacitation visible changes in sperms are little but they are mainly molecular changes in the sperm membrane.

Substances of seminal plasma stick to sperm surface and keep them inhibited. Capacitation involves the removal of these substances.

SERTOLI CELLS

During the process of spermatogenesis the germ cells are supported by the tall columnar cells (Sertoli cells).

Sertoli cells: (a) remain fixed to the basement membrane, (b) they stop dividing before puberty, and (c) they are long-lived and robust.

Functions of Sertoli Cells

1. *Support:* They support a constantly moving population of proliferating cells.
2. *Nutrition:* They provide nutrition to the developing sperm cells.
3. Controlled release of clusters of fully formed sperms from time to time.
4. *Phagocytosis*: Removal of defective cells and cytoplasmic debris.
5. *Blood testis barrier* (BTB): Dyes and radioactive isotopes enter the seminiferous tubule up to a limited distance. The barrier is not at the peripheral boundary of tubule but somewhere inside. Sertoli cells have outgoing processes, which join each other to form a very tight barrier (This may be the site of BTB).
6. *Synthesis and secretion:* In sertoli cells following substances are formed:
   i. *Androgen Binding Protein (ABP)*: synthesized under stimulation of FSH.
   ii. *Inhibin:* Inhibitory hormone working as negative feedback signal from seminiferous tubule to anterior pituitary and cuts down FSH secretion.
   iii. *Estrogen:* Sertoli cells synthesize estrogen in small amounts.

FACTORS REGULATING SPERMATOGENESIS

Hormones

1. Gonadotropin releasing hormone of the hypothalamus (GnRH) stimulates anterior pituitary, which secretes FSH.
2. The FSH in turn stimulates the spermatogenesis. GnRH also stimulates LH.
3. LH (called ICSH = Interstitial cell stimulating hormone in male) secretion in turn, causes secretion of testosterone from the testis.

   Ultimately therefore, the combined presence of FSH and testosterone stimulates the spermatogenesis. This is the fundamental point.
4. High doses of estrogen damage seminiferous tubules and spermatogenesis.
5. Inhibin, produced by Sertoli cells, depresses FSH secretion by negative

feedback mechanism.

6. Prolactin, in some unknown way, potentiates LH in male.

   It appears that, as there is close proximity between the Leydig cells and the seminiferous tubules, the tubules and the precursor cells of spermatozoa are richly supplied by the testosterone produced by the Leydig cells. The process is akin to the paracrine hormonal effect. The testosterone from Leydig cells enters the seminiferous tubules by diffusion.

Temperature

Normal spermatogenesis requires a temperature about 3°C lower than the core body temperature.

Two mechanisms exist for cooling the testes:

1. The testes are located outside the abdomen in the scrotal sac, hanging loosely in the cool air.
2. The pampiniform plexus of veins surrounding the testicular artery forms a counter current cooling arrangement. The large network of veins covered by a thin corrugated skin of scrotum cools the blood returning to abdomen. This cool blood goes in pampiniform plexus and because it is surrounding the testicular artery, the arterial blood supplied to testes is precooled.

   Note:

   i. *Undescended testes (cryptorchidism):* 10 percent of infants may have one or both testes missing from scrotal sac at birth. If the testes, remains in abdomen for more than 5 years, it is permanently damaged and spermatogenesis never occurs even after bringing them down surgically.

   ii. *Varicocele*: Often the drainage of venous blood from plexus surrounding the testes becomes incompetent and big varicosity can be felt around them like a 'bag of worms'. Venous stasis abolishes the temperature gradient and spermatogenesis is markedly depressed.

   iii. *Occupational hazards*: Men who work near boilers, furnaces or open fires often develop low sperm counts and infertility. Therefore, tight fitting woolen or nylon underwear should be avoided, as it will have similar effect in warm climate.

Vitamins

1. *Vitamin E*: It is called antisterility vitamin. Proved in rat and some other mammals, but its need for spermatogenesis in man is doubtful.
2. *Vitamin A:* It is needed for normal health of all epithelial tissues (the germ cells have the same origin).
3. *Vitamin C and* B_{12}*:* Large fluctuations in its supply can disturb spermatogenesis.

ERECTION AND EJACULATION

When a male is sexually stimulated, the penis, which usually hangs limp, becomes hard. This is because of marked vasodilatation of the penile arteries, which fills with blood the corpus spongiosum and the two corpora cavernosa (present in penis). The penis becomes stiff and erect (*an erection*). The rigidity of erect penis makes it easier to insert into the female's vagina during sexual intercourse.

Vasodilatation of penile arteries is brought about by stimulation of parasympathetic nerves – the nervi erigentes. Simultaneously, the arteriovenous shunts are occluded so that

the blood filling the cavernosa is not rapidly drained away. Acetylcholine is the neurotransmitter involved. (Sympathetic impulses traveling via the hypogastric nerves open the arteriovenous shunts again and produce arterial constriction to abolish the erection – detumescence).

Center for reflexogenic erection is in sacral spinal cord S_2-S_4 and is activated by sensory impulses coming from genital area.

Center for psychogenic erection is in cerebrum and limbic system. Impulses travel down to integrating spinal center (T_{12}-L_3). This center also connects with parasympathetic outflow from sacral cord (S_2-S_4).

Ejaculation—Involves

1. *Emission (Under sympathetic control):* During emission sympathetic activation produces smooth muscle contraction in the epididymis, vas deferens, prostrate and seminal vesicle to drive the seminal fluid into the prostratic urethra.
2. Closure of bladder neck (internal sphincter) so that no retrograde or backward ejaculation occurs into the urinary bladder.
3. *Ejaculation proper:* It is brought about by rhythmic contraction of striated muscles of the pelvic floor, aided by muscles of abdomen and thighs as well. This squeezes the urethra forcefully and shoots the fluids out in spurts.

The chief muscles for ejaculation are bulbocavernosus and ischiocavernosus, which are innervated by pudendal nerves.

During ejaculation secretions from the different glands come out in a definite sequence – first the prostratic fluid and sperm rich fraction from the vas and epididymis, last of all the copious alkaline fluid from the seminal vesicles.

After ejaculation, the semen (or seminal fluid) sets into a gel like coagulum but liquefies again in 5 to 20 minutes. The sperms do not gain their full motility and fertilizing capacity unless the fluid liquefies into thin watery medium. The coagulating protein substrates come from seminal vesicles and liquefying enzymes are provided by the prostrate.

Thus, male sexual function is a complex process.

CHAPTER

87

Endocrine Function of Testis

The term androgen means any substance with a male hormone like activity. 95 percent of androgens are from testis.

HORMONES OF THE TESTIS

1. Testosterone.
2. Small amounts of dihydrotestosterone (DHT).
3. Small amounts of estrogen.
   Adrenal cortex of both males and females produces some androgens:
   i. Dihydroepiandrosterone (DHEA), and
   ii. Testosterone.

Testosterone: Mainly secreted by Leydig cells of the testis.

Chemistry (Fig. 87.1)

Testosterone is a 19-C steroid with an OH group present on the 17-C position.

Normal blood testosterone level for adult men is around 600 ng/dl (range 300 to 1000 ng/dl).

In blood almost 97 percent of androgens are carried in combination with proteins – largely with a beta-globulin called as testosterone binding globulin or sex hormones binding globulin (SHBG) – it serves as a carrier for both the male and female sex hormones.

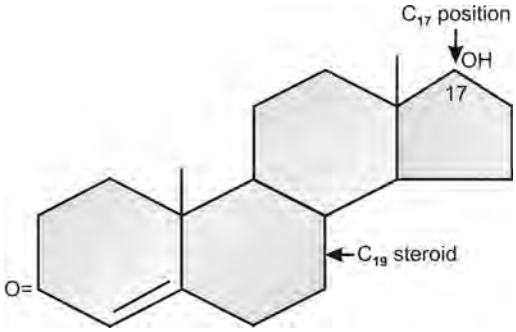


Fig. 87.1: Chemical structure of testosterone

Testosterone is *inactivated* by the liver, which converts it into 17-ketosteroids. This makes oral administration ineffective.

Testosterone gets converted in the tissues into two other important hormones. This creates a wide spectrum of physiological actions. One of them is dihydrotestosterone (DHT), which is twice as potent as testosterone and is produced in many tissues from testosterone. DHT – amplifies androgen action at the cellular level and has some unique actions for the development of male reproductive organs, which cannot be produced by testosterone.

Functions of Testosterone

Testosterone has wide range of actions:

1. On sex organs, secondary sex characters and sex behavior.
2. On metabolism (extragenital).

On Sex Organs

In the Fetus

1. Testosterone begins to be formed at around 7th week of intrauterine life. Prior to 7th week in every fetus both the Wolffian and müllerian ducts exist [From Wolffian ducts, epididymis, vas and seminal vesicles develop, whereas the müllerian duct gives rise to vagina, uterus and the fallopian tubes]. If the testosterone begins to appear, the müllerian duct system disappears and male accessory organs appear. *Absence of testosterone thus causes development of Müllerian duct into the accessory female sex organs and disappearance of the Wolffian duct.*

   Note that this means that if there is no sex hormone (i.e. in absence of both female as well as male sex hormone), the fetus develops female sex organs. This means that every fetus left to itself will become a female gender unless testosterone is present from the 7th week of intrauterine life.
2. Towards the later part of intrauterine life the exposure of the hypothalamus and some other parts of brain to testosterone in the male fetus is one of the fundamental causes of male sex behavior in adult life.

In Puberty

1. Testosterone causes growth of the external genitalia and accessory sex organs in the boys of pubertal age.
2. It also causes appearance of secondary sex characters in boys, i.e. (i) beard, moustache, hairs on the chest and abdomen, as well as the axillary and pubic hairs, (ii) Linear growth, (iii) muscular growth, (iv) deepening of voice, and (v) the male psyche.

In Adult

1. Testosterone is necessary for spermatogenesis and sperm motility.
2. The testosterone is necessary for the development and maintenance of secondary sex characters.
3. Testosterone causes maintenance of the accessory sex organs (i.e. epididymis, vas, seminal vesicles, prostrate and penis).

   Note accessory sex organs are those structures, which form the passage for the gamete).
4. Testosterone is responsible for development of sebaceous glands and acne vulgaris or pimples (which is commonly known as acne). During early youth, the androgen secretion is maximum and acne is seen very frequently in adolescents and young adults.
5. Testosterone maintains the aggressive, competitive, extrovert behavior of males.

On Metabolism

Testosterone is the most powerful *anabolic* substance in the body, which means it causes growth of muscles and bones resulting in positive nitrogen balance.

The muscles grow as well as they become strong. Because of these effects there is sudden spurt of growth in boys of pubertal age and there is linear growth. (=Height increases.)

The adult male therefore, in general is larger and more muscular than female. *To sum up Testosterone affects:*

1. *Protein metabolism* Increases protein synthesis, weight gain and positive nitrogen balance.

2. *Carbohydrate metabolism:* Mildly diabetogenic, promotes neoglucogenesis.
3. *Muscles:* Muscles mass increases – mainly skeletal muscles.
4. *Skeleton:* Increases linear growth and in higher concentration leads to fusion of epiphysis and stops further growth.
5. *Hematopoietic system:* Promotes erythropoiesis.
6. *CNS:* Maintains male aggressive behavior.
7. *Skin:* Promotes hair growth, particularly pubic, axillary and facial hair. Secretion of sebaceous glands increases and skin becomes oily.

Miscellaneous Effects

1. Androgen promotes the growth of hair on the body except on the top of the head. Large amounts of testosterone produce baldness.
2. Acne or pimples – surge of testosterone (or say androgens) at puberty activates sebaceous glands, skin becomes oily and blockage of gland ducts produces pimples. **Remedy**—would be simply wash face frequently.

TESTOSTERONE IN FEMALES

Normally some androgens are produced in females also by: (i) adrenal cortex, and (ii) ovary.

The actions of testosterone in women are: (i) It causes appearance of genital and axillary hairs, (ii) It causes acne vulgaris (pimples).

BIOASSAY OF ANDROGENS

Now even minute quantity can be measured by enzyme-linked immunosorbent assay (ELISA) or radioimmunoassay (RIA). They have replaced bioassay techniques.

Control of Testicular Function

Testis performs two functions: (i) spermatogenesis, and (ii) secretion of testosterone.

Anterior pituitary secretes two gonadotrpins to control two testicular functions (Fig. 87.2).

FSH regulates – spermatogenesis, and
LH regulates – secretion of testosterone.

LH acts on specific receptors on Leydig cells to produce two actions:

1. Differentiation of Leydig cells from precursors at puberty.
2. Stimulation of Leydig cells to produce testosterone.

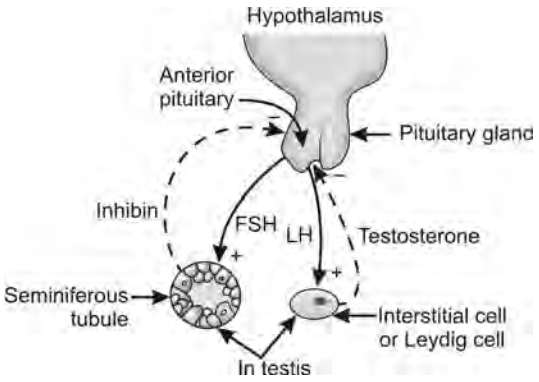


Fig. 87.2: Feedback control system for regulating—Spermatogenesis and testosterone secretion

i. Testosterone entering the bloodstream exerts a negative feedback on hypothalamus – pituitary complex to cut down LH production.

   FSH: Acts on Sertoli cells and stimulate production of ABP (Androgen binding protein) to ensure high testosterone concentration within seminiferous tubules. The action of FSH on spermatogenesis is indirect.

ii. A nonsteriodal water-soluble substance called *inhibin*, which is present in testis and seminal fluid, inhibits FSH production from anterior pituitary. Inhibin is a glycoprotein and apparently is produced by Sertoli cells.

Prolactin

*T*he third gonadotropin along with FSH and LH, is the hormone mainly for lactation, but it is present in human males also. Generally, it seems to supplement the action of LH. Excess prolactin reduces FSH and LH and can cause infertility and impotence.

SECTION XI: SPECIAL SENSES

CHAPTER 88

Vision

There are few organs in the body, which collect information of special significance for survival from external environment and therefore are called organs of special senses. Special senses include vision, hearing, taste and smell.

VISION

Anatomical Considerations

The adult human eyeball is a nearly spherical structure, 2.5 cm in diameter. Only anterior segment of eye, the cornea is transparent. The remainder is opaque. The globe of the eye contains essentially – 3 coats enclosing transparent refractive media (Fig. 88.1).

1. Outermost protective coat consists of sclera and cornea. Cornea is transparent.
2. Middle coat: Mainly vascular consist of (i) Choroid (ii) Ciliary body, (iii) Iris.
3. Innermost layer retina, containing photoreceptors rods and cones responsible for vision.

The eye contains crystalline lens, which is attached to ciliary body by means of suspensory ligaments or zonule. It has broad area of attachment to both: (a) lens, and (b) ciliary body.

Sclera

Consist of dense connective tissue white in color; except in central anterior portion of eye where it forms transparent, cornea.

Choroid

It is a layer of vascular tissue, contains numerous blood vessels. It nourishes the internal structures of eye. It is thin over posterior 2/3 of eyeball, but thickens to form ciliary body anteriority.

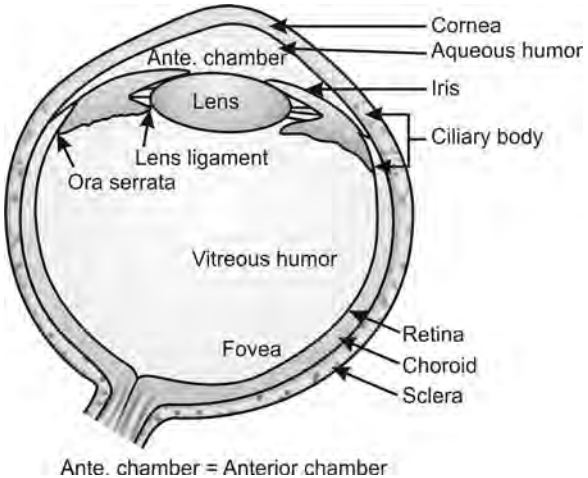


Fig. 88.1: Horizontal section of the eye

Ciliary Body

1. In sagittal section, ciliary body is triangular 6 mm wide.
2. Junction of ciliary body with retina is known as ora serrata.
3. The ciliary body contains circular muscle fibers and longitudinal muscle fibers.
4. Ciliary body is a circular structure, which gives rise to ciliary processes, number about 70-80, extending inward and form corona ciliaris. It is secretory in nature and forms aqueous humor, which fills the space between lens and the cornea. Aqueous humor is a clear liquid and is produced by: (i) diffusion, and (ii) active transport.

Iris

1. In front of the lens is the pigmented and opaque iris (colored portion in the eye by which the person becomes blue eyed or brown eyed, etc.).
2. Iris surrounds the central aperture – pupil.
3. Iris contains circular and radial muscle fibers. Contraction of circular muscle fibers constricts pupil and contraction of radial muscle fibers dilates the pupil.

Retina

Retina lines the inner surface of eyeball. It extends anteriorly almost to the ciliary body. It is organized in 10 layers of which the light sensitive receptors rods and cones form the outermost layer. It contains four other types of neurons: (i) bipolar cells, (ii) ganglion cells, (iii) horizontal cells, and (iv) amacrine cells (Fig. 88.2).

Rods and cones, which are next to the choroid, synapse with bipolar cells and bipolar cells synapse with ganglion cells. The axons of the ganglion cells converge and leave the eye as optic nerve.

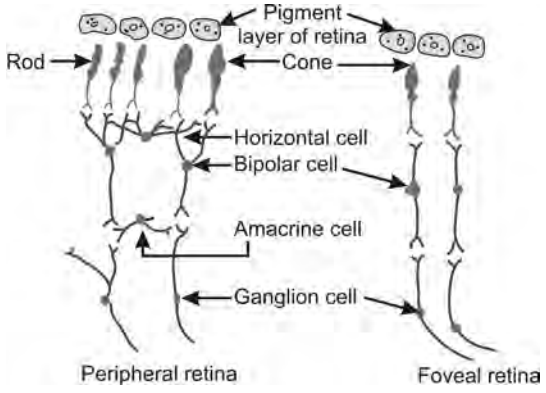


Fig. 88.2: Retina

Horizontal cells connect receptor cell to each other in the outer plexiform layer. The ganglion cells are connected to each other by Amacrine cells in inner plexiform layer. In some instances amacrine cells may be inserted between bipolar cells and ganglion cells. Amacrine cells have no axons and their processes make both pre- and postsynaptic connection with neighboring neural elements. There is considerable overall convergence of receptors on bipolar cells and of bipolar cells on ganglion cells.

Since, the receptor layer of the retina is opposed to the choroid, light rays must pass through the ganglion cells and bipolar cells to reach rods and cones.

The pigmented layer of choroid next to retina absorbs light rays. This prevents reflection of rays back through retina. Such reflection would produce blurring of vision.

The neural elements of the retina are bound together by glial cells called Muller's cells.

The optic nerve leaves the eye and retinal blood vessels enter at a point 3-4 mm medial to end slightly above the posterior pole of the eye. This region is visible through ophthalmoscope as the *optic disk*. There are no visual receptors overlying the disk and

consequently this spot is blind (the blind spot). At the posterior pole of the eye, there is yellowish-pigmented spot—*Macula densa*. This marks the location of *fovea centralis.*

Fovea Centralis

(a) Thinned out, (b) Rod free portion of retina, (c) Where cones are densely packed, (d) There are very few cells and no blood vessels overlying the receptors, (e) The fovea is highly developed in humans, (f) It is the point where visual acuity is greatest, (g) When vision is fixed on a particular object the eyes are normally moved so that light rays coming from the object fall on the fovea.

The arteries, arterioles and veins in superficial layers of the retina near its vitreous surface can be seen through ophthalmoscope (Fig. 88.3). It is of great value in the diagnosis and evaluation of diabetes mellitus, hypertension and other diseases affecting the blood vessels.

Nourishment of Retina

The retinal vessels supply the bipolar cells and ganglion cells, but the receptors are nourished for the most part by the capillary plexus in the choroid. Therefore, retinal detachment damages the receptor cells.

PATH OF LIGHT RAY

The light rays falling on the eye pass through cornea → pupil → aqueous humor → lens → vitreous humor → blood vessels, nerve fibers and cell bodies to reach receptor cells – rods and cones.

The rods and cones are first order neurons and electrical impulses from these neurons proceed in reverse direction of rays of light to the bipolar cells (second order neurons) and then from there to ganglion cells (3rd order neurons) and finally through optic nerve.

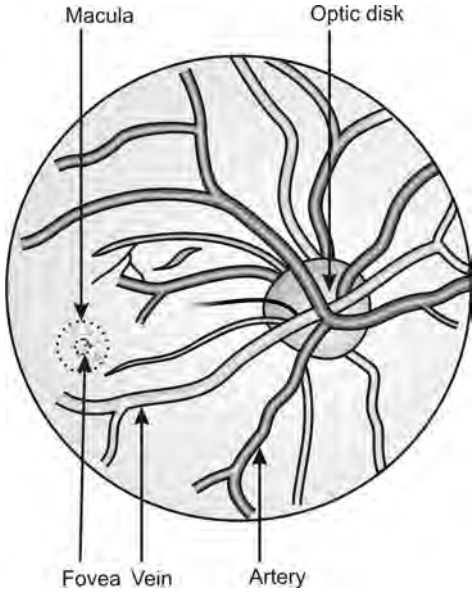


Fig. 88.3: Retina seen through ophthalmoscope

RECEPTORS (FIG. 88.4)

Each rod and cones are divided into:

1. Outer segment
2. Inner segment
3. Nuclear segment
4. Synaptic zone

Rods are named for the thin rod like appearance of their outer segment.

Cones generally have thick inner segments and conical outer segment although their morphology varies from place to place in the retina.

The Outer Segments

Are modified cilia made up of regular shelves of flattened saccules or disks composed of membrane. These disks and saccules contain the photosensitive compounds that react to light, initiating action potentials in the visual pathways.

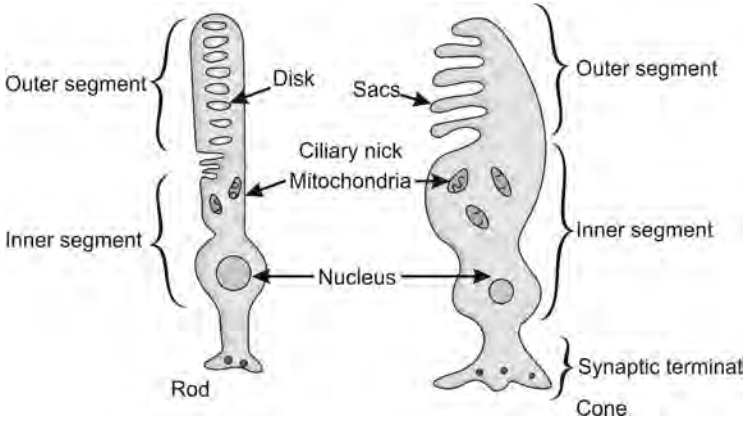


Fig. 88.4: Rod and cone

In cones, the saccules once formed in the outer segments by infolding of the cell membrane, but in rods, the disks are separated from the cell membrane.

The Inner Segments

Are rich in mitochondria. They are particularly important for providing energy for function of photoreceptors.

The Synaptic Zone

It is the portion of the rod and cone that connects with the subsequent neuronal cell—horizontal and bipolar cell.

Rod outer segments are being constantly renewed by formation of new disks at the inner edge of the segment and phagocytosis of the old disks from the outer tip by cells of the pigment epithelium.

Cone renewal is a more diffuse process and appears to occur at multiple sites in the outer segments.

Fovea

The fovea contains no rods, and each foveal cone has a single midget bipolar cell connecting it to a single ganglion cell, so that each foveal cone is connected to a single fiber in the optic nerve (See Fig. 88.2).

In other portions of the retina, rods predominate and there is a good deal of convergence. Flat bipolar cells make contact with several cones and rod bipolar cells make contact with several rods.

There are approximately 6 million cones and 120 million rods in each human eye but only 1.2 million nerve fibers in each optic nerve, the overall convergence of receptors through bipolar cells on ganglion cells is about 105:1.

The rods are extremely sensitive to light and are the receptors for night vision (*scotopic vision*). The scotopic visual apparatus is not capable of: (a) resolving the details and boundaries of objects or (b) determining their color.

This cones have: (1) much higher threshold, (2) much greater acuity and responsible for (a) vision in bright light (*photopic vision*) and (b) for color vision.

There are thus two kinds of inputs to the CNS from the eye:

1. Input from the rods and
2. Input from the cones

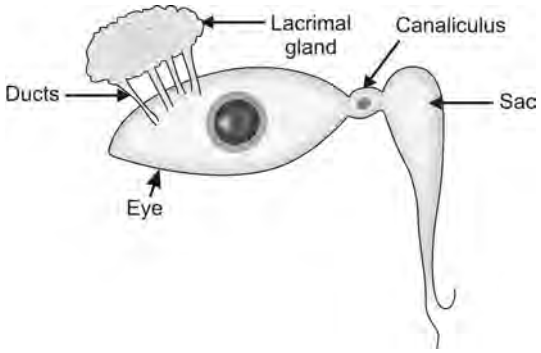


Fig. 88.5: The lacrimal apparatus

Existence of these 2 kinds of inputs, each working maximally under the different conditions of illumination, is called duplicity theory.

Protection:

1. The eyeball is protected from injury by the bony walls of the orbit.
2. The cornea is moistened and kept clear by tears that course from the lacrimal glands (Fig. 88.5). It lies in the upper and outer corner of the orbit. The tears course across the surface of the eye to empty via lacrimal duct into the nose. Blinking helps to keep the cornea moist.

Lacrimal gland is lined by cylindrical cells and a layer of flat epithelial cells, which form the basement membrane. These basal cells have contractile properties and may squeeze the fluid out of the cells into the ducts (usually twelve in number).

The gland has rich blood supply.

The nerve supply is from: (a) ophthalmic division of trigeminal, (b) sympathetic fibers from carotid plexus, (c) fibers from sphenopalatine ganglion, and (d) fibers from facial nerve.

TEARS

1. Can be produced reflexly by psychic stimulation, which is restricted to human beings and appear only when infant is 4 to 5 months old.

   Infants below this age cry lustily but shed no tears.
2. Tears can also be produced reflexly by sneezing coughing and vomiting.

Tears pass over the surface of the eyeball as a capillary layer by the action of lids. This collects in the lacrimal lake at the inner canthus and is drained through the ducts into the nose.

Tears contain proteins, urea, sugar, sodium chloride and an enzyme lysozyme, which destroys many harmful organisms.

OPTICAL SYSTEM OF THE EYE

The optical system of the eye is composed of:

(i) Those structures through which light has to pass and (ii) which together focus on image of the external object on the retina.

The *light has to pass through:* (i) The cornea, (ii) The aqueous humor, (iii) The lens, and (iv) The vitreous humor.

The Eye and Light Refraction

The light rays bend (get refracted) when they pass from one medium into a medium of different density, except when it strikes perpendicular to the interface.

Refraction by the eye is the result of bending light at several surfaces, which have different refractory indices (Fig. 88.6).

1. The refraction first takes place due to the cornea. Cornea together with aqueous humor behind it behaves like a plano convex lens (refractive index 1.33).
2. After passing through the cornea rays of light pass through lens (average refractive index 1.40).
3. After passing through the lens the light pass through vitreous humor (refractive index 1.34).

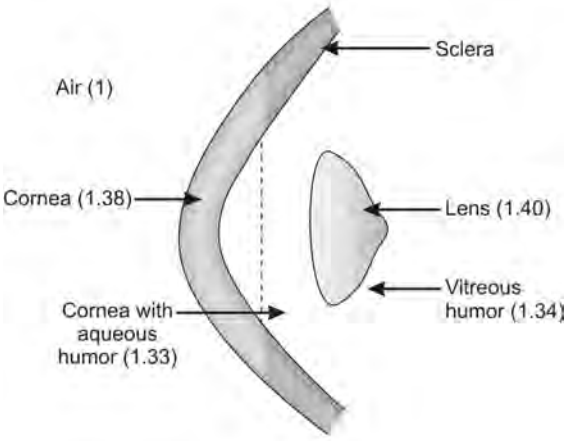


Fig. 88.6: The refractive indices of different media

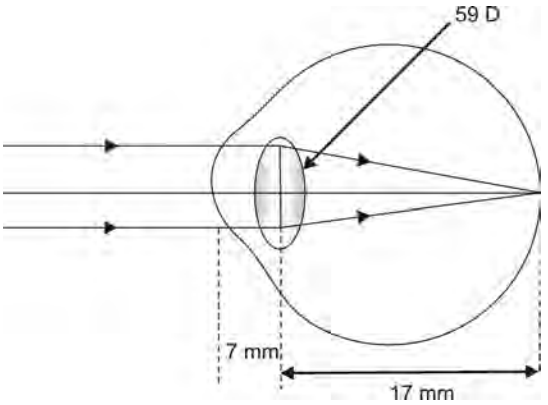


Fig. 88.7: The reduced eye

The greatest amount of refraction of light takes place at the corneal surface. This is because the difference in the density between air and cornea is far greater, than between any other adjacent media for example, between aqueous humor and lens.

Lens contributes less to the refraction of light but variation in lens curvatures, such as occurring with accommodation are of great importance in vision.

REDUCED EYE

The eye, with its multiple surfaces of refraction is too complex for construction of an image. It has been seen that if we consider the eye to have only a single convex lens of 59 D (Diopters) with its optical center (called nodal point) 17 mm in front of retina, we get a situation, which is almost identical with the normal eye. Such a theoretical eye is called reduced eye. The principle plane of the reduced eye is 7 mm behind the anterior surface of the cornea. In such an eye the image can be easily constructed using the basic principles of optics (Fig. 88.7).

The normal optical system is such that light rays from a distant object (more than 6 meters away) are approximately parallel and will therefore be brought to focus on the retina.

Aqueous Humor

1. It is contained in the anterior chamber and posterior chamber.
   i. Anterior chamber is the space between cornea and anterior surface of lens.
   ii. Posterior chamber is the name given to a small space between lens and iris.
2. It is thin watery fluid.
3. Contains crystalloids in concentration similar to plasma.
4. Contains great deal of hyluronic acid, which is kept in depolymerized state by hyaluronidase present in ciliary body. Therefore, viscosity of aqueous humor is low.
5. It is formed continuously in posterior chamber by the ciliary body by diffusion and active transport.
6. It passes through pupil into anterior chamber and then through angle between

iris and cornea into canal of Schlemm, which drains into ocular vein. Thus, it is removed continuously.

7. Function - provides nutrition to cornea and lens.
8. Aqueous humor is principle determinant of intraocular pressure. The normal IOP in the eyeball is 15-20 mm Hg. It depends on:
   a. Rate of formation of aqueous humor,
   b. Ease with which it is drained away.

Normal IOP is required for maintaining the spherical shape of the eyeball. But if it exceeds the normal limits it exerts more pressure on the retina and damages photoreceptors. Abnormal increase in IOP is known as *Glaucoma.*

Vitreous Humor

It is transparent jelly like substance occupying the portion of the eyeball lying behind the lens and ciliary processes.

Its chemical composition is similar to aqueous humor but it contains two additional proteins mucoid and vitrein. Glucose is less probably because of rapid utilization of the retina.

CHAPTER

89

Accommodation and Optical Defects

ACCOMMODATION

Normal resting eye is adjusted to parallel rays and normally the optical system is such that the image of distant objects are focused on the retina because the rays are parallel (distant means more than 6 meters away).

The images of the near objects will be focused behind the retina unless the diopteric power of the lens is increased. The rays from the near objects are divergent. In mammals the problem is solved by increasing the curvature of the lens.

The ability of the eye to focus objects at various distances on retina is due to a mechanism, which allows change in the curvature of anterior surface of lens. This mechanism is known as *accommodation.*

As the object is moved closer and closer to the eye, at certain point, the eye can no longer increase its diopteric power and the object becomes indistinct.

1. *Near point:* The nearest point when object is seen clearly with maximum accommodation is near point.
2. *Far point:* Position of object is such that its image is formed on retina of completely relaxed eye.

In normal emmetropic (optically normal) eye the far point is at infinity.

Near point varies according to age. For example:

- At 10 years – 9 cm
- At 60 years – 83 cm.

Cause

Lens becomes hard which means elasticity of lens is decreased and with accommodation lens curvatures cannot be increased more.

At 40-45 years, The near point recedes far enough so that close work becomes difficult—the condition is known as *Presbyopia.* It is corrected by prescribing convex lens.

3. *Amplitude of accommodation:* The difference between refractory powers of eye when completely relaxed and when accommodated maximally is amplitude of accommodation.

Mechanism of Accommodation

Lens

1. The crystalline lens is transparent, elastic and biconvex. The anterior curvature of the lens has a radius of 11 mm while that of posterior surface is 6 mm. The focal length is 44 mm. The power of lens is expressed in diopters. A diopter is the reciprocal of focal

length expressed in meters. Lens has a refractory power of 23D.
2. Lens is enclosed in a capsule, which is also elastic.
3. The suspensory ligaments (zonule) are attached to the periphery of the elastic capsule and the ciliary body (Fig. 89.1). Therefore, the traction on the suspensory ligaments and the capsule can be altered by movements of the ciliary processes.
4. The lens is composed of concentrically arranged layers. The center is optically more dense than the periphery resulting in nucleus of high refractory power and outer cortex of low refractory power.
5. Lens is a living structure with its own metabolism. It contains lens fibers, which are modified cells.
6. The transparency of lens may be lost leading to a condition called cataract.
7. Lens has no blood vessels but satisfies its requirements from aqueous humor. The refractory power of the crystalline lens of the eye can be increased by 29D.

The basic mechanism of accommodation is (Fig. 89.2):

1. *At rest:* The lens is held under tension by lens ligaments and the shape of the lens is moderately convex, because lens capsule is elastic and lens substance is malleable.
2. When near object is seen, the ciliary muscles contract, (a) The ligament of the lens becomes lax, (b) at once the lens bulges and increase its curvature to increase its diopteric power. During accommodation mainly the anterior surface of the lens bulges.

The radius of curvature of anterior surface of lens is 11 mm at rest. It becomes 6 to 7 mm when eye is accommodating maximally for near vision. The posterior surface of lens hardly alters its radius of curvature, which is 6 mm at rest and 5.5 mm in full accommodation.

This can be proved by the experiment of Phakoscopy.

Bulging forward of the anterior lens surface is due to the relaxation of tension of lens capsule, which permits the elastic lens to assume more spherical form.

In order to appreciate these changes it is necessary to understand some of the details of the anatomy of ciliary region:

1. The crystalline lens is surrounded by a elastic capsule, which in turn is surrounded by a zonule (suspensory ligament). Zonule is composed of delicate connective tissue fibers (Fig. 89.1).
2. The suspensory ligament splits medially into anterior and posterior laminae, which enfold the capsule and blend with it near the equator.
3. Laterally the two laminae fuse and zonule is attached to the inner surface of the ciliary body.

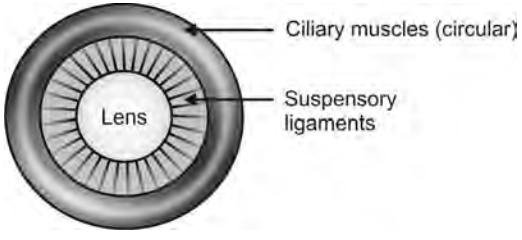


Fig. 89.1: Arrangement of lens, suspensory ligaments and ciliary muscle (circular)

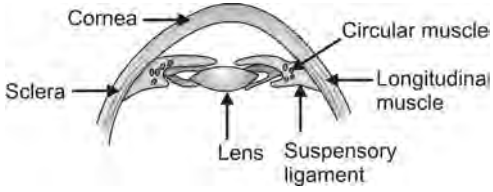


Fig. 89.2: Mechanism of accommodation

4. Ciliary body is a circular zone of tissue which extends forwards from ora serrata towards the circumference of lens.

Ciliary body contains: (i) Smooth ciliary muscle and (ii) Ciliary processes.

Ciliary smooth muscles consist of: (a) Radial fibers, which originate near the corneoscleral junction and are inserted near the posterior margin of ciliary body, (b) Circular or sphincteric muscle fibers, which lie more centrally.

Contractions of both sets of ciliary muscle cause relaxation of lens ligaments. Circular muscles produce sphincter like action and longitudinal muscles (or radial) bring the whole ciliary body forward and inward.

The lens assumes more spherical shape like that of balloon.

Accommodation Reflex or Near Response

In addition to accommodation, the visual axis converge and pupil constricts when an individual looks at a near object.

This is three-part response:

1. Accommodation, i.e. change in diopteric power of lens (contraction of ciliary muscles).
2. Pupillary constriction – to shut off more peripheral parts of lens. This allows light rays from near object to fall on only center of lens in which accommodative changes are most pronounced (contraction of sphincter pupillae).
3. Convergence of the eyeball (contraction of medial recti). This three part response is known as accommodation reflex or near response.

PUPIL

1. It is central aperture in iris. Its diameter can be varied from 2 to 8 mm.
2. Normal size 3-4 mm. It varies with age. In childhood and adolescent age pupils are of maximum size. In advanced age it is constricted. Pupil in women is larger than men.
3. If two pupils are unequal in size—it is known on anisocoria.

Iris contains two muscles: (a) dilator pupillae, (b) constrictor pupillae or sphincter pupillae

Dilator pupillae: has radial fibers, which extend from ciliary border of circular muscles to the root of iris. Contraction of dilator pupillae cause increase in diameter of pupil.

Constrtictor pupillae: Contains circular muscle fibers, which encircle pupil. Their contraction reduces the diameter of the pupil.

These two muscles together with muscles of ciliary body form intrinsic muscles of the eye.

Sphincter pupillae: It is innervated by parasympathetic nerve fibers.

Dilator pupillae: It is innervated by sympathetic nerve fibers.

Other Papillary Reflexes

1. When light is directed into one eye the pupil constricts. This is *pupillary light reflex.*
2. Pupil of the other eye also constricts. This is known as consensual light reflex. Pupillary light reflex is protective.

PATH OF LIGHT REFLEX

1. The optic nerve fibers that carry the impulses initiating these responses leave the optic nerves near the lateral geniculate bodies on each side; they enter the midbrain and terminate in *pretectal nucleus.*
2. From this nucleus the second order neurons project to the ipsilateral *Edinger-Westpal*

nucleus and the contralateral Edinger-Westpal nucleus.
3. Third order neurons pass from this nucleus to the *ciliary ganglion* in the oculomotor nerve.
4. Fourth order neuron pass from this ganglion to the ciliary body—to sphincter pupillae.

This pathway is dorsal to the pathway of near response; therefore the light response is sometimes lost while the response to accommodation remains intact—*Argyll Robinson pupil.*

One cause of this abnormality is CNS syphilis.

Function of Pupil

1. Pupil adjusts the light entering in the eye and falling on retina.
2. It controls the depth of focus of optical system of eye. Smaller pupil increases the depth of focus.
3. By cutting off peripheral rays it helps to avoid errors of refraction and thus provides better-defined images.

Retinal Image

In the eye, light is actually refracted at the anterior surface of the cornea and at the anterior and posterior surfaces of the lens. In reduced eye the optical center is 17 mm in front of the retina, which lies at the junction of middle and posterior third of the lens. This is the point through which the light rays from an eye pass without refraction. All other rays entering the pupil from each point on the object are refracted and brought to a focus on the retina.

i. If the height of the object AB and the distance from the eye of the observer are known the height of the retinal image can be calculated because Δ AnB and Δ anb are similar triangles.

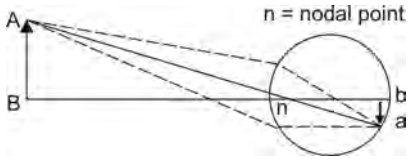


Fig. 89.3: Image formation (reduced eye)

2. Angle AnB is the *visual angle* subtended by the object AB (Fig. 89.3).
3. It should be noted that retinal image is inverted. The connections of the retinal receptors are such that from birth any inverted image on the retina is viewed right side up and projected to the visual field. This perception is present in infants and is innate.

OPTICAL DEFECTS AND ERRORS OF REFRACTION

Common defects in the image forming mechanism (optical defects) and Errors of Refraction.

The eye is affected by such errors of refraction as:

1. Chromatic aberration
2. Spherical aberration

} Present in normal eye also and minimized by papillary mechanism.

Chromatic Aberration

1. It is manifestation of different refraction suffered by colors comprising the white light. These different colors comprising the white light depending on their wavelengths are brought to focus at different distances behind the lens.
2. The red light with longer wavelength is refracted the least and blue light most. If the eye looks at bright light the middle wavelengths are focused. The blue rays meet in front of retina and red rays behind and neither is brought to a point focus (Fig. 89.4).

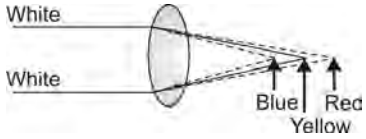


Fig. 89.4: Chromatic aberration

3. Greater the aperture of pupil, greater are the errors of chromatic aberration because those rays passing near the center of the lens are proportionately less affected than the rays passing through the periphery of lens.

Spherical Aberration

1. Crystalline lens of the eye is not nearly so regularly formed as the lenses made by good optician.
2. The light rays passing through peripheral edges of the eye lens are not brought to really sharp focus with other light rays.
3. In the crystalline lens the central part possesses greater refractory power than the peripheral part. This defect is known as spherical aberration.
4. Increasing the papillary aperture progressively decreases the sharpness of the focus. This explains why the visual acuity is decreased at low illuminations because the pupil gets dilated. In bright light pupil is small.

Errors of Refraction

The optically normal condition of the eye is known as *Emmetropia* in which the parallel rays are focused on the retina in relaxed state (without the use of accommodation).

When the refractive state of the eye differs from that of emmetropia it is known as ametropia.

Ametropia Types:

1. Myopia
2. Hypermetropia
3. Astigmatism
4. Presbyopia

Myopia (Near Sightedness)

1. In myopia, the anteroposterior diameter of the eyeball is too long. Therefore, incident parallel rays are brought to focus in front of the retina.

   It can also be caused by more than normal curvature of the refracting surface.
2. Myopia is said to be genetic in origin.
3. There is no mechanism to decrease refractive power of the eye; therefore he cannot see the distant object.
4. As the object comes nearer to his eye it finally comes near enough that its image will be focused on retina with relaxed ciliary muscle, because the incident rays to cornea become divergent. This becomes his far point.
5. Then when the objects come still closer to the eye, the person can use his power of accommodation. Thus, the person can only see things closer to his eyes. In other words, he becomes short sighted.
6. The far point in emetrope is at infinity. The far point in myope is at finite distance and may be only few inches from the eye in severe myopia.
7. Range of accommodation in myope is much less than normal because the far point and near point are closely approximated (Fig. 89.5).
8. Can be corrected by biconcave glasses, which cause divergence of the incident parallel rays (Fig. 89.6).
9. As the myope ages, his near point retreats and he may not need glasses to read fine print because his near point in youth is so closer to corneal surface that even in old

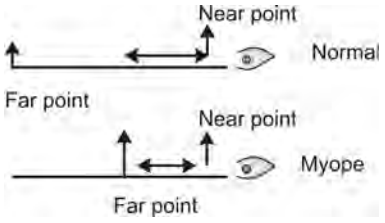


Fig. 89.5: Short sightedness in myope **(↔)** Indicates range of accommodation

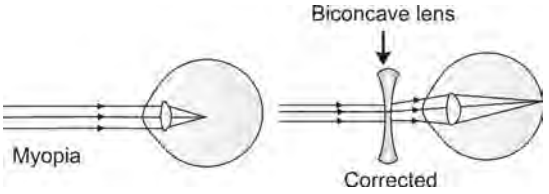


Fig. 89.6: Myopia

age his near point may be at a distance which is normal for young subject.

Hypermetropia

1. In some individuals the eyeball is shorter than normal and the parallel rays of light are brought to focus behind the retina. This abnormality is called *hypermetropia* or *farsightedness*. It can also be caused due to less than normal curvature of refracting surface.
2. Mechanism is present in the eye, which can increase refractory power. Therefore, a hypermetrope will use his accommodation even for a distant object. Thus, for all distances of objects, he has to use his accommodation (Fig. 89.7).
3. If he uses small part of accommodation to visualize object at distance, he has sufficient accommodation power left for near vision. But constant use is very tiring and he gets blurring of vision and headache.

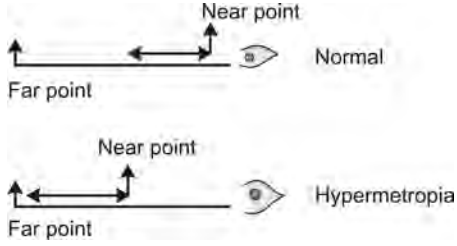


Fig. 89.7: Far sightedness in hypermetropia (↔) Indicates range of accommodation

4. Because he has to use accommodation for distant objects his near point recedes. His near point is more distant than emetrope. He becomes far sighted. He cannot see closer object properly.
5. In hypermetropia, there is hypertrophy of ciliary muscles because of constant use.
6. This defect can be corrected by using glasses with biconvex lenses, which increases convergence of light ray incident upon cornea (Fig. 89.8).

Astigmatism: As the name suggest this is an error of vision in which the light rays are not brought to a point focus on the retina.

Common cause of the condition is that the curvature of the cornea is not uniform and the focus for horizontal rays differs from that for vertical rays. Hence, astigmatic subject looking at a piece of graph paper may focus on the vertical lines and may fail to focus the horizontal ones and *vice versa*. The defect most commonly is due to difference in the horizontal and vertical curvatures of the

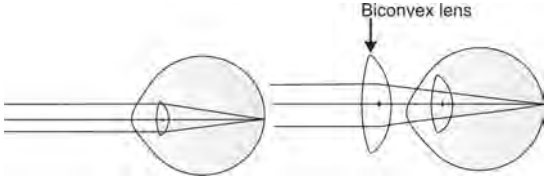


Fig. 89.8: Hypermetropia

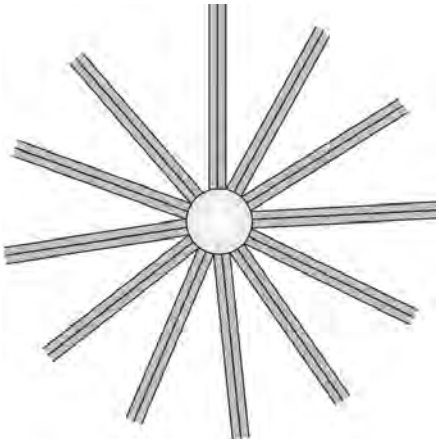


Fig. 89.9: Chart for determining axis of astigmatism

cornea. Occasionally, the same abnormality affects the lens. If the curvature is greater along the vertical meridian astigmatism is said to be 'with the rule'. If the horizontal curvature is greater the astigmatism is said to be 'against the rule'. Many a times the defective curvature may not be exactly in horizontal or vertical axis.

Several methods are there for determining the abnormal axis. A chart composed of parallel black bars for determining axis of astigmatism can be used (Fig. 89.9).

In the chart some of the parallel bars are vertical, some horizontal and some at various angles to the vertical and horizontal axis.

In astigmatic one of these bars will be out of focus or appear hazy. This will be the axis of astigmatism.

Presbyopia

Presbyopia is the normal recession of the near point due to age and is due to loss of elasticity of lens, the eye cannot accommodate for the near object. His near point recedes. By about 40 to 45 years the person develops presbyopia. It can be corrected by biconvex glasses.

Contact Lenses

1. They are made up of either glass or plastic and fit snugly on anterior surface of cornea. They are held in place by thin layer of tears.

   The refraction now will take place at the anterior surface of contact lens instead of anterior surface of cornea.
2. Contact lens is important in odd shaped cornea. In this there is severe abnormality in vision and no lens can correct it except contact lens.

Other advantages: (a) This lens gives broader field of vision, (b) Lens kept few cm in front of the eye affect the size of object and therefore the size of image, but contact lenses has little effect over the size of the object and image when person sees through this lens, (c) Cosmetic advantage.

CHAPTER

90

Physiology of Retina

Action of light on photosensitive compounds in the rods and cones generate action potential. When light is absorbed by these substances their structure changes, and this change triggers a sequence of events that initiates neural activity.

PHOTOCHEMISTRY OF RETINA

Rods and cones contain pigment molecules in the outer segment. The pigment in the rod is rhodopsin, and cone pigments are of three types and accordingly there are three different types of cones.

On exposure to light these photopigments decomposes. This change is responsible for initiating the neural activity.

Rhodopsin and three cone pigments differ primarily in the wavelength of light to which they are maximally sensitive.

The photosensitive compounds in two eyes of humans and most other mammals are made up of a protein called an *opsin* and *retinene* (the aldehyde of vitamin A). Since retinene is aldehyde, they are also called as *retinals.* Vitamin A itself is alcohol and therefore called *retinol.* Retinene$_1$ is present in humans and retinene$_2$ in most animal species.

Rhodopsin

The photosensitive pigment in rods in called as rhodopsin or visual purple. It's opsin is called scotopsin. Rhodopsin has peak sensitivity to light at wavelength of 505 nm.

Cone Pigments

There are three different kinds of cones in primates. These receptors subserve color vision and respond maximally to light at wavelength of 440, 535 and 565 nm.

Each contains retinene$_1$ and an opsin. This opsin resembles rhodopsin and spans the cone membrane 7 times but has a characteristic structure in each type of cone.

There are three types of cones and three types of cone pigments.

A cone pigment called iodopsin has been isolated. It is most sensitive to red light. It is made up of retinene$_1$ and photopsin (a protein different from scotopsin).

Effect of Light on Photoreceptors

1. In dark retinene$_1$ in rhodopsin is 11 cis retinene$_1$.
2. When light energy is absorbed by rhodopsin it immediately begins to

decompose which leads to instantaneous change of the cis form of retinene into all transform.

3. All trans retinene has same chemical structure as cis form, but different physical structure. That means all trans retinene is an isomer of cis form.

   The cis form is a curvical molecule, but trans form is a straight molecule. Therefore, reactive sites of all trans retinene no longer fit with that of reactive sites of scotopsin and it begins to pull away from scotopsin.
4. During this process series of intermediaries are formed. All of these are loose combinations of all trans retinene and scotopsin. One of these is metarhodopsin II. This appears to be a key compound in initiating closure of Na^+ channels in outer segment (Fig. 90.1). [In dark the sodium channels in outer segment are open. Therefore sodium pumped by inner segment enters in the outer segment keeping the photoreceptor hypopolarized].
5. The final step is the separation of $retinene_1$ from opsin (bleaching) (Fig. 90.2).

Regeneration of Rhodopsin

1. Some rhodopsin is regenerated directly.
2. Some all trans retinene is reduced by alcohol dehydrogenase in presence of NADH to vitamin A_1.
3. Vitamin A_1 reacts with scotopsin to form rhodopsin (Fig. 90.2).

Resynthesis takes place in inner segment and the rhodopsin formed migrates to outer segment. Although some regeneration can take place in bright light, it mainly takes place in dark.

Amount of rhodopsin in the receptors therefore varies inversely with the incident light.

Transduction (Fig. 90.3)

Means conversion of visual stimulus to electrical changes in photoreceptors (generation of receptor potential).

1. Photoactivation of rhodopsin molecule is accompanied by a conformational change, which in turn brings about a similar change in a membrane protein – transducin in the plasma membrane of outer segment. It is a G protein.

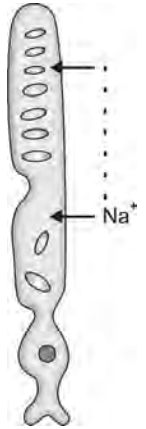


Fig. 90.1: In dark- open Na^+ channels of outer segment

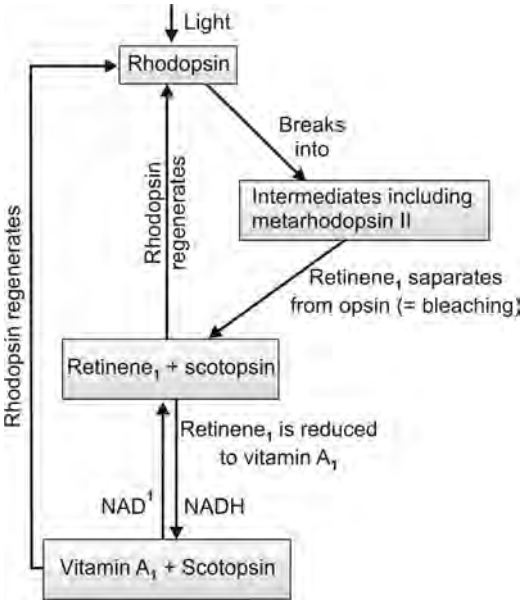


Fig. 90.2: Effects of light on rhodopsin

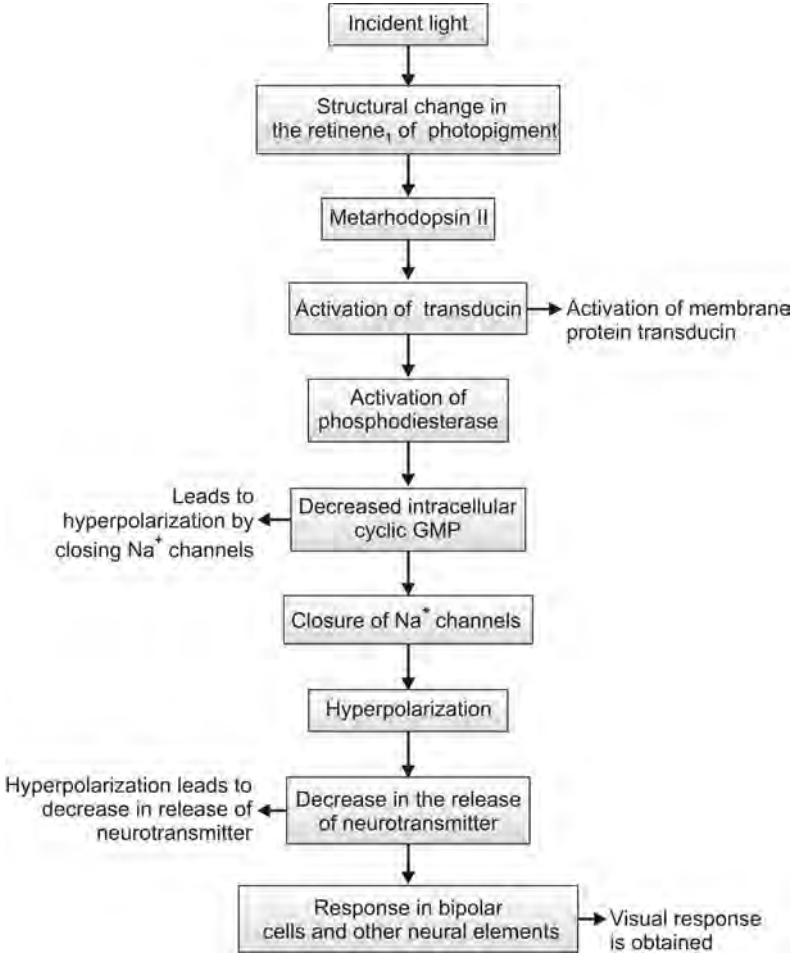


Fig. 90.3: Sequence of events involved in phototransduction of rods and cones
(Phototransduction means conversion of visual stimulus to electrical changes)

2. The conformational change in transducin activates enzymes phosphodiesterase which hydolyzes 3′,5′ guanosine monophosphate (cGMP). This leads to reduction in the level of cGMP in cytoplasm.
3. cGMP keeps the Na^+ channels in the upper segment open. If they are open the sodium pumped out by lower segment enters outer segment. Therefore, resting photoreceptor is hypopolarized (Fig. 90.1).
4. Reduction of cGMP by light stimulus leads to hyperpolarization (as compared to the resting potential inside of photoreceptor becomes more negative).
5. Degree of hyperpolarization is related to light stimulus, (i.e. intensity or brightness of light) to which it is directly proportional. Thus, hyperpolarization of rods and cones has feature of receptor potential.
6. The receptor potential of visual receptors is unique in the whole body, being a hyperpolarization potential.
7. Rods and cones release a neurotransmitter (glutamate) at rest. The light stimulus and resulting hyperpolarization leads to a decrease in the rate of release of the neurotransmitter (Fig. 90.4).

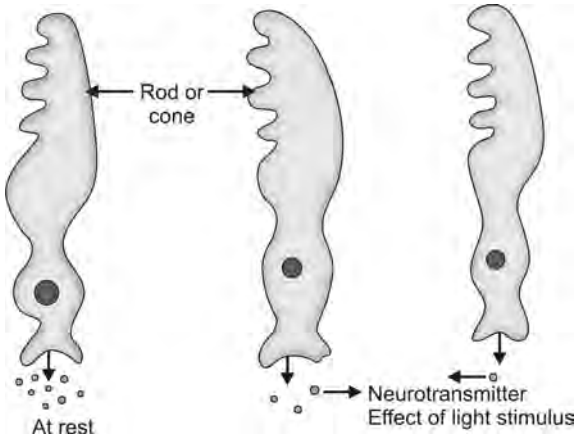


Fig. 90.4: Activation of photoreceptors

Reduction of cGMP by light stimulus leads to hyperpolarization and this ultimately leads to decrease in the rate of release of neurotransmitter.

LIGHT AND DARK ADAPTATION

Dark Adaptation

It is common knowledge that on passing from a brightly lit room into a dark hall, vision at first is very poor but gradually his vision improves even in dark. Improvement of vision in the dark room or dark adaptation has two distinct phases.

1. *The first phase or rapid phase*: Brings about a small improvement in vision within few minutes. This is due to neural adaptation of receptor cells. The receptor cells, which had adapted to persistent light stimulation, recover their sensitivity when light stimulus is withdrawn.
   In light, large portion of photochemicals both in rods and cones have been reduced (a) to retinene and opsin, and (b) most of the retinene in rods and cones is converted into Vitamin A. Because of these two effects the sensitivity of the eye to light is reduced (known as light adaptation).

   When the person comes in dark, because of very less quantity of photosensitive pigments in rods and cones his vision is very poor. But his vision goes on improving as time passes in dark, because all the retinene and opsin in rods and cones become converted to light sensitive pigments.
2. *The second phase or slow phase*: Brings about marked improvement in vision in about an hour. This phase is due to chemical adaptation. During this rods, replenish their rhodopsin by conversion of large amount of vitamin A into retinene which is converted into light sensitive pigments. Final limit being determined by the amount of opsin present in rods and cones.

   Because of these two phases the visual receptors gradually become so sensitive that even the minutest amount of light causes excitation. The process is known as dark adaptation.

At first sensitivity of vision quickly reaches a fairly steady value in few minutes, which is maintained for another few minutes. Then sensitivity shows further increase, which occurs slowly but is of much great degree. This second phase is due to dark adaptation of rods because it does not occur in congenitally night blind (with absent rod function) (Fig. 90.5).

The early phase is due to cone adaptation. Cones show rapid dark adaptation but they increase the sensitivity only slightly.

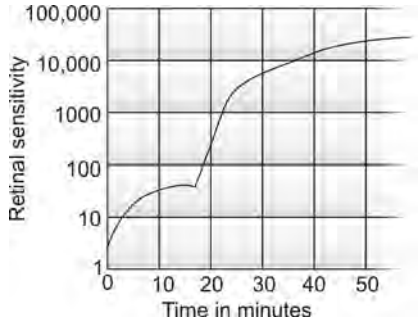


Fig. 90.5: Dark adaptation curve

Night Blindness

Since retinene is derivative of vitamin A, replenishment of rhodopsin may suffer in vitamin A deficiency. Hence, impaired dark, adaptation is one of the earliest symptoms of vitamin A deficiency. Severe vitamin A deficiency leads to night blindness.

Light Adaptation

This occurs in few minutes when a subject enters the lighted room after sitting in dark or dimly lit room.

First sensations are those of dazzle, which may be painful but these pass off as the eyes become less sensitive:

a. Because the photopigments in rods and cones become converted to retinene and opsin, and
b. Most of the retinene is converted to vitamin A.

Because of these two effects the total amount of photopigments is considerably reduced. This reduces the sensitivity of eye to light and eye becomes light adapted (Fig. 90.6).

Retina is considered to have sensitivity of 1 when maximally light adapted.

Light adaptation is very quick as compared to dark adaptation. Therefore, when a dark-adapted person is exposed to light he gets adjusted in few minutes.

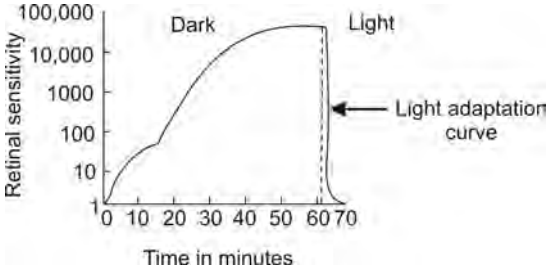


Fig. 90.6: Light adaptation curve

Negative After Image

If one looks at a scene for a while, the bright portion of the image causes light adaptation of the retina, while the dark portions of the image cause dark adaptation.

Areas of the retina that are stimulated by light become less sensitive whereas areas that are exposed only to dark portions gain in sensitivity. If the person then moves his eyes away from the scene and looks at a bright white surface such as wall, he sees the same scene that he had been viewing but the light areas of the scene now appear dark and the dark areas light. This is known as negative after image. It occurs due to light and dark adaptations.

VISUAL ACUITY

Visual acuity is the degree to which the details and contours of the object are perceived.

It is tested by ability of the subject to recognize test letters on a chart (Snellen's chart Fig. 90.7). These letters because of the size and distance subtend known visual angle.

The letters are black on white background and illuminated suitably, possess, details such as spaces and breadth of stroke, so that they subtend a known definite visual angle at a particular distance. Each line of letters has a figure of distance noted beside it.

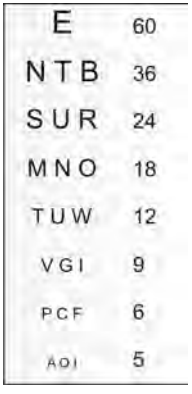


Fig. 90.7: Snellen's chart

Normal person who stands at 6 meters distance can read with each eye up to 6 meters line and his vision is 6/6.

If a person standing at 6 meters cannot read further than 18 meters line with left eye closed, his vision of right eye is 6/18.

Various Factors Affect Visual Acuity

A. Visual acuity depends on:
   i. Type of stimulus
   ii. Illumination
   iii. Time of exposure
   iv. Brightness and contrast.
B. Normal and abnormal errors of refraction play important role:
   i. Chromatic aberration tends to reduce visual acuity. Monochromatic light increases visual acuity.
   ii. Spherical aberration is reduced by pupillary constriction.
   iii. Astigmatism, myopia, hepermetropia are the usual causes of low visual acuity.

Visual acuity is maximum at fovea centralis, where cones are closely packed and where each cone has connection with single ganglion cell. Peripheral retina has visual acuity *less* than 1/30th of fovea.

Visual Fields and Binocular Vision (Fig. 90.8)

Visual field of each eye is the portion of the external world visible out of that eye. It is cut medially by the nose and superiorly by the roof of the orbit. Peripheral portions of the visual fields are mapped with an instrument called *perimeter,* and the process of mapping is known as *perimetry.* One eye is covered while the other is fixed on a central point. A small target is moved toward this central point along selected meridians; and along each the location where the target first becomes visible is plotted in degrees of arc away from the central point.

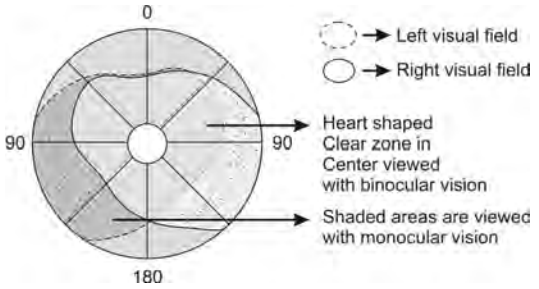


Fig. 90.8: Monocular and binocular visual fields

The central visual fields are mapped with a tangent screen. It is a black screen across which a white target is moved. By noting the locations where the target disappears and reappears *blind spot* can be marked which correspond to optic disk in the retina where photoreceptors are absent. In a similar fashion, objective scotomas can be marked which are due to disease.

The central parts of the visual fields of the two eyes coincide or overlap. Therefore, anything in this portion of the field is viewed with binocular vision. The impulses set up in the two retinae by light rays from an object are fused at cortical level into a single image.

The points on the retina on which the image of the object must fall if it is to be seen binocularly as a single object are called corresponding points, otherwise double vision or diplopia results.

Binocular vision is important for appreciation of depth and proportion.

CHAPTER

91

Color Vision

Human eye can recognize about 150 different colors (technically called as hues) in the visible spectrum (400-750 nm).

Color perception may be defined by three attributes: (a) hue, (b) saturation, (c) brightness.

Colors can be divided into: (1) Chromatic series, and (2) Achromatic series.

CHROMATIC SERIES

The different colors are:

1. Violet
2. Blue
3. Blue green
4. Green
5. Yellow
6. Orange
7. Red.

These colors can be seen in the visible spectrum 400 to 750 nm. Violet at the lowest wavelength in the spectrum and red at the highest wavelength in the spectrum.

ACHROMATIC SERIES

Whites and grays are colors included in achromatic series. In common language they denote lack of color.

Objects reflecting to our eye all the visible rays of sunlight give us a white sensation.

Black is a sensation caused by withdrawal of light. In order to see black one must have retina because in the region of blind spot one does of see black but sees nothing.

Objects absorb certain wavelengths and reflect others and depending on rays of which wavelength are reflected we perceive color.

Color Saturation

Means the amount of color present in it. A less saturated color is closer to white. Pale or pastel shade is the non-technical name for unsaturated color.

Brightness

It is measure of reflection of light falling on the object. It's apparent intensity ranging from dim to dazzling.

Effects of Color Mixing

visible spectrum is a stimulating agent for vision. It is formed by red, orange, yellow, green, blue green, blue and violet.

Results of color mixing are shown by color triangle (Fig. 91.1).

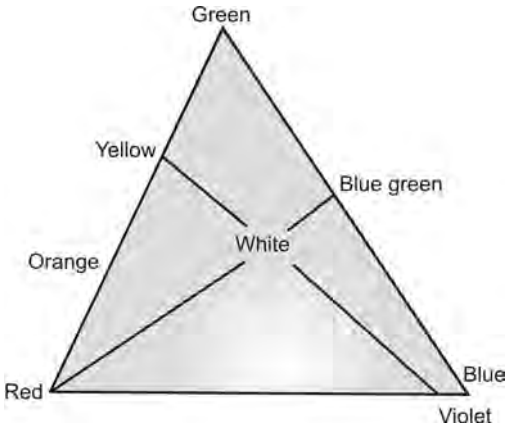


Fig. 91.1: Color triangle

1. Mixture of red and green gives intermediate colors
   i. Orange with more red.
   ii. Yellow with more green.
2. Mixture of green and violet gives intermediate colors
   i. Blue green with more green
   ii. Blue with more violet.
3. Red and blue green mixing gives a sensation of white, yellow and violet mixing gives a sensation of white.

These pairs are known as *complementary colors*. Complementary colors are pairs of colors, a mixture of which produces a sensation of white.

Primary Colors

Are 3 selected spectral colors from which all colors and white can be obtained by proper mixing. The three spectral primary colors are, (a) Red, (b) Green and (c) Blue.

After Images

After one stops looking at a color he may continue to see it for a short time – (positive after image) or he may see its complementary color (negative after image). This is a retinal phenomenon.

Color Contrasts

If a piece of blue paper is laid upon a yellow paper, the color of each of them is heightened. This is known as color contrast.

Perception of white light: About equal stimulation of red green and blue cones gives the sensation of seeing white.

Perception of different colors: Stimulation of three types of cones at different degrees gives sensation of different colors.

For example:

1. Ratio of stimulation of three types of cones– red, green and blue 99: 42: 0 will give sensation of orange.
2. Ratio of stimulation of three types of cones– red, green and blue – 0:0:97 will give sensation of blue.
3. Ratio of stimulation of three types of cones – red, green and blue – 31:67:36 will give sensation of green, and
4. Likewise 83:83:0 is interpreted as yellow. (Fig. 91.2).

PHOTOCHEMISTRY OF COLOR VISION

Photochemicals of cones have almost same composition as that of rhodopsin in rods, only difference is in protein portion.

There are three different types of photochemicals present in different cones, which makes these cones selectively sensitive to different colors namely blue, green and red.

The photosensitive pigments are called:

1. Blue sensitive pigment (short wave pigment).
2. Green sensitive pigment (middle wave pigment).

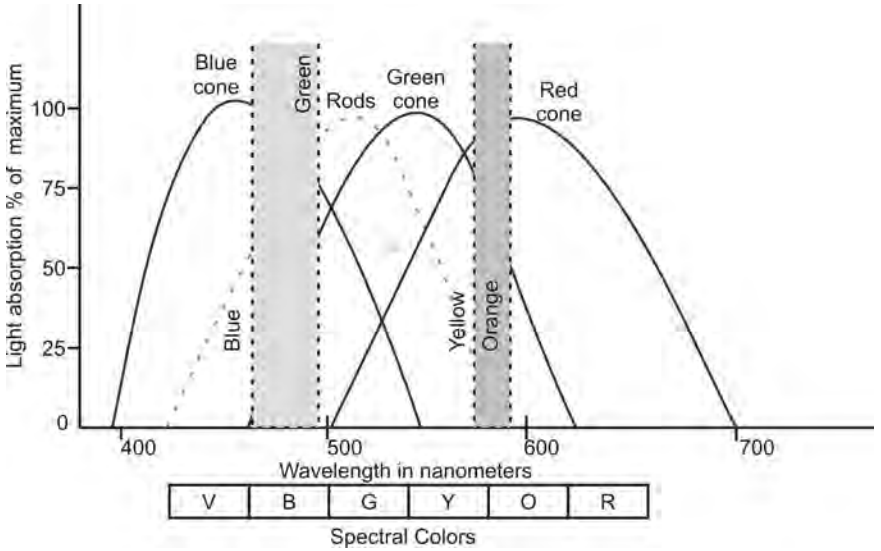


Fig. 91.2: Graph of light absorption by respective pigments of rods and three color receptive cones of humans

3. Red sensitive pigment (long wave pigment).

Peak absorption of light in different cones occurs at different wavelength.

For example:

1. Blue sensitive pigment absorbs maximum light at 445 nanometers.
2. Green sensitive pigment absorbs maximum light at 535 nanometers.
3. Red sensitive pigment absorbs maximum light at 570 nanometers.

For Rods peak absorption of light occur at 505 nanometers (Fig. 91.2).

The sensations derived from color mixing refer to those produced by mixing lights of different wavelength and not those evolved by mixing pigments (paints).

Young and Helmoltz Theory

Was proposed by Young in 1801 and later modified by Helmotz. According to this theory there are three different types of cones containing three different types of photopigments. Decomposition of each of these substances occurs maximally to different color, which means each of the three types of cone is sensitive primarily to different wavelength.

Appreciation of white results from the stimulation of all three cones simultaneously and equally. Black indicates lack of stimulation.

Correctness of this theory has been demonstrated:

1. One pigment (the blue sensitive or short wave pigment) absorbs light maximally in the blue violet portion of the spectrum.
2. Another pigment (the green sensitive or middle wave pigment) absorbs maximally in the green portion of the spectrum.
3. The third pigment (the red sensitive or long wave pigment) absorbs maximally in the yellow portion of the spectrum.

The primary colors are red, blue and green but the cones with their maximal sensitivity

in yellow portion of the spectrum are sensitive enough in the red portion to respond to red light.

COLOR BLINDNESS AND ANOMALIES

The discovery of color blindness (1794) is credited to the British Chemist and Physicist, John Dalton (of the gas law) who was himself color blind.

Conventional classification of color blindness derived from Young and Helmoltz theory of three specific receptors.

Classification of color blindness: Suggested by Von Kries

- Protanopia
- Deuteranopia
- Tritanopia

] implies defect in -

First (Protos) – red
Second (deuteros) – green
And third (trios) – blue

] receptor

The suffix – (a) anomaly – indicates color weakness.

For example: protanomaly (b) anopia – indicates color blindness.

For example: protanopia.

There are three categories of color blinds

1. Trichromats (have 3 cone systems one is weak)
   i. Protanomalous
   ii. Deuteranomalous
   iii. Tritanomalous
2. Dichromats (have 2 cone system)
   i. Protanope
   ii. Deuteronope
   iii. Tritanope
3. Monochromats (have one cone system).

Normal Persons are Trichromats

Normal persons and anomalous trichromats require 3 primary colors to match whole variety of spectral colors, but protanomalous are less of sensitive to red and therefore use more red in matching and deuteranomalous require more green to match than normal person.

Dichromats: Are so named because they can match the spectrum as they see it with only two primary colors:

1. Protanope – with green and blue
2. Deuteranope – with red and blue
3. Tritanope – rare (insensitive to blue).

Monochromats are very rare.

Causes of Color Blindness can be Classified

1. *Aquired*
   - Retinal
   - Cerebral
   - Systemic
   - Toxic
   - Avitaminosis

   ] Disorders

   For example, difficulty with blue and yellow is usually aquired.

2. *Congenital*

For example: Red, green blindness (when either red or green cones are lacking).

Inheritance of Color Blindness

Inheritance of especially red green blindness is sex linked and results from absence of appropriate color genes in the X chromosomes. This lack of color genes is a recessive trait. Since, all the male's cells (except germ cells) contain one X and one Y chromosome in addition to 44 autosomes, colour blindness is present in males, if the X chromosome lacks the color gene. On the other hand the normal female cells have 2 X chromosomes, one from each parent, and since these abnormalities are recessive, females do not suffer, but she is a carrier of the disease and passes on to her sons (half of them). Therefore, sex linked color blindness skips generation.

Color blindness is therefore more common in males –8 percent and only 0.5 percent females suffer from it. It passes from father to grandson by ways of a daughter.

Out of 8 percent color blind males –2 percent protanopes and 6 percent deuteranopes.

Tests for Color Blindness

1. *Ishihara charts*: Commonly known as hidden digit test. Consist of book of plates containing digits of spots of color in the field composed of spots of confusion color; spots of several colors are used.

   One number is seen by the normal eye and another by color weak person.
2. *Edridge Green Lantern test*: Person has to identify the color of a small illuminated area the size of which can be varied.
3. *Holmgren s test:* Number of skeins of wool are used to match 3 standard colors.

Importance

In certain profession like pilots, engine drivers, bus drivers it is very important that the person should not be color blind.

CHAPTER

92

The Visual Path

The visual fibers arise from ganglion cell layer of retina, which is connected by bipolar cell layer with rods and cones.

These fibers pass backward along the optic nerve to the optic chiasma where partial decussation takes place. The fibers from *nasal sides* of retinae *cross* and those from the *temporal sides* of the retina remain uncrossed (Fig. 92.1).

Left optic tract conveys fibers from left halves of both retinae. Each half of retina receives light rays from the opposite half of the field of vision. Therefore, left optic tract corresponds to the right or opposite half of field of vision.

The fibers from the macula lutea – fibers from nasal half of both macula cross and those from the temporal side remain uncrossed. *Optic tracts* thus formed wind round the outer side of crura cerebri and end in two main areas:

1. *Superior colliculi* or in nearby pretectal area which are not concerned with conscious vision, but serve as a center for visual reflexes.
2. In *lateral geniculate body (LGB)* both anatomical and electrical studies have shown that there is an orderly point-to-point (topographical) projection of the retina first (a) in the lateral geniculate body and, then (b) in the occipital cortex.

Gray matter of lateral geniculate body show 6 distinct layers, numbered 1 to 6 (Fig. 92.2). The fibers from retina of the contralateral side end in layers 1, 4, 6 and fibers from equivalent spots from ipsilateral retina end in LGB in layers 2, 3, 5.

From LGB fresh relay arises which pass back in optic radiation to the occipital cortex. These fibers pass through internal capsule, deep in the substance of temporal lobe, round the outer surface of the lateral ventricle to reach the half vision center in the occipital lobe.

In man, this center is situated in: (a) Cuneus and (b) Lingual gyrus above and below *calcarine fissure*, on the medial aspect of the lobe (area 17). The center is called half center, because like optic tract each occipital center represents the opposite half of field of vision.

Macula has a very large central representation and occupies mainly the posterior part of medial surface with forward running tongue. Each occipital half vision center represents the homolateral halves of two retinae. For example, left will represent left half of two retinae, therefore opposite half of field of vision, i.e. right half of field of vision (Fig. 92.3).

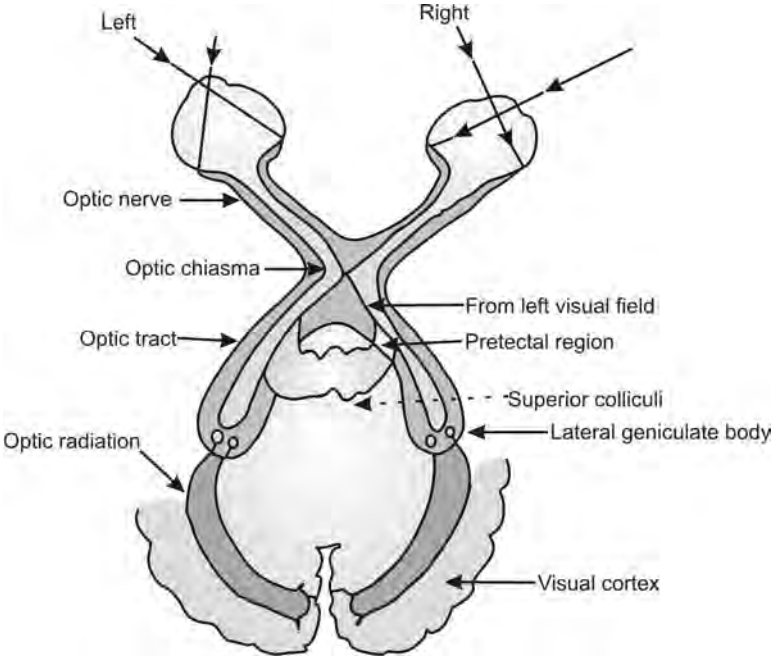


Fig. 92.1: Visual path

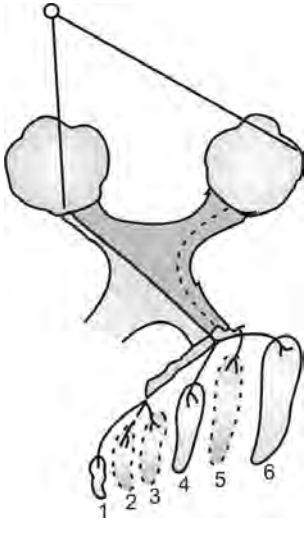


Fig. 92.2: Projection of optic tract fibers to LGB

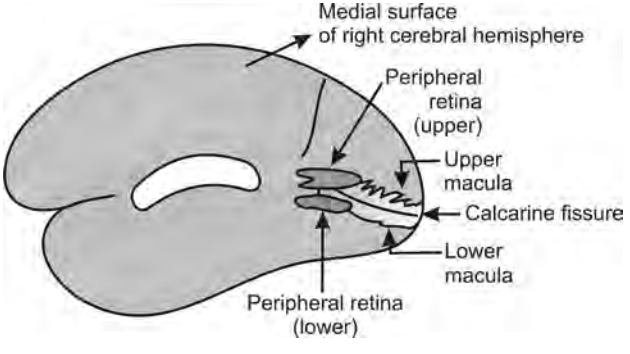


Fig. 92.3: Medial view of right cerebral hemisphere—visual half center

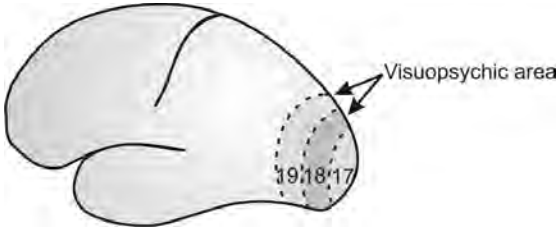


Fig. 92.4: Lateral surface—Left cerebral cortex (visuopsychic area)

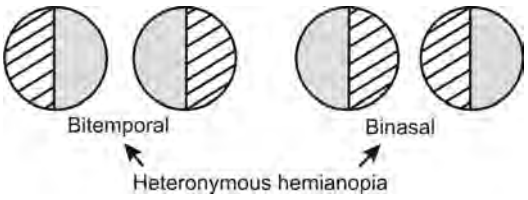


Fig. 92.5: Heteronymous hemianopia

Above the calcarine fissure (cuneus) — Upper half of the retina (Lower half of field of vision)

Below the calcarine fissure (lingual gyrus) are represented — Lower halves of the retina (upper half of field of vision)

The region of occipital cortex which surrounds visual receptive are = area 18, 19 and posterior parietal region are believed to function as a *visuopsychic area* (Fig. 92.4).

Activity in this region help us to recognize the nature of seen object, for example, pencil, paper, etc.

One mm of foveal retina is represented by 16 mm of cortex, whereas more peripheral parts of retina receive only about 1/60th of the representation per mm.

EFFECTS OF INJURY

To understand effects of injury, you must know certain definitions.

Hemianopia: Blindness of half of the visual field from causes other than retinal.

1. *Heteronymous hemianopia*: (a) Bitemporal or (b) Binasal loss of both temporal or both nasal fields (Fig. 92.5).
2. *Homonymous hemianopia*: Loss of right or left half of both visual fields (Fig. 92.6).

Quadrantic: Blindness of one quadrant only.

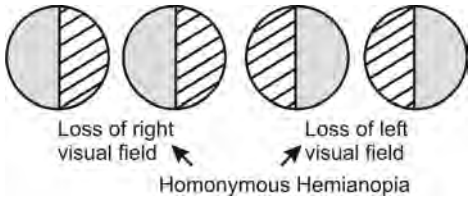


Fig. 92.6: Homonymous hemianopia

VARIOUS INJURIES

1. If optic nerve is cut – blindness of corresponding eye results.
2. Lesion of central part of optic chiasma. For example, by pituitary tumor – will damage crossed fibers from nasal side of both retina results in bitemporal hemianopia.
3. A lesion of outer margin of chiasma may damage fibers from temporal side of retina and cause binasal hemianopia (Fig. 92.7).
4. Any lesion of: (a) optic nerve, (b) optic chiasma or optic tracts up to the point where fibers leave for superior colliculus produce – loss of light reflex from the blind side of retina.
5. A lesion of: (i) LGB, (ii) optic radiation or (iii) occipital cortex produce loss of sight but no loss of light reflex from blind side of retina.

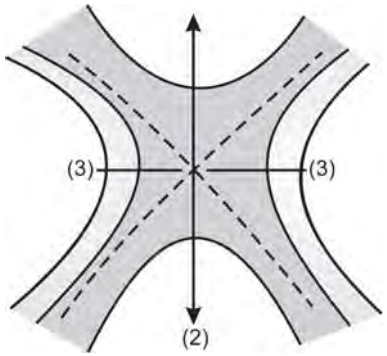


Fig. 92.7: Lesions of optic chiasma: 2. Lesion of central part of optic chiasma, 3. A lession of outer margin of chiasma

6. A lesion of optic tracts or their continuation to occipital cortex – cause homonymous hemianopia. Lesion of left tract or left visual cortex cause loss of right halves of fields of vision.
7. Incomplete lesion of visual cortex – leads to loss of color vision.
8. Lesion of lateral occipital surface Area 18 or 19 or posterior parietal region – keeps the visual sensibility intact but causes disturbances of higher visual function.
   For example, loss of visual orientation:
   i. Localization in space.
   ii. Impaired perception of depth or distance.
   iii. Loss of visual attention and ability to recognize common everyday objects.

CHAPTER

93

Hearing

Auditory system in human being is highly specialized and differentiated. In human beings its main function is communication. In animals purpose of hearing is mainly protection.

This function is carried by:
1. External ear
2. Middle ear
3. Internal ear or cochlea or labyrinth
4. Auditory pathway.

ANATOMY

External ear consists of:
1. Pinna of the ear or auricle and
2. External auditory meatus – It is 2.5 cm long (Fig. 93.1):
   i. It is curved and ends at tympanic membrane.
   ii. Outer 1/3rd is cartilaginous and remainder is bony tunnel in temporal bone.
   iii. The skin of cartilaginous part has many ceruminous gland secreting cerumen or wax to protect from dust or insects.

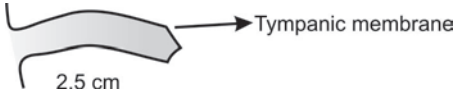


Fig. 93.1: External auditory meatus

Tympanic Membrane

Consists of three layers. Middle layer is connective tissue covered on outer side by skin and on inner side by mucous membrane.

Tympanic membrane is obliquely placed, shaped like shallow funnel with apex of the funnel pointing inwards – called umbo (Fig. 93.2).

Tympanic membrane is attached to bony ring of external auditory meatus and to handle of malleus on inner side. Area of tympanic membrane is approximately 55^2 mm. It can be examined by auroscope.

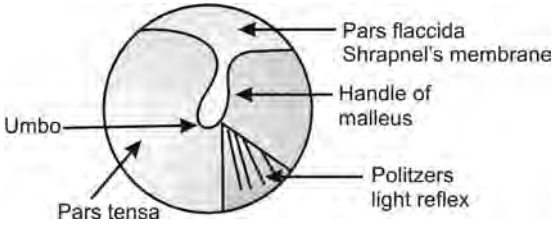


Fig. 93.2: Tympanic membrane

Middle Ear

It is a narrow air filled chamber in temporal bone contains 3 small auditory ossicles or bones suspended (Fig. 93.3).

1. Malleus: handle of malleus is attached to tympanic membrane.
2. Incus, and
3. Stapes – footplate fits in oval window – present in inner wall of middle ear extends across the cavity of ear.

Bones are attached by three ligaments to cavity:

1. Annular ligament of Stapes – surrounding footplate (attached to margin of oval window).
2. 3 ligaments supporting head and processes of malleus.
3. 1 supports the short process of incus.

Muscles: Two minutes muscles aid in controlling movement of ossicles:

1. *Tensor tympani:* Lodged in upper tunnel passing from anterior wall and inserted on handle of malleus.

   This muscle keeps the tympanic membrane tensed.
2. Stapedius from posterior wall is inserted in the neck of stapes.

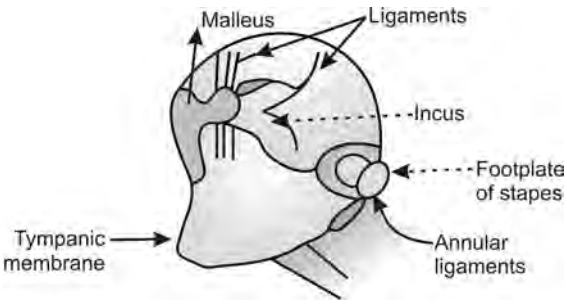


Fig. 93.3: Middle ear with three ossicles

FUNCTIONS OF MUSCLES

1. Tensor tympani keeps the tympanic membrane taught as it is attached to the handle of malleus. When it contracts it pulls the tympanic membrane inwards and increases its tension.
2. *Stapedius*: It is the smallest muscle in the body. As it is inserted in the neck of stapes when the muscle contracts, it tends to pull the stapes out of the window.

Attenuation reflex (Tympanic reflex): When the middle ear muscles contract they pull the handle of malleus inwards and footplate of stapes outward. This decreases sound transmission.

Loud sounds initiate a reflex contraction of these muscles called attenuation reflex or tympanic reflex. This reflex is protective, preventing sounds of high intensity from causing excessive stimulation of the auditory receptors and their damage. Reflex occurs after a latent period of 40-160 milliseconds so it does not protect against brief intense stimulation such as produced by gunshots.

Effect of reflex: Reduction of transmission due to increase in stiffness of vibrating parts.

FUNCTION OF OSSICLES

They increase the efficiency of transmission of sound waves to inner ear by two mechanisms: (a) Acting as bent lever increases the force of movement and (b) Cross-sectional area of tympanic membrane is approximately 55 sq mm and that of footplate of stapes is 3.2 sq mm. Sound vibration is transmitted from larger area to smaller area, therefore it is transmitted with greater force (or pressure).

During transmission of sound vibration from air outside the tympanic membrane to the fluid of the internal ear considerable energy

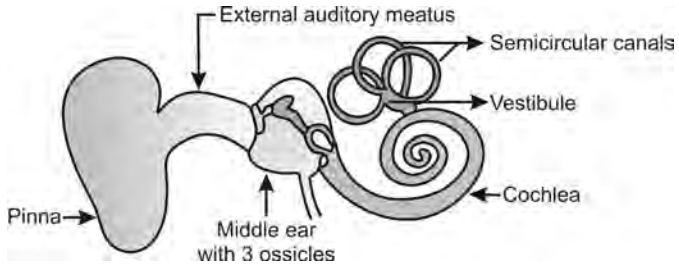


Fig. 93.4: The human ear showing external, middle and internal ear

is lost and excursion is minimal in liquid medium. To overcome this difficulty the force or pressure of sound vibration, is increased by the two mechanisms mentioned above: (i) bent lever and (ii) transmission of sound vibration from larger area to smaller area.

Eustachian Tube

Connects pharynx and middle ear. Its pharyngeal opening opens during swallowing and yawning due to contraction of tensor palati.

Function of Eustachian tube: is to equalize air pressure on either side of tympanic membrane.

INTERNAL EAR (FIG. 93.4)

Consists of membranous labyrinth inside bony labyrinth. Membranous labyrinth includes:

1. Cochlea
2. Vestibule – which include: (i) Utricle, (ii) Saccule
3. Three semicircular canals.

A function of cochlea is hearing and vestibule and semicircular canals are responsible for maintenance of posture and equilibrium.

Cochlea (Fig. 93.4)

35 mm long, coiled bony tube like shell of a snail, takes 2 ¾ turns round central bony pillar modiolus. Through its axis auditory nerve passes. The bony canal is tapering from base to apex (2 mm at base 0.9 mm at apex). Bony edge or spiral lamina projects in canal, winding round modiolus like edge of the screw and makes incomplete partition. Partition is made complete by basilar membrane (BM) on which organ of Corti are situated. Reissner's membrane (RM), stretches from upper surface of spiral lamina to bony wall, little above the attachment of basilar membrane.

The lumen of cochlea is divided by 2 membranes, basilar membrane and Reissner's membrane into three compartments (Fig. 93.5):

1. Between RM and BM – is scala media or cochlear duct or cochlear partition. It contains endolymph, which has composition like ICF. It is secreted by striae vascularis.
2. Above RM – scala vestibuli
3. Below BM – scala tympani

   Both contain perilymph which has composition like ECF. Communicate with CSF through perilymphatic duct.

   At the apex of cochlea there is a small opening *Helicotrema* – through which scala vestibuli and scala tympani communicate.

Scala media ends blindly at apex. At base it communicates with vestibule.

Scala vestibuli ends at the oval window, which is closed by the footplate of stapes.

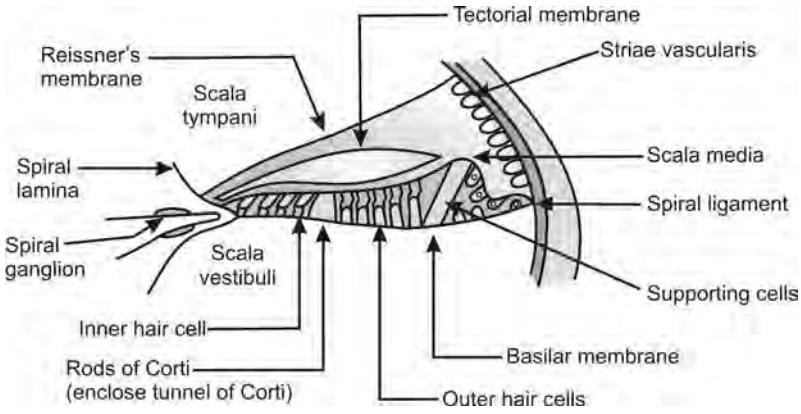


Fig. 93.5: Cross-section of cochlea. Showing organ of Corti and three scala of cochlea

Scala tympani ends at round window that is closed by flexible *secondary tympani membrane.*

On basilar membrane: Lie organ of Corti, which project in scala media. At the junction of basilar membrane and bony spiral lamina, projecting in scala media stand 2 rods of Corti, which meet at the apex enclosing tunnel of Corti (which contain cortilymph).

Tunnel of Corti separates

1. Inner row of single hair cells, and
2. Outer row of three hair cells.

Hair cells are supported by supporting cells. Their pharyngeal processes form *reticular lamina* through which hairs project. Over hanging the hair cells is thin, viscous but elastic *tectorial membrane.*

Cochlear Nerve Endings

Nerve fibers from outer hair cells cross tunnel of Corti to meet nerve fibers of inner hair cells and reach the bipolar cells of spiral ganglion situated in osseous spiral lamina. When hair cells are stimulated auditory impulse arise, which is carried by auditory nerve.

ELEMENTARY PHYSICS OF SOUND

Sounds: Are vibrations of bodies, which can evoke an auditory sensation in normal air.

Tones: Are produced by vibrations as regular as movements of pendulum.

Noises: Are produced by irregular vibrations.

Sound vibrations are transmitted, by creating areas of rise and fall in pressure. It means areas of compression and rarefaction in the molecules of external atmosphere.

Two physical properties of sound: (i) Frequency and (ii) Intensity are of special interest because they are related with perception of pitch and loudness of sound (Fig. 93.6).

Intensity or Loudness: It is determined by amplitude of vibration.

Pitch: It is determined by frequency of vibration.

Frequency is expressed as cycles per second or Hertz.

Physical unit of *intensity* is called *Bel* after Alexander Graham Bel, the inventor of telephone. Decibel (dB) is 1/10th of Bel – this unit is commonly used.

Fig. 93.6: Frequency and amplitude

Pitch: Sounds can be low pitched or high pitched and sounds of same intensity rise in pitch, as frequency is higher.

Human ear can perceive sound of 20 to 20000 cycles per sec or Hz. This is known as pitch range or frequency range. Dogs can perceive higher frequencies.

Human voice Has a pitch range of 300 – 3000 vibration per sec.

Intensity

- Sounds can be soft or loud
- Soft sounds are with small intensity
- Loud sounds are with high intensity.

Threshold of audibility: Lowest intensity that will give, just the sound sensation is known as threshold of audibility.

Timbre: It is characteristic quality of sound, which allows the ear to distinguish it from others of same pitch and loudness. Thus the same note of same intensity is perceived differently when played on piano, violin, trumpet, etc.

Fundamental tone: The tone of lowest frequency and highest intensity is known as fundamental tone. All other tones are *overtones*.

Analytical capacity: Human ear is capable of distinguishing the different components of a compound sound. This is known as analytical capacity, e.g. orchestra.

Localization of sound: Ear can localize sound at its source and can recognize the direction from which it is coming by three mechanisms:

1. Difference in time of arrival of sound to each ear. If sound reaches both ears simultaneously it is located, as its source in the median plane of the subject, e.g. Walkman. If sound reaches one ear first it will be localized on that side.
2. Different intensity of sound as it enters two ears. Sound belongs to the side of the ear in which it is perceived loudest.
3. If sound arises in two ears in different phase of wave it is localized where the crest of the wave arrives first.

MASKING

It is common knowledge that the presence of one sound decreases an individual's ability to hear other sounds. Weaker sounds are completely inaudible in presence of loud sounds. This phenomenon is known as *masking*.

Auditory fatigue: Develops if ear is being stimulated continuously. It is transient loss of sensitivity due to prolonged hearing of loud sounds. Recovery is rapid within few seconds to few minutes.

CHAPTER

94

Physiology of Hearing

FUNCTIONS OF EXTERNAL EAR

1. *Pinna:* (i) Takes up sound waves and (ii) Contribute to localization. It has been found that hearing is impaired when irregularities of pinna are filled with wax.
2. *External auditory meatus:* (i) Amplifies the sound and directs it to the tympanic membrane, (ii) Protects the tympanic membrane by hairs present in it and by its waxy secretion, and (iii) Warms the air.

FUNCTIONS OF TYMPANIC MEMBRANE

Pressure change caused by the sound wave make the tympanic membrane vibrate; reproducing the motions of these waves and transmitting it to handle of malleus.

FUNCTION OF MIDDLE EAR

Main function of middle ear is to transmit sound vibrations to internal ear.

1. Sound vibrations are transmitted from tympanic membrane to the footplate of stapes with greater force by two mechanisms: (i) Bent lever of chain of ossicles, and (ii) Transmission of sound vibration from larger area (tympanic membrane) to the smaller area (footplate of stapes).
2. Middle ear can protect itself and internal ear from harmful effects of excessively intense sounds by *tympanic reflex*.

Transmission of Sound Waves

Impact of sound wave on tympanic membrane makes it vibrate. These vibrations are transmitted to ossicles and footplate of stapes moves in and out of oval window, causing pressure changes in the perilymph of the scala vestibuli. These pressure changes travel up the scala vestibuli and down the scala tympani and end on the membrane of round window.

Level at which the pressure wave passes from the scala vestibuli to scala tympani varies with the frequency of sound wave.

PHYSIOLOGY OF INTERNAL EAR

Certain anatomical features of basilar membrane.

1. 35 mm long.
2. Composed of gelatinous fibers, which run laterally from osseous spiral lamina to spiral ligament.
3. No 20,000–30,000 (number of fibers of basilar membrane).
4. Length of the fibers increases from base to apex and diameters of fibers decreases from

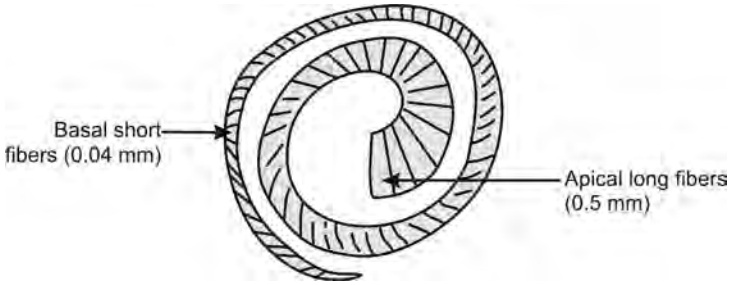


Fig. 94.1: Basilar membrane

base to apex. (e) Basilar membrane is broadest at the apex (0.5 mm) and narrow at the base 0.04 mm (Fig. 94.1).

5. So fibers at the base are short and thick, therefore still and vibrate to higher frequency and fibers to the apex are long and thin, therefore vibrate to lower frequencies.

Production of Traveling Waves

The movement of the footplate of the stapes sets up a series of traveling waves in the perilymph of the scala vestibule. As the wave moves up the cochlea its height increases to a maximum and the then drops off rapidly. The distance from the stapes to this point of maximum height varies with the frequency of the vibrations initiating the wave.

High-pitched sounds generate waves that reach maximum height near the base of the cochlea, low-pitched sounds generate waves that peak near the apex.

The bony walls of the scala vestibuli are rigid, but Reissner's membrane is flexible. Basilar membrane is not under tension. Therefore, both membranes are depressed into the scala tympani at peak of these waves.

Each wave is weak at the onset but becomes strong when it reaches the portion of basilar membrane that has natural resonant frequency equal to the sound frequency. At this place the basilar membrane vibrates back and forth with such great ease that the energy in the wave is completely dissipated. Thus, the wave ceases at this point and fails to travel the remaining distance (Fig. 94.2).

The principle method by which sound frequencies are discriminated from each other is based on the place of maximum stimulation of organ of Corti on the basilar membrane.

The intensity of sound depends on the length of the basilar membrane that is set in vibration.

The displacements of fluid in the scala tympani are dissipated into air at the round window by bulging of the membrane covering the round window.

Tops of the hair cells of organs of Corti are held rigid by reticular lamina. Reticular lamina is rigid and is continuous with rigid triangular structure called rods of Corti, which rests on basilar fibers. Therefore, basilar fibers, rods of Corti and reticular lamina all move as a unit.

Hairs of hair cells are embedded in tectorial membrane when the basilar membrane is depressed and elevated the hairs shear back and forth against tectorial membrane. This causes bending of the hairs and generates action potential in auditory nerve.

ELECTROPHYSIOLOGY OF EAR

The processes of hair cells (called sterocilia) project into the endolymph whereas bases of hair cells are bathed in perilymph. The fluid

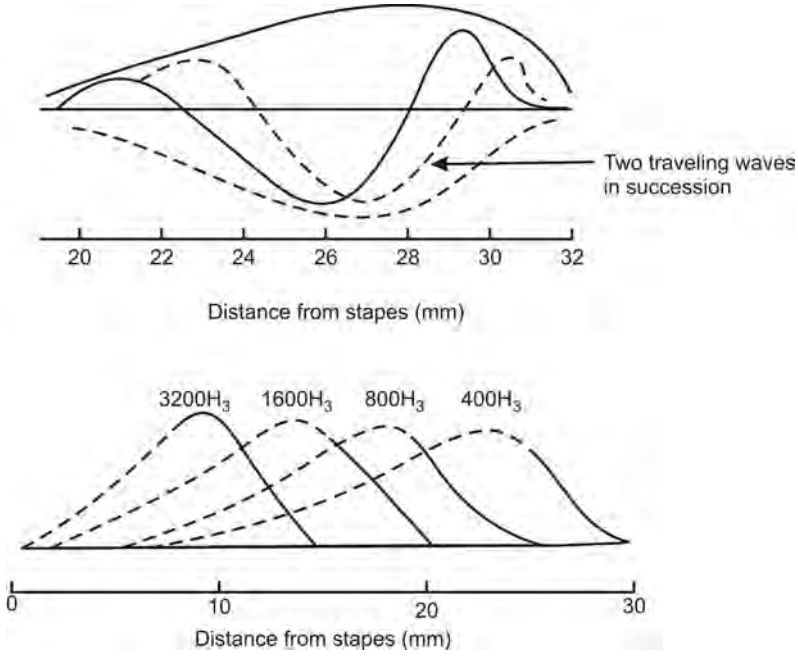


Fig. 94.2: Traveling waves

in scala tympani and scala vestibuli resemble ECF. It communicates with CSF and has high concentration of Na^+ and low concentration of K^+ ions.

The endolymph is formed by stria vasularis and has high concentration of K^+ and low concentration of Na^+, stria vascularis has (i) high concentration of $Na^+ - K^+$ ATPase, and (ii) it appears that there is a unique electrogenic K^+ pump in the stria vascularis. Therefore, scala media is electrically positive relative to the scala vestibuli and scala tympani and electrical potential of + 80 mv exist between endolymph and perilymph.

Bending of hairs of hair cells in one direction depolarizes the hair cells and bending of hair cells in opposite direction hyperpolarizes them. This in turn excites the nerve fibers synapsing with their bases.

To explain fully the electrical potentials generated by hair cells we need to explain *endocochlear potential*—electrical potential of + 80 mv exist all the time between endolymph and perilymph with positivity inside the scala media and negativity outside. This is called the endocochlear potential and is generated by continual transport of positive potassium ions into scala media by the stria vascularis (Fig. 94.3).

Importance of Endocochlear Potential

Hair cells have a negative intracellular potential of –70 mv with respect to perilymph but –150 mv with respect to endolymph at the upper surfaces, where the hairs project into the endolymph. This high electrical potential at the tips of the sterocilia greatly sensitizes the cell there by increasing its ability to respond to the slightest sound.

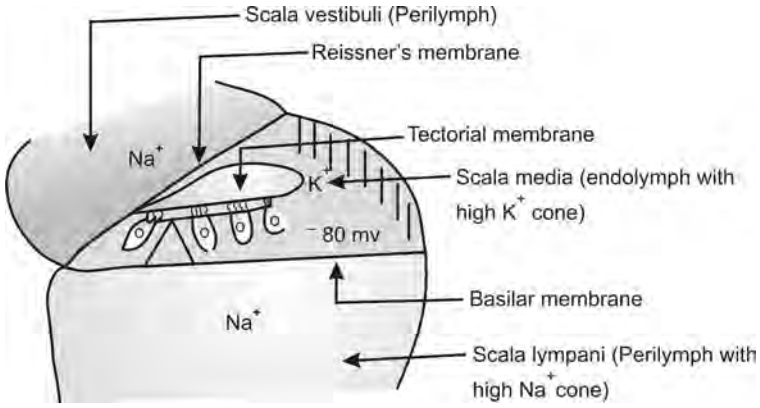


Fig. 94.3: Endocochlear potential

Cochlear Microphonic Potential

It is one of the electrical responses of the cochlea to the sound.

Movement of the hair cells against the tectorial membrane gives rise to voltage change across the hair cells. Whenever the basilar membrane moves upwards, the free ends of hair cells become negative to basal ends. It is generated by bending of hairs (Fig. 94.4).

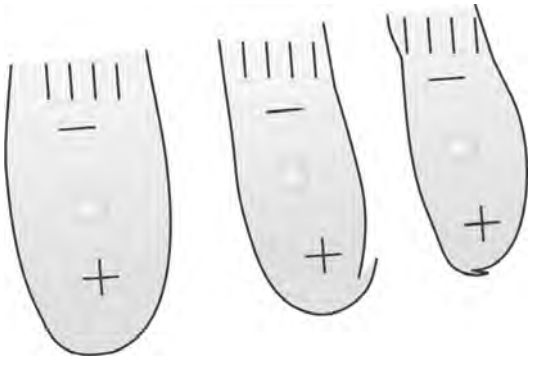


Fig. 94.4: Cochlear microphonic

This voltage change of hair cell is referred to as microphonic effect of the cochlea. The potential changes follow faithfully the sound waves and have the same frequencies. They were first recorded by Wever and Bray in 1930.

If music is played into experimental animals ear, the music can be reproduced by feeding cochlear microphonic in audio amplifier.

Differences from Action Potential

1. The cochlear microphonics are not abolished by general anesthesia, cold or ischemia, which abolish action potentials.
2. The cochlear microphonic potentials can be recorded from any part of the internal ear whereas the action potentials are recorded only from the auditory pathway (Fig. 94.5).
3. The waveform of cochlear potential is almost identical with that of stimulating sound and this can be followed up to 16,000 Hz.

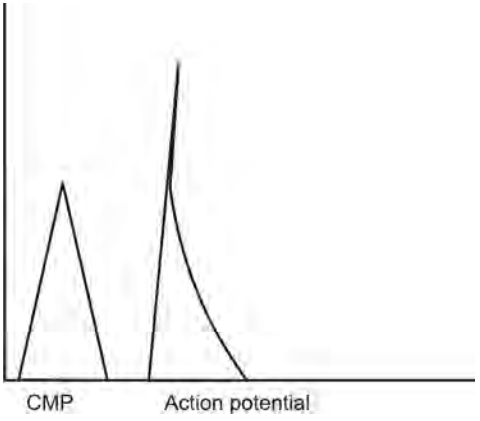


Fig. 94.5: Cochlear microphonic potential and action potential

4. These potentials unlike action potentials are not all or none, but show gradation.
5. The latent period is short 1/8th of action potential.

AUDITORY PATHWAY

From cochlea to temporal cortex auditory impulses pass at least through four neurons (Fig. 94.6).

1. Neurons of first order are situated in the modiolus as spiral ganglion of the cochlea. They are bipolar cells. Each has a short dendrite ending on external or internal hair cells and long central process, which goes to from cochlear division of 8th nerve.

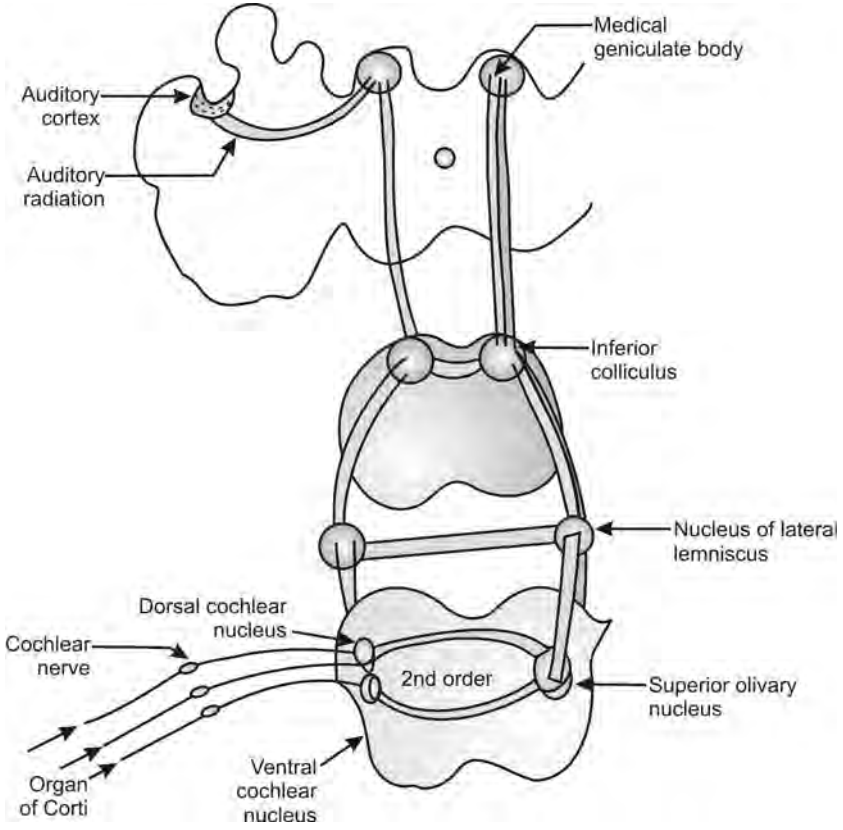


Fig. 94.6: Auditory pathway

They pass out of temporal bone through internal meatus. The fibers enter the cochlear nuclei located in the upper part of the medulla.

2. Second order neurons pass mainly to the opposite side of the brainstem through the trapezoid body to superior olivary nucleus.
3. Some of the second order fibers ascend on the same side to superior olivary nucleus of same side.
4. Most of the fibers coming to superior olivary nucleus on either side terminate here but some pass on through this nucleus.
5. From superior olivary nucleus auditory pathway passes up through lateral lemniscus and many fibers terminate in nucleus of lateral lemniscus but some bypass.
6. Most of the fibers terminate in inferior colliculus. Few fibers pass onto higher level without termination.
7. Few fibers cross from nucleus of lateral lemniscus through commissure to contralateral nucleus. Others cross through inferior collicular commissure.
8. From inferior colliculus the pathway passes through the peduncle of inferior colliculus to medial geniculate body. Where all fibers synapse. From here auditory tract spreads by way of auditory radiation to auditory cortex located mainly in superior temporal gyrus – primary auditory cortex, Brodmann's area 41, in the sylvian fissure and is not normally visible on the surface of the brain.

Auditory association areas remain close to it occupying superior, middle and inferior temporal gyri, areas 20, 21, 22. Here full meaning of particular sound is interpreted (Fig. 94.7).

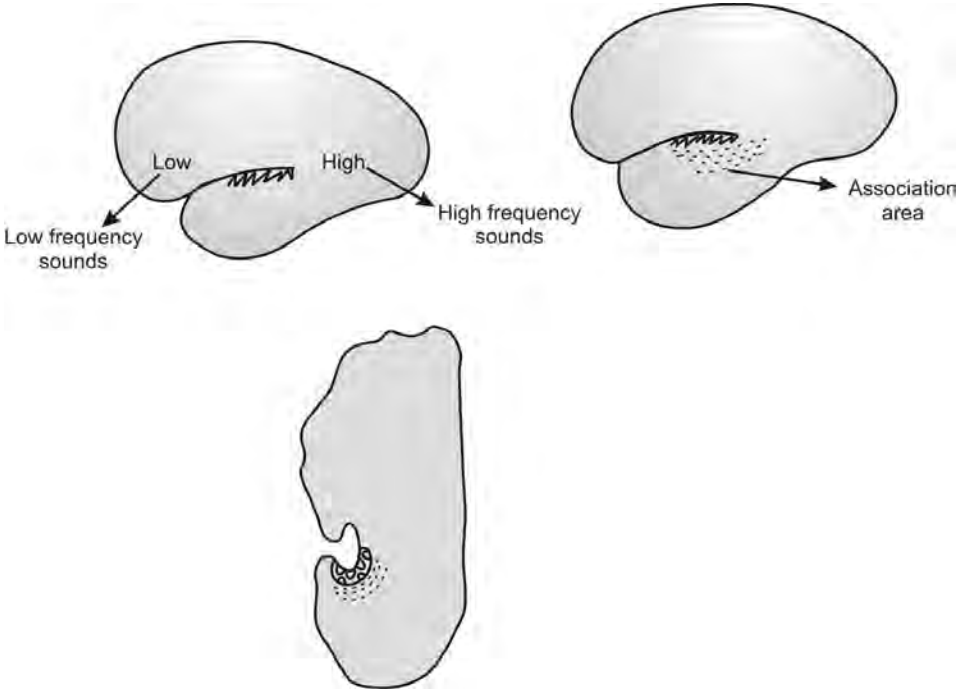


Fig. 94.7: Auditory areas

Important Points

1. Impulses from any one ear are transmitted through auditory pathways of both sides. There is slight predominance is contralateral pathway. Crossing of fibers take place at least at three different places.
2. Many contralateral fibers from auditory tract pass directly into the reticular activating system of brainstem. This system projects diffusely upwards in cerebral cortex and downward in spinal cord.
3. Impulses from cochlea to temporal cortex pass at least through 4 neurons, sometimes as many as 6 neurons. Therefore, some fibers in the tract are more direct and impulses through them reach ahead of others although originating exactly at the same time.
4. Important pathways exist from auditory system to cerebellum: (i) from cochlear nucleus, (ii) from inferior colliculi, (iii) from reticular nucleus, (iv) from cerebral auditory areas.
   They activate cerebellar vermis instantaneously if there is sudden noise.
5. High degree of spatial orientation is maintained in the tract form cochlea to auditory cortex and there is localized projection of cochlea in medial geniculate body and auditory cortex, so that a tone of a given frequency stimulates a definite place in the cochlea and is transmitted along a definite path to a definite place in auditory cortex.

DEAFNESS

Clinical deafness may be due to:

1. Impaired sound transmission in the external or middle ear—*conduction deafness* or
2. Damage to neural pathways or hair cells—*nerve deafness or sensory neural deafness.*

Causes of Conduction Deafness

1. Plugging of external ear by wax or by foreign body.
2. Destruction of auditory ossicles.
3. Thickening of tympanic membrane following repeated infection.
4. Abnormal rigidity of the attachment of stapes to oval window (otosclerosis).

Causes of Nerve Deafness

1. Toxic degeneration of 8th nerve following administration of aminoglycoside antibiotics – gentamicin or streptomycin.
2. Tumor of 8th nerve and cerebellopontine angle.
3. Vascular damage in medulla.
4. Damage to outer hair cells by prolonged exposure to noise.

Conduction or Nerve Deafness

Can be differentiated by simple tuning fork test:

1. Weber
2. Schwaback
3. Rinne—named after persons who developed them.

Audiometry

Auditory acuity is commonly measured with audiometer.

1. Subject is made to hear pure tones of various frequencies through earphones.
2. At each frequency the threshold intensity is determined.
3. It is plotted on a graph as percent of normal hearing.

4. It provides objective measurement of degree of deafness and a picture of the tonal range most affected.

Hearing Aids

Internal ear or cochlea is embedded in bony cage in temporal bone. Vibration of skull can cause vibration of fluid in the cochlea. Therefore, if a tuning fork or electronic vibrator is placed on any bony protuberance of skull—person hears a sound.

Energy available even with very loud sound is not sufficient to cause hearing through bones. Therefore, special electromechanical sound transmitting device is applied directly to the mastoid process (usually).

Hearing aid is given:

1. In conduction deafness.
2. Partial nerve deafness (or sensorineural deafness).

In severe sensorineural defects, there is no use of any type of hearing aid.

CHAPTER

95

Taste

Sensation of taste is relatively complex. Taste is a chemical sense, but it is influenced by:

1. Sense of smell, and
2. Touch and pain receptors of mouth.

The way the food tastes is influenced by its, (a) temperature, (b) physical consistency as well as its, (c) chemical nature. Taste is also influenced by the, (d) condition of adaptation of taste receptors. As compared to other sense organs they are highly adaptable, (e) Taste of a given substance may be significantly influenced by the nature of the material to which the taste receptors have been exposed in the immediately preceding interval.

SIGNIFICANCE OF TASTE

All of us will agree that taste adds an important dimension to human experience or it contributes to our enjoyment of eating.

It also contributes to our rejection of certain food. But it plays important role in maintaining appropriate physiological balance in animals. For example, animals having certain food deficiencies select those foods, the taste of which is associated with substances in which they are deficient.

Tongue

It is mainly concerned with taste and taste buds are the sense organs for taste.

PRIMARY TASTE SENSATIONS

In humans, there are four basic or primary tastes:

1. Salty
2. Sour
3. Sweet
4. Bitter.

These four basic sensations were described by Fick in 1864.

According to some there are two other tastes (5) Metallic (6) Alkaline.

From the four basic tastes we get almost numberless varieties of gustatory experiences. These derived tastes are due to:

1. Blend of primary taste sensations or their interaction.
2. Blending with general sensation in the mouth. For example, touch, pain. In "hot" taste there is element of pain stimulation (chilli sauce).
3. Blending with sensation of smell.

Specific receptors for four primary tastes are distributed in specific regions over the tongue (Fig. 95.1): Therefore:

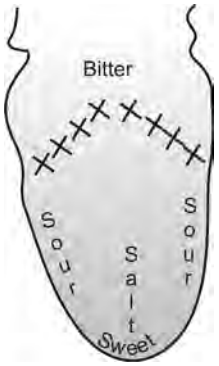


Fig. 95.1: Distribution of the primary taste sensations on the tongue

1. Bitter substances are tasted on the back of the tongue.
2. Sour along the edges.
3. Sweet at the tip and
4. Salt on the dorsum anteriorly.

(Apart from tongue some receptors are also present on palate, pharynx and epiglottis).

The taste buds in different regions of tongue are not histologically different, but existence of physiologic differences have been demonstrated by recording receptor potentials from single taste cells in animals. These studies show that:

1. Some taste cells respond best to bitter stimuli.
2. Others respond to salt, sweet or sour stimuli.
3. Some respond to more than one modality, and
4. Some to all.

Taste buds: Are sense organs for taste.

Distribution

Most are present on tongue. Some are present on soft palate, epiglottis, pharynx and anterior pillars of tonsils.

Taste buds of tongue are located on the lingual papillae (the many small elevations with which surface mucosa of the tongue is studded).

There are three main types of papillae. (Fig. 95.2): (a) Filiform, (b) Fungiform, and (c) Circumvallate.

Filiform: Are minute conical structures covering anterior 2/3 of dorsal surface of tongue. They rarely contain taste buds.

Fungiform

1. Are rounded structures.
2. Numerous near the tip of the tongue.
3. Each holds up to 5 taste buds in the epithelium covering its surface.

Circumvallate

Papillae are the largest and are prominent structures arranged in a V formation (with the vertex towards back) on the back of the tongue. Each contain up to 100 taste buds, usually located along the sides of the papillae.

There are a total of about 10,000 taste buds.

Individual taste bud is ovoid measuring 50 – 70 μm.

It contains:

1. Gustatory receptor cells, and
2. Supporting or sustentacular cells (tall columnar cells).

(The receptor cells are thin and are neuroepithelial in nature). Each one of these

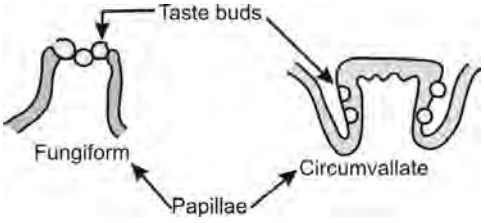


Fig. 95.2: Papillae with taste buds

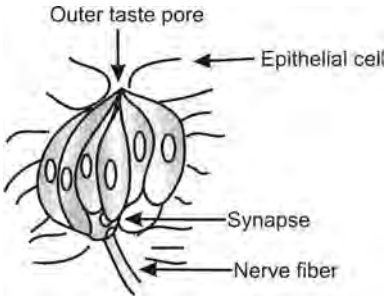


Fig. 95.3: Taste bud

cells ends in short hair like processes, which are known as microvilli, which project into the taste pore (an opening in lingual epithelium). The necks of these cells are connected with each other and to surrounding epithelial cells by tight junctions (Fig. 95.3). So that only apical microvilli are exposed to the fluids in the oral cavity.

Each taste bud is innervated by about 50 nerve fibers and each nerve fiber receives input from an average of 5 taste buds.

Receptor cells are regenerated from basal cells and are continuously replaced with a half time of 10 days.

Substances Evoking Primary Taste Sensations

1. *Acid tastes Sour*: H^+ ions stimulate the receptor. For any given acid sourness is generally proportional to the H^+ concentration, but organic acids are more sour, even with lower H^+ concentration as compared to mineral acids. This is probably because they penetrate more easily and H^+ concentration achieved in taste bud is high. For example, acetic acid.
2. A *salty* taste is produced by Na^+ some organic compounds also taste salty. Familiar example is NaCl for salty taste.
3. Most *sweet* substances are organic, for example, lactose, maltose, glucose. But polysaccharides, glycerol, some alcohols, and ketones and number of other compounds with no apparent relation to any of these, e.g. chloroform, taste sweet.

   Artificial sweetners: Such as saccharin and aspartame are in demand sweetening agents, because very small amount produces satisfactory sweetening. The same is produced by much greater amount of sucrose, which is calorie rich.
4. Usually quinine sulfate is used to taste *bitter* taste. Other organic compounds, which taste bitter, are morphine, nicotine, caffeine and urea, strychnine, etc.

   Inorganic salts of magnesium, ammonium, and calcium also tastes bitter.

The bitter taste is due to cat ions.

Threshold of Primary Taste Sensation

It is minimum concentration of different substances necessary to arouse a primary taste sensation.

Factors Influencing Taste Sensation

1. *Area*: Intensity of taste sensation depends upon the total surface area stimulated. For example, a single papilla when stimulated by a drop of solution produces a weak sensation than the same solution tasted by whole tongue.
2. *Temperature:* Taste sensation is modified with temperature. In the range of 30-40°C maximum sensation is observed.
3. *Individual variation:* There is individual variation of taste sensation. Concentration of a substance, which can be tasted by one person, may not be detected by other person. Differences are usually quantitative but can be qualitative also. For example, variation in the ability to taste phenylthiocarbamide (PTC). Human race can be divided into those who can taste it bitter,

and who cannot taste it. The ability to taste it is inherited as Mendelian recessive trait.

4. *Adaptation*: Taste sensation is quickly adapted and threshold of stimulus for a particular substance is increased. As for instance after taking sweets if anyone takes tea with usual sugar then the sweet sensation is somewhat decreased.
5. Clearly identifiable taste defects: Two conditions.
   i. *Familial dysautonomia*: It is familial disorder of taste sensation in which subject cannot identify even a saturated solution of NaCl by taste.
   ii. *Selective taste blindness*: In this the threshold for stimulation of taste by a particular substance is increased and normal taste sensation for other modalities.
6. *Acceptance and rejection of foods*: Taste sensation is also related to food habit – some like sweet, whereas others like salty. Acceptance and rejection also depends on metabolic state of an individual, e.g. hypoglycemic patient takes more sugar.

Receptor Stimulation

The gustatory receptor cells are chemo-receptors that respond to substances dissolved in the oral fluids bathing them. These substances act on the microvilli, which are exposed in the taste pore, and evoke generator potential, which generate action potential.

THE PATH OF TASTE (FIG. 95.4)

1. The nerve fibers, which penetrate basement membrane of taste buds, are dendritic

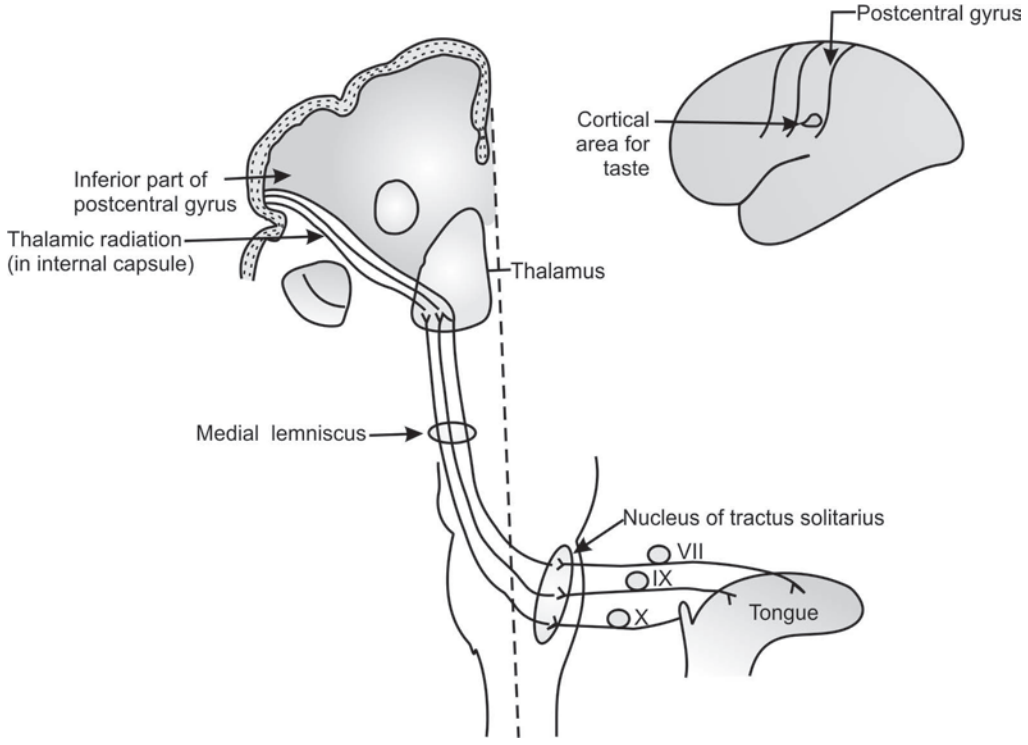


Fig. 95.4: Pathway for taste

branches of neurons. Each of which innervate number of taste cells.

2. They arise in taste buds of anterior 2/3 of the tongue travel in chorda tympani branch of the facial nerve and those arising in taste buds of posterior 1/3 of the tongue travel in glossopharyngeal nerve. The fibers from areas other than the tongue travel via the vagus nerve.
3. For fibers, which are carried by facial nerve, cell station is geniculate ganglion (which is first order neuron).
4. For fibers, which are carried by glossopharyngeal nerve, cell station is petrous ganglion (1st order neuron).
5. The taste fibers in 3 nerves (facial, glossopharyngeal and vagus) unite in the medulla oblongata to enter the nucleus of tractus solitarius.
6. From nucleus of tractus solitarius 2nd order neuron arise, cross the midline, pass through medial lemniscus or fillet and relay in specific nucleus of thalamus.
7. Here third order neuron arise, pass through posterior limb of internal capsule and end in inferior part of postcentral gyrus of cerebral cortex.
8. The sensation of touch, pain, temperature = hot or cold (common sensibility) are carried by lingual branch of trigeminal nerve, cell bodies of which are situated in semilunar ganglia and pursue similar course and end in inferior part of postcentral gyrus.

CHAPTER

96

Sense of Smell (Olfaction)

Like taste smell is also a chemical sense and their receptors are chemoreceptors that are stimulated by molecules in solution.

For smell they must be in gaseous from. After reaching nose the vapors get dissolved in mucus secreted by olfactory epithelium.

Smell receptors are distance receptors (telereceptors) sense of smell is most primitive of all special senses and is much more acute than taste.

In many animals, e.g. dogs the sensation of smell is much more acute than in man. Such animals are known as *macrosomatic.* In these animals, smell plays important role: (i) in protecting the animal, (ii) in search of food and in reactions of sex. In comparison to them man is *microsomatic.*

Sense of smell often blend with taste and general sensations and become complex admixture for example: (a) sweet smell (chloroform), (b) pungent smell (ammonia).

Sense of smell can be measured by an instrument olfactometer and with it we determine minimum identifiable odor (MIO) of a substance.

OLFACTORY MUCOUS MEMBRANE

The olfactory receptors are located in the specialized portion of the nasal mucosa, yellowish pigmented olfactory mucous membrane. Olfactory epithelium is continuous with nonsensory nasal mucosa. It occupies small area in humans about 5 cm^2 in the roof of nasal cavity near the septum (Fig. 96.1). Includes superior nasal concha and upper 1/3 of nasal septum also. It contains supporting cells and progenitor cells for the receptors. Interspersed between these cells are 10-20 million receptor cells.

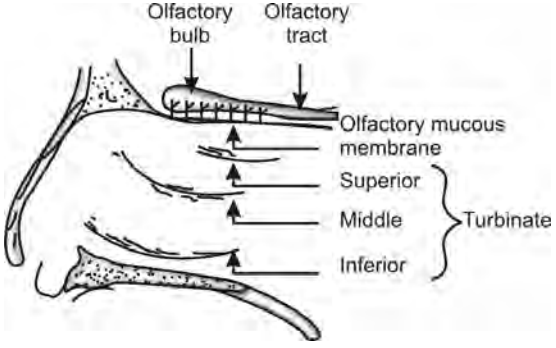


Fig. 96.1: Olfactory mucous membrane

Each olfactory receptor is a neuron (bipolar cell) and the olfactory mucous membrane is said to be the place in the body where the nervous system is closest to the external world.

Each neuron has a short, thick dendrite with an expanded end called an olfactory rod (Fig. 96.2). From these rods cilia project to the surface. Cilia are *unmyelinated* processes. There are 10 – 20 cilia per neuron.

The axons of the olfactory receptor pierce the cribriform plate of the ethmoid bone and enter the olfactory bulbs.

Olfactory neurons are constantly being replaced with a half time of a few weeks.

The olfactory mucous membrane is constantly covered by mucus. This mucus is produced by Bowman's gland, which are just under the basal lamina of the membrane.

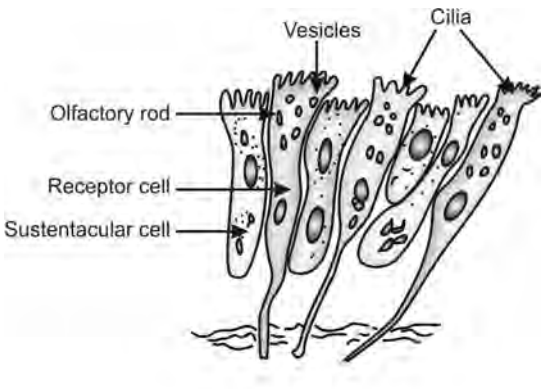


Fig. 96.2: Structure of the olfactory mucous membrane

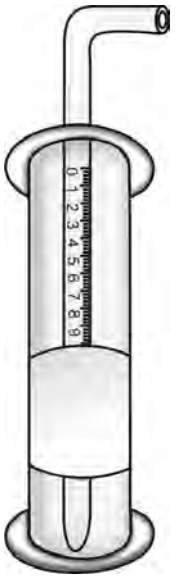


Fig. 96.3: Olfactometer

Olfactometry

1. By *olfactometer of Zwaardemaker* which consist of glass tubes sliding over another tube (Fig. 96.3).
   Inner tube: It is graded in 10 equal divisions of 0.7 cm each. Both ends are open; but outer end is curved and tapering which can be introduced into the nostril.
   Outer tube: Its inner wall is coated with odorous substance, outer end is closed. Subject breaths in and inhales the substance other nostril is kept closed. Intensity of smell is increased with gradual withdrawal of the outer tube.
2. By blast method of Elsberg and Levy – a controlled volume of odor-laden air is forced into the nose. Blast of such air is given successively to just perceive the odor. Minimum volume of odor-laden air necessary for identification is called minimum identifiable odor (MIO).

Classification of Odors by Zwaardemaker

1. Alliaceous – example – hydrogen sulfide, chlorine.
2. Ambrosial – example – Amber, musk.
3. Aromatic – example – Camphor, cloves, lavender
4. Caprillic – example – cheese.
5. Empyreumatic – example – coffee, benzene.

6. Ethereal – example – ether, fruit.
7. Fragrant – example – flowers, vanilla.
8. Nauseating – example – feces.
9. Repulsive – example – bed bug.

PHYSIOLOGY OF OLFACTION

Olfactory receptors respond only to substances that are in contact with olfactory epithelium and are dissolved in the thin layer of mucus that covers it, which is a secretion from Bowman's gland. Secretion of Bowman's gland contains both water and oil. Therefore, odoriferous substances, which are soluble both in water and oil produce strong odor.

The portion of the nasal cavity containing the olfactory receptors is poorly ventilated. Most of the air commonly moves smoothly over the turbinate with each respiratory cycle, although eddy currents pass some air over the olfactory mucous membrane. Eddy currents are probably setup by convection as cool air strikes the warm mucosal surfaces. The amount of air reaching this region is greatly increased by sniffing. In this the lower part of nares contract on septum. This helps to deflect the airstream upward, sniffing is a semi reflex response that usually occurs when new odor attracts attention.

Substances, which remain in gaseous state produce strong odor, e.g. turpentine and non-volatile substances, remain odorless, e.g. heavy metal.

Odorant receptors are present on the cilia of the olfactory receptor cells. Second messenger helps in producing generator potential.

Olfactory Discrimination

Man can distinguish more than 2000 different odors.

Olfactory Adaptation

It is a common knowledge that when one is continuously exposed to even the most disagreeable odor, perception of the odor decreases and eventually ceases. This phenomenon is due to rapid adaptation or desensitization that occurs in olfactory system.

Chemical Compounds and their Relation to Olfactory Sensation

The intensity of olfactory sensation varies with different chemical compounds. If the chemical compounds belong to homologue series. For example, alcohol series, the odors increase in strength from, lower to higher one, e.g. from methyl, ethyl, propyl, butyl to amyl.

Relation of Odorous Substances

(a) Weaker odors are masked by stronger ones, (b) If odorous substances are equal in strength then odors of both are perceived, (c) Some of the odorous substances are antagonistic to each other.

From the study of structure of molecules of odorous substances it is found that each smell is evoked by characteristic structure of the molecule. For example, camphorous material has egg shaped molecule whereas musky molecules are flat disks. Amoore studied all known odorous substances and concluded that smells were mixture of 7 primary smells: (1) Camphorous, (2) Musky (3) Floral, (4) Peppermint, (5) Ethereal, (6) Pungent, (7) Putrid, and molecules of substances producing these smells have a particular shape. So, it was possible to predict the smell of newly synthesized compound.

Several clues in recent years have indicated that there may be as many as 50 or more

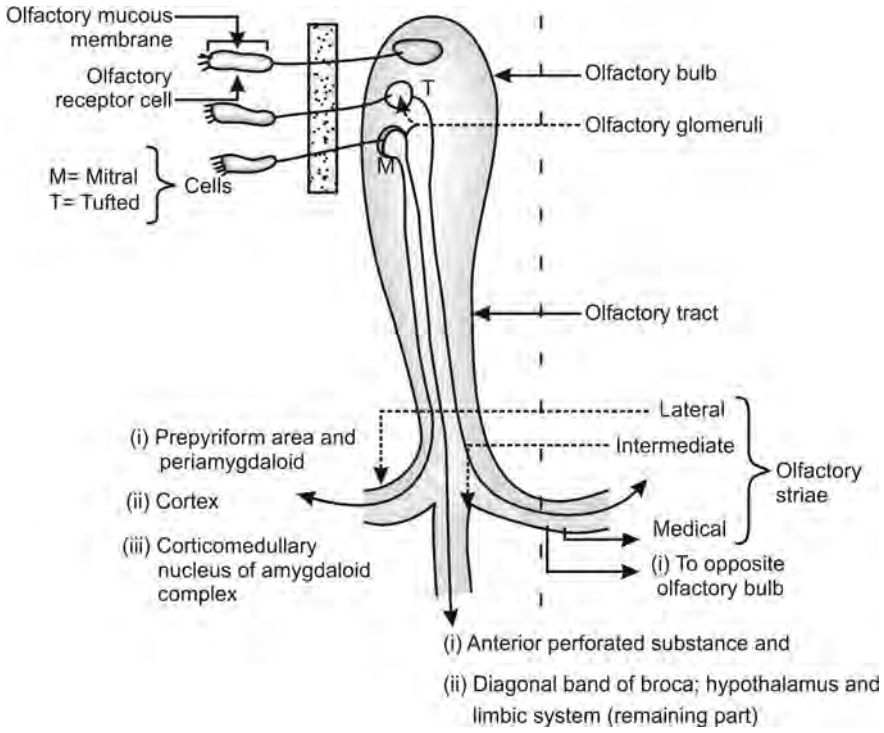


Fig. 96.4: Olfactory tract (arrows indicate the regions where the striae will terminate)

primary sensations of smell. Marked contrast to only 3 primary colors detected by the eye and 4 primary tastes detected by tongue.

OLFACTORY PATH OR OLFACTORY TRACT (FIG. 96.4)

Receptor cells or bipolar cells of olfactory epithelium are first order neurons. Each receptor cell gives rise to one axon, which join with those coming from other receptors to form olfactory nerves (20 olfactory nerves). Olfactory nerves are unmyelinated and have got neurilemmal sheath, which is continuous with subarachnoid space. Virus of acute anterior poliomyelitis probably passes through this olfactory route and reach CNS.

Olfactory nerves pierce cribriform plate of ethmoid bone and enter olfactory bulb. Here axons make the synapse with dendrites of *mitral cells* and tufted cells superficially located, to form the complex globular structures, which are know as *olfactory glomeruli.* Approximately 26,000 receptor cells converge on each glomerulus. Mitral and tufted cells are second order neuron and their axons constitute olfactory tract.

There are three of these olfactory tracts: (a) Medial (b) Intermediate, and (c) Lateral.

The lateral tract ends in: (i) Prepyriform area, and (ii) Periamygdaloid cortex, and (iii) Fibers also pass to medial group of amygdaloid nuclei and a few fibers to central

amygdaloid nucleus. Probably involved in emotional responses to olfactory stimuli.

1. The primary olfactory cortex in human being is pyriform cortex and periamygdaloid cortex.
2. Entorhinal cortex area 28 is secondary olfactory area because it receives fibers from primary olfactory cortex; it is concerned with olfactory memories.
   ***Note*:** No relay in thalamus and no neocortical projection.

ABNORMALITIES OF OLFACTORY SENSATION

Include:

1. Anosmia (absence of sense of smell).
2. Hyposmia (diminished olfactory sensitivity).
3. Dysosmia (distorted sense of smell), e.g. (Hyperosmia more sensitiveness to odors). Olfactory thresholds increase with advancing age.

CHAPTER 97

Nervous System

The functions of different systems of the body are coordinated by: (1) Nervous system and (2) Endocrine system.

Nervous system is a rapid control device while slower control is mediated by a system of endocrine glands. They are also under control of nervous system directly or indirectly.

Function of nervous system is to enable the individual to adjust his activities in a purposeful and coordinated manner in response to changes continually taking place outside and even inside him. These adjustments in most cases are automatic or reflex in character, independent of consciousness and will.

Nervous system carries these adjustments with (1) Afferent (sensory) nerve, and (2) Efferent (motor) nerve. Sensory nerve comes from receptor, which are evolved to be stimulated by changes in external or internal environment. CNS, thus, receives information from all parts of the body and reacts to them by sending impulses through motor nerves to effector organs, e.g. muscles and glands, which act properly. Thus, we adjust our behavior to suit ever changing environmental conditions.

As evolution proceeded nervous system developed most at its cephalic end into brain, which is very complex in structure and function and assumes greater control over lower segments. Brain of human beings is recognized as God's best creation compared to their evolutionary ancestors.

The highest part of brain (cerebral cortex) mainly exerts controlling and coordinating influences on the various functional levels of CNS like:

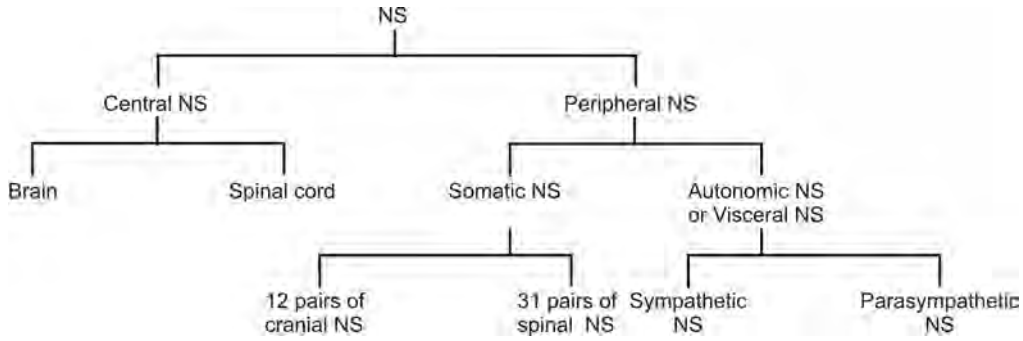
1. Psychical activities of individual.
2. Consciousness of sensations.
3. Retention of memory of such conscious sensations.
4. Development of mind.
5. Resulting into initiation of volitional (=under control of will) activities.

Are all functions of cerebral cortex.

Lower functional levels are concerned with immediate reflex activities.

STRUCTURAL ORGANIZATION

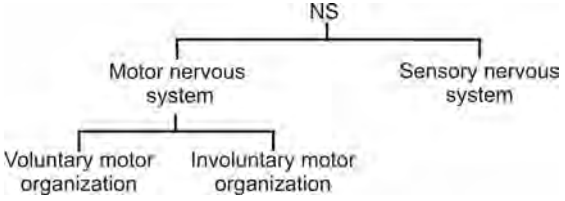
The nervous tissue is made up of nerve cells or neurons. The neurons are organized in nervous tissue. Nervous system is divided into:



Cranial nerves: (1) Olfactory, (2) Optic, (3) Oculomotor, (4) Trochlear, (5) Trigeminal, (6) Abducens, (7) Facial, (8) Auditory, (9) Glossopharyngeal, (10) Vagus, (11) Accessory, (12) Hypoglossal.

Spinal nerves: 8 pairs of cervical nerves, 12 pairs of thoracic nerves, 5 pairs of lumbar nerves, 5 pairs of sacral nerves and 1 pair of coccygeal nerve.

Nervous system can also be divided into:



Central nervous system: Consists of: (1) Brain, (2) Spinal cord (Fig. 97.1).

1. *Brain:* It is lodged inside cranial cavity or skull is made up of, (a) cerebrum and its peduncles, (b) Brainstem – midbrain - pons - medulla, (c) Cerebellum – connected to brainstem by three pairs of peduncles.
2. *Spinal cord:* It is lodged inside the neural canal of vertebrae.

A section of any part of CNS shows: (a) gray matter consisting of closely packed nerve cells and (b) white matter made up of bundles of nerve fibers.

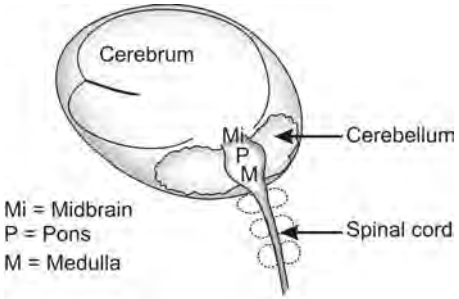


Fig. 97.1: Central nervous system (CNS)

In cerebrum and cerebellum, the gray matter is located outside and white matter is placed centrally.

In brainstem and spinal cord, gray matter is centrally placed and white matter outside.

The whole CNS is safely lodged inside the bony cranial cavity and neural canal of vertebrae. Between the bony covering and the delicate CNS are interposed 3 membranes called as Meninges – which are from out inward – (1) Dura mater, (2) Arachnoid, (3) Pia mater.

Dura mater: It is tough white fibrous tissue attached to the undersurface of the bony wall.

Pia mater: It is the thinnest vascular membrane on the surface of the nervous matter and middle membrane is *arachnoid.*

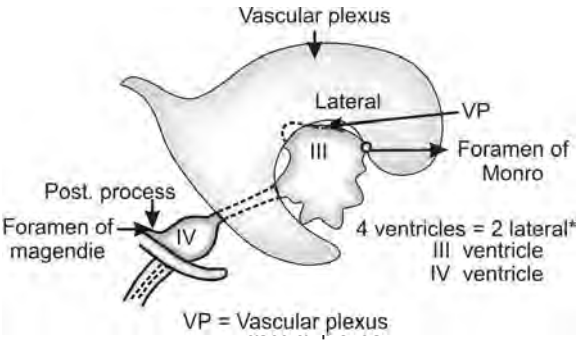


Fig. 97.2: 4 ventricles in brain
(*One each in each cerebral hemisphere)

Between arachnoid and pia mater is the subarachnoid space filled with cerebrospinal fluid (CSF).

Inside the brain are 4 ventricles (Fig. 97.2) intercommunicating with each other and with the central canal of spinal cord. These are filled with CSF secreted by vascular plexuses in the lateral and third ventricle. The CSF goes into subarachnoid space from 4th ventricle and thus CNS is surrounded by a fluid buffer material, both inside and outside and is safe and secure inside the bony coverings.

FUNCTIONAL ORGANIZATION OF CNS

1. Spinal cord
2. Brainstem and subcortical region, and
3. Cerebral cortex.

Spinal Cord

1. Sensory information is first passed into spinal cord through spinal afferents. Some is converted to motor response at a particular segment through a reflex.
2. Gateway for voluntary activities, as the cell bodies of peripheral efferents are located in spinal cord.

Brainstem and Subcortical Part

Information reaching this level subserve various reflexes:

1. Some subconscious activities are controlled from this level, e.g. blood pressure, respiration, heart rate.
2. Some somatic reflexes such as righting reflexes have their centers here.
3. Salivary reflexes and reflexes controlling secretion of digestive juices have also their centers here.
4. Centers for emotion, feeding, sleep, pleasure, anger, pain, etc. are located here.

Cerebral Cortex

This is the highest endowment of human being.

1. Vast information storehouse.
2. Complex voluntary activities and skillful movements are controlled.
3. Seat for higher functions like speech, thought, judgement, orientation of place and time, intelligence, social behavior, etc.
4. Center for: (a) conscious sensations of general sensation like touch, pain, temperature, as well as, (b) special sensations like olfaction, vision, hearing, taste, equilibrium, etc.
5. Concerned with wakefulness and sleep.

Note:

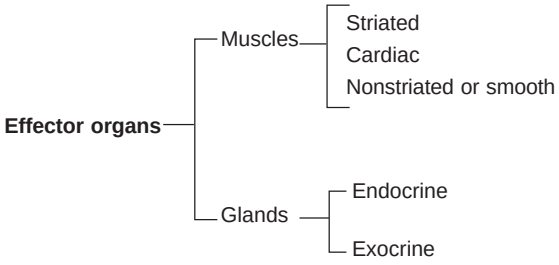
It is the activities of this part, which make the man the superior being in the universe.

Although, CNS functions as single unit reopening to variety of physiological conditions:

Three components are seen if we analyze these actions:

1. *Sensory function:* Impulses pass from receptors to CN.
2. *Motor functions:* Efferent responses mediated by muscle.
3. *Vegetative functions:* Regulation of:
   i. Visceral activities
   ii. Glandular activities

iii. Blood vessels, metabolism and other functions of the body mediated by autonomic nerves.



MOTOR ORGANIZATION

Nerves that regulate actions of muscles and gland are called efferent nerves or motor nerves (for muscle):

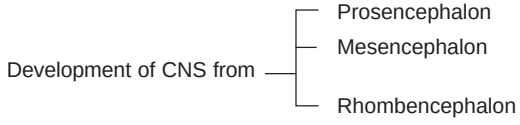
1. Motor nerves control skeletal muscles (voluntary control).
2. Whereas control of cardiac muscle, smooth muscle, exocrine and endocrine glands is under control of sympathetic and parasympathetic division of automatic nervous system (involuntary control).

Voluntary muscles

– Work on command
– But voluntary muscles also work Involuntarily in reflex action for safety; for tone.

Muscles are like aggregation of strings of fibers. These strings of muscle fibers must be at proper tension (i.e. tone), so that they can be put to work at any moment at the command of will or reflexly. For smooth and precise action *tonicity* and *contractility* of muscles. They are under the charge of two separate commands, extrapyramidal system and pyramidal system respectively.

Like this there is division of labor and 2 systems work in complete harmony with complete understanding between themselves.



CHAPTER

98

Structure and Functions of Nervous Tissue

Structural units of CNS are called neurons. They are embedded in supporting framework of neuroglia. The neurons display wide diversity in their sizes and shapes but have some features in common.

CYTOLOGY OF NEURONS

Neuron comprises of (Fig. 98.1):

1. A cell body (Soma)
2. Two types of processes: (i) Dendrites and (ii) Axon.

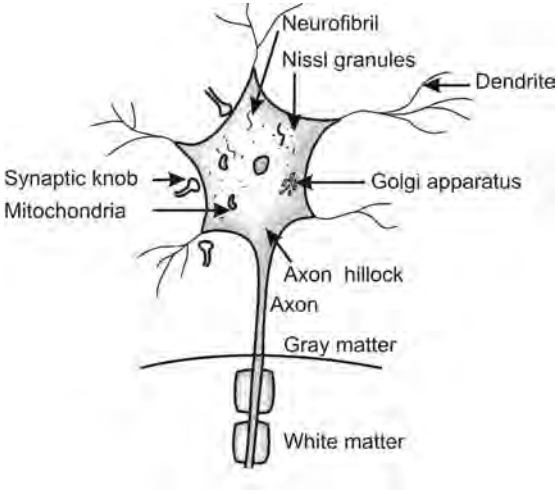


Fig. 98.1: Neuron

Dendrites: Many from single neuron:

1. Their characters are repeated branching
2. Short course
3. Varying caliber
4. Irregular number.

Axon

1. Single from each neuron.
2. Arises from conical expansion of the cell called axon hillock.
3. Length of axon varies and long axons are called nerve fibers.

As a general rule, the dendrites convey impulses towards the neuron and axons away from the neuron.

Cell Body (Soma)

Consist of cytoplasm and large spherical nucleus in the center of the cell.

Neuron is termed:

1. Unipolar
2. Bipolar
3. Multipolar depending on number of processes.

Examination of properly stained section of the cell body shows that it contains all the structures such as mitochondria, endoplasmic reticulum, Golgi apparatus and pigment. In

addition, it contains Nissl granules and neurofibrils. Nissl granules are peculiar to soma.

Nissl Granules

Are cluster of particles, which stain intensely with basic dyes, particularly with methylene blue. It contains ribonucleic acid (RNA). They are absent in the region of axon hillock and disappear when axon is cut. The dissolution of the granules in an injured cell is known as chromatolysis.

Neurofibrils

Are delicate thread like structures which course through the cytoplasm of the cell and form complex network in the cells, but run parallel to each other in dendrites and axon.

Nerve Fibers

Are the axonal processes of nerve cell together with their covering sheaths. Their cytoplasm (axoplasm) also contains all the intracellular structures found in nerve cells except Nissl granules. Supporting cells are called glial cells in CNS and Schwann cells in peripheral nervous system are closely applied to axon.

Nerve fibers are of two types:

1. Unmyelinated
2. Myelinated.

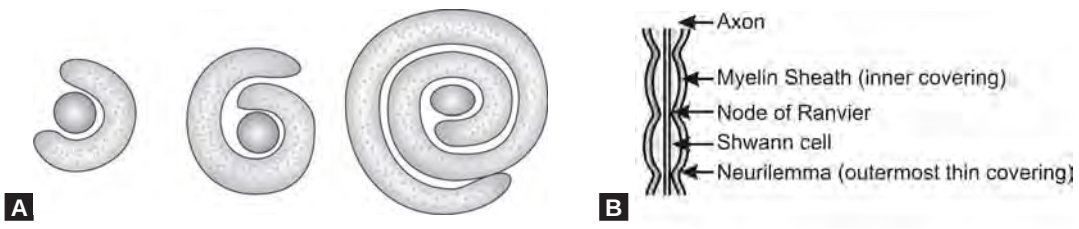
In myelinated nerve, the axon is surrounded by layers of lipoprotein lamellae, termed as *myelin sheath.* The thicker the nerve greater are the number of lamellae. In peripheral nerve myelin sheath is enclosed by neurilemma (Figs 98.2A and B).

In the unmyelinated nerve the axon is enveloped in its whole length by the Schwann cell and it's membrane. In the myelinated nerve, the Schwann cell has rotated several times round the axon, wrapping a spiral of lipid protein around it. However, the myelin lamellae are not continuous along the entire length of nerve fiber. They are interrupted at regular intervals to leave short segments covered only by Schwann cells. In the peripheral nerve such segments are the *nodes of Ranvier.*

PHYSIOLOGY OF NEURON

When the nerve is appropriately stimulated it conducts and invisible message termed nerve impulse. The whole activity of the nervous system depends on this ability to transmit impulses. The nerve impulses cannot be detected by any of our senses. It is also difficult to define it. The usual definition *is* Physicochemical change transmitted by nerves. Passage of impulse is associated with electrical changes (action potential), which is associated with:

- ↑O_2 uptake
- – ↑ CO_2 output
- – ↑ Heat production (↑ = increased)



Figs 98.2A and B: A. Myelination, B. Myelinated nerve fiber

A stimulus has been defined as a sudden change in the environment of a tissue, which causes it to react (which in case of a nerve is to set up an impulse).

For experimental purposes, electrical stimuli are employed because of their many advantages:

1. The strength of stimulus can be measured accurately.
2. It is easily reproducible and
3. It leaves the nerve undamaged.

SYNAPSE

Functional junction between one neuron and the next is called as synapse. The word synapse was coined by Sharrington—to denote the locus of contact between one neuron and another.

Morphology of Synapse

The axon of the presynaptic neuron looses it's myelin sheath and breaks into a number of fine terminals, which may come into relationship with the dendrite of the postsynaptic cell or with its soma.

So, two types of synapses are recognized:

1. Axodendritic
2. Axosomatic.

Morphological and functional properties are similar in all synapses. The presynaptic teledendron (or branch of axon) before making contact with postsynaptic cell widens itself to form a *synaptic knob* or bouton or end feet or presynaptic terminal.

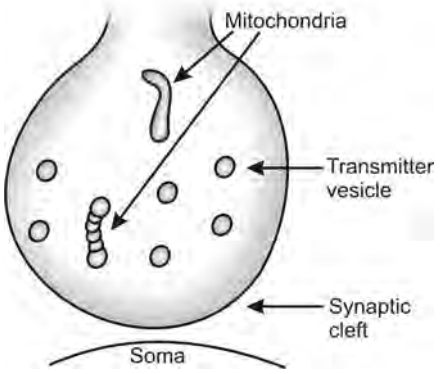


Fig. 98.3: Synaptic knob

Synaptic Knob

Electron microscopic study shows that they are oval or round, contain (a) vesicles containing transmitter substances, and (b) mitochondria which produce ATP used to resynthesize transmitter substance (Fig. 98.3).

1. There is no anatomical continuity between one neuron and another and there is a cleft (200 – 300 A°) between the synaptic knob and the next neuron.

Function of synapse: It is to transmit impulse from one neuron to the next that is from presynaptic terminal to the postsynaptic neuron.

CHAPTER

99

Synaptic Transmission

Impulses are transmitted in CNS through a succession of neurons one after the other.

SEQUENCE OF EVENTS DURING SYNAPTIC TRANSMISSION

Presynaptic terminal is excited by spread of action potential (impulse) – membrane depolarization – emptying of some vesicles in cleft – cause change in permeability of post-synaptic membrane which leads to excitation or inhibition.

Action of Transmitter Substance on Postsynaptic Neuron

Postsynaptic membrane contain specific receptor molecule, which binds with the transmitter substance. React, so that the permeability of postsynaptic neuron is increased to:

1. Most ions when the receptor is excitatory.
2. K and Cl ions when receptor is inhibitory.

Chemical and Physiological Nature of Transmitter Substance

1. Whether a transmitter will cause excitation or inhibition is determined not only by the nature of transmitter but also by the nature of receptor in postsynaptic membrane, e.g. norepinephrine in CNS – inhibitory, in other parts excitatory.
2. Each single neuron releases only one type of transmitter and it releases it, at all its nerve terminals. Release of different types of transmitters in CNS requires different types of neurons.
3. Transmitters and their principle sites.
   i. Acetylcholine excitatory in (Fig. 99.1):
      a. Autonomic ganglia
      b. Neuromuscular junction
      c. CNS
      d. Postganglionic parasympathetic nerve ending.

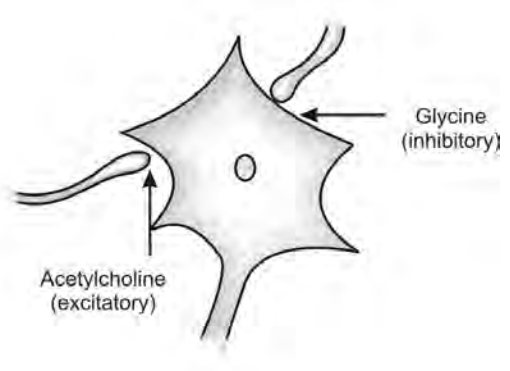


Fig. 99.1: Excitatory and inhibitory transmitter

e. Postganglionic cholinergic sympathetic nerve.

ii. Norepinephrine: Postganglionic sympathetic nerve endings CNS– Reticular formation, brainstem

iii. Dopamine—Corpus striatum

iv. Serotonin—Median raphe nucleus of brainstem—hypothalamus.

v. Inhibitory transmitters:
   a. Gamma aminobutyric acid (GABA) in CNS
   b. Glycine in spinal cord.

vi. Newer transmitter:
   a. Glutamic acid
   b. Aspartic acid
   c. P substances
   d. Endorphins
   e. Enkephalins
   f. Neurotensin
   g. Purines
   h. Histamine
   i. Prostaglandins
   j. Cyclic AMP, GMP.
   k. Hormones – Somatostatin
      - MSH
      - MSH RIH
      - LHRH
      - Oxytocin
      - Vasopressin.

ELECTRICAL EVENTS DURING NEURONAL EXCITATION

1. Resting membrane potential in neuronal soma is – 70 mv (Fig. 99.2) (which is less than peripheral nerve and muscle, i.e.– 90 mv).
2. Lower value is important because it allows both positive and negative control and degree of excitability of neuron is controlled.

   For example, when more negative then neuron is less excitable and when less negative then neuron is more excitable.

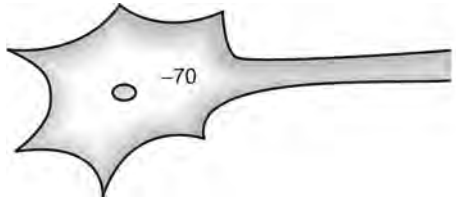


Fig. 99.2: Resting membrane potential

3. Inside soma is highly conductive electrolyte solution and diameter is large therefore any change in potential in anyone part causes almost equal change in potential at all other points in soma. Important because it plays role in summation of signals entering from multiple sources.
4. *Exhcitatory postsynaptic potential (EPSP):* Increase in potential from –70 to –59, i.e. to a less negative value is called EPSP (Fig. 99.3). Release of excitatory transmitter causes increased permeability to all ions and because of electrochemical gradient Na moves in. Big channels open, which allow passage of Na.

   EPSP is not all or none like action potential. Different inputs can sum to produce larger EPSP.

   Discharge of single synaptic knob can never increase neuronal potential from –70 to –59. This requires simultaneous discharge from many knobs (10 to 100). Process is called *summation.*

   When EPSP is high enough it excites action potential in initial segment of axon (axon hillock = first 50–100 micron) because although negative potential is same every

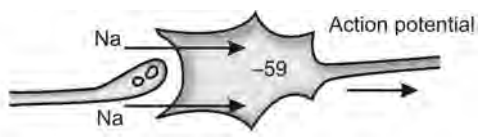


Fig. 99.3: EPSP

where, in soma there is physical and geometric difference in different parts of soma. The most excitable part of soma is initial segment of axon. Where rise of 11 mv can fire action potential, i.e. potential rise from – 70 mv to –59 mv will cause firing of action potential (–70 ± 11 = –59) –59 mv is the threshold value. In soma rise of +30 mv fires action potential.

c. *Inhibitory postsynaptic potential (IPSP)*: Inhibitory transmitter open pores, which allow transmission of ions below certain size (i.e. small channels open). This increases permeability of potassium ions and chloride ions. Therefore, efflux of potassium ions takes place and Cl ions get in (Fig. 99.4). This decreases membrane potential. 5 mv decrease results into IPSP or hyperpolarized state.

Inhibition is required for:

1. When one muscle contracts, its antagonist relaxes (by reciprocal innervation).
2. Restraint on muscular activity.
3. Negative feedback – inhibition to control complex neuronal circuits from over-action.

Inhibition four types:

1. Inhibition caused by inhibitory synapses— (just described).
2. Presynaptic inhibition.
3. Clamping (Fig. 99.5).
4. Renshaw cell inhibition.

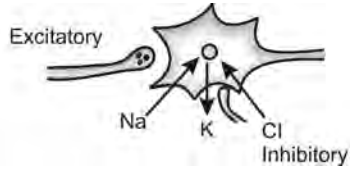


Fig. 99.5: Clamping

Presynaptic Inhibition (Fig. 99.6)

1. Excitatory knob.
2. Inhibitory knob (releasing GABA).

When the inhibitory knob lands on the excitatory knob, this decreases the release of excitatory knob and next neuron will not be excited.

Clamping of Resting Membrane Potential

One of the means of inhibition when sodium enters inside because of excitatory transmitter, potential is not able to reach excitatory value, because of rapid flux of potassium and chloride. So there is tendency of K and Cl to maintain potential near resting value-clamping (when inhibitory pores, are wide open).

Renshaw Cell Inhibition

When motoneuron is stimulated branch of this motor nerve fiber will stimulate the Renshaw cell and the Renshaw cell will in turn inhibit the motoneuron. Renshaw cell secretes acetylcholine at its nerve ending. That is why

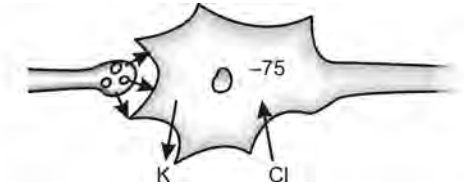


Fig. 99.4: IPSP

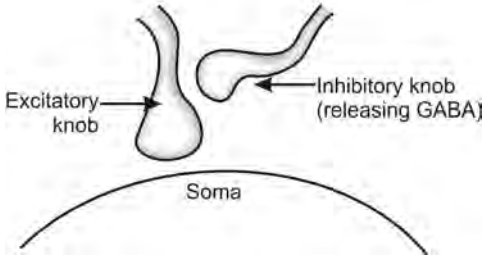


Fig. 99.6: Presynaptic inhibition

there in prolonged Renshaw cell discharge with anticholinesterase (Fig. 99.7).

PROPERTIES OF SYNAPTIC TRANSMISSION

1. *Summation of postsynaptic potential*: If many knobs fire simultaneously effect is summated. Three types of summation:
   i. Spatial summation many knobs fire simultaneously and the effect is summated (Fig. 99.8).
   ii. Temporal summation same knob fires successively (Fig. 99.9).
   iii. Simultaneous summation of inhibitory and excitatory knobs (Fig. 99.9).
2. *Facilitation of neuron:* When few excitatory knobs fire the postsynaptic potential developed is nearer to threshold value (Fig. 99.10). Importance – diffuse signals in NS facilitate large group of neurons so that they can respond quickly and easily to signals from secondary sources.

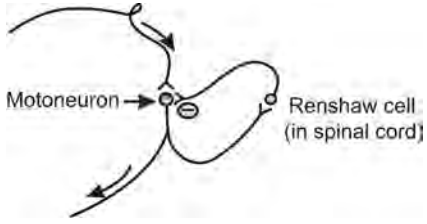


Fig. 99.7: Renshaw cell inhibition

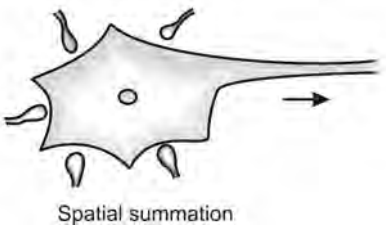


Fig. 99.8: Summation

Special Aspects of Synaptic Transmission

1. It follows principle of *forward conduction.*
2. *Synaptic delay*: Time is required for transmission of impulse from presynaptic knob to postsynaptic neuron because time is consumed for:
   i. Release of transmitter.
   ii. Diffusion of transmitter in synaptic cleft.
   iii. Action of transmitter on postsynaptic membrane.
   iv. Inward diffusion of sodium ions.
   Minimal time is 0.5 m sec.
3. *Fatigue*: If presynaptic knob is repeatedly stimulated there occurs exhausation of transmitter resulting into fatigue.
4. *Post-titanic facilitation*: If titanic current is followed by rest period synapse becomes more responsive explanation – because of repetitive stimulation transmitter vesicles become more mobile and empty rapidly.

Fig. 99.10: Facilitation of neuron

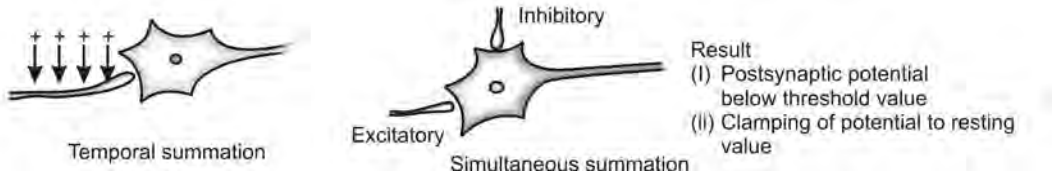


Fig. 99.9: Temporal and simultaneous summation

5. Effect of acidosis and alkalosis:
   pH change from 7.4 to 7.8
   — Results into convulsions
   pH change from 7.4 to 7
   — Results into coma, e.g. diabetic coma.
6. Effect of hypoxia – Cessation of O_2 for few seconds – results into inexcitability of neuron.
7. Effect of drugs:

   Caffeine
   Tea
   Theophylline
   Theobromine
   ↑ Excitability by decreasing threshold for excitation

Strychnine poisoning

– Inhibit the action of inhibitory transmitter. Therefore, neuron, becomes so excited that it fires repeatedly. Severe convulsions result.

Hypnotics
Anesthetics
↑ Threshold for excitation and decrease neuronal activity

Note ↑ = increase

8. In parkinsonism—tremor is because of injury to inhibitory system, which restrains normal motor activity.

CHAPTER

100

Reflex Action

Basis of function of nervous system is reflex action by which it is automatically regulating the different functions of all systems of the body, e.g. heart and digestive system.

DEFINITION

It is the action in which the sensory impulse is automatically converted into a motor effect through the involvement of center (in CNS).

It is an automatic action produced by a reflex pathway consisting of:

1. Sensory path
2. Center (Spinal cord or brain)
3. Motor path, e.g. (a) Painful stimulation will cause withdrawal reflex. That part of the body is withdrawn for protection, (b) All internal organs are functioning automatically with reflex action with (CNS) as a center.

REFLEX PATHWAY OR ARC

Reflex arc consist of (Fig. 100.1): (A) Afferent limb—consisting of receptor and sensory (or afferent) nerve, (B) Efferent limb—consisting of motor nerve and effector organ, (C) Center.

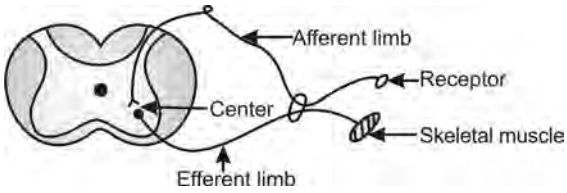


Fig. 100.1: Reflex arc

The different reflex pathways are:

1. Simple reflex path (Fig. 100.2) (2 nuerons are involved), e.g. stretch reflex.
2. Intercalated reflex pathway, (3 neurons) e.g. crossed extensor reflex.
   = when painful stimulus is prolonged the opposite limb is extended.
3. Multineuron or complex reflex paths – many
4. Axon reflex—false reflex, because it is without a center.
   i. If integration between the afferent and efferent limb occurs at a segment of spinal cord – spinal reflex.
   ii. Integration may occur somewhere in brainstem-brainstem reflex, e.g. reflexes concerned with posture and equilibrium, control of BP, etc.
   iii. Integration in cerebral cortex–cortical reflex.

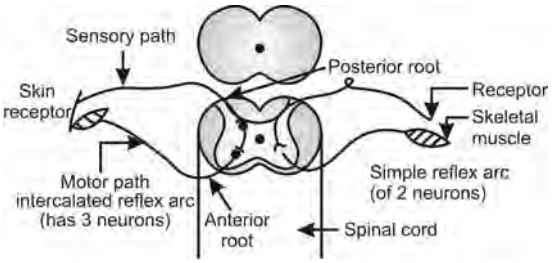


Fig. 100.2: Simple and intercalated reflex arc

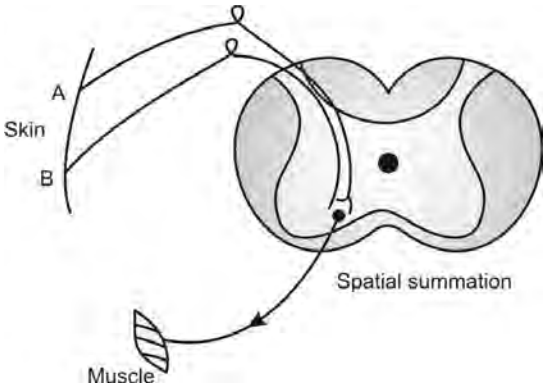


Fig. 100.3: Spatial summation

PROPERTIES OF REFLEX ACTION

Localization

One particular local path has to be stimulated to get that particular reflex action, e.g. biceps jerk—we can only get by stimulating biceps tendon.

Facilitation

Effects of second stimulus is always higher, thereby giving better contraction. Explanation—passage of previous reflex impulse facilitates the transmission of consecutive impulse.

Cause: (Beneficial effect by reducing synaptic resistance), e.g. of reducing synaptic resistance—warming up before actual race, always helps.

Summation

Summations are of two types: (i) Temporal, (ii) Spatial summation.

i. *Temporal summation*: A single subthreshold stimulus may not be effective but 3 to 4 stimuli given in quick succession at the same point will be effective to get the reflex contraction as it is reaching a threshold value. This is known as temporal summation.
ii. *Spatial summation*: When different spots (e.g. A and B) are stimulated with subthreshold stimuli separately no reflex contraction takes place (Fig. 100.3).
   — But when (A) and (B) are stimulated simultaneously, i.e. at the same time, they will be summed up at the center reaching a threshold value and reflex contraction will take place.

Latent Period

It means the time taken for the reflex action (by its sensory and motor path and the center).

– Majority of the time taken is at the synaptic junctions (at the center) and not in sensory and motor paths, hence known as *central delay* or *latent period.*

Irradiation (Fig. 100.4)

It means as the strength of stimulus for reflex action is increased there is reflex contraction of more number of muscles, e.g. if there is mild pinprick of a finger, there is only withdrawal of the finger whereas a strong pinprick causes withdrawal of the upper limb.

This is due to irradiation of impulses from the center above and below.

Reciprocal Innervation

It means when the flexors (e.g. biceps) are contracting extensors (e.g. triceps) are relaxing and *vice versa* (Fig. 100.5). This is because the

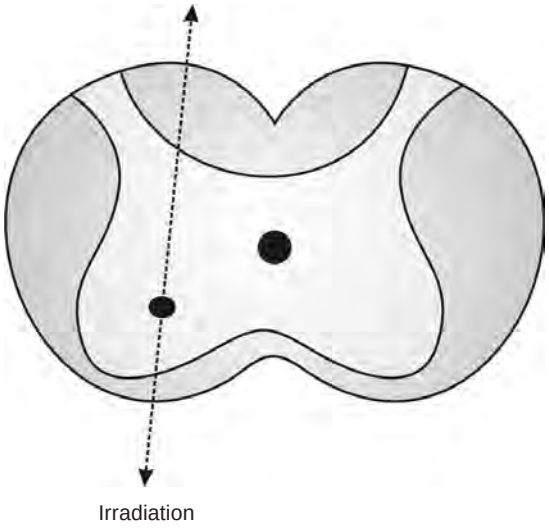


Fig. 100.4: Irradiation

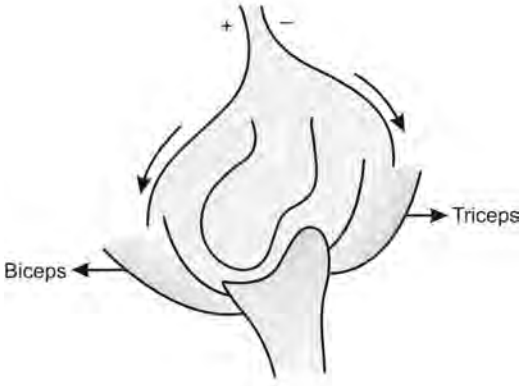


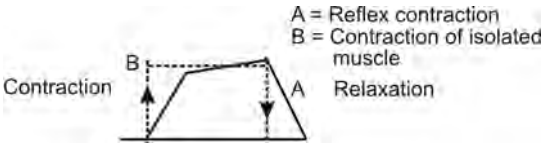
Fig. 100.5: Reciprocal innervation (+ ⟶ stimulation
– ⟶ Inhibition)

nerve, which is stimulating and contracting the biceps is at the same time relaxing the triceps by its another branch which is inhibitory.

It is important in day-to-day activities. This makes the movement smooth and efficient, other wise it would have been jerky.

Recruitment and After Discharge

A = Reflex contraction
B = Contraction of isolated muscle.



Recruitment

The motor components of many reflexes gradually increase to a maximum when a stimulus of unaltered intensity is merely prolonged. It is due to progressive activation of more number of motor neurons therefore the terminology recruitment. In isolated muscle all the muscle fibers contract at the same time.

After Discharge

This means even after stopping the stimulus some tension or contraction remains in the muscle after reflex contraction but in isolated muscle the tension falls immediately.

Therefore, in reflex contraction, relaxation is smooth and gradual. This is due to discharge of impulses from the center even after stoppage of stimulus. Hence, called as *after discharge*.

Importance

By this, our contractions and relaxations of the muscles for day-to-day activity are smooth and not jerky and this helps for our efficient activity.

Block or Resistance or Fractionation

When a stimulus applied directly to the motor nerve of a muscle the amount of contraction becomes much higher than when the same muscle is made to contract reflexly (that is by stimulating appropriate sensory nerve). This indicates that one fraction of sensory impulse is lost in the CNS, to overcome the synaptic resistance (Strength of impulse is reduced

while crossing the synapse). Only fraction of impulse is allowed to pass through the nerve for action.

Occlusion and Subliminal Fringe

Occlusion (Fig. 100.6)

When A and B afferent nerves are stimulated separately each stimulate 9 motoneurons, but when A and B are stimulated together we get contraction of 12 units instead of 18 units. This is because of central overlap, as 6 motoneurons are common to both.

Subliminal Fringe

When A & B afferent nerves are stimulated separately the impulse becomes adequate for some synapse but is inadequate for others. When two are simultaneously stimulated such subliminal stimuli coming from two sources will be summated together so the effect will be stronger than sum total of effects produced by separate stimulation.

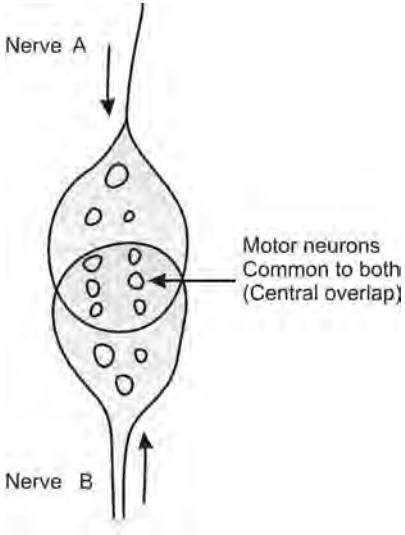


Fig. 100.6: Occlusion

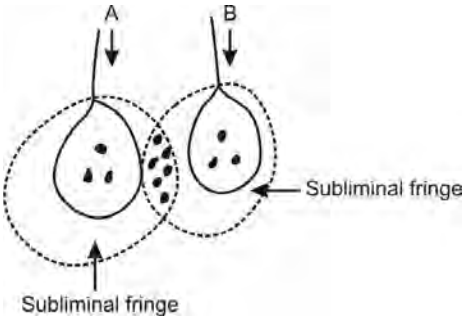


Fig. 100.7: Subliminal fringe

When A & B are stimulated separately we get contraction for 3 units each, but when A & B are simultaneously stimulated we get contraction of 12 units instead of 6. This is because when A & B are separately stimulated 6 other units are stimulated with subliminal strength therefore they are not contracting. But when A & B are stimulated together these two subliminal stimuli for 6 units are summated to become minimal or threshold stimuli. Therefore, 6 units are now effective giving stronger contraction (Fig. 100.7).

Fatigue

If a particular reflex is repeatedly elicited the response becomes progressively feebler and finally disappears altogether. It is a reflex fatigue of muscles or fatigue in a reflex contraction. The seat of fatigue is the synapse (at center) of spinal cord or brain and not the neuromuscular junction as in the isolated muscle.

Fatigue comes first in synapse then in motor endings and lastly in muscle (Fig. 100.8). Proof – After reflex fatigue if motor pathway is stimulated we get normal contraction.

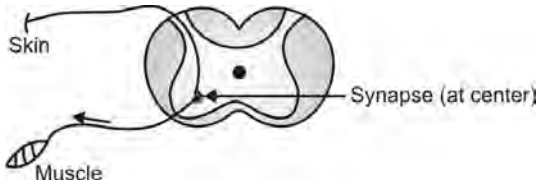


Fig. 100.8: Seat of fatigue

REFLEXES OF THE BODY

Reflexes are of two types:

1. Unconditioned reflex
2. Conditioned reflex.

1. *Unconditioned reflex:* It is present from birth and so no condition is attached for the reflex action, e.g. all the visual reflexes, action of heart, lungs, intestine, etc.
2. *Conditioned reflex*: It is not inborn but is acquired by experience and there are conditions attached for this reflex, e.g.
   i. Sight of good food preparation will produce reflex salivation.
   ii. Smell of good food preparation only, gives reflex salivary secretion.
   iii. Sound of bell at the mealtime in hostel will produce reflex salivary secretion for a students living in hostel and not for others.
   iv. Some develop the conditioned reflex of taking a cup of tea or cigarette first thing in the morning for a sense of defecation.

   Pavlov was the great Russian scientist who was famous for using the conditioned reflexes in dogs to study many of the physiological processes, e.g. (i) Reflex mechanism of secretion of gastric and salivary juice secretion, (ii) Some important nervous phenomenon.

Reflexes of the body can be divided into:

1. Superficial reflexes
2. Deep reflexes
3. Visceral reflexes.

Superficial Reflexes

Reflexes of the Eye

1. *Conjunctival reflex*: Touching the conjunctiva with cotton will reflexly close the eyelids in normal persons.
2. *Light reflex* or *pupillary reflex*: When light is thrown in the eye by torch there will be reflex contraction of the pupil in normal persons, reflex path – sensory path by optic nerve and motor path oculomotor nerve.
3. *Corneal reflex*: Touching the cornea with cotton or finger causes closure of eyelids.

Reflexes of Abdomen or Abdominal Reflexes

Divided into upper abdominal reflexes (Thoracic 7, 8, 9 segments acting as center) and lower abdominal reflexes (Thoracic 10, 11, 12 segments acting as center) scratching by means of pin in these regions of abdomen will produce contraction of muscle underneath (Fig. 100.9).

Planter Reflex

Scratching the sole of foot from behind forward along the lateral side will produce planter flexion of big toe and planter flexion of other toes (Fig. 100.10).

Babinski's sign: When planter reflex gives dorsiflexion of big toe and fanning of other toes. It is present:

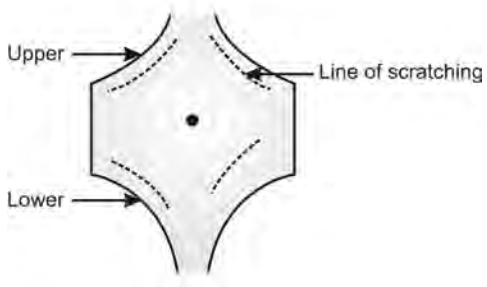


Fig. 100.9: Abdominal reflexes

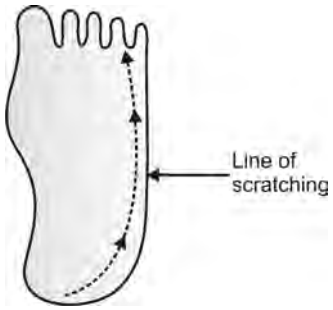


Fig. 100.10: Planter reflex

1. In upper motor neuron lesion*.
2. It is normally present in newborn babies up to infancy before he starts walking.
   i. *Anterior horn cell from where motor nerve takes origin is a lower motor neuron. This is controlled by upper motor neuron situated in brain.
   ii. Pyramidal tract is not myelinated before 18 months. Order of myelination is first sensory, second motor and third association areas.

Deep Reflexes or Jerks— (Deep Proprioceptive Reflexes)

A tendon of a muscle is stimulated by the hammer and we get reflex contraction of the muscle, known as jerk or *tendon reflex.*

There are four deep reflexes:

1. Biceps jerk
   Center 5th and 6th cervical segment.
2. Triceps jerk
   Center 7th and 8th cervical segment.
3. Knee jerk
   Center 2nd, 3rd and 4th lumbar segment.

D. Ankle jerk
   Center 5th lumbar and sacral 1 and 2 segments.

Tendon reflexes: Are stretch reflexes, e.g. knee jerk is monosynaptic stretch reflex.

Importance of deep reflexes or jerks: These reflexes show characteristic variations in many diseases and are of great diagnostic value:

1. If the jerks are exaggerated than normal it means upper motor neuron damage (Present in brain).
2. When the deep jerks are absent it means lower motor neuron damage, e.g. anterior horn cell damage in diseases like peripheral neuritis, anterior poliomyelitis, etc.
3. And gives an idea of the site of lesion.

Reinforcement

The jerk may be reinforced by a strong simultaneous voluntary act, e.g. clenching of jaw, squeezing of the hands, etc. reinforcement is due to irradiation.

CHAPTER

101 Sensations Receptors and Pain

The world around us is recognized through our sensory mechanism. Every sensation is mediated through some specialized neural structures–receptors. Receptors convert stimuli into impulses, which by specialized pathways, end in cortex, activate the cortical structures and we perceive sensations.

CLASSIFICATIONS OF SENSATIONS

1. Sensations are classified in two major groups:
   i. General sensations, e.g. touch, pain, temperature.
   ii. Special sensations, e.g. vision, hearing, smell and taste.
2. Sensations can also be classified as:
   i. *Exteroceptive:* When stimuli are outside the body.
   ii. *Proprioceptive:* When stimuli are from muscles, tendons and joints.
   iii. *Interoceptive:* When stimuli are from inside the body.
3. *Head classified* general sensations into three groups: (i) Epicritic, (ii) Protopathic, (iii) Deep sensibility.
4. General sensations can also be classified into two groups: (i) Cutaneous, and (ii) Deep.

Epicritic or *fine* sensations are: (1) Light touch, (2) Tectile localization, (3) Tectile discrimination, (4) Appreciation of finer grades of temperature between 25° and 40° C.

They are mediated by A group of nerve fibers.

Protopathic: Or curde sensibilities are primitive and more widely distributed sensations. They are: (1) Touch (crude) = simple appreciation of touch, (2) Pain, (3) Temperature (crude).

- Above 40° and below 25°C
- Only recognized as hot and cold.

For protopathic sensations stimuli must be strong enough to arouse sensations, once aroused it is diffuse, poorly localized and unpleasant. They are mediated by C group of nerve fibers.

Deep sensibility: It is produced by stimulation of structures in deeper layers of skin, muscles, bones and joints. They are well localized. They are: (1) Pain, (2) Pressure, (3) Sense of position and movement, and (4) Vibration sense.

Cutaneous sensations: Are sensations aroused by stimulation of skin. They are: (1) Touch, (2) Cold, (3) Hot or heat, (4) Pain, (5) Pressure. All except pain are mediated by receptors. In general receptor has a lamellated connective tissue capsule enclosing a soft cellular core in which the axon ends after loosing the myelin sheath.

Touch Sensation (or Tectile Sensation)

(1) Light touch, (2) Tectile localization, (3) Tectile discrimination, (4) Itching.

Light touch is subserved by three types of receptors:

1. *Meissner s corpuscles* (Fig. 101.1)
   i. Situated in papillae of skin just beneath the epidermis.
   ii. Unevenly distributed, spares on front of forearm, numerous on lips, tongue, hand, foot.
   iii. Elliptical in shape.
   iv. Irregularly coiled nerve ending enclosed by connective tissue capsule.
2. *Merkel s disks* (Fig. 101.2)
   i. Group of 3 cup shaped disks, which have reticulated appearance.
   ii. Nerve fiber breaks in branches one going to each disk.
   iii. Found on fingertips, lips, and mouth.
3. Basket like arrangement of nerve fibers.
   i. It is seen surrounding the base of hair follicles (Fig. 101.3).
   Consist of short vertical filaments each one ending in a small bulbous expansion stimulated by movement of hairs.

Light touch can be tested by placing a:

1. Wisp of cotton on the skin.

Fig. 101.1: Meissner's corpuscle

2. By the use of Von Frey's hair aesthesiometer.
   i. Consist of a series of hairs attached at right angle to a holder.
   ii. Pressure in grams required to bend each hair is marked on the instrument.
   iii. Which hair on bending gives rise to a sensation of touch is found out. This is the sensitivity to touch (in terms of pressure).

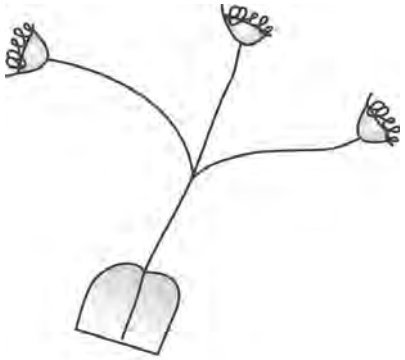


Fig. 101.2: Merkel's disks

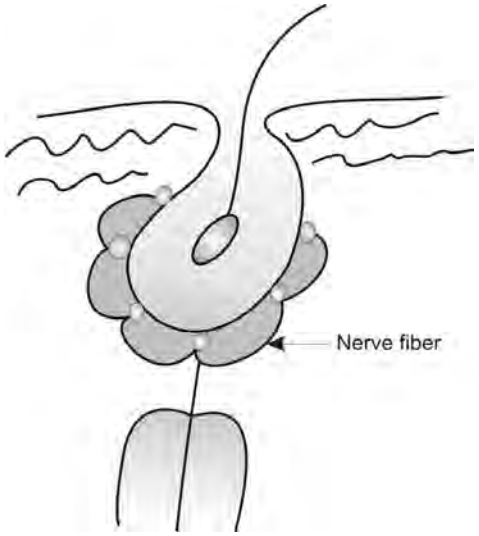


Fig. 101.3: Hair follicle

Tactile Localization

When the skin is stroked gently a normal subject is able to locate the place stimulated. This faculty of localizing the point touched is aquired by experience and is not inborn.

Tectile Discrimination

This is the ability to discriminate between two individual points touched, or to recognize them as separate points. If two points are touched simultaneously it is felt as two points, if the distance between the two is sufficiently great.

If the 2 points of a compass (compass aesthesiometer) are applied to the finger tip, subject feels both the points if they are more than 2 mm apart, if the distance between two points is less, only a single sensation is experienced. On tongue minimum distance to feel 2 points could be 1 mm, whereas on back 60-70 mm. In limbs the power to discriminate gradually diminishes from distal to proximal parts.

Tickling

This is caused by light stimulation of skin and is due to the combined effect of stimulation of touch receptors and pain nerve ending.

Itching

This is a sensation usually felt near the site of injury or during the healing process of an injury.

1. It is due to liberation of a chemical substance from damaged cells of the skin, which act on nerve endings. The sensation of itching is also produced by combined stimulation of pain and touch receptors, but proportion is different from that causing the sensation of tickling.

Temperature Sensation

Or heat and cold sensation.

Cold sensation is mediated by the end bulb of *Krause (Fig. 101.4).* These are less in number than touch receptors and pain nerve ending found mostly in the dermis of the skin.

Warmth is subserved by *end organ of Ruffini (Fig. 101.5).*

They are found near the plexus around the blood vessel in the deeper part of skin and subcutaneous tissue.

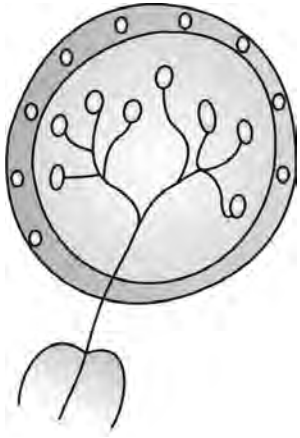


Fig. 101.4: End bulb of Krause

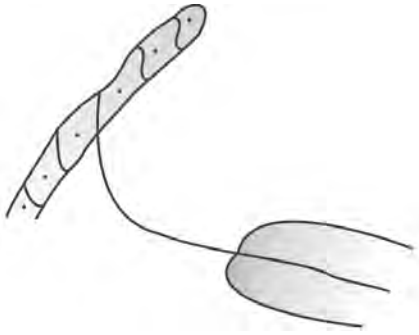


Fig. 101.5: End organ of Ruffini

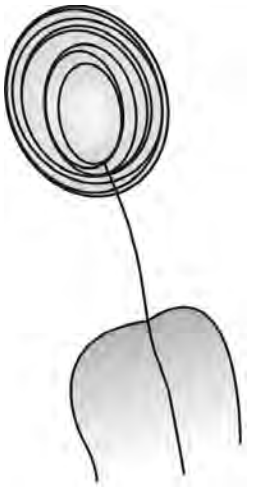


Fig. 101.6: Pacinian corpuscle

Sense of temperature is tested by temperature aesthesiometer.

Pressure

Receptors for pressure are *Pacinian corpuscles (Fig. 101.6).*

Oval is shape, composed of concentric laminae like skin of onion. Afferent fibers penetrate the center. Pressure causing elongation (or distortion) of the organ and stretching of nerve fiber is adequate stimulus. They are found in joints, tendons, periosteum, mesentery, and fascia covering the muscles, deep subcutaneous tissue and in dermis of skin.

It is not a true cutaneous sensation.

PAIN

It is subserved by unmyelinated nerve fibers, which terminate in superficial layer of dermis, in delicate loop lying paralled to surface of the skin or long naked ending.

- Bare nerve ending mediating pain are also present in the cornea and periosteum and parietal pleura where receptors for touch and temperature are usually absent.

Pain nerve endings have no specificity and respond to any types of stimulus: (i) Mechanical, (ii) Electrical, (iii) Thermal, (iv) Chemical. All of them cause or threaten injury, and pain nerve endings respond to it but do not give specific information about the specific stimulus.

– Pain can also evoke reflex action (for protection) (All stimuli which threaten the welfare of the tissues and give pain are called nociceptive stimuli).

Function of Pain

Protective, because when person has pain, he will take measures to prevent further damage. Unless you have had pain you do not know pain.

Difference between pain and others: Pain has built in unpleasant component other sensations may be pleasant.

Exception: War injury, people do not feel pain immediately.

Pain is described in terms of stimulus, e.g. stabbing pain, pearcing pain, gripping pain, pricking pain, etc.

Types of Pain

1. Superficial, e.g. pin prick
2. Deep
   i. Somatic, e.g. tearing of tendon
   ii. Visceral, e.g. stomach pain.

Additional feature of visceral pain is referred pain.

Referred Pain

It is often felt in an area of the skin supplied by the same spinal segment as an irritable viscus, convergence the pain pathways from the body surface and the viscus occur in the

cells of posterior horn and some ascending fibers of the cord are common to the skin and visceral pathways. An impulse from viscera reaching the point of convergence may appear to have originated in the body surface, e.g. (a) Pain arising in the central portion of the diaphragm is referred to the top of the shoulder, (b) Heart pain is referred to the left arm.

Physiological Changes During Pain

Cutaneous Pain

1. Increases heart rate
2. Increases blood pressure
3. But no visceral effects.

Severe Visceral Pain

1. Decreases heart rate
2. Decreases blood pressure
3. Causes nausea, vomiting, sweating, etc.
   For example, attack of appendicitis – causes decrease in HR, decreased blood pressure nausea, vomiting and referred pain to umbilicus.
   For example, myocardial pain may be associated with cold sweating, passing of stools, etc.

A single painful stimulus applied to skin gives rise to two pain sensations fast and slow separated by short interval.

1. The first or the fast pain is short and sharp and is the one rapidly conducted by the A δ group of fibers—(diameter is 1.5 micron and rate of conduction 30 m/sec).
2. The second is more prolonged and severe and is conducted slowly by *C* group of fibers. Therefore, lasts long. Rate of conduction slow, i.e. 1 m/sec and diameter of nerve fibers is less.
3. A third type of pain response follows certain types of injuries like scorching and scalding. It is due to release of chemical substances from the damaged tissues.

Deep Pain (Somatic)

Muscles, tendons, joints and fascia are susceptible to painful stimulation, just like skin. Bare nerve endings are present in these areas.

1. A muscle is insensitive to cutting and pricking but pain is produced by pressure and tension and also by chemical agents.
2. Periosteum and cancellous bones are sensitive but compact bone is not.
3. Walls of arteries are insensitive but walls of the veins are susceptible to pain sensation.
4. Lungs, visceral pleura and pericardium have no pain fibers, whereas parietal pleura and peritoneum are very sensitive.

Deep pain is not accompanied by protective reflexes. Pain is produced by:

1. Physical stimuli–like

i. Prick or cut
ii. Tension: (a) In hand inflammation—exudates is increased—Tension is increased therefore pain, (b) Pulling of hair—Pain, (c) Dilatation of blood vessel—Headache.
iii. Compression: (a) Increased intracranial pressure, e.g. intracranial tumor—Pain, (b) Prolapsed intervertebral disk—roots of nerves are compressed—Pain.
iv. Thermal – stimuli – cause pain.
v. Osmotic – hyperelectrolyte solution-pain.

2. Chemical stimuli—(1) Extrinsic, e.g. acids, alkalies, (2) Intrinsic are more important.

i. Acids – e.g. HCl – responsible for pain in gastric ulcer.
   Proof – give antacid – pain goes off.
   Give H_2 blocker – pain goes off.
ii. 5 hydroxytryptamine – comes out on lysis of platelets.
iii. Potassium—Present inside RBC. If suspension of RBC applied to a blister no pain. Snakebite – causes lysis of RBC – pain.

iv. Histamine
v. Proteolytic enzymes – like kinins, trypsin.

Natural Pain Producing Substance

1. Bee sting – produce histamine
2. Red ants – produce formic acid
   This is nature's gift to animals for chemical warfare
3. Prostaglandins
   i. Pain producing
   ii. Synthesized from arachidonic acid
   iii. Inhibited by aspirine. Therefore, gives relief.
4. Lewis P factor–collection of various substances–Adenyl nucleotides, potassium, myoglobin and acid metabolites.

   P factor is washed away by increased blood flow.

Specific Pathway for Pain

Lateral spinothalamic tract sensation reaches post-central gyrus in parietal lobe.

1. There is pain-inhibiting system working in the body. When pain is there pain-inhibiting system is also stimulated and pain becomes less as threshold for pain is increased.

There are opiate receptors in brain and spinal cord, which can bind endogenous opiates (enkephalins and endorphin). Enkephalin and endorphin are produced in the human body and act like opium alkaloids (e.g. morphine). Whenever pain in there nerve fibers secreting endogenous opiates (i.e. enkephalin and endorphin) are stimulated.

They bind with the opiate receptors and block the pain entry resulting in decreased pain perception.

2. Some people believe when enkephalins and endorphins are absent the person has low threshold for pain. Therefore, he has to take morphine or opium to inhibit pain and he may become drug addict.
3. *Acupuncture*: The needle is pierced and rotated so the enkephalins come out from spinal cord from same segment, which relieves pain.

KINESTHETIC SENSATION

Proprioceptive Sensation is also Known as Kinesthetic Sensation

This is the function of *proprioceptors* or *kinesthetic receptors.* These receptors are present in skeletal muscles and tendons and convey information to CNS about: (a) Position and (b) Movement of different parts of the body. As a result of the messages thus received by the center, contractions of individual group of muscles are coordinated to produce on effective smooth movement, which would be impossible in absence of such impulses from the periphery. For this reason they are called kinesthetic receptors (Kinetic denotes movement and aesthesia = sensation). Most of these impulses do not enter consciousness. The receptors for this purpose are: (1) Muscle spindles, (2) Golgi corpuscles, (3) Pacinian corpuscles. Free nerve endings are also present.

Kinesthetic Sensation is divided into two:

1. *Conscious kinesthetic:* Which we can feel (relayed to cerebrum).
2. *Unconscious kinesthetic:* Which one cannot feel or appreciate (relayed to cerebellum).

Muscle Spindle (Fig. 101.7)

It is fusiform body

1. 1-4 mm long and 0.1 to 0.2 mm broad
2 Lying parallel to and in between muscle fibers in the fleshy part of the muscle.
3. Each consists of 3-6 intrafusal fibers, which arise proximally from extrafusal fibers and end distally in the aponeurosis of the tendon.

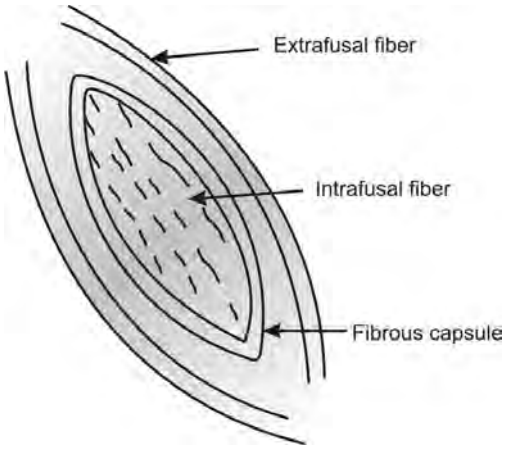


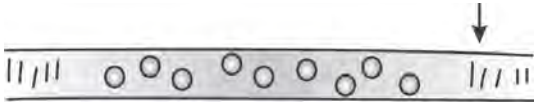
Fig. 101.7: Muscle spindle

4. Enclosed in fibrous capsule.
5. *Intrafusal* fibers have two striated poles separated by noncontractile, nonstriated central nuclear bag.

Nuclear Bag Fibers

Striated pole

6. *Some intrafusal* fibers show dispersal of nuclei—*nuclear chain fibers.* Striated pole



These fibers differ from extrafusal fibers.

7. Each spindle has an afferent and efferent nerve fiber.

Afferent fiber enters through the middle, looses the myelin sheath and ends in one of the two ways:

1. Some become flat and wind themselves in rings or spirals around the middle of the intrafusal fiber they are known as *annulospiral nerve endings* or *primary endings* or *Large IA.* It winds round both nuclear bag and nuclear chain fibers.
2. Other fibers ramify mostly on polar regions like a spray of flowers resembling a Japanese Orchid and are called floral Spray nerve endings or secondary endings or *Group II* afferents.

Efferents fibers are γ efferents: Which arise in γ motoneuron of the anterior horn of the spinal cord. The α motoneurons supply the extrafusal fibers (Figs 101.8A and B).

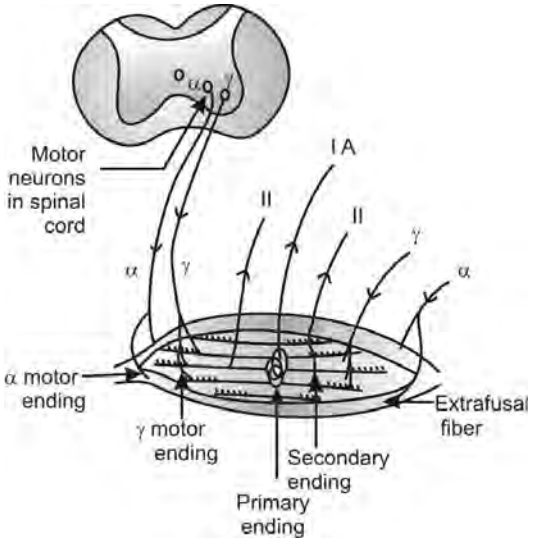
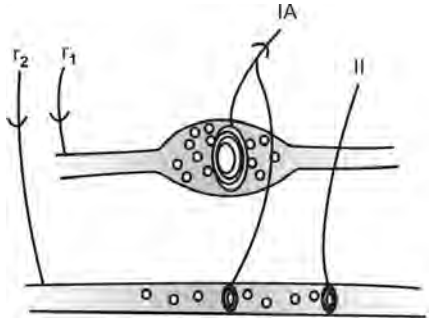


Fig. 101.8A: Muscle spindle—nerve supply



γ1 for dynamic response supply—nuclear bag fibers
γ 2 for static response supply—nuclear chain

Fig. 101.8B: γ motoneurons

Muscle spindles are the receptors for:

Stretch Reflex

Whenever the spindle is stretched the afferent impulses, pass via I and II afferents and enter the dorsal root of the spinal cord. These afferents synapse directly with the α motoneurons. Their motor nerve fibers transmit the reflex signals back to the same muscle containing the spindle and the muscle contracts. This reflex is known as the *stretch reflex (Fig. 101.9).*

Golgi corpuscles: Are situated in tendon close to the muscle fibers, surrounded by lymph sacs and enclosed in fibrous capsule.

Afferent nerve enters the center and ramifies.

1. They respond to tension.
2. Detect the position and movement of the part.

Vibration Sense

This is the ability to perceive stimuli of vibratory nature, e.g. vibrating tuning fork placed on the bone. The receptors are present in the bones, tendons and periosteum. Therefore, it is a deep sensibility.

Stereognosis

The ability to appreaciate the form of a three-dimensional object by its size, shape, texture, and weight without seeing the object.

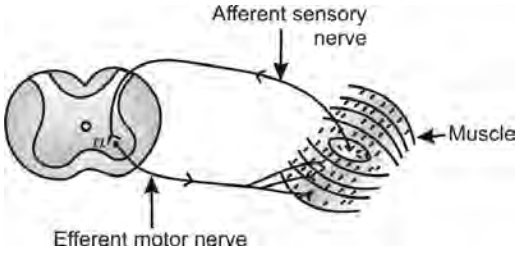


Fig. 101.9: Stretch reflex

It is a complex perception, depending on the synthesis of several somatic sensations subserved mainly by touch and pressure receptors and is one of the most sophisticated sensation present.

CLASSIFICATION AND PROPERTIES

Different Sensory Receptors (End Organs)

Receptors are specialized end organs at peripheral end of sensory or afferent nerve.
Energy that stimulate them:

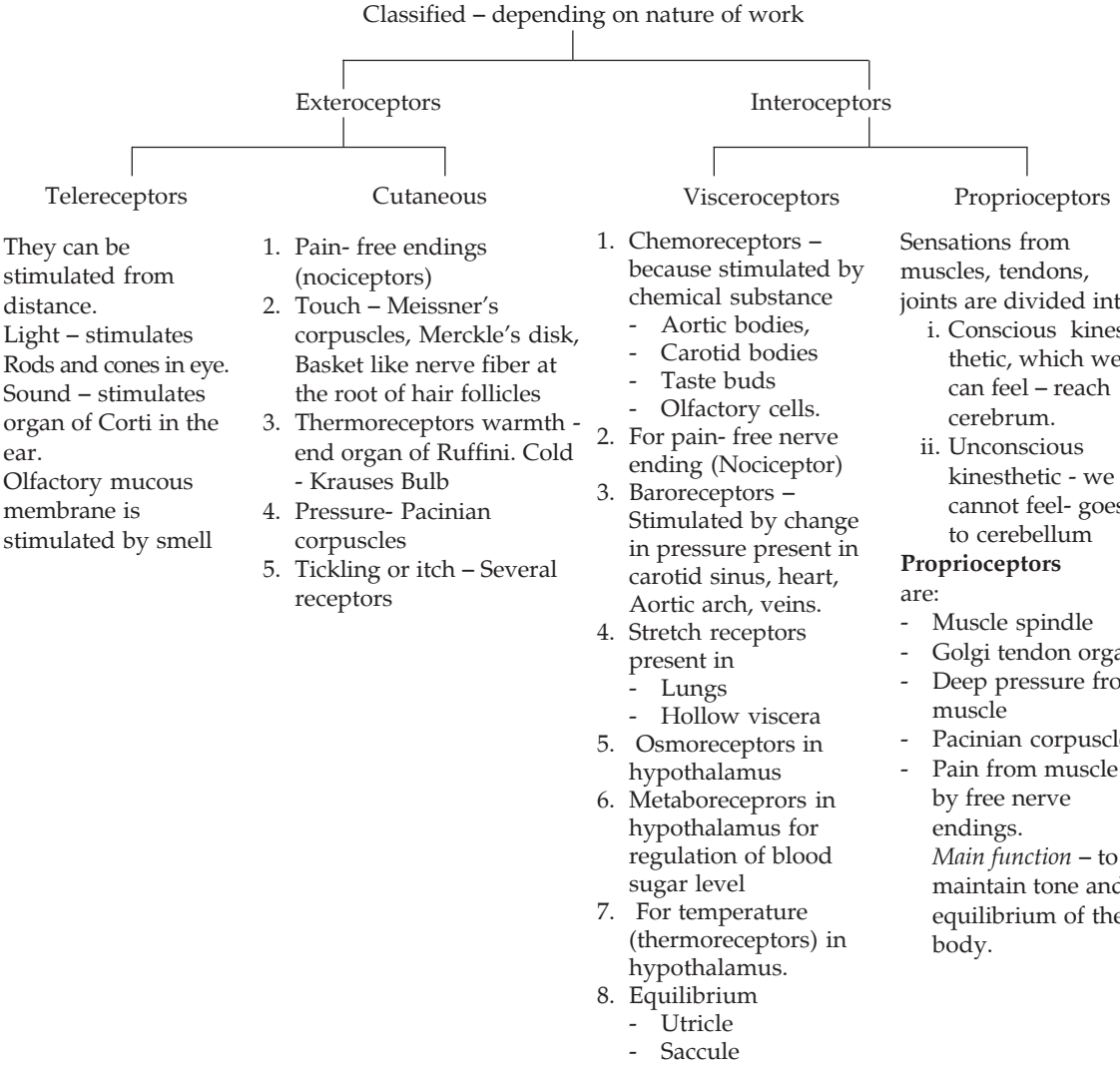
1. Thermal
2. Chemical
3. Mechanical
4. Electromagnetic
   i. Job is to collect information from both outside as well as inside.
   ii. In general, the receptors have a lamellated connective tissue capsule enclosing a soft cellular core in which the axon ends after loosing myelin sheath.

Properties of Receptors

1. *Excitability*: That is they can be stimulated by any common stimulus, e.g. thermal, mechanical, electrical stimulus, which will produce depolarization by ionic exchange of Na^+ & K^+ and generate – generator potential when this goes up to a threshold value – action potential is fired.
2. *Specificity*: That particular specific end organ should be stimulated to get the specific sensation, e.g. for cold sensation, end bulb of Krause are to be stimulated.
3. *Specific projection*: For each sensation there is a specific separate pathway, which is projected to specific part of the brain to get the specific sensation.
4. *Recruitment*: If the strength of stimulus is more, adjoining sensory end organs will be stimulated so we feel spreading of that

sensation more and more from the stimulated part.

5. *Summation*: Stimuli may be summated together to form threshold stimulus for stimulating the end organ.
6. *Fatigue*: Prolonged stimulus may fatigue the end organ.
7. *Intensity discrimination*: If the strength of stimulus is more, intensity of the sensation will be more.
8. *Adaptation*: If the stimulus is for longer time the end organs will adapt to it so that the sensation may be felt to a lesser degree than before. Property of adaptation is present in different degrees in different receptors. Some are rapidly adaptable others are not, e.g. receptors in muscles and tendons do not adapt which has a special significance for maintenance of tone of the muscle.



CHAPTER

102

Spinal Cord

It is not possible to consider the CNS as consisting of a number of separate parts each with a distinct function of its own. In fact effectiveness of the CNS depends on integrated nature of its activity. However, some of the parts like spinal cord deserve special consideration, for understanding the full significance of the nature of the coordinated actions of the nervous system.

Spinal cord gives off 31 parts of spinal nerves in a symmetrical manner. Each nerve has two roots (Fig. 102.1):

1. An anterior or ventral
2. A posterior or dorsal.

The anterior roots are efferent in nature and motor in function.

Posterior roots consist of afferent sensory fibers.

Both the roots contain fibers of widely – differing diameters and a mixed nerve consists of fibers, which are connected to both these roots.

– Anterior root arises as a series of rootlets.

– Posterior root fibers on their way to cord relay in posterior root ganglion.

In spinal cord, gray matter is found in the center and white matter in the periphery as

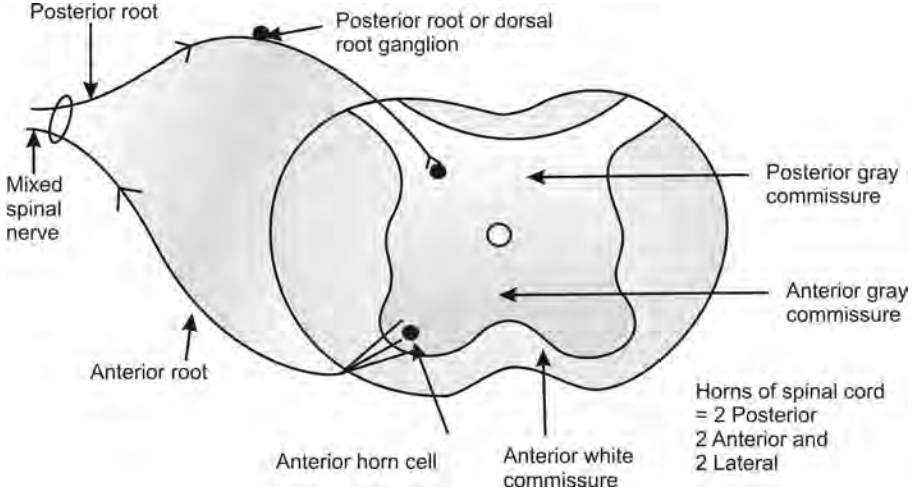


Fig. 102.1: Spinal cord—Horns and roots

fiber tracts. This arrangement is exactly opposite to that found in the brain.

– The gray matter in the center of the spinal cord forms a peculiar type of design which is more or less like a butterfly and reasembles the letter H and has 2 posterior horns, 2 anterior horns and 2 lateral horns (Fig. 102.2).

THE NERVE CELLS OF THE SPINAL CORD

The nerve cells of spinal cord are all multipolar in type and have different sizes. The population of these cells also varies from region-to-region and cells tend to collect in columns or pools.

1. The cells are of Golgi types I and II.
2. Type II cells with short axons are found mainly in the posterior horn of the gray matter. These short axons pass towards the anterior horn of the same or opposite side.
3. Type I cells usually send out their axons into the tracts of the spinal cord.
4. Important groups of cells of the posterior horn are the substantia gelatinosa Rolandi (The chief sensory nucleus) and the Clarke's column.
5. In the lateral portion of the gray matter – especially in the thoracic region are a column of cells which give origin to axons that pass out through the anterior roots as white rami communicates to the sympathetic chain.
6. In the anterior horn of gray matter there are group of cells known as the anterior horn cells. The axons of these cells – streaming out through the anterior nerve roots are the motor components of the spinal nerves.

The White Matter

The white matter around the gray matter contains the ascending and descending pathways called tracts.

These fibers are in general divided into four groups:

1. Long path afferent axons carrying the sensory impulses such as tracts of Goll and Burdach in the posterior column.

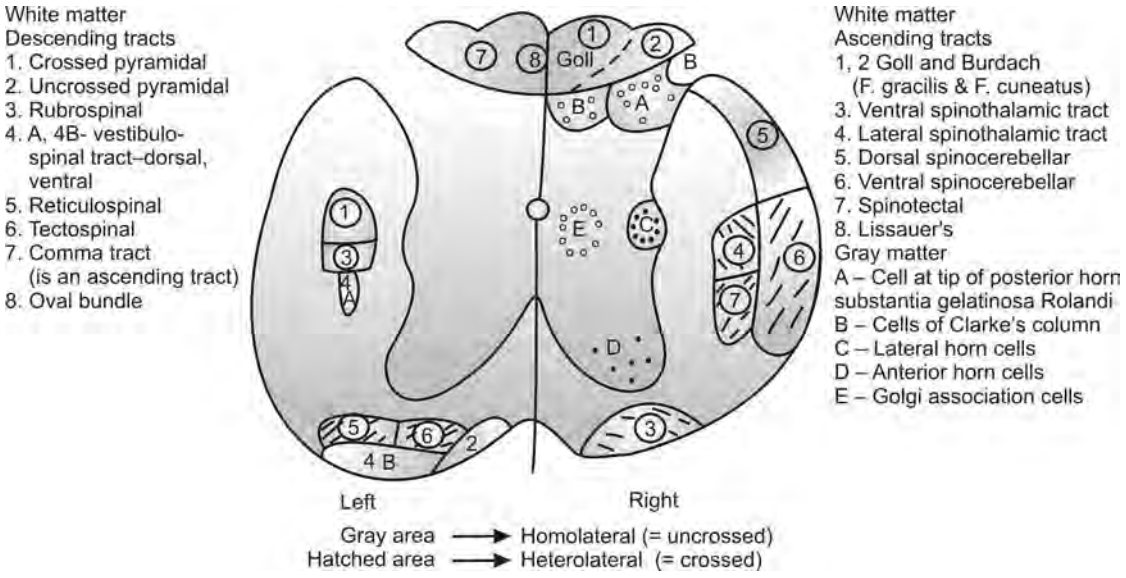


Fig. 102.2 : TS spinal cord

2. Long path efferent axons carrying motor impulses from higher centers to the periphery, e.g. corticospinal or pyramidal tracts.
3. Association or intrinsic tracts which connect adjacent segments of the spinal cord.
4. Commissural fibers which connect opposite halves of the same segment of the spinal cord (Fig. 102.2).

EXTENT OF SPINAL CORD

Extends from foramen magnum to lower border of L1 (Fig. 102.3). Spinal cord is not segmented internally but conventionally divided into spinal segments:

- Cervical 8
- Thoracic 12
- Lumbar 5
- Sacral 5
- Coccygeal 1

Length of spinal cord in male — 45 cm
female — 43 cm

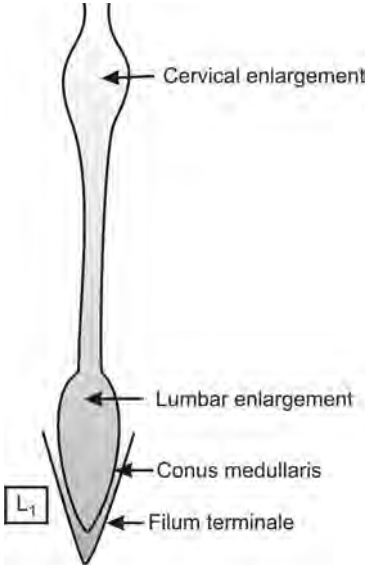


Fig. 102.3: Extent of spinal cord

Diameter of width — 1.2 cm
Weight — 35 grams

At its upper end is medulla and its lower end is known as conus medullaris.

It shows two dilatations (swellings):

1. One in cervical region
2. One in lumbar region.

Because of more gray matters to support limbs.

White matter increases in upper spinal cord.

1. Length of vertebral canal and spinal cord is not equal because vertebral canal grows faster. At birth the spinal cord ends at lower border of L_3. But at adult stage it ends at lower border at L_1.
2. Because vertebral canal is longer than spinal cord (1) there is discrepancy between the vertebrae and spinal segment.
   In cervical segment, discrepancy is of 1 segment.
   In thoracic segment, discrepancy is of 2 segments.
   In lumbar segment, discrepancy is of 3 segments.
3. The roots of lower spinal nerves are stretched (Fig. 102.4).

Meninges: The spinal cord is covered over by meninges from inside to outside they are:

1. Pia mater
2. Arachnoid mater
3. Dura mater (Fig. 102.5).

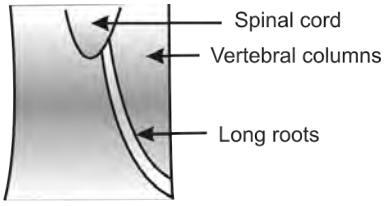


Fig. 102.4: VS lower end of spinal cord

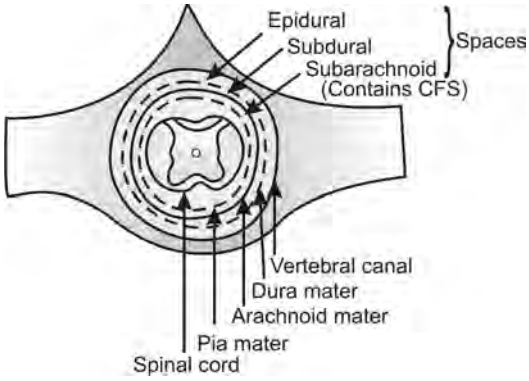


Fig. 102.5: TS vertebral canal

Some Interesting Facts

1. Groups of neurons present in CNS are called nucleus and group of neurons present outside CNS are called ganglia.
2. When nerve fibers come out of spinal cord they form peripheral nerve. Whereas nerve fibers pass into CNS they form tracts.
3. When many tracts come together they form fillet or funiculus, e.g. medial fillet consist of tracts of Goll and Burdach and spinothalamic tract.
4. When number of such tracts join two parts, e.g. (a) Midbrain to cerebral cortex, they are known as cerebral peduncles, (b) Cerebellar peduncle joins cerebellum to brainstem.

CHAPTER

103

Ascending or Sensory Tracts

Ascending tracts consists of:

1. *Major tracts:*
    i. Tract of Goll and Burdach
    ii. Spinothalamic tract—Lateral spinothalamic tract, anterior spinothalamic tract.
    iii. Dorsal and ventral spinocerebellar tracts.
2. *Minor tracts:* They relay to four extrapyramidal nuclei of brain:
    i. Spino-olivary relays to olivary nucleus.
    ii. Spinovestibular relays to vestibular nucleus.
    iii. Spinoreticular relays to reticular nucleus.
    iv. Spinotectal relays to superior colliculus.

TRACTS

1. Comma tract of Schultze
2. Lissauer's tract.

MAJOR TRACTS

Tracts of Goll and Burdach (Fig. 103.2): (1/2 touch (F) + 1/2 kinesthetic (C)) carries 1/2 touch, i.e. fine touch, and 1/2 kinesthetic, i.e. only conscious variety.

Origin

It arises as axons of dorsal root ganglia, i.e. their central processes. The peripheral processes end at the receptors (Fig. 103.1).

1. The sensation are carried first by corresponding spinal nerves then through the

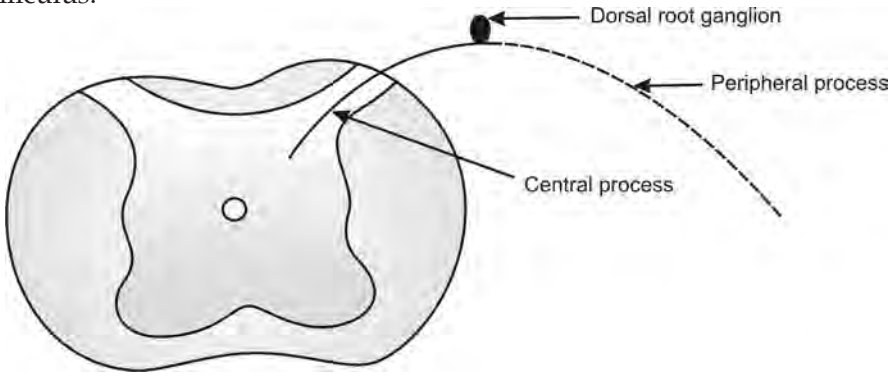


Fig. 103.1: TS spinal cord—Central and peripheral process

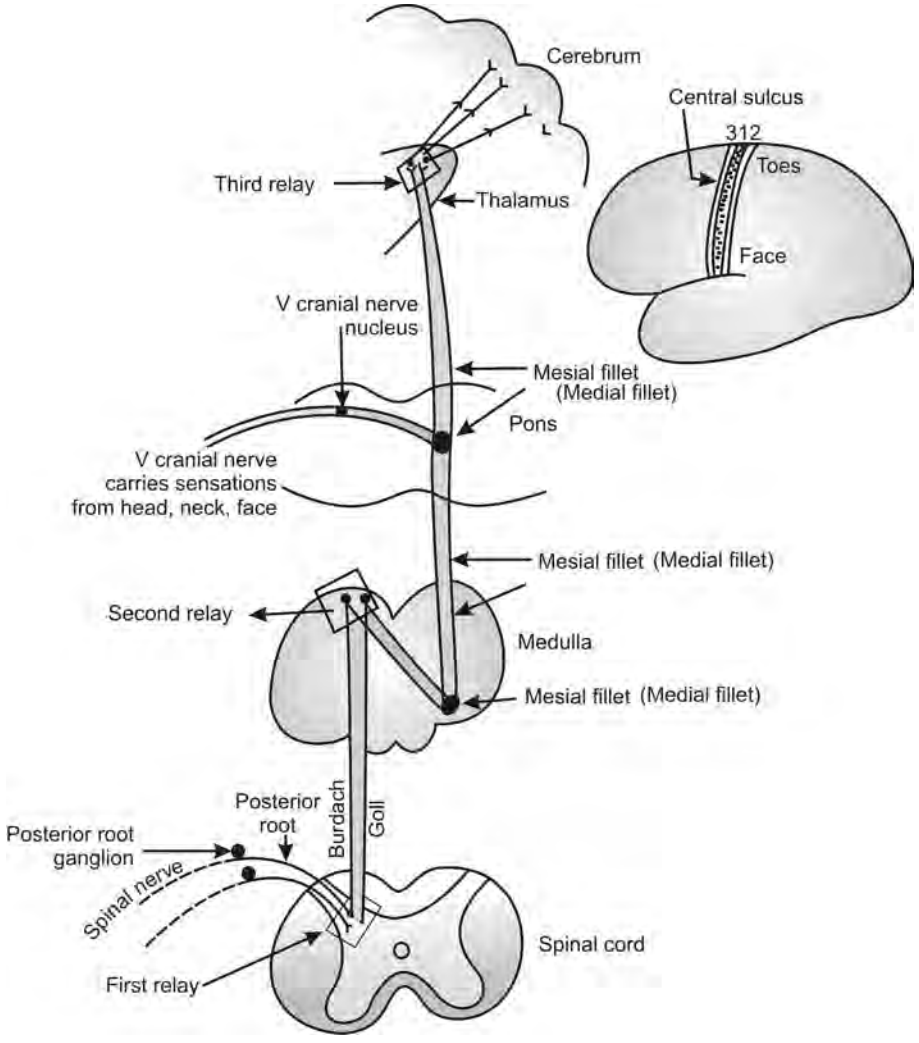


Fig. 103.2: Tract of Goll and Burdach

posterior nerve root making *1st relay* in the posterior horn cell.

2. It then forms 2 separate bundles of Goll and Burdach in the posterior column of the same side.
3. They proceed upwards on the same side up to medulla where there is *second relay*. Tract of Goll relays to nucleus gracilis. Tract of Burdach relays to nucleus cuneatus.
4. Then they cross over to opposite side in medulla as arcuate fibers to form medial fillet or medial lemniscus.
5. It proceeds upwards to pons, where fibers from V cranial nerve carring same sensations (i.e. fine touch and conscious kinesthetic) from the region of head, neck and face of opposite side join.

6. So from here onwards medial fillet or medial lemniscus represents 1/2 touch (fine) and 1/2 kinesthetic (conscious) sensations from whole of the opposite half of the body.
7. Medial fillet or medial lemniscus ascending upwards makes the third relay in the ventral posterior part of lateral nucleus of thalamus situated at the base of the cerebrum.
8. From here fibers spread upwards to reach sensory areas of cerebrum 3, 1, 2 in post-central gyrus where face is represented down and toes in the midline.

   Tract of Goll and Burdach carries:
   1. Fine touch
   2. Tectile discrimination
   3. Tectile localization
   4. Sense of position (Canscious kinesthetic sensation)
   5. Sense of vibration
   6. Stereognosis (Sense of knowing the object by feel).

Spinothalamic Tract (Fig. 103.3)

(Carries 1/2 touch + pain + temperature
|→(Crude)

1. Sensations first are carried by corresponding spinal nerve, pass through posterior nerve root via posterior nerve root ganglion.
2. First relay takes place in posterior horn cells. Then fibers cross immediately to opposite side forming two separate tracts:
   i. Anterior or ventral spinothalamic tract carries 1/2 touch (Crude).
   ii. Lateral spinothalamic tract – carries temperature and pain).
3. Then they proceed upwards to medulla to join with medial fillet (it is also known as mesial fillet or medial lemniscus).
4. Then pass to pons as medial fillet where it is joined by fibers from V cranial nerve of opposite side carring same sensations (1/2 touch (curde) + pain + temperature) from head, neck and face.
5. Medial fillet relays to ventral posterior part of lateral nucleus of thalamus. This is the second relay.
6. From here fibers spread upwards to reach sensory areas of cerebrum 3, 1, 2 in postcentral gyrus where face is represented down and toes in the midline.
7. From the description of tract of Goll and Burdach and spinothalamic tract it is clear that sensory area of one side of cerebrum represents whole of the opposite half of the body for the sensation of touch, pain, temperature and conscious kinesthetic.

   Hence, damage to sensory area of one side will produce loss of sensations of opposite side of the body.

Spinocerebellar Tract

They are two: (1) Dorsal, and (2) Ventral Spinocerebellar tracts, i.e. (Flechsig's) and (Gower's):

Carrying unconscious kinesthetic sensation (Fig. 103.4):

1. These sensations from muscles, tendons and joints are carried first by spinal nerve, pass through posterior nerve root enter the spinal cord and relay in Clarke's column of cells, near posterior horn cell forming:
   i. Dorsal spinocerebellar (Flechsig's) tract.
   ii. Ventral spinocerebellar (Gower's) tract.
2. They ascend on the same side in the lateral column of spinal cord. Ventral spinocerebellar tract is made up of fibers arising from Clarke's column of both sides. It is comprised mostly of crossed and partly of uncrossed fibers.

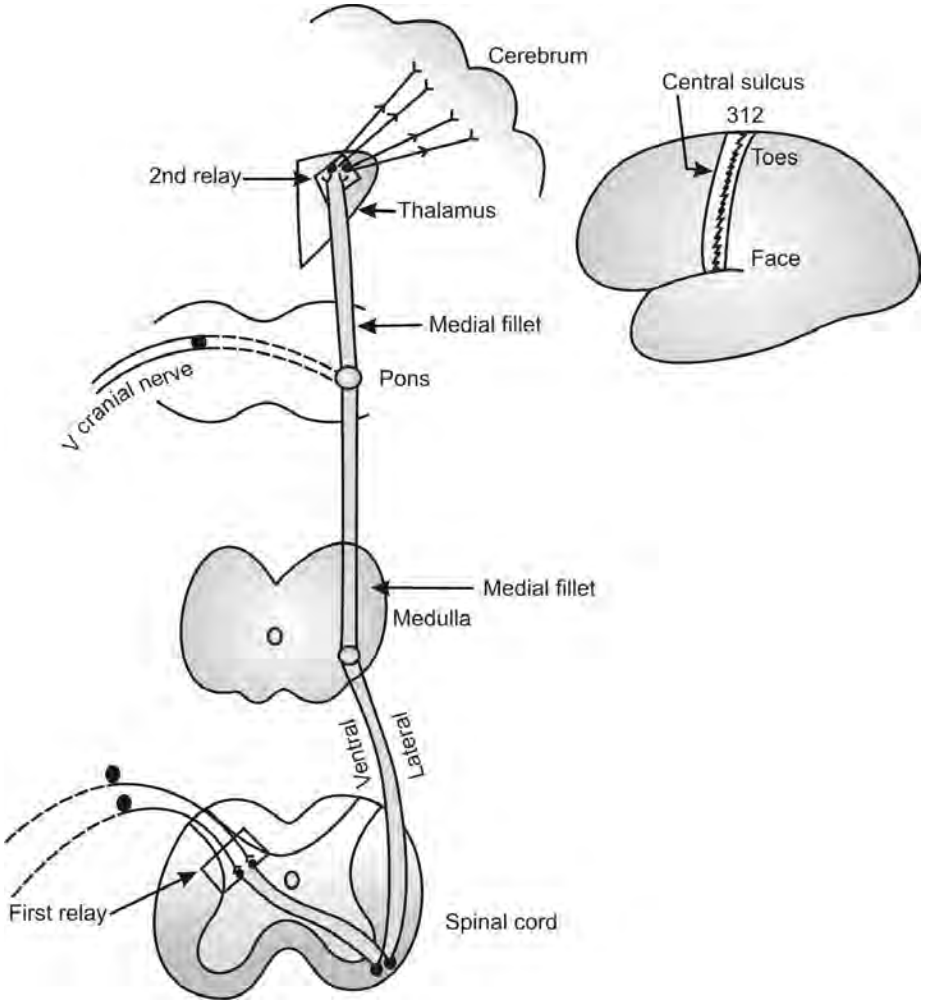


Fig. 103.3: Spinothalamic tract

3. Dorsal spinocerebellar tract reaches the medulla and enters the cerebellum of same side through inferior cerebellar peduncle.
4. Ventral spinocerebellar tract crosses medulla, pons and reaches the level of red nucleus in the midbrain. Here the fibers turn sharply backward and downward and enter superior cerebellar peduncle of the same side.
5. Unconscious kinesthetic sensations are represented on the same side of the cerebellum because the crossed fibers from ventral spinocerebellar tract again cross through middle cerebellar peduncle and end ultimately in the same side cerebellum (Fig. 103.4).

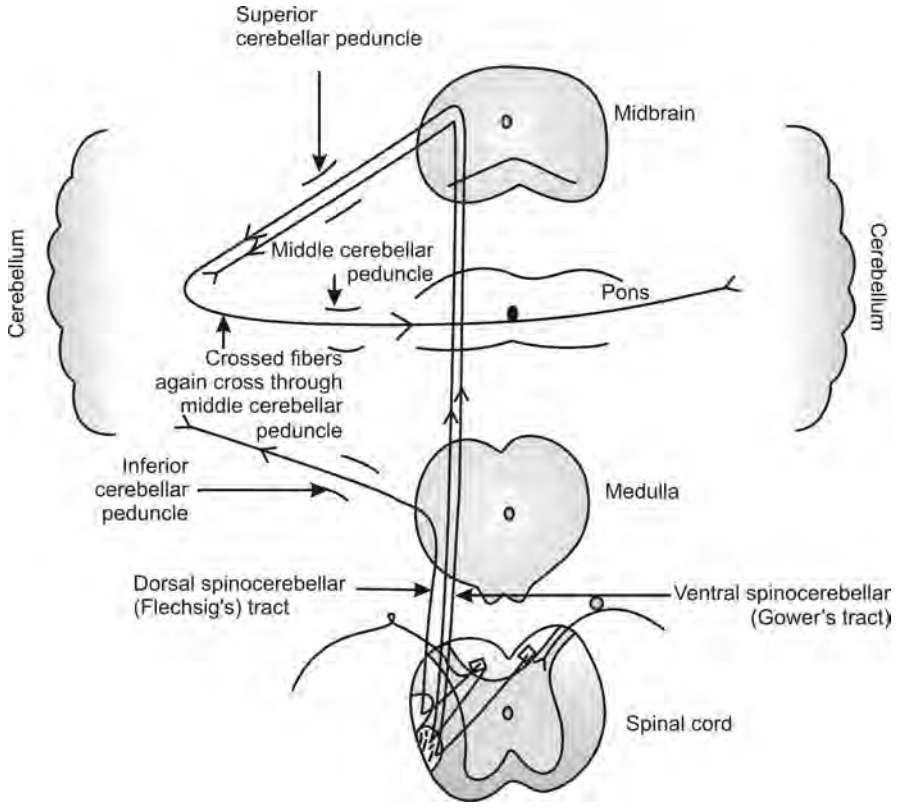


Fig. 103.4: Dorsal and ventral spinocerebellar tracts

MINOR TRACTS

1. *Spino-olivary*: It originates in posterior horn cells of opposite side, ascends in the anterior funiculus and ends in inferior olivary nucleus of medulla. From here it is relayed to cerebellum via inferior cerebellar peduncle. It carries proprioceptive impulses from the muscles.
2. *Spinotectal*: Fibers are derived from chief sensory nucleus of opposite side, ascend in lateral funiculus and terminate in superior colliculus of the midbrain. It subserves spinovisual reflexes.
3. *Spinovestibular:* It is for postural reflexes.
4. *Spinoreticular*: It is for alertness of mind.
5. *Comma tract of Schultz:* It is in reality a descending tract. It begins from posterior horn cells and goes down few segments only.

Function

They are responsible for local reflexes and bind together these segments for common reflex action.

Lissauer's Tracts

These are locally ending tracts, run for few segments and are supposed to be 1st neurons of spinothalamic tract.

CHAPTER

104

Descending or Motor Tracts

Descending or motor tracts have been divided into two groups:

1. *Pyramidal tracts or corticospinal tracts*:
    i. Direct pyramidal (Uncrossed) or anterior corticospinal tract.
    ii. Indirect pyramidal (Crossed) or lateral corticospinal tract.
2. *Extrapyramidal tracts:* These are five in number and arise from five extrapyramidal nuclei.
    i. Olivospinal from olivary nucleus.
    ii. Vestibulospinal from vestibular nucleus.
    iii. Reticulospinal from reticular nuclei.
    iv. Tectospinal from superior colliculus.
    v. Rubrospinal from red nucleus.

PYRAMIDAL TRACT

Starts from pyramidal cell layer of cerebral cortex of the motor area – number 4, in front of central sulcus, face representation is downwards while toes are represented upwards (Fig. 104.1).

1. Pyramidal tract passes downward as corona radiata to the internal capsule on the lateral side of thalamus and occupies anterior 2/3 of posterior limb of internal capsule.
2. Then it passes down. In midbrain it occupies the middle 3/5 of lateral surface. Here the temporopontine and frontopontine fibers are placed laterally and medially respectively.
3. Then it passes down. In the pons it is divided into large number of bundles because it has to pass through many nuclei of pons called nuclei pontis.
4. Then fibers pass to medulla where 90 percent of the fibers cross to the opposite side, known as *crossed pyramidal tract*, while remaining 10 percent of the fibers remain uncrossed known as *uncrossed pyramidal tract.* The crossing is known as the *great motor decussation*. It occurs at the lower border of medulla. The pyramidal tract fibers produce an elevation on the ventral side of the medulla. One on each side known as *pyramid*. Therefore, it is known as pyramidal tract and also because it arises from pyramidal cells in area 4 of cerebral cortex.
5. While descending through brain pyramidal tract fibers give off collaterals, which terminate on the extrapyramidal system and via interneurons on the cerebellum. Therefore, extrapyramidal system and cerebellum are fired concomitantly.

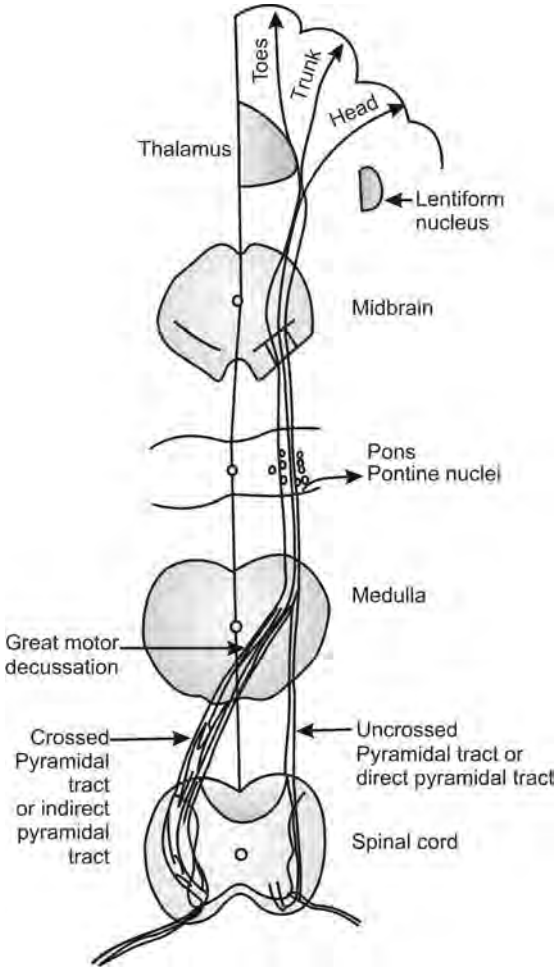


Fig. 104.1: Pyramidal tract

6. Fibers pass down in the spinal cord as crossed pyramidal tract. They make connection with anterior horn cells passing through the gray matter of the spinal cord.

Functions of Pyramidal Tract

It is concerned with motor activity of the body, i.e. voluntary contraction of skeletal muscles.

The pyramidal fibers from one side of the brain are crossing to opposite side. Hence, if there is damage to one side of the brain (commonly damage to internal capsule), there is paralysis of opposite side of the body. This paralysis will be of upper motor neuron type.

Role of Uncrossed Fibers

About 10 to 15 percent uncrossed fibers are present only up to 12th thoracic segment, which supply thoracic muscles of respiration. Hence, when there is lesion of internal capsule of right side, thoracic muscles of left side do not become completely paralyzed because left side is also supplied by uncrossed fibers of left side.

EXTRAPYRAMIDAL TRACTS (FIGS 104.2A and B)

They are:

1. Olivospinal tract
2. Vestibulospinal tract
3. Reticulospinal tract
4. Tectospinal tract
5. Rubrospinal tract.

1. *Olivospinal tract:* Originates from olivary nucleus of medulla and crosses to opposite side.

All these four tracts after crossing descend to spinal cord, and finally will make connection with anterior horn cells. Thus, controlling the voluntary muscles.

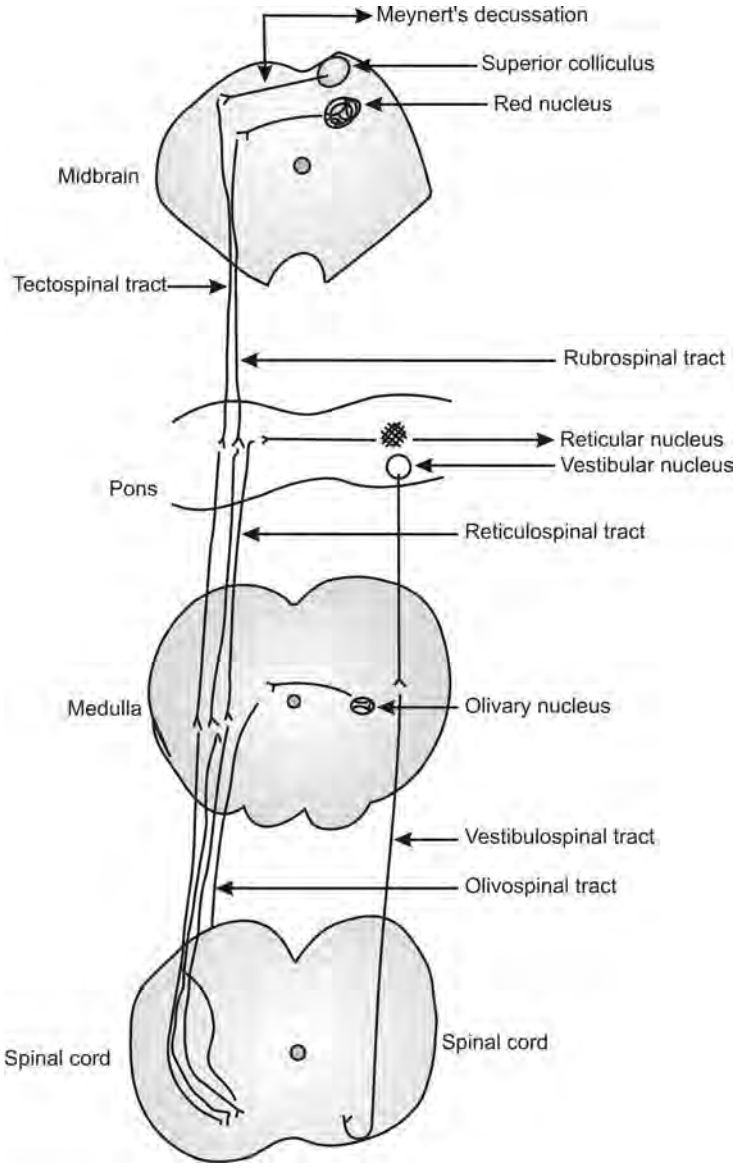


Fig. 104.2A: Extrapyramidal tracts

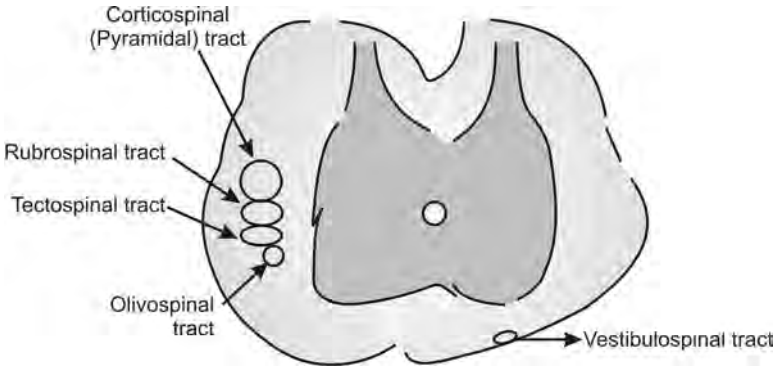


Fig. 104.2B: TS spinal cord showing situation of extrapyramidal tracts

2. *Vestibulospinal tract:* Originates from vestibular nucleus of pons but remains on the same side of the spinal cord. It also makes connection with anterior horn cells and control voluntary muscles.

Rubrospinal tract is always in front of pyramidal tract in spinal cord, therefore it is also called as pre-pyramidal tract.

3. *Reticulospinal tract*: Originates from reticular nucleus in pons and crosses to opposite side.
4. *Tectospinal tract:* Originate from deeper layers of superior colliculus. Crosses at once to opposite side. The decussation is known as Meynert's decussation.
5. *Rubrospinal tract*: Originates from red nucleus in the midbrain, crosses immediately to opposite side. The decussation is known as Forel's decussation.

Extrapyramidal System and Functions

Extrapyramidal system consists of: (a) Part of cerebrum known as extrapyramidal areas no. 6 and 8, (b) Caudate nucleus of corpus striatum, (c) Five extrapyramidal nuclei, and (d) Their five extrapyramidal tracts, i.e.

1. Tectospinal tract
2. Rubrospinal tract
3. Vestibulospinal tract
4. Reticulospinal tract, and
5. Olivospinal tract.

FUNCTIONS

1. The most important function being maintenance of normal tone of the muscles, thereby control posture and equilibrium of the body. Thus, the control of tone, posture, and equilibrium is 90 percent function of EPS.
2. It is responsible for automatic associated movements, e.g. swinging of arms while, walking will be absent when this system is damaged.
3. Extrapyramidal pathways can act as an alternate pathway for voluntary move ments (Main is pyramidal pathways). Pyramidal tract work on the background of extrapyramidal system, because extrapyramidal system maintains tone, therefore pyramidal system is able to move muscle.
4. Some voluntary movements in times of emergency, e.g. when there is paralysis of one side of the body the person may be able to stand and even walk slowly with support of another person but actual voluntary movements are not possible.
5. But in lower animals it is the seat of motor activity.

CHAPTER

105 Upper Motor Neuron Lesion, Lower Motor Neuron Lesion and Internal Capsule

LOWER MOTOR NEURONS

Lower motor neurons are:

1. Anterior horn cells, which are in continuation with anterior nerve root and their spinal nerve (Fig. 105.1).
2. Motor cranial nerve nuclei with their corresponding nerves especially v, vii, ix and x cranial nerves.

Effect of lower motor neuron lesion: If anterior horn cell, anterior nerve root and corresponding spinal nerve (or motor cranial nerve) are damaged, it will produce following symptoms:

1. Paralysis of the muscles supplied by that nerve. Here the muscles paralyzed in lesion are less in number in comparison with upper motor neuron lesion.
2. Complete loss of tone of the paralyzed muscles as the reflex arc for the muscle tone is broken. This type of paralysis with loss of tone is called *flaccid type of paralysis.*

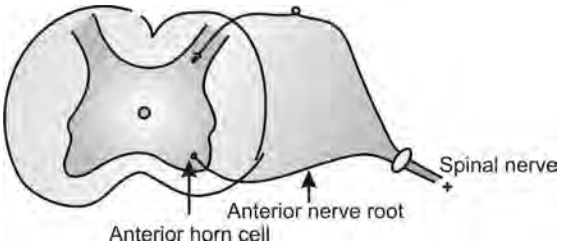


Fig. 105.1: Lower motor neuron

3. Loss of superficial and deep reflexes. Again because the reflex arc is broken. The same reflex arc for muscle tone is required.
4. There will be degeneration of the muscles concerned. This is due to the fact that the muscle is cut of from its anterior horn cell, which is supposed to supply vital nutrition.
5. Because the muscle has degenerated the reaction of degeneration will be positive.

Normally KCC > ACC, i.e. contraction by cathode closing current is greater than anode closing current, but because of degeneration of muscle ACC > KCC.

UPPER MOTOR NEURONS

The neurons, which are at higher level than anterior horn cells and are concerned with motor activity and control anterior horn cells are called upper motor neurons.

EFFECT OF UPPER MOTOR NEURON LESION

The lesion is at a higher level, may be to pyramidal tract or to extrapyramidal tract and the lesion may be at (Fig. 105.2):

1. Cerebral cortex
2. Internal capsule
3. Spinal cord.

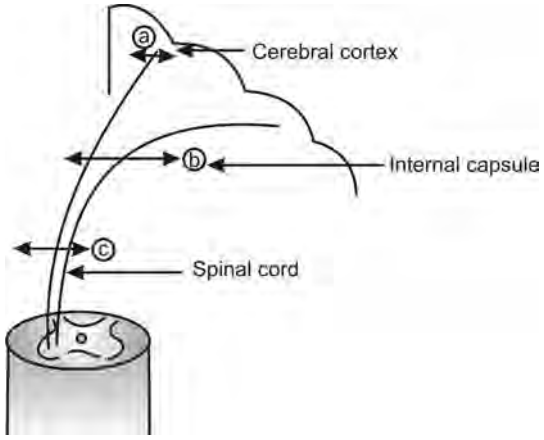


Fig. 105.2: Possible sites of UML (a,b,c)

It will produce following symptoms

1. Paralysis of muscles of opposite side of the body, but large number of muscles are affected.
2. Tone of muscles concerned is exaggerated. This is due to cutting of the inhibitory influence for the muscle from the upper motor neuron, therefore the tone is increased. This is known as *spastic paralysis*.
3. *Deep reflexes*, i.e. jerks are exaggerated, again because of the inhibitory action from UMN is lost.

   Superficial reflexes are lost because reflex pathway for this is complex, center is in brain, as it is cut off so reflex is lost completely.
4. There will be no degeneration of muscles concerned, as they are not cut off from anterior horn cells, which is vital for their nutrition.
5. Because there is no degeneration of muscles, reaction of degeneration will be negative, i.e. KCC > ACC.
6. *Babinski s sign*: Positive. That is the planter reflex, which is normally planter flexion now becomes dorsiflexion of great toe and fanning of other toes.

Importance of UMN and LMN Lesion

By the symptoms we know definitely whether the UMN or LMN are damaged and the location of damage can also be known which helps in the treatment.

INTERNAL CAPSULE

This is an important area at the base of the cerebrum on lateral side of thalamus and caudate nucleus (Fig. 105.3).

It is V shaped pointing outwards.

All the pyramidal fibers are passing through this small area along with some other important fibers, e.g. sensory, visual and auditory fibers.

The pyramidal fibers while passing through the internal capsule are rotated through 90° so that head is anteriorly represented and legs posteriorly.

- This area of brain is very important clinically because many fibers pass through this area.

Internal capsule consists of:

Anterior limb, genu and posterior limb.

Genu

It is nothing but the bend between anterior and posterior limb.

It is occupied by pyramidal fibers for head, neck and face region. This has comparatively large representation.

Posterior Limb

Anterior 2/3 of posterior limb is occupied by the pyramidal fibers for thorax, abdomen and legs.

Behind the pyramidal fibers are three important sensory fibers passing through the posterior limb.

1. *Mesial fillet:* Which has relayed already to thalamus and now passing as thalamic

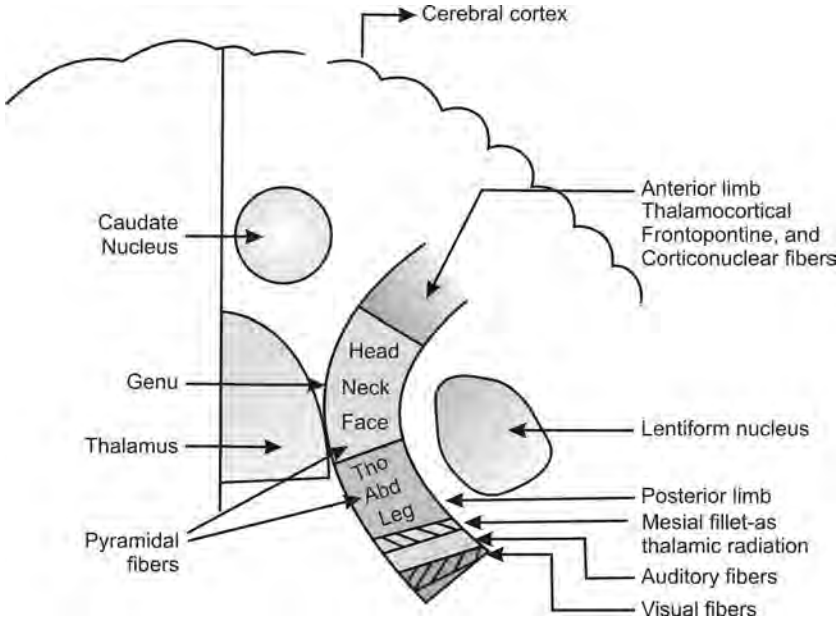


Fig. 105.3: Internal capsule

radiation, representing touch, pain, temperature and kinesthetic (conscious), sensations of opposite side of the body.
2. Auditory fibers of the same side.
3. Visual fibers of the same side.

Clinical Importance

As all the pyramidal fibers pass through this small area of internal capsule. Damage to this area produces paralysis of opposite side of the body including, head, neck, face. Usually, this occurs in old persons suffering from hypertension and atherosclerosis.

Hemiplegia

Paralysis of 1/2 of the body including head, neck, face (of opposite side).

CHAPTER

106 Lesions of Spinal Cord—Hemisection and Complete Section

HEMISECTION OF SPINAL CORD (FIG. 106.1)

Definition

Lesion involving lateral 1/2 of spinal cord.
It is due to injury:

1. A stage of spinal shock first appears during which
   i. Subject may become unconscious.
   ii. Muscles are flaccid.
   iii. Reflexes are abolished.
2. In patients who survive, this stage gradually passes off and
3. Typical features of lesion gradually develop, helpful for localizing the site of injury.

Typical features of spinal hemisection.
Degenerative changes:

1. Peripheral parts of cut fibers degenerate up to next neuron.
2. Central part of the fibers and related nerve cells may degenerate to a variable extent.
3. There may be transneuronal degeneration.

Functional Changes

1. A band of cutaneous hyperesthesia is seen above this level on the same side of lesion, corresponding to distribution of next higher sensory nerve and is due to irritation of sensory fibers (Fig. 106.1).

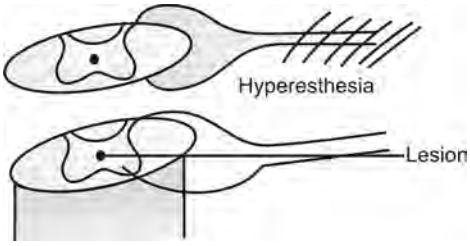


Fig. 106.1: Spinal hemisection— functional changes above the lesion

At the Level of Lesion (Fig. 106.2)

1. There is complete loss of sensation due to severance of posterior nerve root fibers on the same side.

Opposite side: Some loss of pain sensation because pain fibers of spinothalamic tract cross horizontally in the same segment.

2. Flaccid type of paralysis (LMN type) present on the same side.
3. Vasomotor paralysis in the affected segment on the same side.

Below the Level of Lesion

1. Sense of position, movement, fine touch, tectile localization and tectile discrimination, carried by tract of Goll and Burdach (which do not cross in spinal cord) are lost on the same side.

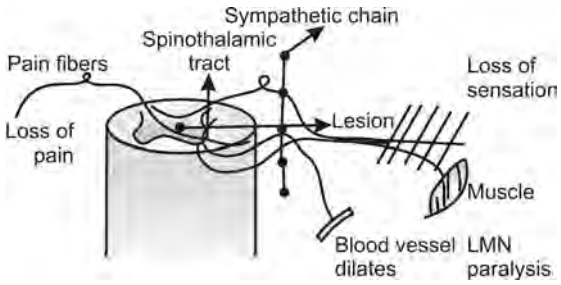


Fig. 106.2: Spinal hemisection—functional changes at the lesion

Loss of sense of position and muscles sense, lead to ataxia (Loss of coordinated movements).

2. Unconscious kinesthetic sensations from muscles to cerebellum carried by spinocerebellar tracts are not completely interrupted because each ventral spinocerebellar tract carries impulses from both sides of the body.
3. Pain and temperature are lost on the opposite side. They are carried by spinothalamic tract and these fibers cross shortly after entering the cord but no loss of pain and temperature on the same side.
4. The touch fibers have double pathway in spinal cord, so in hemisection touch fibers, which have crossed from the opposite side to anterior spinothalamic tract as well as fibers from same side going in tracts of Goll and Burdach are affected.

Thus fine touch, tactile localization and tectile discrimination	Lost on the same side and rest of the touch intact on same side.
Reverse occurs on opposite side – fine touch, tectile localization, tectile discrimination	Intact on opposite side Rest of the touch is lost

Net result is – there is no complete loss of touch on either side.

5. Extensive paralysis of UMN type occur below the level of lesion on same side.
6. Vasomotor paralysis – due to interruption of pathways from lateral horn cells to anterior nerve root causes dilatation of the blood vessels at and below the level of lesion on the same side. Skin becomes red at first later becomes cyanosed or blue.

Thus, below there is extensive sensory loss but little motor loss on opposite side. While on the same side there will be extensive motor loss but little sensory loss. This syndrome is known as *Brown Sequard syndrome (Figs 106.3A and B)*.

EFFECT OF COMPLETE TRANSVERSE SECTION OF SPINAL CORD

1. In higher animals, the spinal cord has few autonomous functions.
2. Simple spinal reflex is profoundly influenced by higher centers.
3. Sudden and complete interruption of the continuity of the spinal cord occurs as a result of injuries like gunshot wounds, fracture dislocation of vertebrae or may result from acute inflammation of spinal cord known as transverse myelitis.

Effects can be Divided in Three Stages

1. Stage of spinal shock (Stage of flaccidity).
2. Stage of reflex activity (Stage of recovery).
3. Stage of degeneration (Stage of reflex failure).

Stage of Spinal Shock

The higher the animal is in the phylogenetic scale the longer is the duration of the spinal shock.

1. In cat – few minutes
2. In dog – few hours
3. In monkeys – few days
4. In man – few weeks.

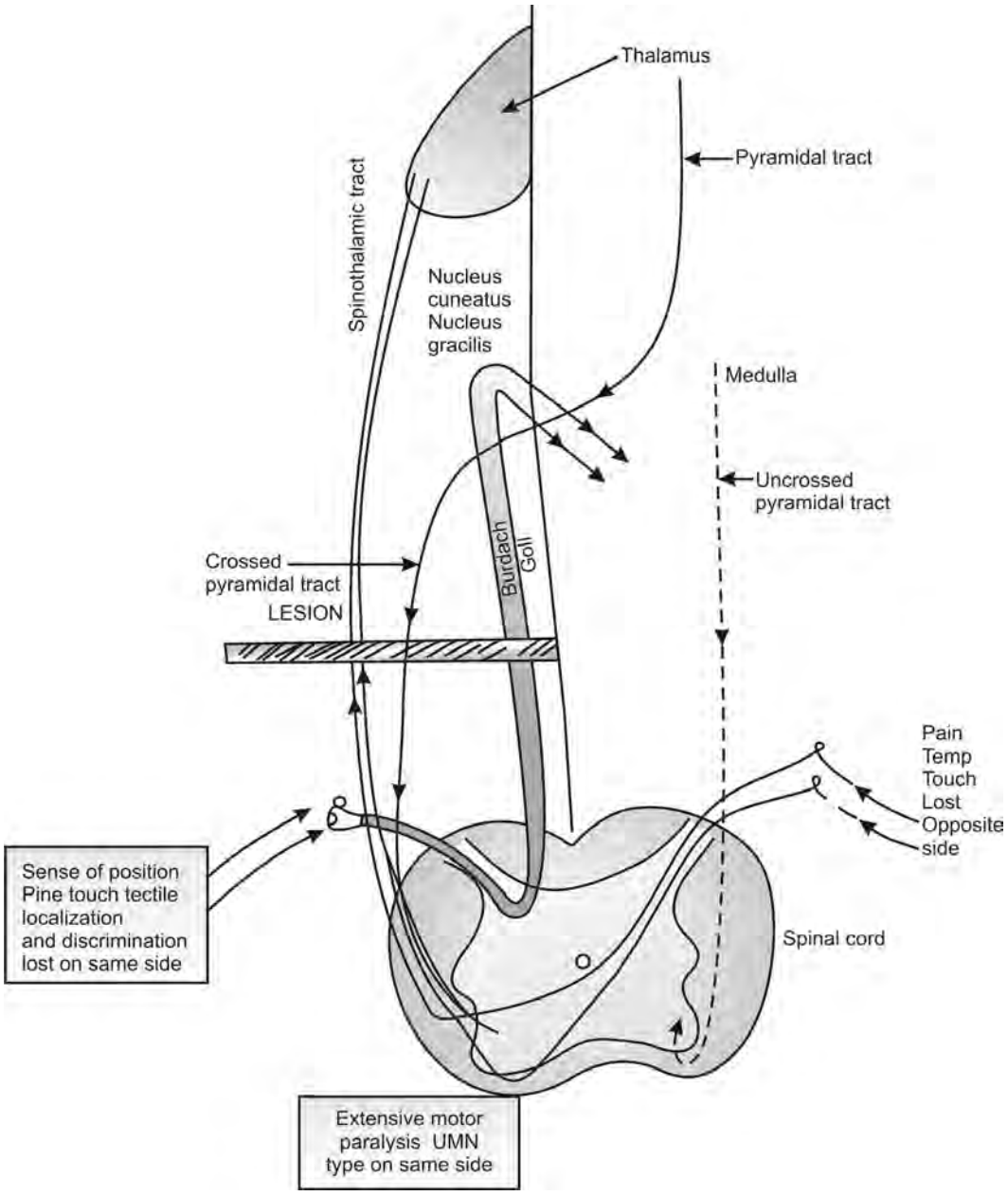


Fig. 106.3A: Hemisection of spinal cord
(Brown Sequard syndrome)

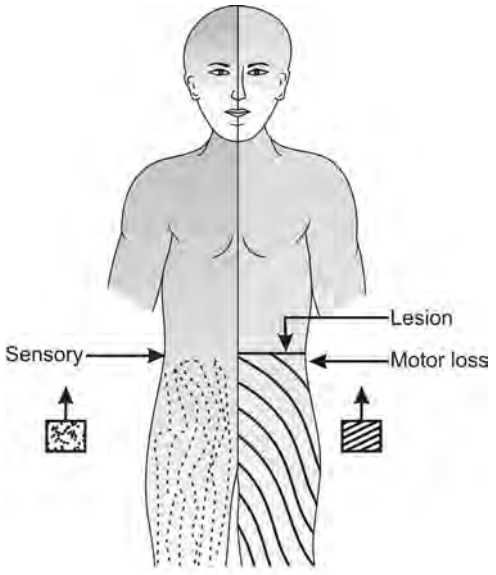


Fig. 106.3B: Brown Sequard syndrome

General Features

At the moment of section the subject feels as though he is cut into two.

1. The higher centers are unaffected and mind is clear.
2. Motor functions – muscles become paralyzed and flaccid.
3. Quadriplegia (paralysis of all four limbs) if lesion is higher in cervical segments.
4. Paraplegia (paralysis of lower limbs) if lesion is lower down.

Reflex functions: All reflexes both superficial and deep are lost.

Sensory functions: All sensations below the lesion are lost.

Sphincters: The sphincter vesicae and anal sphincters, which were paralyzed recover tone rapidly and produce tonic contraction – resulting in retention of urine and faces.

By overstretching, sphincters may be forced open sometimes and little quantities of urine may escape at intervals.

This is retention with overflow.

Frequent catheterization of bladder to remove urine has to be done at this stage.

Blood Pressure

The higher the transection, the greater is the fall of BP. If the section is in cervical region – there is profound fall in BP, if transection is lower than the 2nd lumbar segment the fall in BP is not significant.

Bedsore: The paralyzed limbs are cold and blue and absence of vascular tone reduces circulation-causing stagnation. Slight pressure causes edema. The limbs are prone to bedsores.

Cause of Shock

Spinal shock is not due to fall of BP. Because if it is due to fall of BP all parts should suffer, but in spinal shock effects are seen below the level of lesion.

Stage of Reflex Activity

In man, this stage may last from weeks to years and sometimes this stage may never appear at all when the first stage merges with the third.

1. Functional activity returns first to smooth muscle.
   i. Detrusor muscle recovers partially – and bladder evacuates automatically.
   ii. So also rectum.
   iii. Tone returns to smooth muscles of blood vessel as lateral horn cells of spinal cord begin to act independently. BP is then restored to normal.
2. Activity next returns to voluntary muscles.
   i. Some tone is recovered after 2-3 weeks.
   ii. Isolated cord always favors flexor neurons, so flexor tone predominates – Paraplegia in flexion.

iii. Limbs tend to be in a partially flexed positions.
iv. Hip and knee flexed.
v. Ankle, toes dorsiflexed.

3. The first reflex to return: *Babinski s sign*
   i. Later protective withdrawal reflex (flexor reflex), e.g. scratching of thigh: produces flexion of foot, knee, hip, accompanied by crossed extensor reflex in animals, i.e. spreads to extensors of opposite limb.
   ii. Extensor reflexes (deep reflexes) difficult to elicit. Knee jerk returns 1-5 weeks after flexor reflex, relaxation of quadriceps is sudden and complete due to diminished tone. Ankle jerk returns still later.
4. *Mass reflex:*
   i. Exaggeration of flexor reflex.
   ii. Seen after several months.
   iii. Stimulus applied to an area of skin irradiates in spinal cord and a diffuse response involving a large number of voluntary flexor muscles results.
   iv. Any area of skin below the lesion can be stimulated to get the response.
   v. *Type of stimulus*: Should be painful or unpleasant like pricking, scratching. Response-flexion of lower extremities, flexor spasm of abdominal wall, profuse sweating below the level of lesion, evacuation of bladder and rectum.
5. *Bladder and rectum:* After spinal section detrusor contracts reflexly due to stimuli caused by the distention of the bladder, relaxation of sphincter fails to occur resulting in retention.
   i. *In later stages*: The spinal centers take over the function so contraction of detrusor with relaxation of sphincter results when about 600 ml urine is accumulated.
   ii. Evacuation can also occur by extravasical stimulus.
   iii. Evacuation of rectum is also similar.
6. Lastly tone of extensor muscle is restored in 6 months.
   i. Sweating commences below the level of lesion.
   ii. Skin circulation improves and limb becomes warmer.

Stage of Degeneration

The isolated cord has less power of resistance. Therefore, infection followed by toxemia leads to degeneration of spinal cord.

i. The spinal reflex centers become functionless.
ii. This stage preceeds death by a short interval.

The general features are:

1. Gradual decline in the ability to elicit reflexes.
   The first reflex to disappear is extensor response.
2. Flexor reflex is elicited with great difficulty.
3. Mass reflex also disappears.
   Muscles: Loss of tone in muscles and muscle wasting is there
   Bedsores: Trophic changes in skin and bedsores develop.
   Bladder : Bladder tone is lost, dribbling of urine occurs.
4. Bladder infection occurs.
5. Hypercalcemia
6. Calciuria

   ] due to infection

   Death—due to uremia or septicemia.

In man—second stage can continue for months or years in absence of infection. If infection occurs in first stage itself, it merges in third.

INCOMPLETE TRANSECTION OF SPINAL CORD

Bilateral lesions usually destroys pyramidal tracts leaving vestibulospinal and reticulospinal tracts intact, so that the influence of brainstem on spinal cord is maintained (whereas in complete transection, cord below is cut off from higher centers).

The manifestation of stage: (1) and (3) are similar to those of complete transection but second stage, i.e. *stage of reflex activity* shows certain characteristics features.

1. Paraplegia in extension—Because tone in extensor muscles return,
   i. Hip, knee extended,
   ii. Ankle, toes planter flexed.
2. Muscles are spastic, extensor activity predominates.
3. Deep reflexes are exaggerated.
4. Extension thrust reflex present – with legs flexed, if foot is pressed contraction of quadriceps and posterior calf muscle.
5. Abdominal superficial and mass reflex absent.
6. Spontaneous extensor movement early and infrequent.
7. Flexor reflexes appear much later.
8. Gentle flexion of one limb causes extension of opposite limb (Phillipson's reflex). The flexed limb becomes extended and the other one is flexed. In this way movement alternates in the limb— producing stepping movement.

This shows that in incomplete transection the range of reflex activity is greater and movements of locomotion can be carried out to some extent reflexly and unconsciously by lower parts of CNS.

CHAPTER

107

Brainstem

Brainstem includes:

1. Medulla oblongata,
2. Pons,
3. Midbrain.

MEDULLA OBLONGATA—FUNCTIONS

1. It forms a pathway for the ascending and descending tracts.
2. Performs many vital functions subserved by centers situated in this region. Important ones are:
   i. Respiratory center
      a. Inspiratory center
      b. Expiratory center
   ii. Cardiac center
      a. Cardioinhibitory center
      b. Cardioacceleratory center.

      Many reflexes in CVS are integrated at the medullary level.
3. Vasomotor center
   i. Situated in floor of IV ventricle.
4. Deglutition center
5. Vomiting center

   All these centers are influenced by higher centers situated in cerebral cortex and hypothalamus.
6. Nucleus of XIIth, XIth, Xth, IXth cranial nerve and part of nucleus of VIIIth and Vth cranial nerve are also located in medulla (Fig. 107.1).

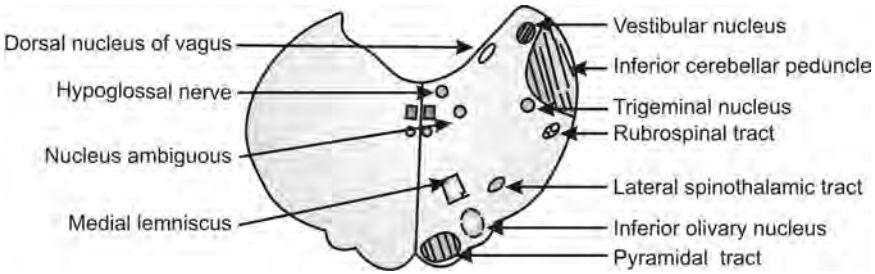


Fig. 107.1: TS upper part of medulla

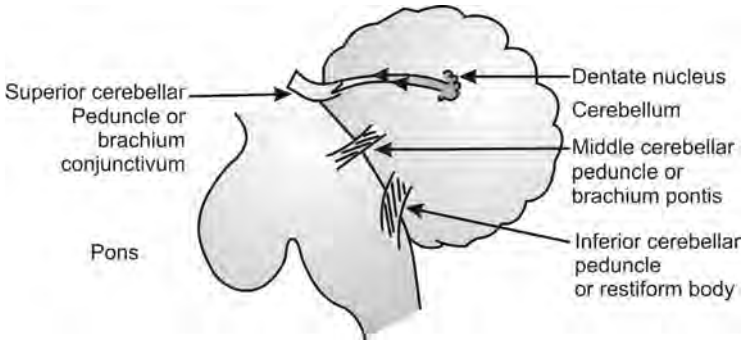


Fig. 107.2: Pons and cerebellar peduncles

PONS

It forms bridge between medulla and midbrain.

1. Numerous nerve fibers, which are axons of pontine nuclei units laterally to form middle cerebellar peduncle or brachium pontis—which is the pathway connecting cerebellum with the cerebral cortex (Fig. 107.2).
2. Nuclei pontis divide pyramidal tract into several bundles.
3. At the cephalic and lateral walls converge to form the aqueduct of Sylvius.
4. Above it on each side is the superior cerebellar peduncle, which carries fibers from dentate nucleus of cerebellum.

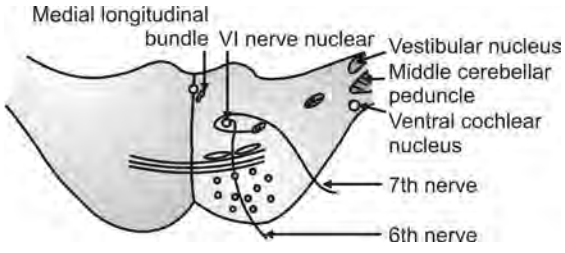


Fig. 107.3: TS of lower part of pons

5. In pons medial fillet is joined by fibers arising from Xth, VIIth and Vth cranial here.
6. Center in pons are – fascilitatory reticular nucleus.
7. Pneumotaxic center.
8. Nucleus of VIIIth, VIIth, VIth and part of Vth cranial nerve (Fig. 107.3).

MIDBRAIN (FIG. 107.4)

Lies between pons and diencephalon.

Consist of two structures: (1) Tectum–2 superior colliculi and 2 interior colliculi, (2) Cerebral peduncles

Between them lies the aqueduct of Sylvius.

Superior Colliculus

1. It is a small structure.
2. It is important center for visual reflexes.
   i. Through tectospinal tract superior colliculus reflexly alters the position of the eyes, head, trunk and limbs in response to retinal reflexes.
   ii. Colliculonuclear fibers pass to 3rd nerve nucleus from superior colliculus to cause constriction of pupil during light reflex.

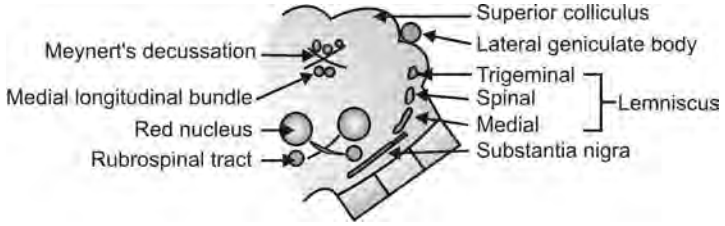


Fig. 107.4: TS of midbrain passing through superior colliculus

3. There are four layers of gray matter and fibers – majority are from optic tract.
4. Its main function is integration of optical and postural reflexes.

Inferior Colliculus

1. Consist of single layer of gray matter on which lateral fillet synapses.
2. It is a center for auditory reflexes.
3. Stimulation of inferior colliculus also produces vocalization.

Cerebral Peduncles

1. Unite the pons with cerebrum.
2. Each peduncle consists of three parts and they are from before backwards:
   i. Basis pedunculi
   ii. Substantia nigra, and
   iii. Tegmentum.

Basis Pedunculi

1. It is occupied by pyramidal fibers in middle 3/5.
2. Frontopontine and corticonuclear fibers in the medial 1/5th.
3. Temporopontine fibers in lateral 1/5th.

Substantia Nigra

1. Consists of two types of cells.
2. Ventrally the cells are small and unpigmented.
3. Dorsally they are larage and pigmented with melanin, rich in iron.
4. It receives sensations from body surface, organs of hearing and sight. Probably it is center for integration of these afferent impulses essential for performance of skilled movements.

The substantia nigra is connected by:

Afferent fibers with (Fig. 107.5):

1. Globus pallidus
2. Frontal cortex
3. Mesial fillet
4. Lateral fillet
5. Superior colliculus
6. Mammillary bodies
7. Caudate nucleus
8. Putamen

Efferent: Fibers to:

1. Red nucleus
2. Subthalamic nuclues
3. Thalamus
4. Globus pallidus.

Tegmentum

1. Lies dorsal to substantia nigra and is actually upward continuation of reticular formation of pons.
2. Three decussations take place here:
   i. Superior cerebellar peduncle
   ii. Meynert's decussation
   iii. Forel's decussation.
3. Red nucleus is situated here.

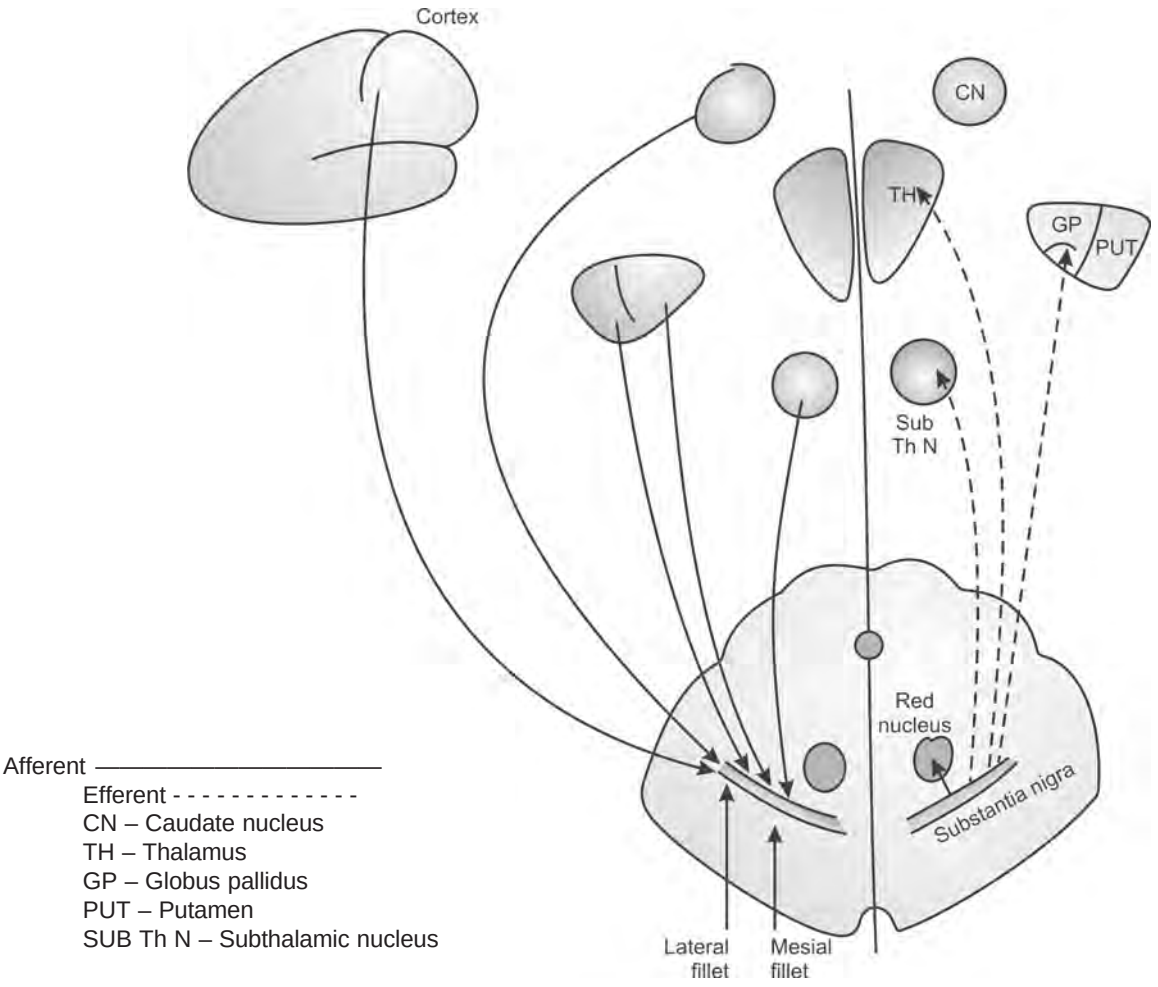


Fig. 107.5: Connections of substantia nigra

4. Medial longitudinal bundle lies close to midline.
5. Mesial fillet passes through tegmentum.
6. Lateral fillet turns dorsally to end in inferior colliculus.

Red Nucleus

It is large oval or round mass of gray matter, placed in medial part of tegmentum, extending from caudal broder of superior colliculus to hypothalamus. Fibers of IIIrd nerve stream through it. It contains 2 groups of cells.

1. Large cells in posterior 1/3 form nucleus magnocellularis – Fibers cross to opposite side and form rubrospinal and rubrobulbar tract.
2. Small cells in anterior 2/3 form nucleus pulvocellularis – fibers synapse mainly with cells of relicular formation to form rubroreticular tract.

Connections of red nucleus (Fig. 107.6).

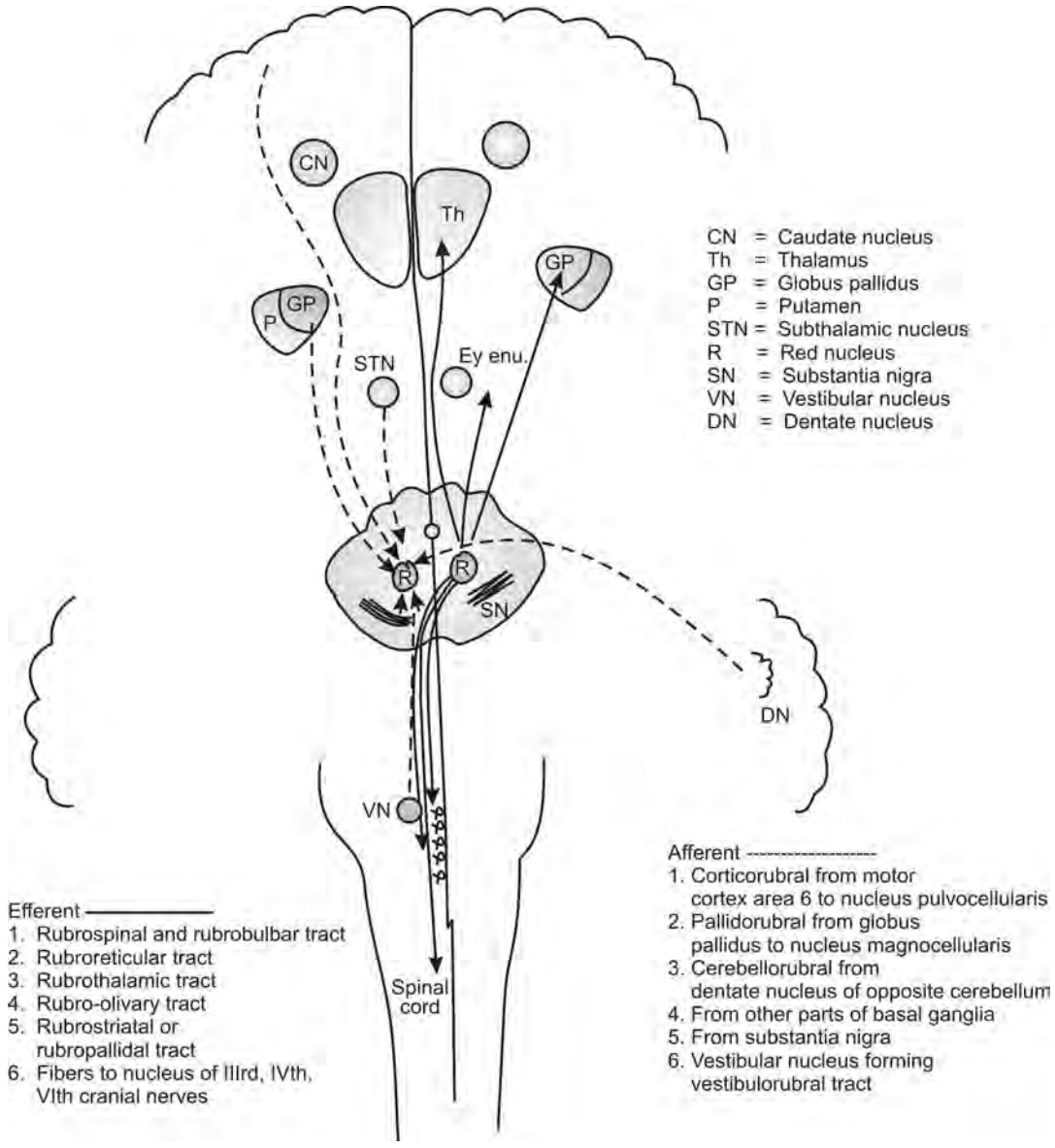


Fig. 107.6: Connections of red nucleus

Efferent

1. Rubrospinal and rubrobulbar tract.
2. Rubroreticular tract.
3. Rubrothalamic tract.
4. Rubro-olivary tract.
5. Rubrostriatal tract or rubropallidal tract.
6. Fibers to nuclei of IIIrd, IVth, VIth cranial nerves.

Afferent

1. Corticorubral from motor cortex area 6 to nucleus pulvocellularis.
2. Pallidorubral from globus pallidus to nucleus magnocellularis.
3. Cerebellorubral from dentate nucleus of opposite cerebellum through superior cerebellar peduncle to nucleus mangocellularis.
4. From other parts of basal ganglia especially subthalamic nucleus.
5. From substantia nigra.
6. Vestibular nucleus forming vestibulorubral tract.

Functions of Red Nucleus

1. It is an essential part of extrapyramidal system, controls performance of complex muscular movements.
2. Important integrating center where impulses received from various sources are ogranized before transmission to spinal cord.
3. By its connection with cerebellum and through it to vestibular apparatus and muscles, it plays important part in maintaining tone especially in animals.
4. Red nucleus is center for all righting reflexes except visual.

***Nuclei of* Vth, IIIrd, IVth and VIth cranial nerves** are present in midbrain.

Vth cranial nerve: Motor part supplies muscles of mastication.

Sensory part: Carries sensations from face, part of skull, cornea, conjunctiva and anterior 2/3 of tongue.

3rd cranial nerve: Fibers take a curved course through red nucleus.

Sensory part: Receives proprioceptive impulses from external ocular muscle and maintain reflex tone in these muscles and delicate adjustment in gaze.

Motor part: Supply extrinsic muscles of eye except superior oblique and lateral rectus muscle.

Autonomic part: Known as Edinger Westphal nucleus.

Fibers pass along 3rd nerves to ciliary ganglion.

Postganglionic fibers along short ciliary nerve supply sphincter pupillae.

CHAPTER

108 Thalamus

The diencephalon is that portion of central nervous system which intervenes between the cerebral hemisphere (telencephalon) above and midbrain (mesencephalon) below. It consists of thalamus, epithalamus, meta-thalamus (i.e. lateral geniculate body and medial geniculate body) and hypothalamus.

THALAMUS

The thalami are two large oval convex cell masses of 4 cm in length, situated at the base of the cerebral hemispheres and above the cerebral peduncles. They are obliquely placed in such a way that their anterior ends converge together whereas their posterior ends diverge from each other and as they diverge posteriorly they enclose a space between them known as 3rd ventricle.

It's main function in lower animal is center for all types of sensations. In man it is used for appreciation of crude sensations, and emotions and acts as relay center for large number of fibers.

The thalami are joined in the midline by massa intermedia. Laterally, it is separated from lenticular nucleus by internal capsule, the head of the caudate nucleus lies in front of it, and below is the subthalamic nucleus. It forms the floor of the lateral ventricle. The body of the caudate nucleus is related to the upper part of its lateral surface (Fig. 108.1).

Structure

Structurally, the thalamus consists mostly of gray matter except its superior and lateral surface.

1. Superior surface is covered over by layer of white matter – known as *stratum zonale*.
2. Lateral surface is similarly covered – known as *external medullary lamina*.
3. The gray matter of the thalamus is sub-divided by a vertical white septum—the internal medullary lamina into medial and lateral masses or parts.
4. In the region of interthalamic adhesion and the adjoining medial mass, there are a group of descrete nuclei known as *midline nuclei*.
5. The internal medullary lamina also shows the presence of cellular masses known as *intralaminar nuclei*.
6. The cell masses in the pulvinar of thalamus constitutes the *Pulvinar nucleus* ˘ expanded posterior end.

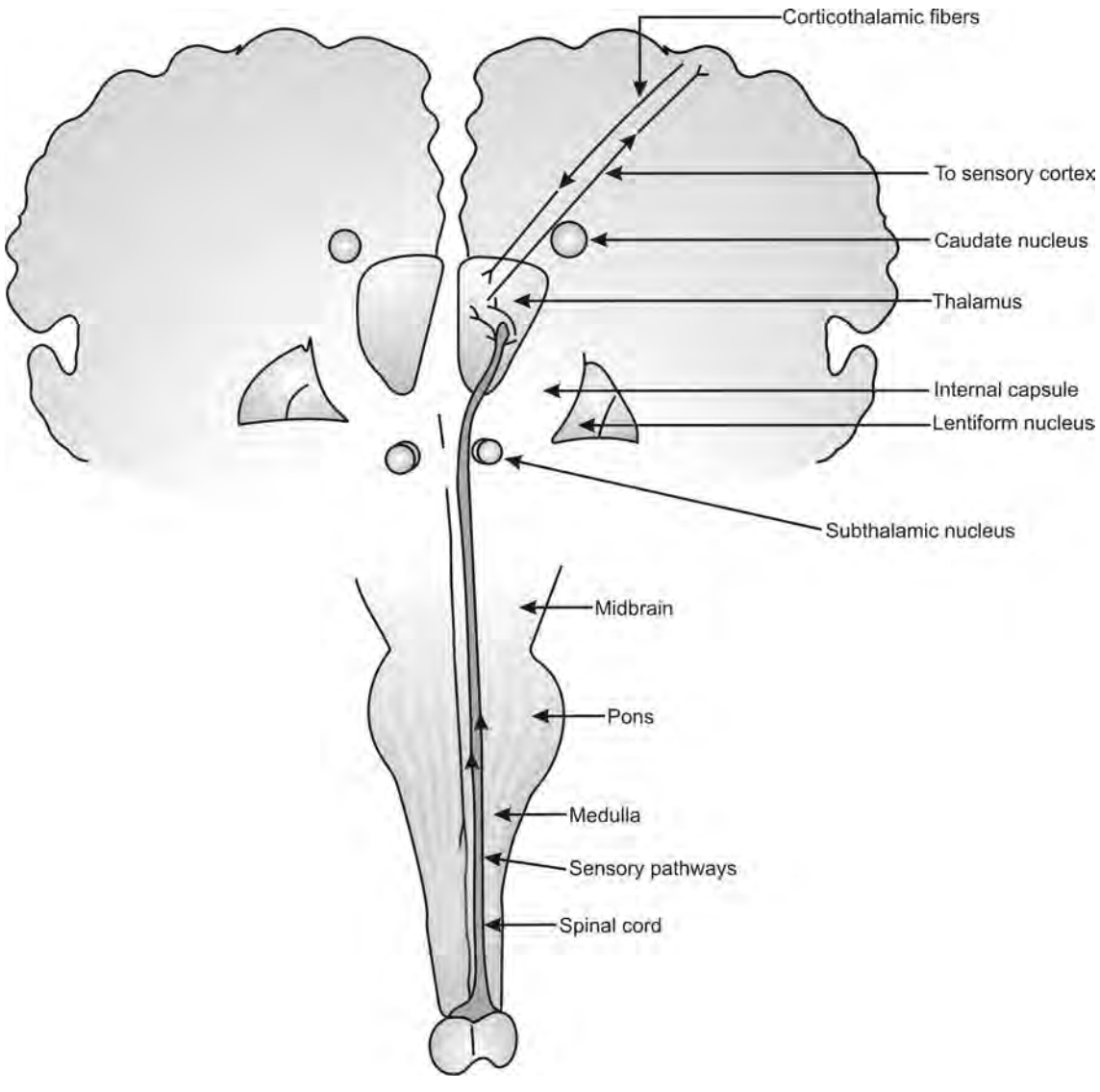
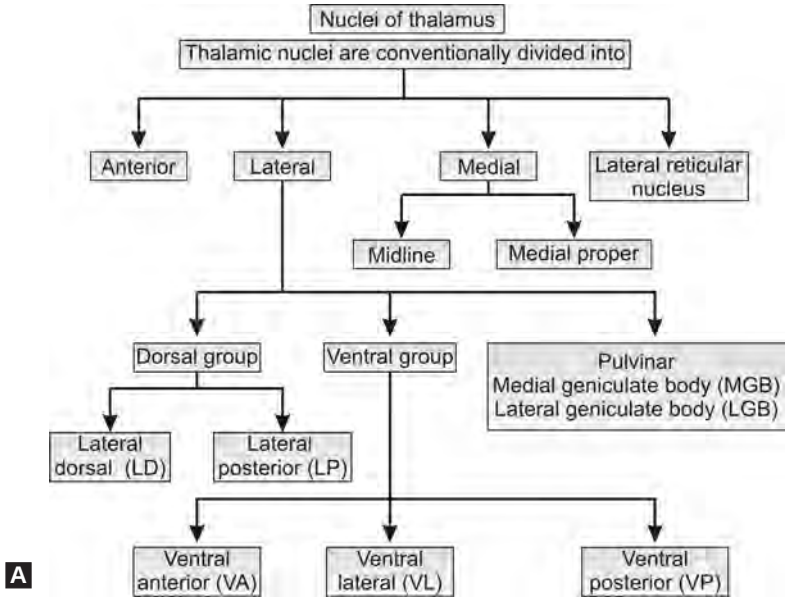
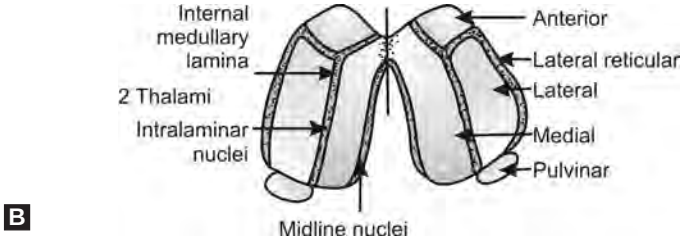
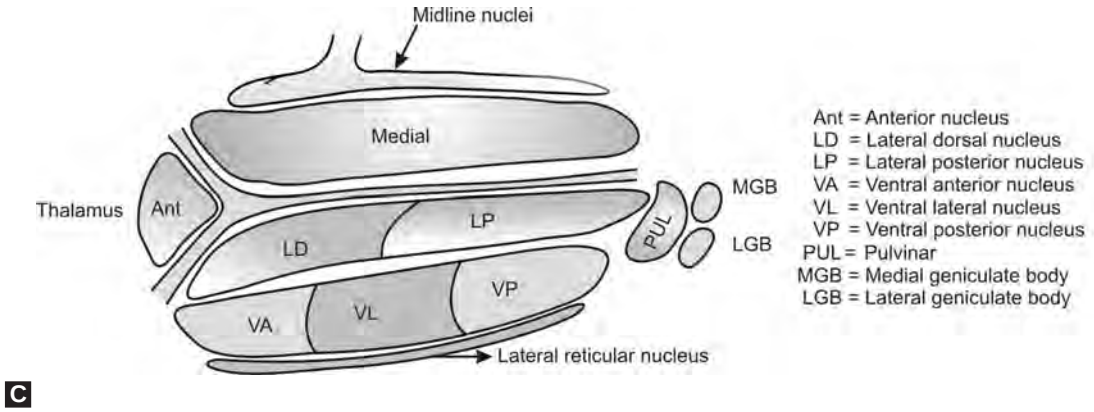


Fig. 108.1: Schematic relations of thalamus and representation of nerve paths and centers for sensations showing all sensations reaching destination in lateral part of thalamus, relaying in medial portion of thalamus and remaining sensations in the sensory cortex

THE NUCLEI OF THALAMUS (FIGS 108.2A TO C)





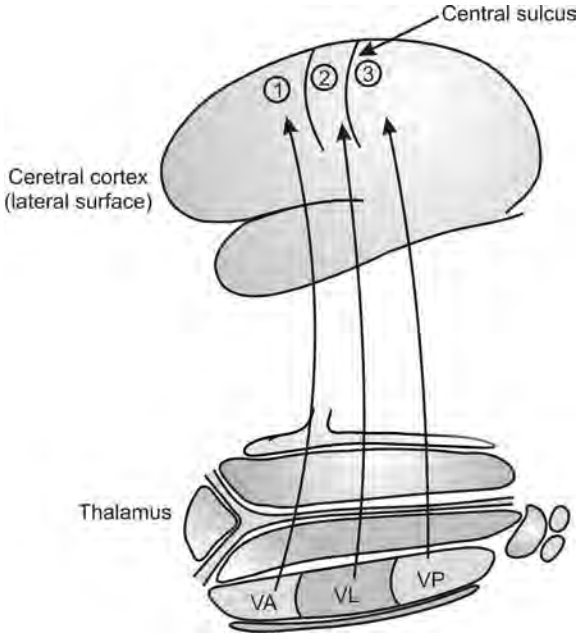


Figs 108.2A to C: Nuclei of thalamus

CONNECTIONS OF THALAMUS

Efferent (Fig. 108.3) for efferent connections remember:

1. Lateral surface of cerebral cortex.
   Number the three areas premotor, motor and sensory area as (1), (2) and (3). These are efferent connection of VA, VL and VP nuclei respectively (Fig. 108.3).
   VA to (1) (Premotor)
   VL to (2) (Motor)
   VP to (3) (Sensory).
2. On medial surface there is precuneus, turn laterally to find supraparietal and infraparietal areas.
   Number these as (1), (2) and (3).
   These are efferent connections of LD, LP and pulvinar nuclei respectively (Fig. 108.4).



1. = Premotor area, VA = Ventral anterior nucleus
2. = Motor area, VL = Ventral laleral nucleus
3. = Sensory area, VP = Ventral posterior nucleus

Fig. 108.3: Efferent connections of ventral group

   LD to Precuneus
   LP to superior parietal area
   Pul to Infraparietal area.
3. Efferent connection of all reticular nuclei, i.e. lateral reticular nucleus, intralaminar nuclei, midline nucleus is cerebral cortex by diffuse cortical connections.
4. Efferent connection of anterior nucleus is cingulated gyrus.
5. Efferent connection of medial nucleus is:
   i. Prefrontal lobe
   ii. Corpus striatum.
6. Efferent connection of medial geniculate body is auditory cortex.
7. Efferent connection of lateral geniculate body is visulal cortex.

In additions, all nuclei of thalamus are interconnected, e.g. from lateral nucleus to medial nucleus, from anterior nucleus to lateral nucleus, and from medial nucleus to lateral nucleus, etc.

Once we know the efferent connections we can build the afferent connections.

Afferent Connections (Fig. 108.5)

VA nucleus: Receives afferents from corpus striatum anterior and medial nuclei of thalamus.

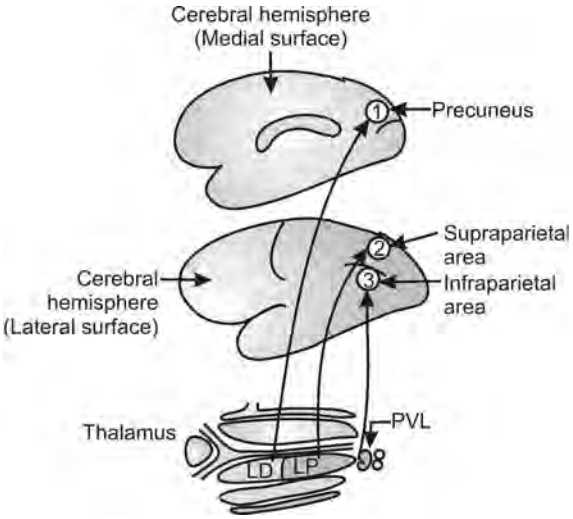
VL nucleus: Because it projects to motor cortex its afferents are:

1. Dentatorubrothalamic tract
2. Rubrothalamic tract.

VP nucleus: Because it projects to sensory area its afferent connections are:

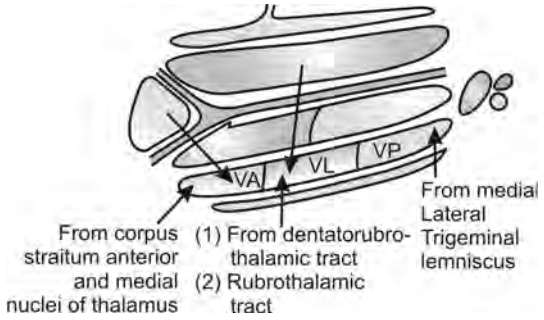
   1. Medial lemniscus
   2. Spinal lemniscus
   3. Trigeminal lemniscus.

1. Afferent connection of LD, LP and pulvinar nuclei are: other nuclei of thalamus (Fig. 108.7).
2. Afferent connections of all reticular nuclei is from reticular formation of brainstem.



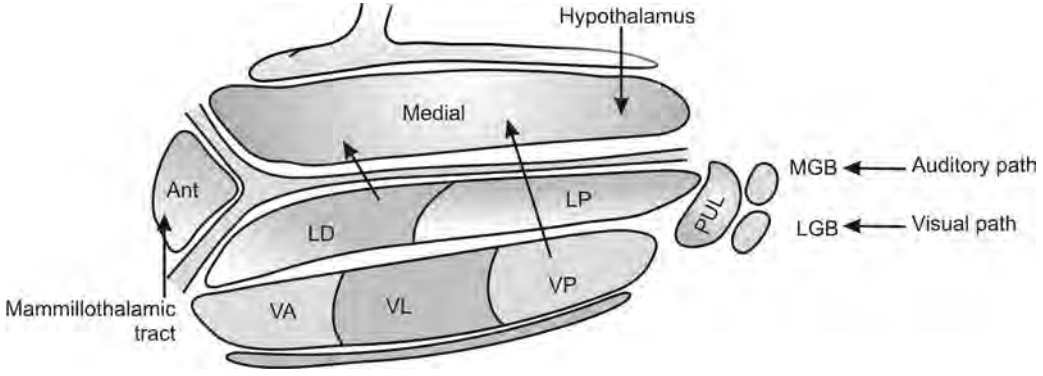
1 = Precuneus
2 = Supraparietal area
3 = Infraparietal area
LD = Lateral dorsal nucleus
LP = Lateral posterior
PUL = Pulvinar

Fig. 108.4: Efferent connections of dorsal group and pulvinar



VA = Ventral anterior nucleus
VL = Ventral lateral nucleus
VP = Ventral posterior nucleus

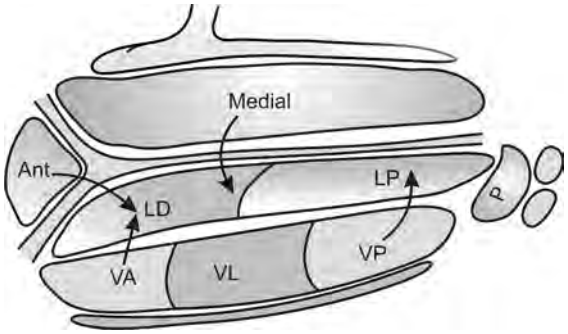
Fig. 108.6: Afferent connections of ventral group



MGB = Medial geniculate body, LGB = Lateral geniculate body
LD = Lateral dorsal nucleus, VP = Ventral posterior nucleus

Fig. 108.5: Afferent connections of medial nucleus, anterior nucleus and MGB and LGB

3. Afferent connection of anterior nucleus is from mammillary body—Mammillothalamic tract.
4. Afferent connection of medial nucleus is hypothalamus and lateral nucleus of thalamus.



Ant = Anterior nucleus, LD = Lateral dorsal nucleus, LP = Lateral posterior nucleus, VA = Ventral anterior nucleus, VL = Ventral lateral nucleus, VP = Ventral posterior nucleus, P = Pulvinar

Fig. 108.7: Afferent connections of LD, LP and pulvinar

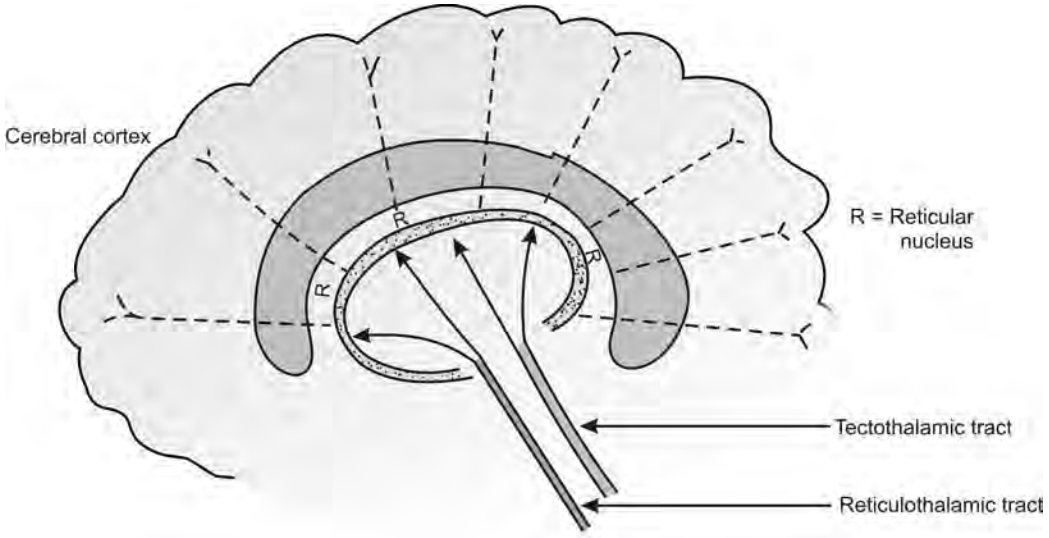


Fig. 108.8: Reticular nucleus surrounds the thalamus like shell and nerve cells their in project to various parts of cortex

5. Afferent connection of medial geniculate body is auditory path.
6. Afferent connection of lateral geniculate body is visual path.

In summary the connection are:

Afferent Connection

1. *Medial lemniscus:* Continuation of fasciulus gracilis and cuneatus carry proprioceptive impulses and fine touch tectile localization and tectile discrimination to ventral posterolateral nucleus of thalamus (Fig. 108.6).
2. *Spinal lemniscus:* It carries touch (crude), pain and temperature sensation to ventral posterolateral nucleus of thalamus.
3. *Trigeminal lemniscus:* It carries all sensations from trigeminal areas to ventral posterolateral nucleus of thalamus.

4. Sensory visceral fibers from the hypothalamus terminate in medial nucleus of thalamus.
5. *Mammillothalamic tract:* It carries olfactory sensation to anterior nucleus of thalamus.
6. *Cerebellar efferents:* From opposite side terminate into ventral lateral nucleus (Dentatorubrothalamic tract).
7. *Rubrothalamic fibers:* From opposite side terminate into ventral lateral nucleus.
8. *Corticothalamic fibers:* From different areas of cerebral cortex.

Efferent Connections

1. Thalamocortical fibers distributed to postcentral area and other areas of cerebral cortex.
2. Efferent fibers to corpus striatum.
3. Efferent intrathalamic connections.
4. Efferents to hypothalamus and midbrain.

CHAPTER

109 Functional Significance of Thalamus

FUNCTIONS OF THALAMUS

1. *It is a great relay station:* Thalamus forms the important relay station for all sorts of sensory impulses and therefore establishes important correlation between different types of sensations. The somatic sensory impulses coming from right side of the body are relayed into left thalamus and from there into left cerebral hemisphere. Thus, thalamus represents sensory input of opposite half of the body.

   Compared to postal service the thalamus is like Royal mail service where all sensory impulses are analyzed, correlated with different areas and finally are dispatched to their respective destinations.

   i. Olfactory sensations received from mammillary bodies are relayed to hippocampal region (cingulate gyrus).
   ii. Except pain all sensations received from medial, spinal and trigeminal lemniscus are relayed to post-central gyrus, areas 3, 1, 2 of cerebral cortex.
   iii. Cerebellar impulses are relayed to areas 4 and 6 of frontal lobe. Through this path cerebellum guides and controls cerebrum in making the movement initiated precise in rate, range, force and direction and for coordination of movements.
   iv. Including metathalamus, i.e. LGB and MGB visual impulses project to lateral geniculate body (LGB) and it projects to calcarine cortex (or geniculocalcarine cortex).

   MGB receives topically organized projection of auditory fibers from cochlear—nuclei and inferior colliculi, which they relay to auditory areas of cerebral cortex.

2. *Association or modulation function:* Practically all thalamic nuclei receive fibers from certain related parts of the cerebral cortex and there is thalamocortical projection of main sensory paths. This suggests that the thalamus and the sensory cortex somehow function together rather than independently in control of sensory system. When the word association is used to describe this function it does not have technical meaning, but is used to describe what is not clearly sensory or motor. There are thalamo-cortical-thalamic connections, which modulate the diencephalic and telencephalic levels of function.

It determines whether the impulses from the periphery will be transmitted in or may be modulated so one subject may be hypersensitive while other remains unresponsive to the same stimulus. Because it has widespread afferent and efferent connections with cortex, it helps cortex in appraisal of various inputs.

3. *Arousal:* Nucleus of midline, intralaminar and reticular nuclei are believed to constitute an essential part of ascending reticular activating system (ARAS) or the arousal mechanism responsible for wakefulness and consciousness. ARAS originates in the reticular formation of the tegmentum and project to cerebral cortex and keep it in waking state (Fig. 109.1).
4. It is responsible for production of electrical activity of brain cells and therefore responsible for electroencephalogram (*EEG*).
5. *Center for crude sensations:* In lower animals, it is center for all types of sensation but in man cerebral cortex takes up more and more of this function. So epicritic sensations are perceived in cerebral cortex and only crude sensations are appreaciated in thalamus.
6. *It acts as affect and emotional reflex center:* The sensation is perceived as pleasant or unpleasant, this perception is known as affect. There is no other area in brain, which can determine affect. The medial nucleus of thalamus is responsible for it. When the cerebral cortex is removed the sensations are perceived as extremely pleasant or unpleasant. As emotion is an affective sensation it is possible that thalamus by projecting the fibers to prefrontal lobe, determines the conscious nature of emotions.

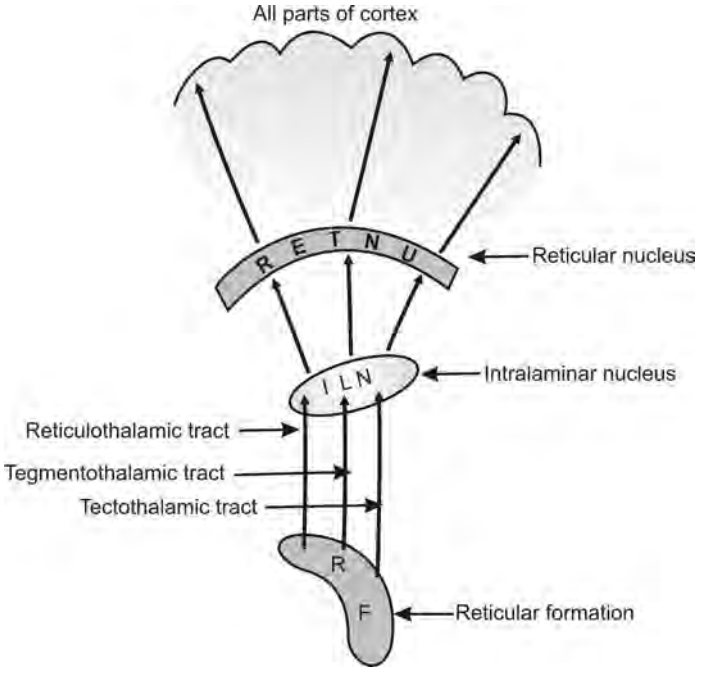


Fig.109.1: Ascending reticular activating system (ARAS)

7. *Maintains personality and behavior:* By virtue of its connections with hypothalamus and prefrontal lobe, the thalamus (medial nucleus) is reflex center for emotional exteriorization, which determines our personality and social behavior. Emotional reactions such as rage are mediated through thalamus.
8. *It differentiates the modalities of sensations:* Expermentally when cortical areas are stimulated only tingling sensations are aroused in that particular region. So it is possible that thalamus determines the modalities before signal for sensation is relayed to sensory cortex. The paleosensibilities (pain, heat and cold) are distinguished in thalamus, whereas neosensibilities (touch, pressure) are distinguished in cortex. It was prevalent thought that pain was a thalamic sensation. But relief of pain in the amputation stump by removal of sensory cortex – suggests that it is not wholely true.

THALAMIC SYNDROME (FIGS 109.2A AND B)

Sometimes as a result of thrombosis of the local artery supplying thalamus or due to hemorrhage, there is lesion of nuclear masses on outer side of the thalamus (VP and VL). As a result, the:

1. Mesial fillet is not allowed to proceed to cerebrum. There will be loss of finer sensations – (epicritic sensibilities):
   i. Loss of light touch
   ii. Loss of tectile localization
   iii. Loss of tectile discrimination
   iv. Loss of intermediate grades of touch
   v. Loss of appreciation of small movements of joints (Fig. 109.2A).
2. Only crude sensation will be appreciated on opposite side of the body.
3. Cerebellar afferents of one side are relayed to opposite cerebrum. This is not possible due to damaged nuclei, which leads to loss of kinesthetic sensations. So
   i. There is loss of coordination = Ataxia
   ii. There is profound muscular weakness
   iii. There is decreased muscle tone (Fig. 10.9.2B)

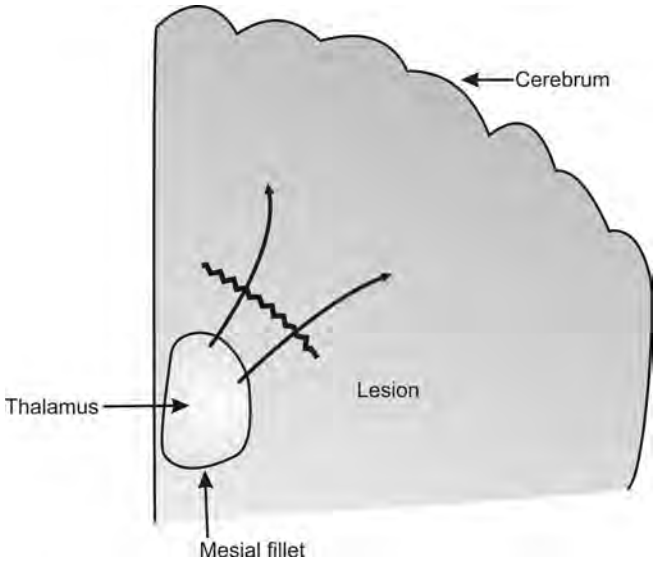
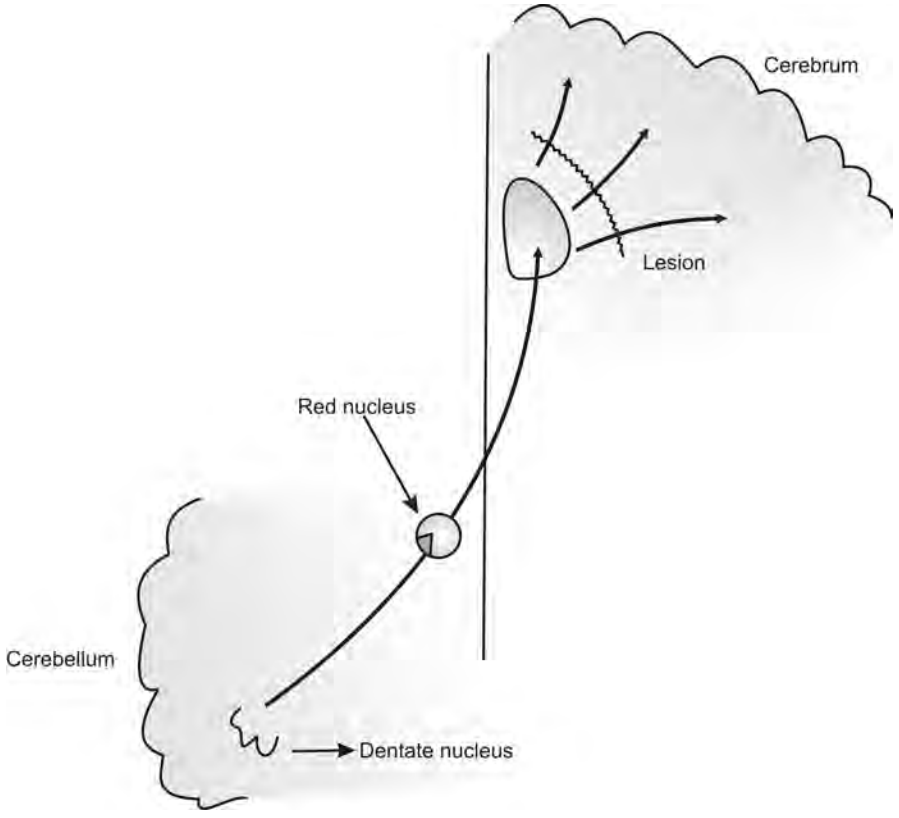


Fig. 109.2A



Figs 109.2A and B: Thalamic syndrome

All these symptoms and signs occur on opposite side of the body.

4. They may be accompanied by altered emotional effects because it is detached from cerebrum, which is another emotional center.
5. Slight painful or pleasurable sensation appears as extremely painful or extremely pleasurable sensation.

Sensory functions of thalamus can be studied by cutting off its connections with cerebral cortex. By this procedure the thalamus becomes isolated from the cortex and its independent functions can be revealed. Such a preparation can be called thalamic animal. The features are similar to thalamic syndrome.

CHAPTER

110

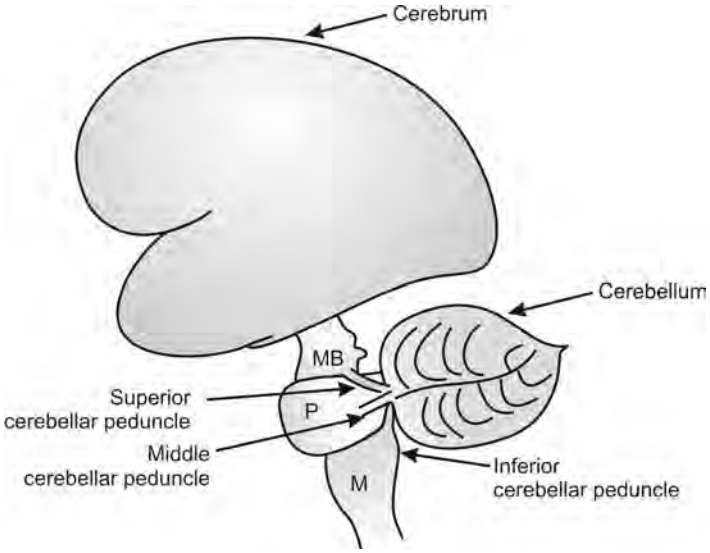
Cerebellum

INTRODUCTION

Cerebellum is largest part of hindbrain and lies behind pons and medulla oblongata (Fig. 110.1A). It is oval in form and broader transversely than anteroposteriorly. Its weight is about 150 gm and bears a ratio of 1:8 in weight with that of cerebrum. (i.e. cerebellum is 1 and cerebrum 8). In infants, the ratio is 1:20.

It is connected with brainstem with superior, middle and inferior peduncles. The cerebellar surface has characteristic patterning, being divided by parallel and curved furrows into numerous laminae of folia (Folia = lexaves) (Fig. 110.1B).

It consists of: (1) 2 large lateral portions known as a cerebellar hemispheres and (2) A small central portion known as vermis. It is so called because it resembles a worm bent on itself to form a complete circle.



MB = Midbrain, P = Pons, M = Medulla

Fig. 110.1A: A cerebellum

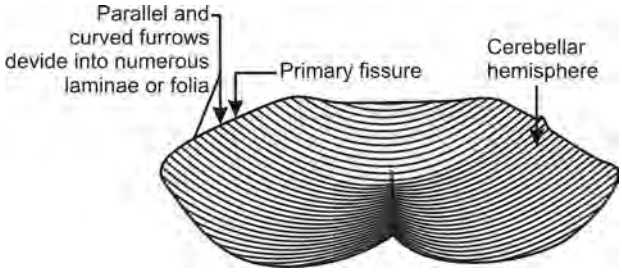


Fig. 110.1B: Cerebellum superior surface

Anatomical subdivisions do not correspond with functional subdivisions. It is divided into (Fig. 110.2).

1. *Paleocerebellum:* Older part of the cerebellum phylogenetically.
2. *Neocerebellum:* New part of the cerebellum.

Paleocerebellum is Divided Intob

1. Archicerebellum (flocculonodular lobe). Believed to be most ancient part of cerebellum from phylogenetic point of view. It includes: (a) Nodule, (b) Flocculi
2. Paleocerebellum proper : Which includes
   i. Paraflocculi
   ii. Pyramis
   iii. Uvula.
3. Physiological anterior lobe of cerebellum. It includes:
   i. Lingula
   ii. Lobus centralis
   iii. Culmen
   iv. Lobus simplex (Fig. 110.2).

Neocerebellum consist of:

1. *Ansiform lobule*: Which is the major portion of the cerebellar hemisphere. Ansiform lobule reaches greatest development in human brain (function – tone adjustment and muscular coordination required for skilled movements).
2. Paramedian lobule.

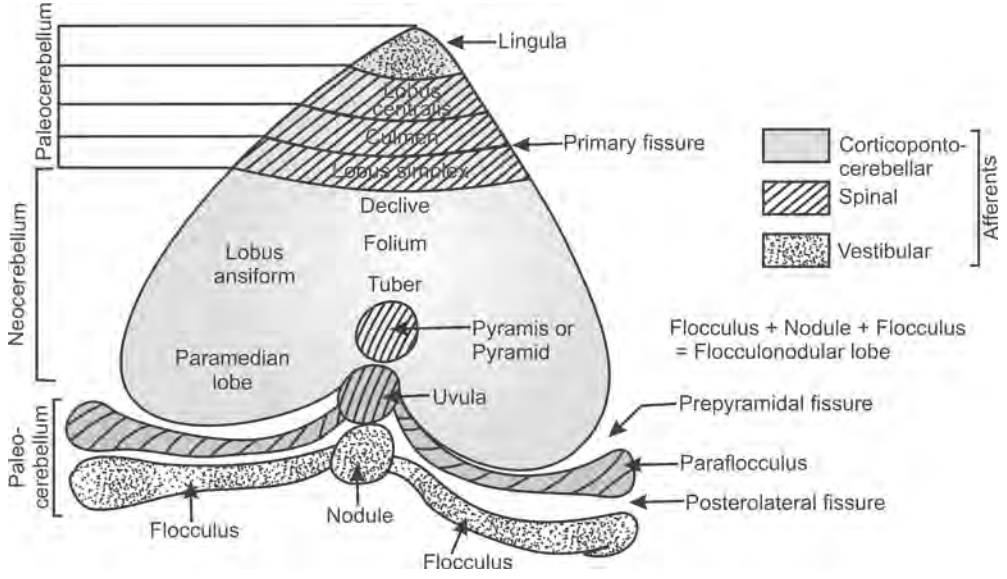


Fig. 110.2: Schematic diagram of primate cerebellar cortex laid out flat and looked at from dorsal surface

3. Declive–which is greater part of lateral hemisphere
4. Folium, and
5. Tuber of vermis.

CEREBELLAR CORTEX (FIG. 110.3)

Surface of cerebellum is covered by a gray cortex, which is thrown into numerous fine convolutions. Deep inside is white matter. The cells that lie in the gray matter have a regular pattern, which is repeated as a pattern is repeated on wallpaper. The arrangement of elements in a pattern was first described by Spanish Neuroanatomist – Raman Y Cajal (1888), who studied the sections stained with silver nitrate and examined under a conventional light microscope. Now, we can study the same with electron microscope, but this has not altered much the picture, which shows Cajal's skill and patience in preparing and examining sections.

Three layers are recognized:
1. Inner granular
2. Middle layer of Purkinje cells
3. Outer molecular.

Inner granular layer: contains

Small granular cells have multiple small dendrites and one long axon – which ascends to molecular layer bifurcates into transverse branches parallel to surface and communicates with many cells.

Intermediate layer of Purkinje cells: These cells are the characteric feature of cerebellum. They have large flask shaped bodies with:
1. Freely branching dendrites extending into the molecular layer.
2. One axon passing down to the cerebellar nuclei.

Molecular layer (Outer): consist of: (a) Small stellate cells, (b) Basket cells – send transverse fibers ending round bodies of many Purkinje cells and receive impulses from granular cells.

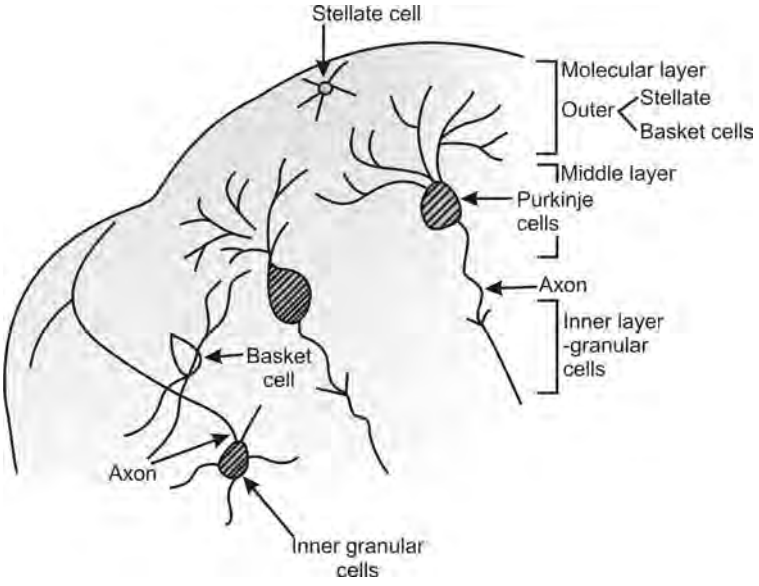


Fig. 110.3: Cerebellar cortex

Afferent fibers – carry:
1. Kinesthetic impulses
2. Vestibular impulses, and
3. Cortical impulses – via pontine nuclei.

Efferent fibers: Leave cerebellum in two stages:
1. From the cortex to the deep nuclei and
2. From the deep nuclei to extracerebellar regions and efferent fibers communicate with motor centers at all levels of central nervous system.

CEREBELLAR NUCLEI

Cerebellum contains 4 pairs of separate gray masses, one on each side (Fig. 110.4).
1. Nucleus festigius (nucleus of roof) (2 nuclei = nuclei festigii)
2. Nucleus globosus
3. Nucleus emboliformis.
   These three are phylogenetically older than.
4. Nucleus dentatus.

Festigial nuclei: Ancient of all, lie near midline on either side of roof of 4th ventricle:
1. They receive fibers from
2. Paleocerebellum and
3. Vestibular nucleus and 8th nerve, through inferior cerebellar peduncle.
4. They send fibers to vestibular nucleus.

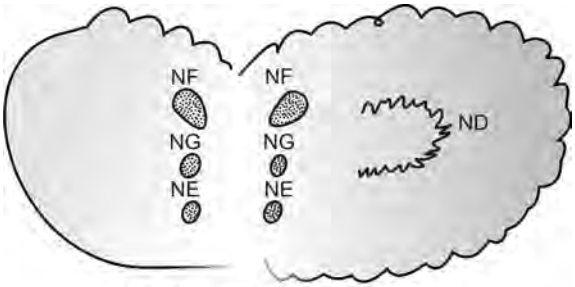


Fig. 110.4: Cerebellar nuclei

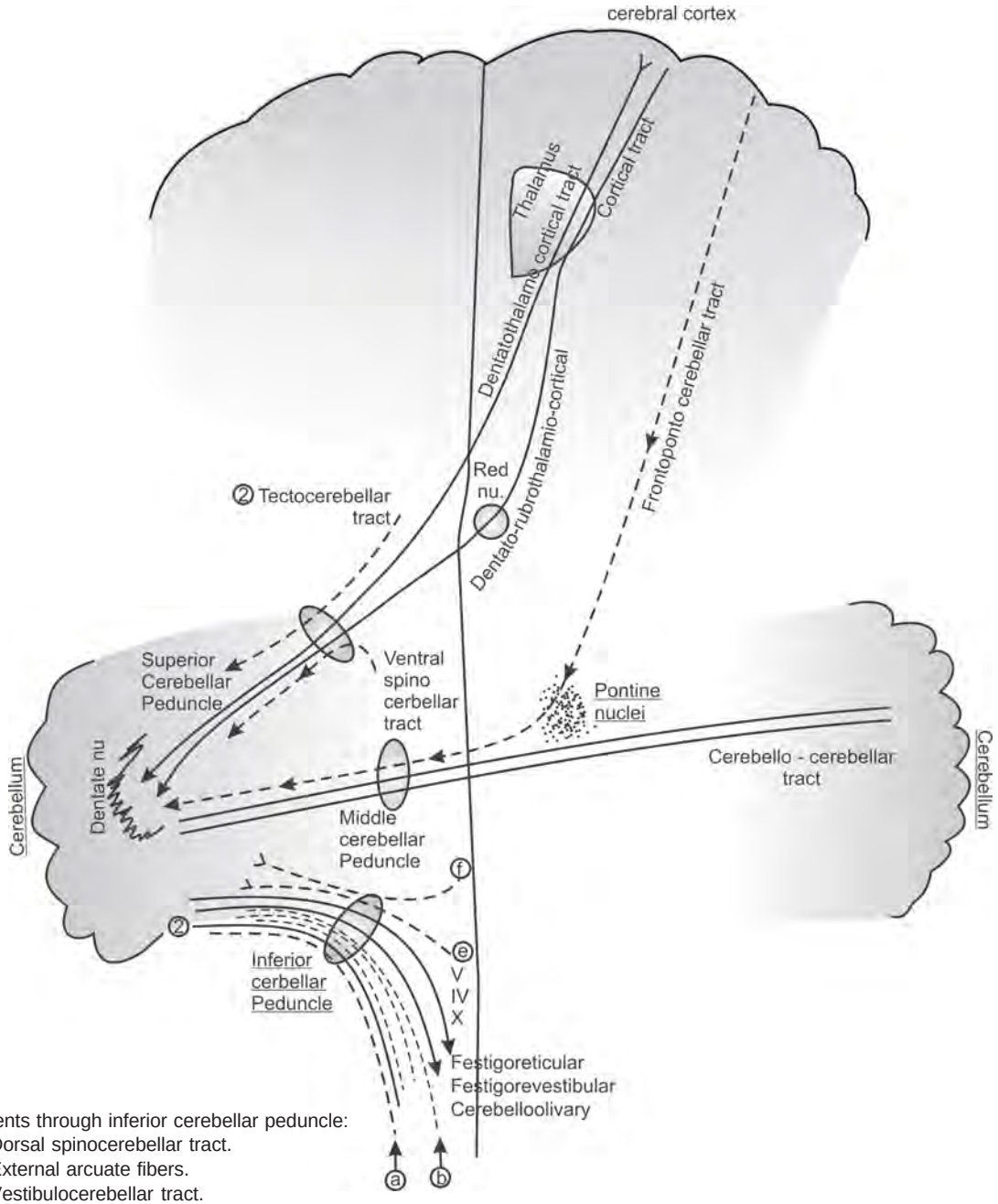
Globosus and Emboliform Nuclei
1. Placed more laterally than roof nuclei
2. They receive fibers from
   i. Anterior lobe
   ii. Globose nuclei also receive fibers from flocculonodular lobe.
3. Both send fibers to Large celled portion of red nuclei.

Dentate nuclei
1. Most laterally placed.
2. Large and crenated mass of gray matter bent actually on itself.
3. It receives fibers from Purkinje cells of neocerebellum, and
4. Send fibers through superior cerebellar peduncle to small celled portion of red nucleus and ventrolateral group of thalamic nuclei.

CONNECTIONS OF CEREBELLUM (FIG. 110.5)

White matter of cerebellum is composed of:
1. *Projection fibers:* Fibers which leave or enter the cerebellum via peduncle.
2. *Association fibers*: Which connect different regions of the same hemisphere.
3. *Commissural fibers*: Connecting cortical areas of the two hemispheres.

The fibers afferent and efferent, connecting the cerebellum with other portions of the nervous system are all carried in three large bundles known as superior, middle and inferior peduncle.
1. Inferior cerebellar peduncle: (Restiform bodies).
   Afferent connections – through inferior cerebellar peduncles.
   i. Dorsal spinocerebellar tract, origin – Clarke's column.
   ii. External arcuate fibers origin-nucleus gracilis-nucleus cuneatus.



Afferents through inferior cerebellar peduncle:

a. Dorsal spinocerebellar tract.
b. External arcuate fibers.
c. Vestibulocerebellar tract.
d. Olivocerebellar tract.
e. Fibers form V, IX, Xth cranial nerves.
f. Tectocerebellar tract.

Fig. 110.5: Cerebellar connections

iii. Vestibulocerebellar tract origin-vestibular nucleus, ends - mainly in nuclei festigii
iv. Olivocerebellar tract origin – olivary nucleus of same side, also opposite side.
v. Fibers from Vth, IXth and Xth cranial nerve.
vi. Tectocerebellar tract, origin – midbrain colliculi.

Efferent connections through inferior cerebellar peduncle:

1. Festigovestibular and festigobulbar (or festigoreticular).
   Origin: Flocculonodular lobe and nuclei festigii.
   End: Vestibular nuclei and medullary reticular formation.
   From medulla fibers descend in spinal cord as vestibulospinal tract and reticulospinal tract.
2. *Cerebello-olivary tract:* Origin–cerebellum
   Ends: Olivary nuclei of both side.

Middle cerebellar peduncle (*Brachium Pontis*)
Afferent connections: Through middle cerebellar peduncle.

1. Pontocerebellar tract
   Origin: Pontine nuclei.
   End: Middle lobe of opposite side.
   Few fibers end in same side hemisphere and vermis.
   Actually: This tract forms secondary neurons of fronto ponto cerebellar tract.
2. Fibers from cerebellum to cerebellum
   Origin: Dentate nucleus of one side.
   End: Cerebellar hemisphere of opposite side.

Efferent connections: Through middle cerebellar peduncle-cerebellocerebellar tract from opposite cerebellum.

Superior cerebellar peduncle˘(Barchium conjunctivum).
Afferent connections: Through superior cerebellar peduncle

1. Ventral spinocerebellar tract
   Origin: Clarke's column.
2. Tectocerebellar tract
   Origin: Superior colliculus.

Efferent connection: Through superior cerebellar peduncle.

1. Fibers arise from dentate nucleus and few fibers from other nuclei decussate in midbrain with fibers from opposite side and descend or ascend as tracts.
   Ascending fibers form: (a) Dentato-thalamocortical tract to VL group of nuclei, from there to area 4 & 6 of motor cortex, and (b) Dentatorubrothalamic tract is a descending tract. Ends in reticular formation of pons, medulla and cervical spinal cord.

So considering connections of cerebellum with extracerebellar nuclei, it may be seen that cerebellum has cerebro-cerebello–cerebral connections, cerebellum makes connections with cerebral cortex (Area 4 & 6) through dentatorubrothalamocortical tract and cerebral cortex (areas 4 & 6) makes connection with cerebellum through fronto ponto: cerebellar tract. Thus, steady voluntary movement is possible, which is initiated by area 4 & 6 of cerebral cortex.

CHAPTER

111 Functions of Cerebellum

From connections two things become clear:
1. Control of cerebellum is ipsilateral.
2. Cerebellum is not concerned with conscious sensations.
3. Disorders of cerebellum produce disorders of motor system only.

Functions may be summarized under three headings:
1. Functions of archicerebellum or flocculonodular lobe.
2. Functions of paleocerebellum excluding archicerebellum.
3. Function of neocerebellum.

FUNCTIONS OF ARCHICEREBELLUM

Its afferent and efferent connections are with vestibular nuclei.
1. Vestibular afferents, i.e. from saccule, utricle and semicircular canals pass directly or after relay in vestibular nucleus via inferior cerebellar peduncle to flocculonodular lobe.
2. Efferents from flocculonodular lobe return via inferior cerebellar peduncle to vestibular nuclei. From these nuclei the vestibulospinal tract connects the spinal motoneurons.

Thus, the flocculonodular lobe is long relay superimposed on vestibulospinal tract for controlling body posture and helps in regulation of posture and equilibrium.
1. *Effects of extripation*: The main disturbance is of equilibrium, which is shown by inability to maintain an erect posture.
2. *Effect of stimulation* of flocculonodular lobe. There are electrical responses in anterior and middle, ectosylvian gyri of the cerebral cortex. This indicates that vestibular receptors have cortical projection.

FUNCTIONS OF PALEOCEREBELLUM EXCLUDING ARCHICEREBELLUM

1. It acts as receptive organ for:
   i. Tectile
   ii. Proprioceptive
   iii. Visual
   iv. Auditory impulses.
2. *Modification of muscle tone and stretch reflexes:* Cerebellum controls the tone of muscles on same side of the body via the γ efferents to muscle spindles.
   i. When cerebellum is removed in the Cat, (or cooled) a rigidity develops, shown by Pollock and Davis in 1930s.

ii. But in human beings from clinical case studies it is clear, that the influence of cerebellum on tone is quite different.

Destruction of cerebellum due to disease or injury produces.

Hypotonia (not hypertonia or rigidity as in cat).

It means that in man cerebellum facilitates the tone. In man the middle lobe of cerebellum is well developed but in subhuman mammals (e.g. cats) the middle lobe is poorly developed (Fig. 111.1).

FUNCTIONS OF NEOCEREBELLUM

1. It guides and controls all voluntary movements so that they may be accurate in time, force, direction and extent. Thus, important for production of coordinated movements like walking, eating, writing, etc.
2. The new concept of cerebellar function is that the organ acts as a comparator of servomechanism.

It receives a: (i) Representation of the corticospinal activity, which is transmitted to

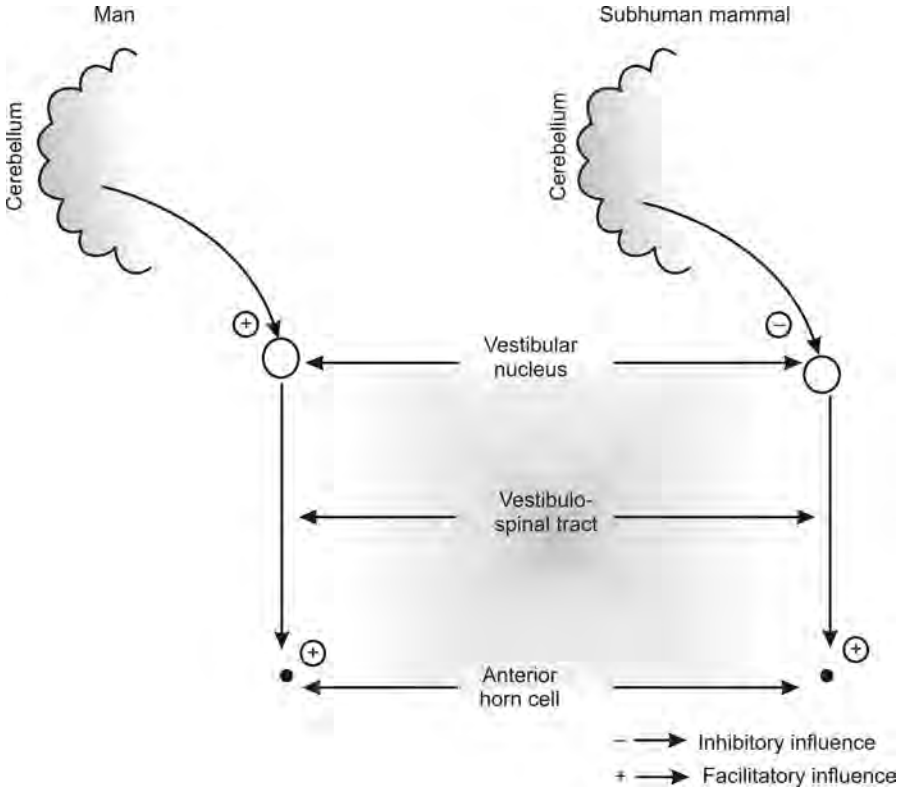


Fig. 111.1: Influence of cerebellum on vestibular nucleus in man and subhuman mammal

the muscle and (ii) Almost simultaneously a representation of the result in terms of the muscle movements from proprioceptors of muscle, (iii) It also receives impulses from eye, ear and tectile receptors.

This allows a comparison of the true corticospinal input and the proprioceptive indication of the position of the limbs.

Then cerebellocortical relays can modify the motor activity by appropriate corticospinal discharge. Literally servomechanism means a system introduced to check the working of another system. Here cerebellum is introduced to check the working of corticospinal activity, so that accurate movement results in time, force, direction and extent.

SUMMARY OF FUNCTION OF CEREBELLUM

1. Cerebellum is concerned with maintenance of normal tone in muscle (Anterior and middle lobe of cerebellum).
2. By adjusting distribution of tone in postural muscles, it helps in maintaining the normal erect posture of the body (flocculonodular lobe- vestibular connection).
3. Keeping in touch with the vestibular apparatus it maintains *equilibrium* of the body in standing, running, jumping, etc. by adjustments of tone amongst various groups of muscles engaged in particular act (flocculonodular lobe—vestibular connections).
4. It maintains integrity of γ efferent system. Ablation of anterior lobes by cooling abolishes gamma discharge to the intrafusal fibers of the muscle spindle.
5. During any voluntary act it synchronizes the firing of protagonist, antagonist and the synergists simultaneously so that the movement is smooth, non oscillating and regular.
6. It controls the range, force, speed and direction of movement for a particular purpose.
7. It may be said that cerebrum initiates the movements and cerebellum regulates them. In other words it is the regulator of neuromuscular apparatus.
8. Lastly the organ acts as comparator servomechanism meaning a control system for maintaining the operation of other system. Here the cerebellum acts as a control system for the operation of cerebrum.

Asthenia — Loss of power
Atonia — Loss of tone
Astasia — Loss of steadiness (e.g tremor)
Ataxia — Loss of equilibrium and loss of coordination.

RESULT OF LESION AND TESTS FOR CEREBELLAR LESION

There are characteristic disturbances of posture and movement. In unilateral lesion the changes are predominantly found on the same side of the body.

1. *Disturbance of Posture*
   i. *Atonia:* There is homolateral atonia. The muscles feel flabby and limbs swing about like a flail.
   ii. *Attitude*: The face is rotated towards the opposite side. The homolateral shoulder is lower than its fellow. The leg is abducted and rotated outwards. The weight is thrown on the sound leg. So the trunk is bent with the concavity towards the affected side.
   iii. *Spontaneous deviation:* If eyes are closed and arms are held straight out in front homolateral arm sways laterally.
   iv. Nystagmus is common in cerebellar lesion.

v. *Deep reflexes:* The knee jerk is characteristically pendular, i.e. after initial response, the leg on falling continues to swing to and fro.

2. *Disturbance of Voluntary Movement*
   i. There is feebleness of movement (Asthenia). The muscles tire easily. Voluntary movements are carried out slowly.
   ii. *Ataxia:* The person will not be able to perform coordinated movement and there will be loss of equilibrium.

Not affected by closing the eyes because conscious proprioception (Knowledge of body parts) is not lost.

Tests for Ataxia

1. *Heel knee test:* Person is asked to put the heel of the affected side on the knee of the opposite side. He is not able to perform this as one action as normal person; instead he will divide the movement into 3-4 parts. First, he will flex the knee and then puts the heel in middle of opposite leg. Finally, he will put the heel over the opposite knee. This is *Decomposition of movements.* That means movement seems to occur in obvious stages.
2. *Finger nose test:* The patient is asked to touch the tip of the nose by index finger of the affected side.

   He is not able to perform this action in one sweep. Either the finger will go away from the nose (i.e. off shoot the mark, which is known as hypermetria), or finger will remain short of nose (fails to reach the mark, which is known as *hypometria).* This means that for coordinated action, even the force applied should be regulated, which he is not able to do. Hypometria and hypermetria together is known as *Dysmetria.*
3. *Pronation and supination test:* (Adiadochokinesis)—This means inability to perform pronation and supination of the hand rapidly. This is known as *Asynergia.* Synergia means synergic action. In asynergia there is lack of coordination between protagonist, antagonist and synergist.
4. *Romberg s sign:* The person is asked to stand erect with eyes closed. Person with cerebellar lesion can do it because conscious proprioception (i.e. knowledge of body parts) is intact. Fasciculus gracilis and fasciculus cuneatus are intact.

   In tabes dorsalis, where conscious – proprioception is not possible, the person will not be able to stand erect with closed eyes.
5. *Gait:* Zigzag gait, when asked to walk along a straight line. This is because his balance is lost and he deviates to the affected side because of incoordination of muscles. He will try to correct himself and gets back to original line, thus producing zigzag gait.
6. *Speech:* Speech is slow and lulling and monotonus, because of incoordination of laryngeal muscles, muscles of tongue, face and palate.
7. *Intension tremor:* Conspicuous feature of neocerebellar lesion. The course tremor 4-6 /sec is most conspicuous when the part is used in a voluntary movement. It becomes progressively exacerbated as the movement develops.

CHAPTER

112

Basal Ganglia

Group of nuclei present at the base of cerebrum and concerned with – muscle tone and control of abnormal movements of the body are included in basal ganglia (Fig. 112.1):

1. Corpus striatum
   - i. Caudate nucleus
   - ii. Putamen
   - iii. Globus pallidus
2. Red nucleus
3. Body of Luys or subthalamic nucleus
4. Substantia nigra.

These represent the subcortical parts of extrapyramidal system. In lower animals, these are the structures, which control motor activity. In human being, cerebral cortex has taken up the functions of basal ganglia to a large extent.

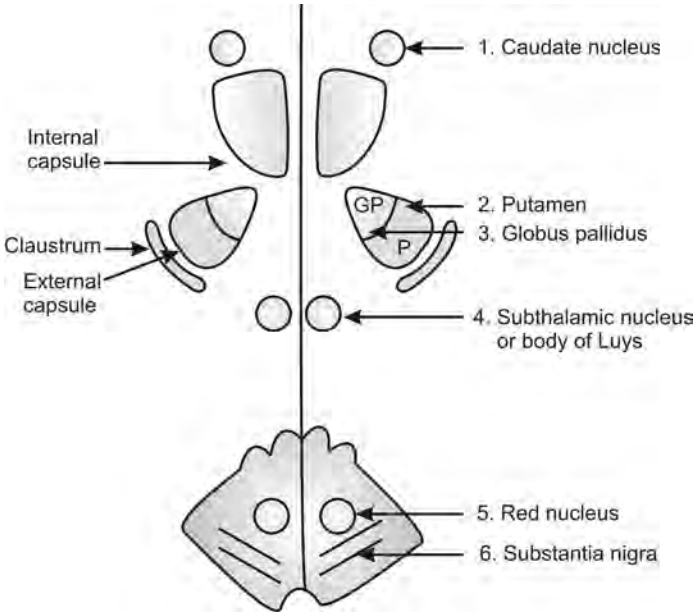


Fig. 112.1: Basal ganglia

CORPUS STRIATUM

They are a set of nuclei on the lateral side of thalamus. It has important role in controlling:

– Voluntary
- Reflex
- Automatic
- Associated

} Movements of the body

And in man most important function of these nuclei will be for control of muscle tone by inhibiting the normal muscle tone activity, i.e. stretch reflex.

Nuclei of corpus striatum are as follows:

Corpus striatum is divided in two parts incompletely by internal capsule:

1. *Caudate nucleus:* Mass of gray matter with large pear shaped head and long tail. Head bulges in lateral ventricle. Tail ends in amygdaloid nucleus (Fig. 112.2).
2. *Lentiform nucleus:* Lies on outer side of internal capsule:
   It is wedge shaped
   i. Outer part is *Putamen:* Inner smaller segment is *Globus pallidus.*
   ii. Beneath the anterior limb of internal capsule the lenticular nucleus is continuous with the head of caudate nucleus.

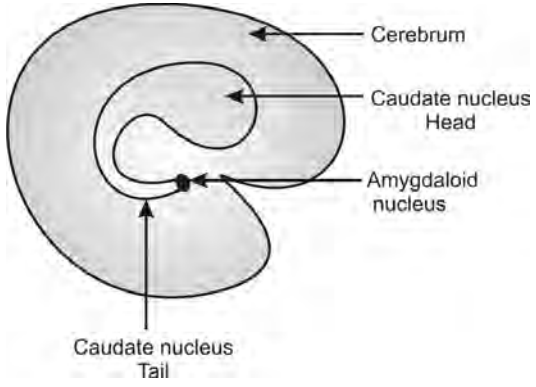


Fig. 112.2: Caudate nucleus

   iii. On other side of lenticular nucleus is a narrow band of white matter-called external capsule. Lateral to it is elongated band of gray matter called claustrum.

Caudate nucleus and Putamen – form neostriatum.

Globus pallidus – forms – Paleostriatum.

Large amount of white matter makes the globus pallidus look pale, hence the name.

Metabolism

1. High oxygen utilization.
2. Basal ganglia are sensitive to hypoxia.
   (i) Syndrome of parkinsonism results.
3. Contain high dopamine
4. Have high copper content – familial disorder of ceruloplasmin (Cu binding protein) metabolism causes Wilson's disease with severe derangement of lenticular nuclei.

Connections

1. *Commissural fibers:* Corpus stratum on one side is joined with opposite side.
2. Interstriate fibers-connections between their own nuclei-caudate nucleus to putamen and then to globus pallidus.
3. Striatopetal fibers or afferent (Fig. 112.3).
   i. *Thalamostriatal:*
      a. Thalamus to putamen and globus pallidus
      b. Thalamus to caudate nucleus.
   ii. Corticostriatal: (a) From suppressor bands (mainly area 4s) to caudate and then to Reticular inhibitory area, (b) from area 4 & 6 to putamen and globus pallidus then via ansa lenticularis to reticular facilitatory area.
   iii. From body of luy's to globus pallidus.

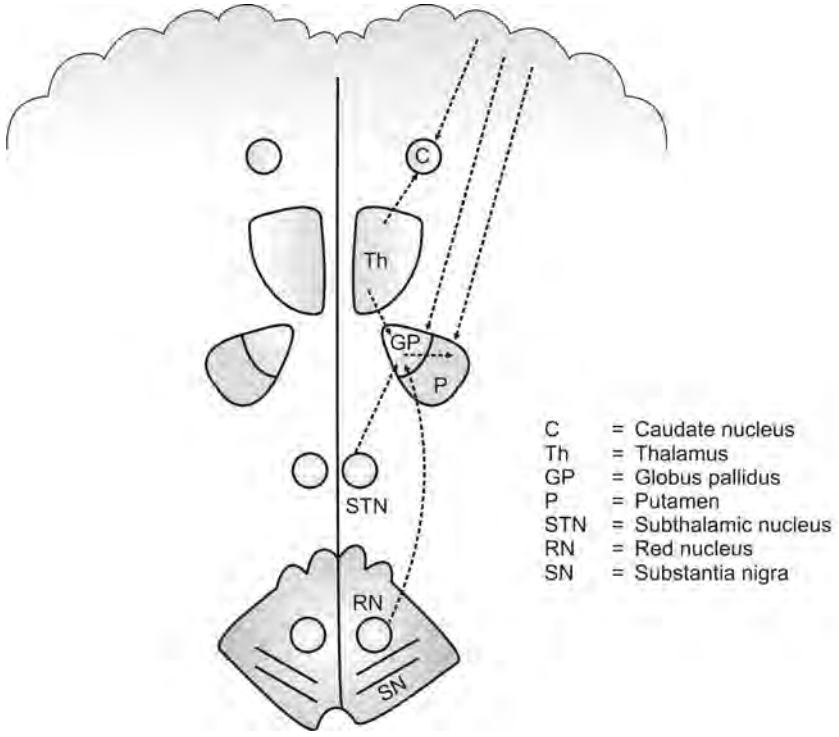


Fig. 112.3: Afferent connections of corpus striatum

iv. Rubrostiatal – from red nucleus to globus pallidus.
v. From hypothalamus.

4. Striatofugal or efferent fibers (Fig. 112.4).
   i. To adjoining nucleus of thalamus, hypothalamus red nucleus and cerebral cortex.
      a. Striatothalamic
      b. Pallidohypothalamic
      c. Striatocortical
      } All arise from globus pallidus
   ii. Ansa lenticularis
      a. Striatoreticular
      b. Striatonigral
      c. Striatorubral
      d. Striatosubthalamic

Ansa Lenticulars (Ansa = Bunch of fibers) passing downward from globus pallidus and making connection with:

1. All extrapyramidal nuclei
   i. Red nucleus
   ii. Vestibular nucleus
   iii. Reticular nucleus
   iv. Olivary nucleus.
2. Motor cranial nuclei (3, 7, 9, 10)
3. Some nuclei of basal ganglia
   i. Body of Luy's (subthalamic nucleus)
   ii. Substantia nigra (Fig. 112.4)

It is through this complex interconnecting system, the motor function is affected profoundly through pathways arising in many of the nuclei and because these pathways are additional to pyramidal, they are called extrapyramidal.

It is by its connections with the extrapyramidal nuclei (and the extrapyramidal tract) the main function, i.e. control of muscle tone is performed.

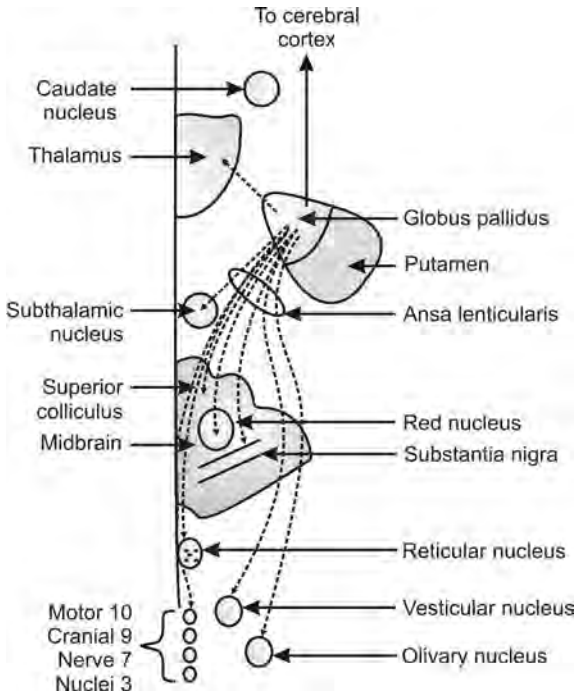


Fig. 112.4: Efferent connections of corpus striatum

FUNCTION OF BASAL GANGLIA

1. *It is primitive motor cortex:* For voluntary muscular movements.
   In lower vertebrates:

Fishes Amphibia Reptiles Birds	It acts as highest motor center for voluntary movement

   In primates: The highest motor center is precentral cortex (area 4 and 6) (Figs 112.5A and B)
   In Monkeys
   i. Ablation of area 4
      —Still some voluntary activity is possible because of area 6 and basal ganglia, e.g. can sit, walk.
   ii. Ablation of area 6 and section of pyramidal tract.
      - Basal ganglia and extrapyramidal tract help in voluntary movements.
2. Regulates tone, posture and equilibrium of the body by making connection with extrapyramidal system (i.e. it controls reflex muscular activity for control of muscle tone and posture).
   i. It has inhibitory control on spinal reflex, which maintain tone (i.e. on stretch reflex).
   ii. Regulates the activity of muscles, which maintain posture by controlling γ efferent activity (Fig. 112.6).

Stretch reflex is basically responsible for muscle tone therefore diseases of basal ganglia produce muscular rigidity in Parkinson's paralysis agitans or parkinsonism whereas lesions in substantia nigra and globus pallidus are responsible for tremors in parkinsonism.

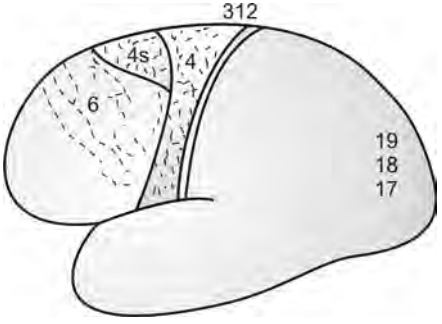


Fig. 112.5A: Lateral surface of cerebral hemisphere

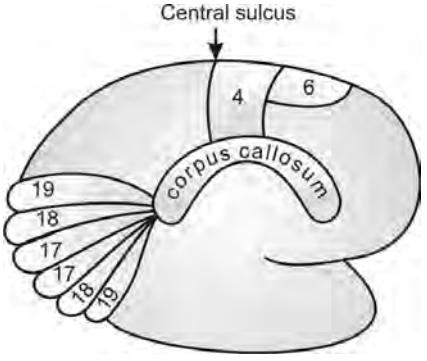


Fig. 112.5B: Medial surface of cerebral hemisphere

3. *Controls automatic associated movements:* (Such as swinging of the arms during walking) normally they are initiated by area 6 and are mediated through corpus straitum.
4. *Checks abnormal involuntary movements:* Therefore in lesion of corpus striatum abnormal involuntary movements occur.
5. *Controls group movements for emotional expression:* Therefore in striatal lesion – there is lack of emotional expression (mask like face).
6. *Red nucleus*

   In summary its functions are:
   i. It is a relay station.
   ii. It is coordination center for many motor and sensory impulses.
   iii. It acts as a center for righting reflexes.
7. *Substantia nigra:* It is center for coordination for those impulses, which are essential for skilled movements.

CLINICAL MANIFESTATIONS ASSOCIATED WITH DISEASE OF BASAL GANGLIA

In diseases of basal ganglia:
Clinical features are:
1. Muscular rigidity
2. Abnormalities in reflex muscular activity.
3. Disturbances in automatic associated movements.

Voluntary movements are impaired but no paralysis.

Clinical Syndromes

1. Paralysis agitans (parkinsonism)
2. Progressive hepatolenticular degeneration or Wilson's disease.
3. Chorea
4. Athetosis
5. Torsion spasm
6. Hemiballismus.

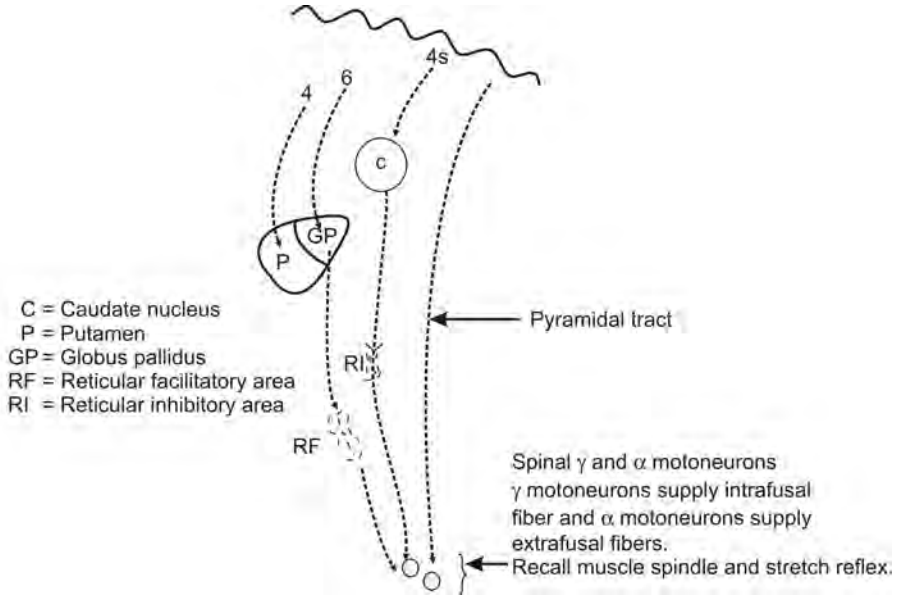


Fig. 112.6: Facilitatory and inhibitory pathways descending on spinal motoneurons

Paralysis agitans or parkinsonism is common. Rest are uncommon.

Parkinson's Disease or Parkinsonism or Paralysis Agitans

It is due to degeneration of corpus striatum in old age.

Symptoms are:

1. Rigidity of muscles
2. Tremors (Coarse)
3. Disturbances of movements
4. Absence of automatic associated movements.

1. *Rigidity*:
   i. Muscle tone of all the muscles of the body both flexors and extensors is increased, but tone in all the flexors is more than extensors, thereby person will assume a state of universal flexion. Man sits like a statue.
   ii. Because of the rigidity of muscles of face he will not be able to have his emotional expression of face, i.e. face becomes expressionless, known as mask like face.
   iii. Rigidity is *lead pipe type* in passive movements – means resistance felt while bending the elbow or any other joint will be uniform throughout as in bending a lead pipe.
   iv. *Deep reflexes:* Will be less than normal because of extreme rigidity.
2. *Coarse tremors*: These are involuntary movements, 4 to 6 times per second, which are more evident in the peripheral region, i.e. head, hands and protruded tongue.

   These movements can never be stopped except in sleep and by painful stimuli.

   They become pronounced during emotional excitement.
3. *Disturbance of movements:* All the disturbances are due to rigidity of muscles:
   i. Normal day-to-day movements will be difficult due to rigidity of muscles, smooth coordinated movement is not possible – *Ataxia*. The movement is weak, slow and irregular.
   ii. There will be poverty of movements, i.e. patients will try to avoid any movement as far as possible *Akinesia*. Also the muscles will get fatigued easily—*Asthenia*.
   iii. *Speech* will be slow and monotonous because of rigidity of facial muscles.
   iv. *Gait*: (means mode of walking) – Short schuffling gait. He takes short quick steps because of rigidity. Schuffling gait means falling forward, which is due to flexion of the body. If asked to check the movement, he cannot do so quickly and there is little falling forward movement.
4. There is absence of automatic and associated movements, e.g. swinging of arms during walking, i.e. poverty of movements is there.

Overall Peculiar features of parkinsonism are:

ART
1. **A**kinesia—Poverty of movements
2. **R**igidity
3. **T**remor of hands and head
4. Universal flexion of body
5. Mask like face
6. Incoordinate movements—Ataxia
7. Asthenia
8. Gait – short and schuffling
9. Speech – slow and monotonous.

Progressive Hepatolenticular Degeneration or Wilson's Disease

Described by Wilson in 1912.

There is disorder of ceruloplamin (copper binding protein) metabolism, which is familial. There is cellular degeneration of putamen and globus pallidus.

Caudate nucleus is not affected, putamen is maximally affected.

Features

Widespread muscular rigidity affecting flexors, extensors, face, trunk, limbs.

1. Face is blank, mouth open.
2. Tremor like involuntary movements, exaggerated during excitement.
3. Cirrhosis of liver, Cu metabolism is upset affecting liver and brain and causing their damage.
4. Emotional disturbances – involuntary laughing, crying.
5. Greenish brown pigmentalion of cornea.
6. Reflexes not affected.

Chorea

Disease causes irregular spasmodic movements not under patient's control (involuntary).

Voluntary movements are jerky.

It is of two types

1. Childhood disease known as rheumatic chorea.
2. Adult type or Huntington's chorea.

Childhood Disease

Also known as St. Vitus's Dance, caused due to rheumatic fever. Therefore, known as rheumatic chorea. The movements are rapid. Two or more limbs are involved. Movements are rhythmic and one movement blending with the other so dancing movements are produced. Therefore, known as St. Vitus's Dance.

Adult Type

It is rare. Also known as Huntington's chorea

1. Familial.
2. Transmitted as dominant trait.
3. Abnormal gesture and distortion of face is produced during speaking.
4. It is disease of small cells in caudate and putamen.

Athetosis

Result due to damage of caudate and putamen during birth. Therefore, manifests in childhood. There are abnormal movements, purposeless and involuntary. No rhythm.

Chorea—Athelosis

There are abnormal involuntary muscular movements quick and jerkey, like twisting of hands and feet. Absent during sleep and predominant during walking.

Torsion Spasm

It is rare. There are abnormal involuntary turning and twisting movements of trunk and neck and distortion of extremities.

Hemiballismus Are Hemichorea

It is produced due to vascular lesion of subthalamic nucleus of Luy's, occurs in old age due to cerebral atherosclerosis.

There are flinging movements of extremities of one side of the body.

Kernicterus

It is a disease of newborn. If the baby suffers from severe jaundice as in Rh incompatibility the basal ganglia are stained yellow.

CHAPTER

113

Cerebral Hemisphere

Cerebral hemisphere constitutes the bulkiest portion of the central nervous system and occupies most of the cranial cavity.

1. When viewed from above the two hemispheres together appear as an avoid mass which is seen to be broader behind than in front.
2. The two hemispheres are completely separated from each other both in front and behind, but in the middle they are connected together at the depth of anteroposterior deep fissure known as longitudinal cerebral fissure (Fig. 113.1).
3. With infoldings of cortical matter and formation of sulci the cortical surface area is enormously increased, particularly in man and it is due to greater cortical surface area, man is superior to animals.
4. The total surface area of adult cortex is approximately 2,200 sq cm which is equal to three times the surface area of the inner surface of the skull. 1/3rd of the total surface of adult cortex lies upon the free surface or crown of convolutions and 2/3rd is buried within the depth of the sulci or fissures.
5. The living cortex shows electrical activity, which is of two types:
   i. S*pontaneous electrical activity:* Continuously manifesting itself, without any stimulus.
   ii. *Evoked electrical activity:* Menifests itself when any suitable stimulus is applied to—sense organ or nerve path or to cortical neurons.

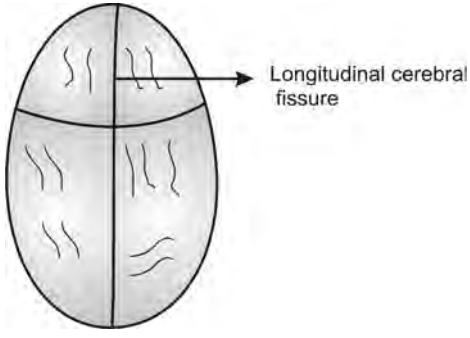


Fig. 113.1: Longitudinal cerebral fissure

Before discussing the physiology of the brain various anatomical divisions are to be known.

SUBDIVISIONS OF CEREBRAL HEMISPHERES

Major landmarks on the lateral surface of cerebrum (Fig. 113.2):

Major landmarks on medial surface of cerebrum (Fig. 113.3):

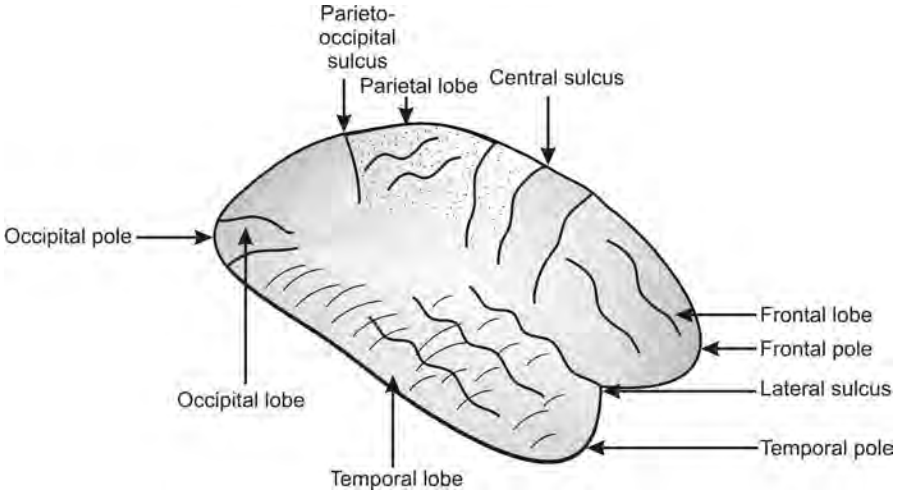


Fig. 113.2: Lateral surface of cerebrum

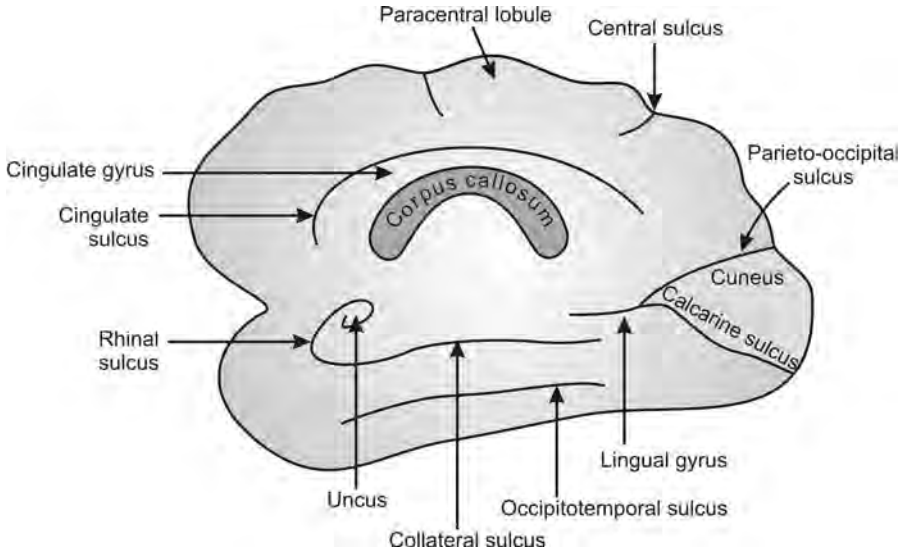


Fig.113.3: Medial surface of cerebrum

Each cerebral hemisphere is divided into: four lobes:

1. Frontal
2. Parietal
3. Occipital, and
4. Temporal.

Lateral and central ┐ Sulci form important landmark in this division ┘

Frontal lobe—on superolateral surface:

1. Precentral gyrus
2. Superior ┐
3. Middle ┘ Frontal gyri ┐ separated by superior and inferior frontal sulci ┘
4. Inferior

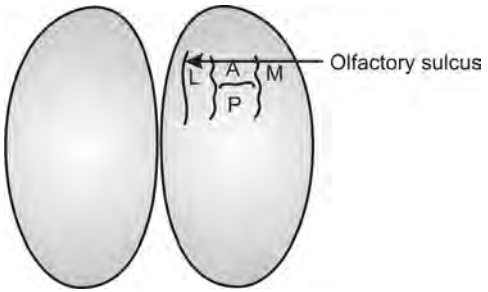
On Orbital Surface

1. Close to medial border olfactory sulcus—contains olfactory bulb and tract.
2. Gyrus rectus on medial side of olfactory sulcus.
3. Remaining portion of orbital surface is divided by H shaped sulcus in four orbital gyri (Lateral, medial, anterior and posterior) (Fig. 113.4).

On Medial Surface (see Fig. 113.3)

Curved sulcus—known as sulcus cinguli divides it into:

1. Outer zone
   i. Medial frontal gyrus
   ii. Paracentral lobule.
2. Inner zone—gyrus cinguli



L= Lateral, M = Medial, A = Anteriar, P = Posterior orbital Gyri

Fig. 113.4: Orbital surface

Parietal lobe—Consists of:

1. Postcentral gyrus
2. Superior ┐
3. Inferior ┘ Parietal gyri separated by intraparietal sulcus.
   i. Supramarginal ┐
   ii. Angular ┘ Gyri

Temporal lobe

1. Superior and inferior temporal sulci
2. Superior, middle and inferior temporal gyri.

On tentorial surface

i. Parahippocampal gyrus
ii. Lateral ┐
iii. Medial ┘ Occipitotemporal gyri

Anterior part of parahippocampal gyrus is curved on itself to:

Form globular swelling
- Uncus.

Occipital Lobe

1. Superior and inferior occipital gyri
2. On medial surface
   Divided by calcarine sulcus into:
   (i) Cuneus and (ii) Lingual gyrus.

FINE STRUCTURE OF CEREBRAL CORTEX

The detailed cell structure of any cortical area is called its cytoarchitecture. In 11 out of 12 parts, cells and fibers of cerebral cortex are arranged into layers or laminae. In 1/12 part they are not arranged.

Allocortex or archipallium—here all types of cells just mingle together.

1. 11/12 parts
   – Laminar arrangement, it is known as
   – Isocortex—neopallium
2. 1/12 parts
   – No laminar arrangement, it is known as Allocortex
   or Archipalium, e.g. olfactory lobe, limbic system.

3. Juxtallocortex or mesocortex: Between allocortex and isocortex a narrow zone showing transitional characters.

Structure of Isocortex or Neopallium

On naked eye examination of a section of brain shows two light bands—outer and inner bands of Baillarger may be distinguished in contrast with gray matter. These bands are produced by nerve fibers running parallel to surface of the cortex.

Structurally greater parts of human cortex are arranged in six layers (Fig. 113.5).

1. Molecular layer
2. Outer granular layer
3. Outer pyramidal cell layer
4. Inner granular layer
5. Ganglionic layer (inner)
6. Fusiform cell layer.

Gray Matter (Cortex)

It forms the surface layer, thickest (4.5 mm) at precentral gyrus and thinnest (1.3 mm) at the frontal and occipital poles, 2/3 of gray matter remains hidden in sulci. It is composed of nerve cells, nerve fibers and neuroglia.

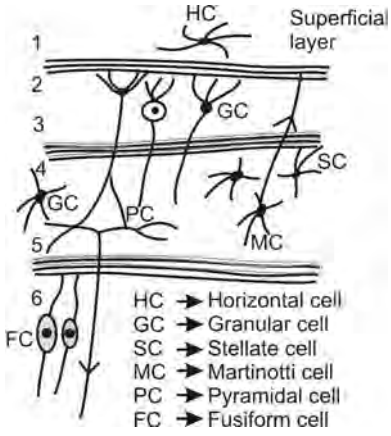


Fig. 113.5: Types of cells in the cortex and six layers

Roughly Five Types

Roughly five types of nerve cells are present

1. *Pyramidal*: Look like pyramids or isosceles triangle—**Heights differ**
   i. Small pyramidal cell 10-20 microns
   ii. Larger pyramidal cells 45-50 microns
   iii. Large pyramidal cells of Betz more than 100 microns present in motor area of precentral gyrus.
2. *Small stellate or granular*: Triangular or polygonal, 4-8 microns, dark staining nuclei, scanty cytoplasm. Some stellate cells resemble pyramidal cells known as stellate pyramidal cell or star pyramidal cell.
3. *Fusiform or spindle cells:* Placed vertically, found in deepest layer of cortex and have long axon.
4. *Horizontal cells of Cajal*
   i. Small fusiform cells
   ii. Found in most peripheral layer.
5. *Cells of Martinotti:* With ascending axons found in all layer.

Pyramidal, fusiform and stellate cells posses descending axons, which leave the cortex as projection and subcortical association fibers, but horizontal cells of Cajal, cells of Martinotti and granular cells have intercortical connection.

White matter: Remains under the gray matter, composed of three groups of medullated fibers.

1. *Projection fibers:* Connecting cerebrum with extracortical areas.
2. *Association (Arcuate) fibers:* Connect different parts of same hemisphere.
3. *Commissural fibers:* Unite two hemispheres.
   i. Corpus collosum
   ii. Anterior commissure—between two temporal lobes.
   iii. Hippocampal commissure, between two hippocampal gyri.

FUNCTIONS OF DIFFERENT LAYERS OF CEREBRAL CORTEX

1. Outer layers of cortex are concerned with associative and intellectual faculties. Therefore, in dementia (mental degeneration) there is atrophy of these layers.
2. Inner layers are concerned with various organic and instinctive faculties and very little difference is observed in these layers between man, monkey and dog.
3. Pyramidal cells are concerned with reception of impulses from various sources, which they convert into efferent discharge.
4. Cells of granular layer have sensory and associative functions.

CHAPTER

114

Functional Areas of Frontal Lobe

EXCITOMOTOR AREAS

It is that part of frontal cortex which on stimulation gives rise to skeletal muscle response. As this region lies in front of central sulcus it is commonly called as (Fig. 114.1):

Precentral motor cortex which includes

- Motor cortex area 4
  - It includes areas 4s, 4α and γ
- Premotor cortex Area 6, 8, 44 and 45

Or in terms of region it includes

- Whole percentral gyrus
- Adjoining paracentral lobule
- On medial surface
- Adjoining posterior parts of superior, middle and inferior frontal gyri

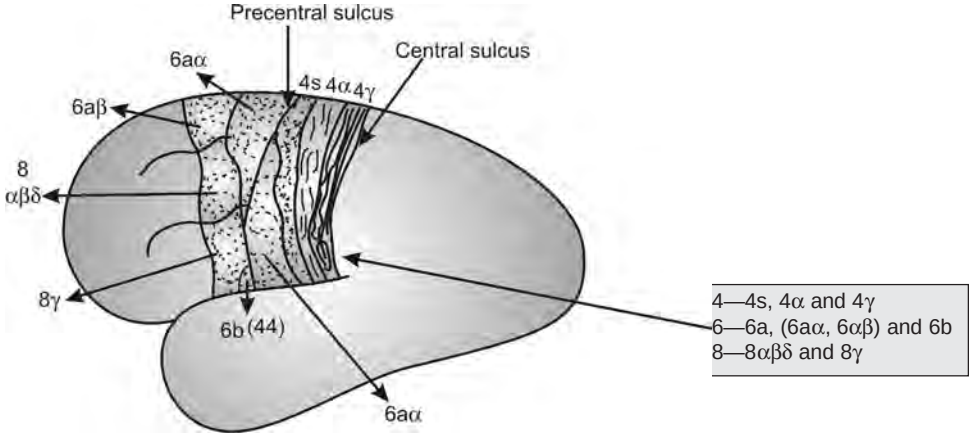


Fig. 114.1: Precentral motor cortex and it's divisions

Area 4: It is motor area of brain

1. Includes:
   i. Whole precentral gyrus
   ii. Adjoining part of paracentral lobule
   iii. Lip of central sulcus
2. It is divided into:
   i. 4 γ—lies most caudally
   Betz cells are present therefore, known as area gigantopyramidalis. Betz cells are not present anywhere else.
   ii. 4α—Forms bulk of area 4 and lies rostrally
   iii. 4s functionally is an inhibitory area. Because stimulation of this area inhibits movements in animals.

Functions of Area 4—center for control of movements:

1. Gives origin to major part of corticospinal tract (Pyramidal tract).
2. Stimulation of area 4 produces coordinated movement of opposite side of the body.

Area 4—Projects also to Pons (frontopontine tract)

1. To corpus striatum
2. To thalamus and subthalamus
3. To red nucleus.

Area 4 and 6 are connected by intercortical fibers.

Area 6—is situated in front of area 4

1. This area contributes:
   i. Descending fibers to pyramidal tract.
   ii. Descending fibers, which do not run in the pyramidal tract and therefore are extrapyramidal.
   iii. Horizontal fibers to excite area 4.

Connections

1. Many pyramidal axons pass without relay to spinal segment. Where they synapse with either internuncial neurons or with motoneurons themselves.
2. Extrapyramidal fibers have many synapses in their descending path, e.g. with nuclei of corpus striatum, hypothalamus and reticular nuclei.
   i. The pyramidal and extrapyramidal projection fibers cause effects on motoneurons of opposite side of the spinal cord.
3. Corticopontine fibers, which relay via nuclei pontis to opposite neocerebellum.
4. Corticothalamic fibers to thalamic nuclei, back to cerebral cortex.

Functions of Area 6

- Divided in two parts 6a and 6b
- 6a subdivided in two parts:
  - 6 aβ
  - 6 aα

1. Stimulation of area 6 predominantly produces excitatory effects: (a) stimulation of 6a causes movements of eyes, head, body towards opposite side (b) stimulations of 6b controls complex movements of jaws, tongue, pharynx, larynx, swallowing and respiratory movements.
2. Extrapyramidal activity—maintenance of tone posture and equilibrium.
3. Writing center: Area 6aα on left side in right handed people is believed to contain center for writing.
4. 6b on the left side in right-handed people contains Broca's area—(Area 44 and 45) which is a center for speech.

Area 8 (Frontal Eye Field)

Two parts—upper 8 α β δ in the middle frontal gyrus

Lower 8γ in the inferior frontal gyrus.

8s is situated in front of area 6—inhibitory area.

Connections

Corticonuclear fibers from area 8 descend first in anterior limb of internal capsule then in medial fifth of cerebral peduncle to pass finally dorsally to the eye nuclei of opposite side.

Function

1. For the conjugate (combined) movements of both eyeballs for seeing an object, otherwise there will be double vision.
2. Opening and closing of eyelids.
3. Sometimes, dilation of pupils and lacrimation.

AREA 44 AND 45 (BROCA'S AREA)

It is situated in posterior part of inferior frontal gyrus.

1. It is a speech center.
2. Present in dominant hemisphere, i.e. in left hemisphere in right handed person.

Damage to Area 4

1. Loss of strength
2. Flaccidity
3. Diminished tendon reflexes
4. Incapability to movements.

Damage to Area 6

Awkwardness of movements with little change in strength:

1. Increased tone (Spasticity)
2. Increased tendon reflexes
3. Forced grasping often associated with autonomic disturbances.

Damage to Broca's Area

Does not prevent person from vocalizing.

1. Person does not speak whole words
2. He speaks simple words.

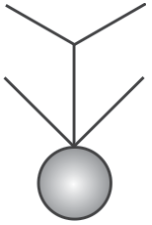


Fig. 114.2: Cortical representation of body in motor cortex

CORTICAL LOCALIZATION

The body is represented in the motor cortex in a reverse way (upside down) (Fig. 114.2).

1. Paracentral lobule controls lower limb below the knee it also includes cortical center for micturition and defecation.
2. The summit of the precentral gyrus controls lower limb above the knee.
3. The remainder of the precentral gyrus controls the rest of the body parts in order from above downwards, the body parts represented are (Fig. 114.3):
   i. Trunk
   ii. Upper limb, hand
   iii. Face, larynx, mouth, lips, jaws, tongue and pharynx.

There is large area for thumb, lips and jaws (so as to have high cortical control).

Supplementary motor area: It is present in man and monkey on medial surface of frontal lobe. It is more anterior and more ventral in position to primary motor area. Here representation of head and upper part is near the margin in forward position and the lower part posteriorly towards corpus callosum and body is represented horizontally (Fig. 114.4).

GENERALIZED FUNCTIONS OF EXCITOMOTOR CORTEX

1. Motor cortex control opposite half of the body.

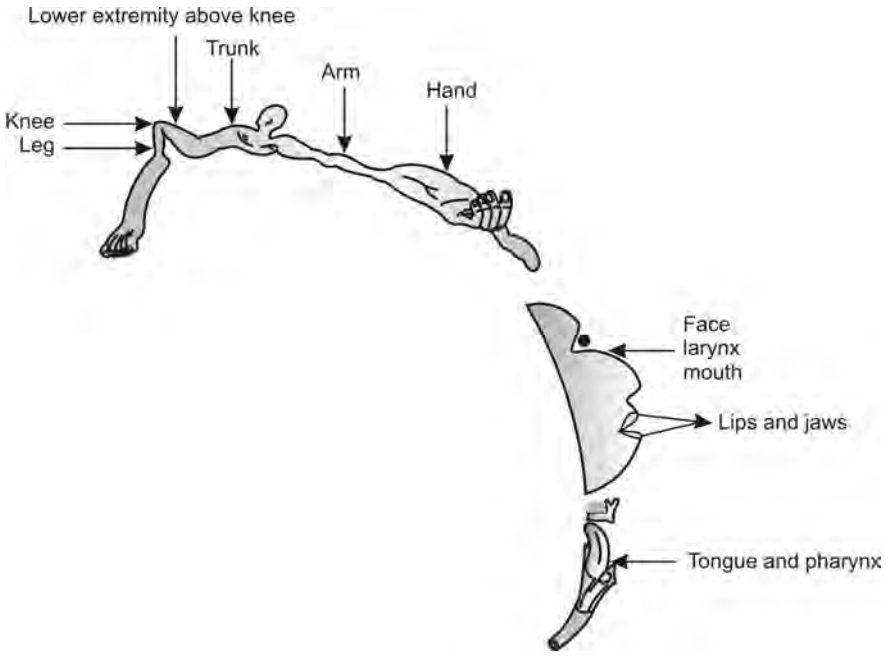


Fig. 114.3: Cortical representation of body

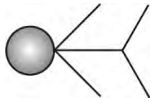


Fig. 114.4: Horizontal representation of the body in supplementary motor area

2. Its main function is to initiate and organize purposeful voluntary movement of the opposite side of the body, e.g. flexion of elbow, extension of thigh, etc.
3. The motor cortex organizes particular movement and not the action of individual muscle, although individual muscles can be made to contract on electrical stimulation of the cortical area.
4. Premotor area coordinates the activities of motor cortex, so that a particular skillful volitional (Voluntary) movement may be smooth, precise and regular, e.g. threading through a needle.
   i. It requires skillful holding of the thread in one hand and needle in the other and then carry out threading through hole of the needle.
   ii. Motor cortex initiates and organizes different movements required for the act of threading through a needle: (1) flexion of elbow, (2) extension of wrist, (3) opposition and flexion of digits and steadiness.

Coordination

Only comes from premotor cortex in order to make the purpose a success. In other words, attempt to thread the needle (initiation and organization of movement) is the work of motor cortex, but to make the attempt a success is the work of premotor cortex.

CHAPTER

115 Prefrontal Lobe or Orbitofrontal Region

SITUATION

1. Anterior to excitomotor cortex.
2. Also extends on medial surface of the hemisphere up to anterior end of corpus callosum.
3. Orbital gyri. Therefore, known as orbitofrontal region.

Thus, it occupies medial lateral and orbital surfaces and comprises of areas 9,10,11,12, 13,14, 23, 24 and 32 (Area 24 is precallosal part of cingulate gyrus) (Fig. 115.1).

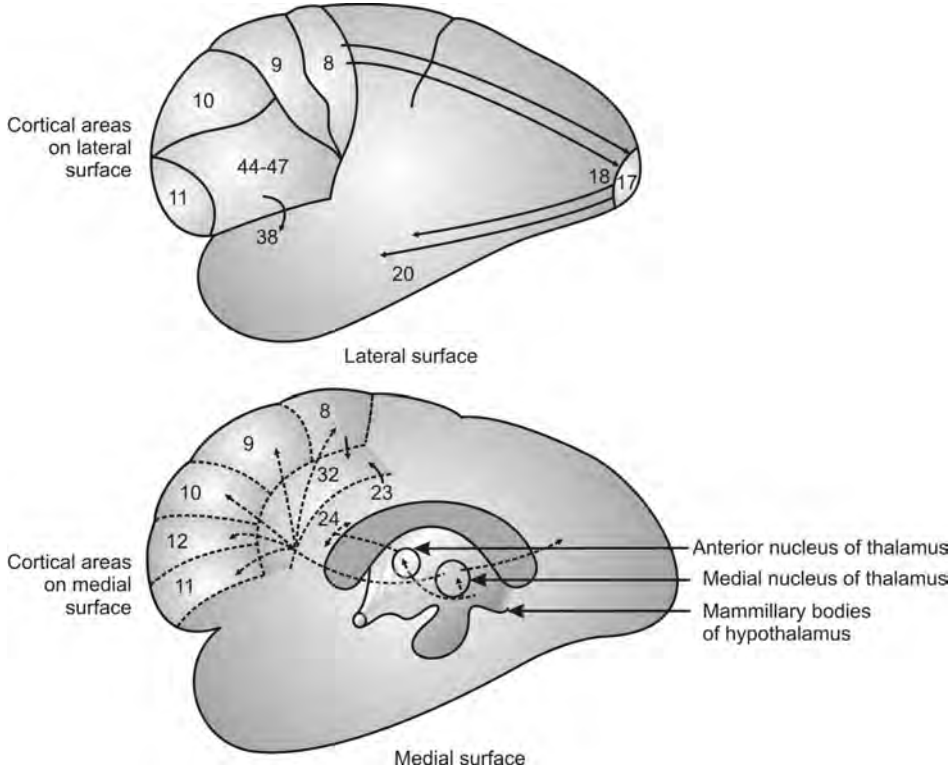


Fig. 115.1: Prefrontal lobe (arrows indicate areas of projection and receiving fibers)

The size of prefrontal lobes increases as one ascends the phylogentic scale.

It is also called silent area of brain because ultill recently, this area was not known to produce any response on stimulation or it was thought to be inexcitable.

Recent observations reveal that stimulation of prefrontal area with low frequency electric current produces–circulatory, respiratory, gastrointestinal, renal and autonomic responses.

Ablation of this area brings about permanent changes in thought process and other symptoms.

Thus, prefrontal lobe in some way is concerned with visceral rather than somatic sensations.

Structure

It is typical 6 layered isocortex.

Connections

1. These are mainly to and from thalamus and hypothalamus.
2. Connections are also established with other regions of cerebral cortex.

Afferent Connections

1. Many fibers pass from medial nucleus of thalamus to most of the areas of prefrontal lobe.

   As the medial nucleus of thalamus receives afferents from posterior hypothalamus, so the impulses that reach the prefrontal lobes represent the resultant of hypothalamic as well as thalamic activity.
2. Fibers from anterior nucleus of thalamus project to precallosal part of cingulated gyrus (area 24).

   Hippocampus sends efferent fibers via the fornix to the mammillary bodies of the hypothalamus. From here a new relay transmits the impulses to the anterior thalamic nucleus. Hippocampus is thus, ultimately projected to inhibitory area (Fig. 115.2).

Closed Circuit Connections with the Thalamus

Like most regions of the cerebral cortex the prefrontal lobes establish to and fro connections with:

- Anterior
- Medial
- Intralaminar

] Nuclei of thalamus

These type of closed circuit connections are responsible for electrocorticogram or electroencephalogram.

Intercortical Connections

1. Area 32—receives fibers from frontal inhibitory areas

   4s, 8s, 24s (s = suppressor) and also from other inhibitory areas – 2s, –19s

   No other connections of area 32 are known.
2. A long tract runs back from the frontal eye field in area 8 to area 18 in occipital lobe

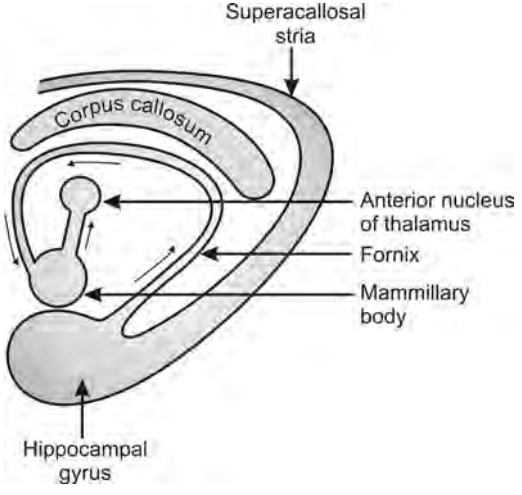


Fig. 115.2: Connection of anterior nucleus of thalamus to hippocampal gyrus

(Area 18 surrounds the visual cortex) and receives afferents from it.

i. Thus, frontal lobes are linked with visual system.

Ablation of Area 8: Causes visual agnosia (Object vision hemianopia), which means — can see the object but cannot recognize it.

ii. Proprioceptive data from eye muscles are integrated in area 8 and through frontal occipital projection (Area 8 to area 18) this data can be correlated with retinal impression.

3. Fibers from prefrontal areas 44-47 and from occipital area 18 pass to temporal lobes. Prefrontal lobes thus, establish connections both direct and round about (i.e. via area 18) with the temporal lobes, which in their turn receive numerous association fibers from most parts of the cerebral cortex.

Efferent Connection (Fig. 115.3)

1. Inhibitory area 8s and 24s discharge to caudate nucleus.
2. Area 10 provides many of the fibers of frontopontine tract which passes in anterior limb of internal capsule to pontine nuclei then to cerebellum of opposite side.

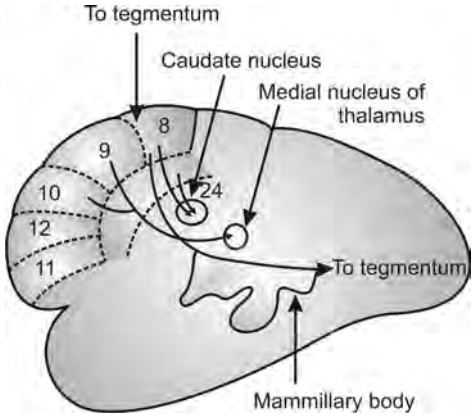


Fig. 115.3: Efferent connections of prefrontal lobe

3. Area 8 has an important projection to the tegmentum of the midbrain—corticotegmental fibers.
4. Areas 9 and 10 send fibers to medial and ventral nuclei of thalamus and to tegmental reticular formation.
5. Hippocampus, uncus, area 13 and amygdala project via fornix to mammillary bodies (hypothalamus).

Significant Points about Connections

1. As the prefrontal lobes are linked up with thalamus and hypothalamus by many fibers which pass in both direction the whole system may be considered as an integrated whole.
2. The prefrontal lobes are linked up with visual cortical areas and the temporal lobes.
3. The prefrontal lobes also affect the autonomic system via the hypothalamus and via midbrain.

EXPERIMENTAL STUDIES

1. Unilateral or bilateral removal of prefrontal lobes does not cause paralysis either in man or monkey.
2. i. Unilateral removal of human prefrontal lobe produces a definite alteration in mental processes.
   a. Loss of initiative and mental alertness
   b. Memory, judgement and intellect show little or no deterioration.

   ii. Removal of dominant hemisphere prefrontal area, i.e. on left side in right-handed person—produces greater alteration in character and intellect than that of nondominant side removal.
3. Even bilateral excision of prefrontal areas is followed by a surprisingly moderate mental defect on superficial examination and observation but detailed examination shows that his mental activity and behavior becomes impaired.

In an operation for removal of tumor, Dandy excised the prefrontal lobes on both sides. In casual acquaintance, he appeared to be normal. It is reported that for an hour he toured the hospital with two visiting neurologists, who failed to notice in him any mental abnormality. A more intimate knowledge showed very definite changes of character and mentality. His mental age was about 13 years; his IQ (Intelligence Quotient) was 80. The main features shown by this subject can be taken as effects of extensive prefrontal destruction.

FRONTAL LOBE SYNDROME

Features are as follows:

1. Impairment of intelligence.
2. Impairment of memory and learning power.
3. He is jolly and is in euphoria (i.e. high spirits).
4. Lack of initiative and difficulty in planning.
5. Impairment of moral and social sense. Loss of love for the family.
6. Lack of restraint—leading to boasting, hostility, aggressiveness.
7. Distractibility and restlessness with difficulty in fixing attention.
8. Hypermotility—which appears to be due to loss of especially area 13 on orbital surface.
9. Flight of ideas, fantasies, emotional instability.
10. Disturbance of orientation in time and space.

The effects of prefrontal lobotomy are highly variable from patient to patient and depend on each patient's preoperative personality and past experiences.

. In chimpanzees, removal of both frontal areas show restlessness and are easily distracted although they remain alert and show keen interest around them. Fulton and Jacobson (1951) reported that after these operation chimpanzees failed to show temper tantrums and other manifestation of frustration. This observation formed the basis for surgical attempts to relieve certain psychoneurosis in man. First employed by the Portugese neurologist Moniz. The operation was called frontal lobotomy or leucotomy, in which fibers connecting prefrontal areas with subcortical centers were cut. Moniz was awarded Nobel Prize.

Recently introduced drugs like tranquilizers are capable of reducing mental tensions and aggressive agitated patients become more manageable. Therefore, lobotomies are performed rarely.

FUNCTIONS OF PREFRONTAL LOBE IN SUMMARY

1. The prefrontal area is region of high associative or synthetic capabilities required for formation of abstract ideas, accurate judgement and for guidance of behavior suitable with social customs.
   i. Planning, forecasting, prediction and forming strategy is with prefrontal area.

   For above function it is known as organ of Mind.
2. Also required for emotional stability. By virtue of its connections with hypothalamus and brainstem it exerts influences on autonomic reactions associated with emotions:
   i Mediated by:
      a. Frontopreoptic
      b. Frontothalamic
      c. Frontohypothalamic, and
      d. Thalamo-hypothalamic pathways
3. Prefrontal lobe exerts inhibitory control over the ideomotor area (supramarginal gyrus of parietal lobe on dominant side) so

that it is kept under restraint for response to various incoming sensory stimuli on the basis of past experience, e.g. in a shop of sweets—sweets are exhibited. Normally, one will buy the seeets and eat, but a person with frontal lobotomy will go ahead with eating without payment.

4. In a nutshell "the relative pitch of one's being is influenced in this region:
   i. From calmness to ectasy,
   ii. From gloom to elation,
   iii. From friendliness to disagreeableness, have their roots in areas 9–12".

CHAPTER

116 Parietal, Temporal, Occipital Lobes and Dominant Hemisphere

PARIETAL LOBE

In parietal lobe the main sensory areas of brain are present.

Functionally following areas are present (Fig. 116.1):

1. Postcentral area or sensory are 3, 1, 2
2. Parietal association area 5 and 7
3. A narrow strip of parietal adversive field 5b, which on stimulation produces motor responses on opposite side of the body.

Sensory area: Also called as primary sensory area, or somatic sensory area or somesthetic area.

Situation

1. Posterior wall and lip of central sulcus.
2. Postcentral gyrus (except lower part).

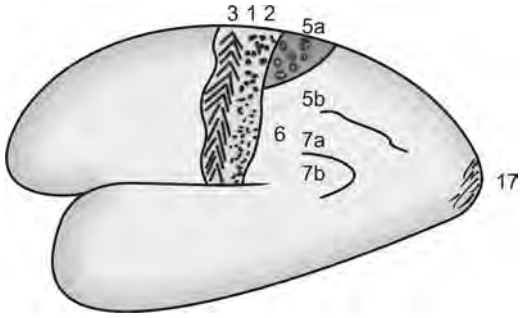


Fig. 116.1: Parietal lobe different areas

3. Extends up to cingulate gyrus on medial surface.

Postcentral area

1. It i s divisible into—anterior (Area 3)
2. Posterior part (Area 1 and 2)

They are characterized by structural difference.

Cortical Localization

1. The sensory areas are also represented in the inverted order, like motor area.
2. The motor center for a particular part lies just in front of the sensory center of the same part like mirror image.
3. The areas representing hand, fingers and thumb are larger as in motor areas.
4. The lowest part represents tongue including taste sensation (i.e. center for taste—in lower part of 3, 1, 2).
5. Penfield and his associates have found precentral and postcentral gyri are knit together by connecting neurons and are interrelated functionally. So, that both together can be called *sensory motor area.*
6. The sensory area just described (3, 1, 2) is primary sensory area somatic area I. More recently discovered sensory area is called somatic area II lies in upper wall of sylvian fissue, i.e. below face area of somatic area

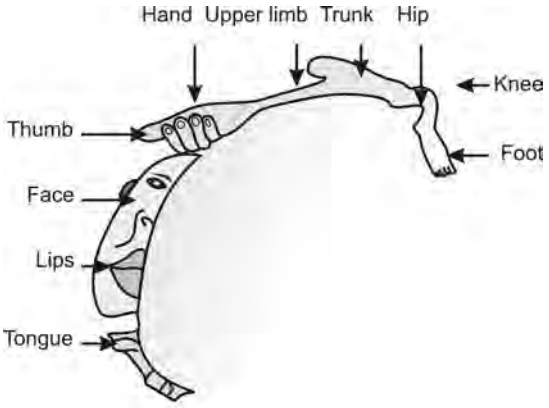


Fig. 116.2: Sensory homunculus

I. In somatic area II order of representation is reverse to that of somatic area I, i.e. face above and foot at the bottom (Fig. 116.2). It is more primitive and receives cruder sensation.

Connections: All sensations passing via medial, spinal and trigeminal lemnisci relay to thalamus from where they project to sensory cortex (except pain).

Parietal association area: Area 5 and 7, i.e. superoparietal lobule, supramarginal and angular gyri.

Note: All sensory areas (both general and special) are surrounded by association areas or psychic areas. For example:

1. For general sensation area 3,1,2—psychic area is 5, 7
2. For vision area 17—psychic area is 18 and 19
3. For hearing area 41, 42—psychic area is 22, 21, 20
4. For taste lower part of area 3, 1, 2
5. For smell area surrounding the amygdaloid nucleus.

In association or psychic area, the past experiences area stored for that particularly sensation.

Effect of stimulation of different parts of somesthetic areas in conscious patients:

There are hallucinations of: (i) tactile stimulations, (ii) feeling of numbness, (iii) tingling, and (iv) sense of movements or pressure are felt on contralateral half of the body but never pain.

The location bearing constant relationship, e.g. if foot area is stimulated—sensations are felt in the foot of opposite side.

Ablation Studies

Show disturbances of cutaneous and kinesthetic sensations in the corresponding region of opposite side of the body.

Functions of Parietal Cortex

Parietal cortex is concerned with following aspects of sensations:

1. Differences in relative intensity of different stimuli, e.g. heat is not merely distinguished from cold but warm objects are distinguished from warmer objects, cold from colder, rough from rougher and so forth.
2. Recognition of spatial relationships:
   i. Tactile localization, i.e. precise point stimulated is accurately located.
   ii. Tactile discrimination (2 point discrimination): Two points of compass placed close together are recognized as two and not as one.
   iii. Extent and direction of small joint displacement can be estimated accurately.
3. Appreciation of similarity and differences in external objects brought in contact with the surface of the body, without the aid of vision. Differences and similarity of size, weight, form and texture are thus, recognized.

4. *Stereognosis*: It is the most elaborate function subserved by parietal cortex. It requires perfect repetition of impulses set up by the stimuli from the object. The sensation produced is compared with previous similar sensory memory. We thus, recognize an object as 1 rupee coin and distinguish it from 2 rupee coin, because of dissimilarity in size.

   Sensations innumerated are lost or impaired in lesion of parietal lobe.
5. Inferior part of postcentral gyrus acts as cortical center for taste. No number is given to this area.

TEMPORAL LOBE

Functionally following areas are present in temporal lobe:

1. *Auditosensory area:* Area 41 and 42 and part of area 22.
2. *Auditopsychic:* Area 22, 21 and 20 or association area.
3. *Temporal adversive area:* Posterior part of area 22 (Fig. 116.3).

Auditosensory area: Consists of area 41 and 42 (Primary cortical center for hearing) situated in tranverse gyrus of Heschl's lying in the floor of lateral cerebral or sylvian fissure.

Adjoining small area of superior temporal gyrus (part of area 22) which lies below and behind central sulcus.

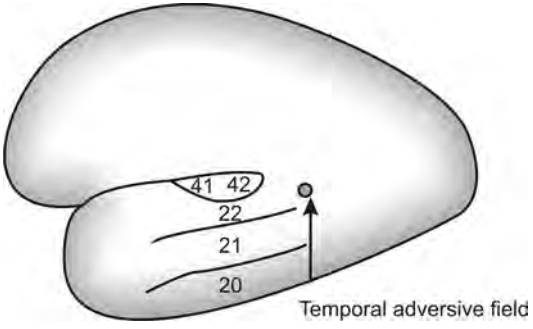


Fig. 116.3: Different areas in temporal lobe

Connections

Fibers from medial geniculate body reach auditosensory area via posterior limb of internal capsule they constitute auditory radiations.

Base

Auditosensory area receives orderly topographic representation of cochlea (Fig. 116.4). Anterior part receives impulses—which originated from cochlear apex and posterior part—receives impulses, which arise from base of cochlea.

This area is auditosensory area I. In auditosensory area II, there is opposite representation.

Function

It is primary center for hearing.

1. Cochlea is bilaterally represented in the center.
2. In the auditosensory area the fundamental auditory sensation—intensity and pitch of sound are perceived. But interpretation, significance and source of origin of sounds require the help of auditopsychic area.

Effect of Stimulation

Stimulation of area 41, 42 and 22 causes hallucinations described as humming, buzzing, whistling and ringing the bell.

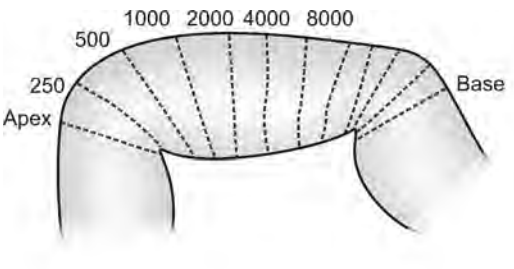


Fig. 116.4: Topographic representation of cochlea in auditosensory area

Lesion of 41 and 42

Unilateral

Produces difficulty to locate the source of sounds coming to the ear without any loss of hearing because each cochlea is bilaterally represented and projects equally to two cerebral hemispheres.

Lesion of 22 (Auditosensory) with intact 41 and 42.

Unilateral (of dominant hemisphere): Leads to difficulty in interpretation of sound. The subject cannot understand spoken language—this is called as *word deafness.* He is able to speak but makes innumerable mistakes of which he is unaware.

Auditopsychic area: 22, 21 and 20 (Association areas) rest of superior temporal gyrus excluding auditosensory area.

Function: It is concerned with:

1. Interpretation of sounds as regards its – origin, source and differentiation by correlating with past experiences.
2. The perception of concrete idea based on sounds is also the function of this area.

The auditopsychic area is represented unilaterally. In the right-handed person it is on the left side (Dominant ˇ hemisphere).

Center for equilibrium: It is located in posterior part of superior temporal gyrus. Stimulation of this part gives rise to a feeling of dizziness, swaying/falling and rotational feeling.

Temporal Lobe Syndrome

Bilateral removal of temporal lobes together with amygdaloid nucleus and the uncus in animals like monkeys leads to some manifestations, which are collectively known as temporal lobe syndrome.

It is characterized by:

i. Emotional changes—animal becomes extremely tame.
ii. Hypersexuality
iii. Visual agnosia—does not recognize the objects by seeing.
iv. It shows tendency to examine all objects by mouth.
v. It shows changes in dietary habits.
vi. It fails to ignore peripheral stimuli.
vii. It shows agnosia in auditory and tectile fields.

Note: Agnosia is a general term used for the inability to recognize objects by a particular sensory modality, even though the sensory modality is intact.

In mansimilar lesions produce following symptoms:

1. Disturbances of speech:
   i. Fails to tell names of common objects.
   ii. He is unable to express (More so when dominant hemisphere is involved).
2. Auditory disturbances—buzzing
   i. Auditory hallucinations—humming, ringing, paroxysmal attacks of tinnitus, seizures and dreamy state.
3. Disturbances of taste sensation—which become unpleasant.
4. Disturbances of smell—which also become unpleasant.
5. Dreamy state—known as psychomotor seizure.
   He gets visual, auditory, olfactory hallucinations, goes in trance like state and fails to observe the reality of his surroundings.
   i. He may take off his clothings or tear off other's clothing.
      That means, does things over which he has no control and returning back to normal, has no memory of what he has done.

6. Disturbance of vision—visual hallucinations, small images and incomplete images. Homonymous hemianopia—due to damage to visual fibers from lateral geniculate body may also occur.
7. Loss of memory—often results from extensive damage.

OCCIPITAL LOBE (FIG. 116.5)

Occipital lobe accommodates:

1. Visuosensory area 17
2. Visuopsychic area 18 and 19
3. Area 19 also contains—occipital eye field (adversive). Stimulation of this area causes conjugate deviations of the eyes to opposite side.
4. Anterior to visuopsychic area—is a suppressor strip:
   Area 19S—which on sitmulation leads to arrest or inhibition of resting electrical potential (Fig. 116.5).

Visuosensory area (Area 17) or striate area: It is confined to the walls of posterior part of calcarine sulcus and extends to cuneus above and lingual gyrus below and occipital pole. This area can be recognized by naked eye, which forms a broad strip of Genari, commonly known as *area striata.*

Functions

1. It acts as a cortical center for vision.
2. It receives, recognizes visual impressions of color, illumination, forms, size and transparency.

Connections

It receives fibers of optic radiation or visual radiation fibers from lateral geniculate body.

Retinal Representation in Visuosensory Area

1. The visuosensory area in each hemisphere represents temporal half of retina on the same side and nasal half of the opposite retina, due to decussation of nasal fibers in optic chiasma.
2. Upper lip of calcarine sulcus represents upper quadrants, whereas the lower lip represents the lower quadrants of retina.
3. Macular areas of retina have a wider representation in visuosensory area.
4. Experimental evidence shows that the retina bears a point-to-point relationship with visuosensory area.

Visuopsychic Area or Area 18 and 19

1. Visuopsychic area surrounds the visuosensory area except anteriorly.

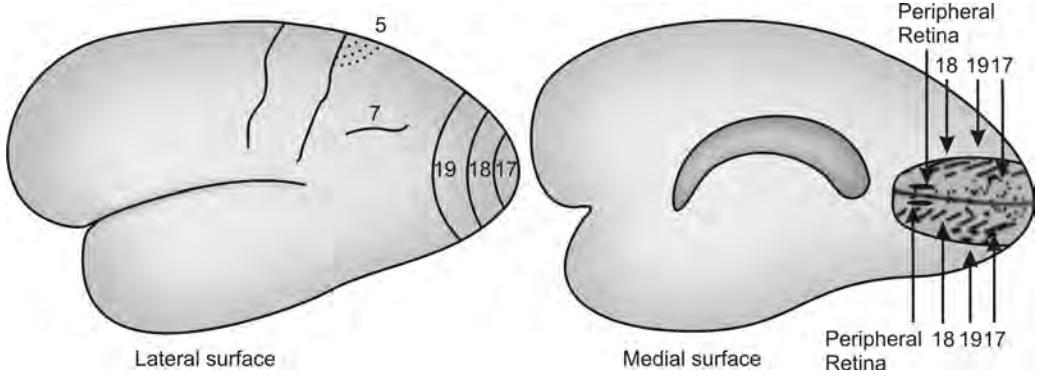


Fig. 116.5: Different areas of occipital lobe

2. Area 18 is called as parastriate area and is second visual area.
3. Area 19 is called as peristriate area.

Effect of Stimulation

Visual hallucination of flashes of light of various colors or definite images is evoked by electrical stimulation of area 18 and 19.

Functions

1. Visual impressions are interpretated.
2. Stores visual memories.
3. Concerned with assessing distance and orientation of an object in space.

Sensory Association Areas

Around the borders of primary sensory areas are regions of sensory association areas. These areas extend 1-5 cm in one or more directions from the primary sensory areas. Each time primary sensory area receives signal. The secondary signals spread in respective association areas:

1. Partly directly from primary are through subcortical fiber tract.
2. Major from thalamus—beginning in sensory relay nuclei—thalamic association areas—association cortex.

General functions of sensory association areas—to provide higher level of interpretation of sensory experience.

Lesion: Reduces the capability of brain to analyze different characteristics of sensory experiences. For example:

1. Damage to temporal lobe below and behind the primary auditory area in dominant hemisphere of brain often causes person to loose his ability to understand words or other auditory experiences even though he hears them.
2. Destruction of visual association area—18 and 19 in occipital lobe of dominant hemisphere do not cause blindness but greatly reduce person's ability to interpret what is seen. Such person loses the ability to recognize the meaning of words—*Word blindness.*

GENERAL INTERPRETATIVE AREA OR WERNICKE'S AREA (FIG. 116.6)

Somatic Visual and Auditory

Association areas—all meet in the posterior part of superior temporal gyrus and anterior part of angular gyrus.

1. This area of confluence is especially highly developed in the dominant side of brain, i.e. left side in right, handed person.
2. This area plays important role in higher levels of brain function. That we call cerebration.
3. Therefore, this area is called general interpretative area, or Wernicke's area— in honor of neurologist, who first described its special significance in intellectual processes.

Damage

1. Person might hear perfectly well—but fails to understand the thought they carry.
2. Person is able to read words—but unable to recognize the thought that is conveyed.
3. Person has difficulty in understanding higher levels of somatic sensory experiences even though there is no loss of sensation itself.

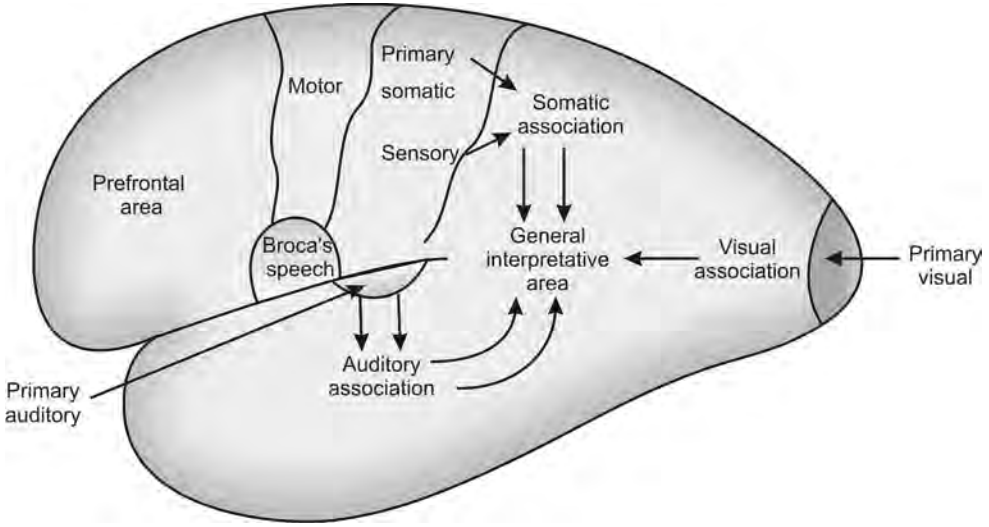


Fig. 116.6: General interpretative area or Wernicke's area

DOMINANT HEMISPHERE

The general interpretative Wernicke's area, functions of speech and motor control areas are highly developed in one cerebral hemisphere than other. This is called as dominant hemisphere. In 9 out of 10 persons left hemisphere is dominant. It depends on handedness. In right handed—left hemisphere is dominant. Handedness is determined genetically.

The other hemisphere is not simple non-dominant. It is concerned with:

1. Recognition of faces
2. Stereognosis
3. Recognition of musical themes.

Therefore, dominant hemisphere and non dominant hemisphere, this concept is replaced by concept of complementary hemispheres.

One—for language function and sequential analytical process (categorical hemisphere).

Other—for visuospatial relations (representational hemisphere).

Lesion

1. Of categorical hemisphere produces language disorders, i.e. aphagias
2. Of representational hemisphere produces
3. Asteriognosis, and
4. Agnosias.

In adults: The defect produced in either hemisphere are long lasting.

In young children: The function of missing hemisphere may be largely taken over by remaining hemisphere, no matter which hemisphere is removed.

Lateralization of Function

CNS is bilaterally symmetrical in its organization.

1. At the level of primary sensory input and final motor output the two halves are autonomous except for the fact that interconnections occur in spinal cord and brainstem such that activities of two halves are naturally integrated, e.g.

ipsilateral flexor reflexes are accompanied by contralateral extensor reflexes.

2. There are many loci where artificial, stimulation yields bilateral responses:
   i. Autonomic responses elicited by hypothalamic stimulation are bilateral.
   ii. When pontine and medullary regions are stimulated respiratory responses are bilateral.
3. Experiments on monkeys, baboons, chimpanzees and cats have shown that the two halves of the cortex are not completely independent.
   i. Similar observations have been made upon a limited number of patients who have required operations in the region of corpus callosum. The most notable defect in them is of:
      a. Speech
      b. Writing, and
      c. Language, where both input and output portions of the system are lateralized, i.e. predominantly developed in one hemisphere.
   ii. Speech and related activities such as reading and writing are represented mainly in the cortex of one hemisphere, i.e. dominant hemisphere.
   iii. For centuries it has been shown that cortical lesion of one side of brain may affect speech whereas similar lesion or other side leaves it undisturbed.
   iv. Speech mechanisms are in the cortex of the side that control the preferred hand.

CHAPTER

117

Conditioned Reflex and Speech

Povlov recognized two distinct classes of reflexes:
1. Inborn or unconditioned reflex
2. Acquired or conditioned reflex.

Ivan Petrovich Povlov

Neurophysiologist, for his monumental work he was awarded the Nobel Prize for physiology and medicine.

Most reflexes are inborn, for example:
1. Withdrawing of limbs due to pinprick.
2. Closing eyelids when suddenly light is flashed.
3. Production of saliva when food is placed in the mouth.

The inborn reflexes are *unconditioned reflexes.*

Most of the spinal and brainstem reflexes are unconditioned reflexes, for example:
1. Flying of birds
2. Postural reflexes
3. Vascular reflexes.

They are different from conditioned reflexes.

CONDITIONED REFLEXES

1. Salivation is produced in a grown up animal or human being on sight or smell of food.

But an infant or newborn pup does not salivate on the sight or smell of food. Therefore, for conditioned reflex to get established:
1. Experience is required.
2. It is a type of learning.
3. Certain conditions must be present.
4. It is aquired by pairing a stimulus with another stimulus that normally produces a response.

   Thus, they are aquired reflexes.

Classical Conditioned Reflexes

Povlov used dogs for experiment and to avoid disturbing influences, carried out work in:
1. Quiet rooms especially built for the purpose.
2. The animals were trained to stand still on table.
3. The experimenter observed the animal's behavior unseen from another room, and he could present food to animal or apply various stimuli by remotely controlled apparatus.
4. The animals were operated so that the dog's parotid duct was exteriorized and a tube connecting it was carried into observer's room and production of saliva could be measured.

He observed:

i. Food in mouth (unconditioned stimulus)—Saliva is produced by unconditioned reflex.
ii. But salivary secretion can take place by a specific stimulus such as sound after training.
iii. This specific stimulus, i.e. sound initially have little effect on salivation but produces "Orienting reflex" (a complex response of alerting or arousal). Involving—changes in heart rate. Changes in respiration and other physiological functions, and sign of attention to stimulus.

In short—'what is it' type of response.

4. The specific stimulus (conditioned stimulus) and unconditioned stimulus are now presented simultaneously or with a short-time interval between them in which conditioned stimulus preceeds unconditional stimulus, on a number of occasions. The procedure is called reinforcement.
5. The result is orienting reflex disappears and conditioned stimulus given alone produces a response resembling that originally produced only by the unconditioned stimulus.
6. Re-inforcement increases the strength of conditioned response.
7. If conditioned stimulus is repeatedly presented without unconditioned stimulus, strength of conditioned reflex progressively (Production of saliva) decreases. This is known as extinction or internal inhibition. Extinction is more rapid than reenforcement.
8. If animal is disturbed by an external stimulus immediately after conditioned stimulus is applied, the conditioned response may not occur. This is known as external inhibition.

The study of conditioned reflexes has provided physiologist with a useful method for examining:

1. The sensory abilities of animals, e.g. about hearing—tone differentiation and limits of differentiation can be tested.
2. Conditioned reflex have been established with many different unconditioned reflexes, e.g. involving reaction of smooth muscle, glands and voluntary responses, and stimuli like:
   i. Visual
   ii. Auditory
   iii. Tactile
   iv. Thermal, and
   v. Olfactory can be used.

Higher Order Conditioning

Conditioned reflex once established can be used for further conditioning, e.g. light followed by bell followed by food.

This is known as higher order conditioning by using this technique one can develop voluntary control over normally involuntary response, e.g. pupillary reflex. This was shown by Hudgins.

A similar technique has been used to establish voluntary control of relaxation in patients suffering from chronic anxiety.

There is difference between the response obtained by conditioned stimulus and an unconditioned stimulus, e.g. the animal does not respond to bell in the same way as food. There is difference in saliva produced by two.

Conditioned reflexes are easily formed when unconditioned stimulus is associated with pleasant or unpleasant affect or experience. When there is stimulation of brain reward system, there is positive reinforcement and when there is stimulation of avoidance system, there is negative reinforcement. Similarly, reward or punishment plays

important role in developing a conditioned reflex. Thus, conditioned reflexes play an important part in the behavior of animal and human being. They are mediated by cerebral cortex and they disappear when cortex is removed.

Povlov's experiment was an example of simple conditioning. For conditioning to occur conditioned stimulus must preceed unconditioned stimulus.

Physiological Basis of Conditioned Reflexes

1. The essential feature of the conditioned reflex is the formation of new functional connection in the nervous system.
2. Stimulus produces changes of arousal both in EEG and behavior.

At the behavioral level similar conditioning of the arousal value of stimuli occurs in human beings, e.g. the mother who sleeps through many kinds of noises but wakes up promptly when her baby cries.

SPEECH

Definition

Speech is meaningful expression of thought by words and symbols in articulate sound.

It is an integrated audito, visuo, and psychomotor mechanism of brain, denoting facultative supremacy of man over animals.

Reading, writing and speech: Are in essential alliance with one another in association with audition and vision.

And any defect in anyone of them has its repercussion on the other—which may lead to various form of defective speech.

Mechanism of Speech

For speech to take place coordinated activities of the: (1) speech center or central speech

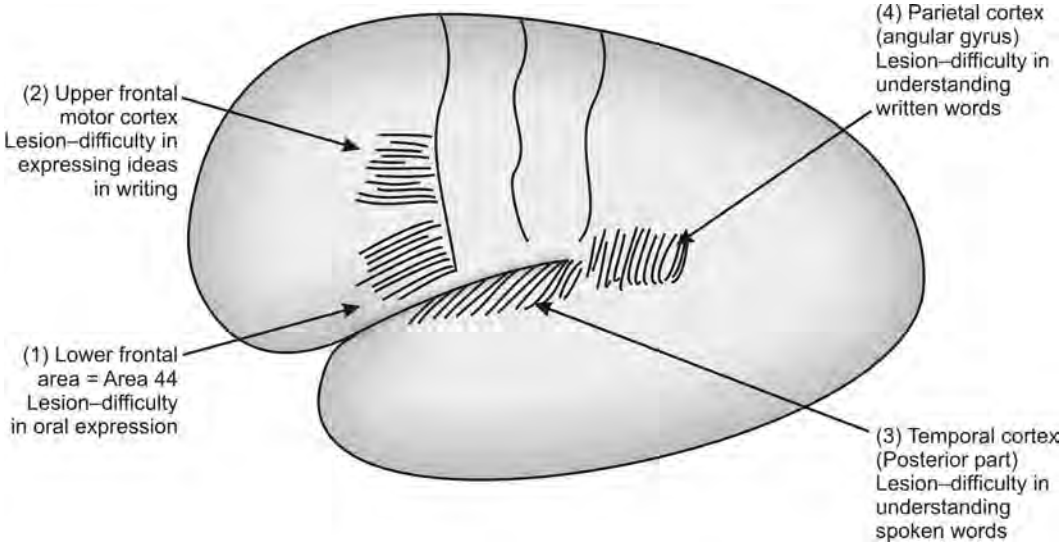


Fig. 117.1: Central speech apparatus—4 areas or speech centers

apparatus and the (2) peripheral speech apparatus, must take place.

Speech Center or Central Speech Apparatus

In right-handed person, the left cerebral hemisphere plays a dominant role in speech mechanism. Four areas have been identified in dominant hemisphere (Fig. 117.1).

Development of Speech

1. Depends on normal hearing.
2 A child born deaf is also dumb. Because for spoken speech:
   i. We must be able to hear sounds which require normal auditory apparatus and auditory path from ear to auditory center and
   ii. Secondly, we must be able to under stand them auditopsychic area must be normal.
      a. Speech demands skilled use of many muscles such as those of tongue, larynx, etc. Therefore:
      b. Excitomotor areas of brain, their descending tracts and related lower motor neurons must all be intact functionally and guided by cerebellar, labyrinthine, muscular and other afferents.
         – The initial speech, noises first appear in a child during the second half of first year, which are gradually differentiated into speech sounds and syllables.
         – By the end of first year the child tries to combine separate syllables into simplest words: Baba, Mama.
         – At this stage he becomes initiative and tries to imitate whatever he hears from the talk of surrounding people and thus, verbal connection develops through the medium of audition and visual stimuli.
         – During second year there is rapid development of child's speech and his stock of words increases up to 200-400, which he reproduces in the form of binomial and trinomial combinations.
         – The first speech by the child is usually defective which he compares with the correct, recognizes the fault and tries again. Thus, by trial and error he picks up the correct sound.
         – Subsequently, grammatical system of speech begins to take shape and he is now capable of showing signs of abstract thinking, expressed in words.

Peripheral Speech Apparatus

Consist of larynx or sound box, pharynx, mouth, nasal cavities, tongue and lips, which work in association with the respiratory organ in a coordinated manner, under the influences of motor impulses from the respective motor area.

APHASIAS

Group of functions related to language are:

1. Understanding the spoken and printed word, and
2. Expressing ideas in speech and writing.

Abnormalities of these functions that are not due to defect of vision or hearing or to motor paralysis are called *aphasias*.

Aphasia is classified in many different ways and nomenclature is chaotic.

In a general way, aphasias can be divided into:

1. Sensory (or Receptive aphasia)
   Subdivided into:
   i. Word deafness—inability to understand spoken word.
   ii. Word blindness—inability to understand written word.
2. Motor (or Expressive aphasia)
   Subdivided into:
   i. Agraphia—inability to express ideas in writing.
   ii. Motor aphasia—inability to express idea in speech. This is subdivided into:
      a. Nonfluent aphasias—in which speech is slow and words hard to come by.
      b. Fluent aphasia—in which speech is normal or even rapid but key words are missing.

Patients with severe degrees of nonfluent aphasia are limited to 2 or 3 words with which they must attempt to express every thing. Sometimes, the words retained are those, which were being spoken at the time of injury or vascular accident that caused aphasia. More commonly they are frequently used automatic words, such as days of week or dirty words or swear words.

In clinical cases:

1. More than one form of aphasia is usually present.
2. Frequently aphasia is general or global involving both receptive functions.
3. Lesion of Area 44—in inferior frontal gyrus (Broca's area) causes nonfluent aphasia.
4. In patient with fluent aphasia, Broca's area is intact and lesions are generally in the temporal or parietal lobe.

CHAPTER

118

Cerebrospinal Fluid

Anatomical considerations: The CNS is enveloped by meninges from without inwards:

1. Dura
2. Arachnoid
3. Pia.

Dura: Consists of fibrous tissue lined by endothelium.

Subdural space contains small amount of fluid resembling lymph.

Pia—invests nervous substances very closely.
Arachnoid—in between

1. Subarachnoid space—which contains CSF
2. There are definite dilalations of sub-arachnoid space called cisternae.
   i. The cisterna magna
   ii. The cisterna pontis
   iii. The cisterna basalis
3. Cisterna magna
   i. Found in interval between the medulla and undersurface of cerebellum.
4. Cisterna pontis
   i. Lies on the ventral aspect of the pons and contains basilar artery.
5. Cisterna basalis
   i. Formed by arachnoid bridging across the interval between lips of temporal lobes and contains circle of Willis.

ii. Rest of the CSF lies in the ventricles
iii. The ventricles establish a connection with the extraventricular fluid through:
   a. The foramen of Magendie
      – In the midline
      – In the inferior part of the roof of the fourth ventricle.
   b. The foramina of Luschka—lateral apertures at the extremities of the lateral recesses of this ventricle that means 4th.
iv. As the arteries and veins enter and leave the brain substance, they are surrounded by the perivascular spaces, which are continuous at one end with the subarachnoid space and at the other with the fine spaces which surround the nerve cells. The flow along these perivascular spaces is normally outward to the subarachnoid space and they serve to remove waste products resulting from cell activity.
v. The dura ends at the lower border of second sacral, and spinal cord ends at the lower border of the first lumbar vertebra. So we can do lumbar puncture in the lower lumber region without fear of injury to the cord. To, collect sample of

CSF, lumbar puncture is done between 3rd and 4th lumbar verterbrae.

A needle of 1 mm bore is inserted between 3rd and 4th lumbar vertebrae with subject lying on the side.

CHOROID PLEXUSES

Some arteries pass through the brain substance to reach the lining ependymal layer in the lateral, third and fourth ventricles (Fig. 118.1). They then break up into complex capillary network which project into ventricular cavities and become lined by the now—much folded ependymal cells. The blood vessels and their lining epithelium constitute the choroid plexuses. The epithelium becomes differentiated.

MECHANISM OF FORMATION AND ABSORPTION

The fluid is formed by secretory activity of the epithelial cells of the choroid plexuses of intraventricular system. The capillaries of the choroid plexuses are covered by a thick, highly differentiated epithelium, which features all the intracellular organelles in profusion, which is required for active transport activity.

1. Rate of formation of CSF in man is 0.2 ml/min.
2. The content of CSF, in man is 130-150 ml of which some 30 ml is in the ventricular system and remainder in subarachnoid space.
3. Formation requires active chemical work. Proof:
   i. Ouabain (which inhibits Na^+—K^+ ATPase)
   ii. Dinitrophenol (which uncouples oxidation from phosphorylation).
   iii. Acetazolamide (which inhibits carbonic anhydrase).
   All diminish the rate of formation of CSF.
4. *Fluid pressure:* The normal pressure of the fluid depends on a balance between its rate of secretion and of absorption.
   The value in man in lateral recumbent position varies between 100 - 200 mm H_2O. Pressure in sitting position is 200 mm H_2O. (higher than in recumbent position).
   i. Rise of venous pressure, e.g. coughing and crying hinders absorption and so raises CSF pressure.
   ii. Compression of internal jugular vein has a similar effect.

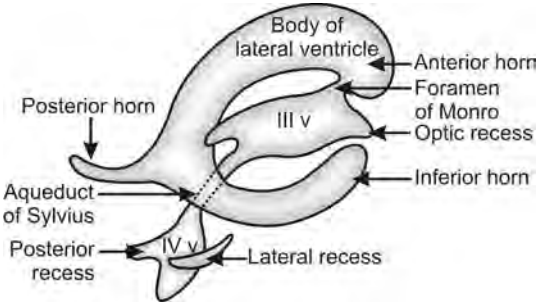


Fig. 118.1: Ventricles (Lateral, 3rd and 4th)

FUNCTIONS OF CEREBROSPINAL FLUID

1. It serves as fluid buffer.
2. It acts as reservoir to regulate contents of cranium, if the volume of blood or brain increase, CSF drains away. If the brain shrinks more fluid is retained.
3. It may serve as a medium for nutrient exchanges in the nervous system. But mainly the brain carries out its metabolic exchanges directly with the blood.

Effect of Cerebral Tumor

1. Expulsion of some CSF
   i. Blood vessels are compressed
   ii. The gyri are flattened and gradually there is general rise of pressure above tentorium and pressure is transmitted

to prolongation of subarachnoid space round optic nerves.

a. First structures in the nerve to suffer from compression are the veins. Blood can still flow in arteries but return is hampered therefore, minute vessels at the nerve head become engorged and swollen and fluid exudes from them. The resulting appearance in ophthalmoscope examination is termed papilledema.

2. Pressure is then exerted on the posterior fossa of the skull, the cerebellum is gradually driven into and through the foramen magnum, fills the aperture like cork, fluid cannot escape in spinal canal (where about 1/5 absorption takes place).
   i. Fourth ventricle foramina are distorted partially and blocked.
   ii. Vicious circle is established.
   iii. CSF cannot escape from ventricles and is not absorbed—hydrocephalus results.
   iv. Death from medullary anemia.

Composition

CSF is clear

1. Colorless fluid
2. Specific gravity 1005
3. Almost protein free (20-30 mg/100 ml)
4. Almost cell free (lymphocytes 5% mm^3)
5. Contains less glucose (70 mg/100 ml) than plasma
6. pH of CSF is 7.3.

There are significant differences between the concentrations of some of the ionic constituents in the plasma ultrafiltrate and the CSF.

Formation and Absorption of CSF

Formaton: Formed by the choroids plexuses - especially large plexuses, which are found in lateral ventricles. CSF passes from foramen of Monro into 3rd ventricle.

Circulation: Through aqueductus Sylvii (Cerebral aqueduct) to 4th ventricle and out through foramen of Luschka and Magendie into subarachnoid space.

Absorption

Route of absorption—CSF is absorbed:

1. Mainly via the arachnoid villi into the dural sinuses and the spinal veins. To a minor degree:
2. Fluid may pass along the sheaths of the cranial nerves into the cervical lymphatics and also into the perivascular spaces.
   i. 4/5 CSF is absorbed via cerebral arachnoid villi.
   ii. Rest of CSF is absorbed via spinal villi.

Arachnoid Villi (Fig. 118.2)

1. Are finger like projections.
2. Lined by flat epithelial cells project into venous sinuses.
3. The Pacchionian bodies (arachnoid granulations) are simply exceptionally large villi; they are few in number and present only in the adult.

Hydrocephalus

Means a pathological accumulation of CSF.

Internal H: Excess fluid in ventricular system (H = Hydrocephalus)

External H: Excess fluid in subarachnoid space.

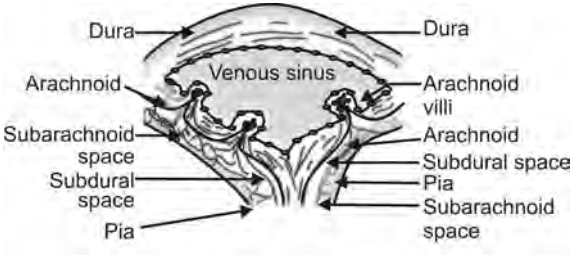


Fig. 118.2: Arachnoid villi

Hydrocephalus is due to the obstructions:
Intraventricular: Blocking the foramen of Monro, the cerebral aqueduct, or the fourth ventricle formina.

Extraventricular:

i. Block at foramen magnum (Prevents the fluid from entering spinal canal) where 1/5 absorption takes place).

   Block at the tentorial opening (cisterna ambiens) prevents the fluid from passing from posterior fossa of the skull into supratentorial subarachnoid space, where most of the absorption normally occurs.

ii. Inflammatory changes in leptomeninges may occlude arachnoid villi.

iii. Thrombosis of the dural sinuses prevents the escape of fluid from subarachnoid space into the veins.

Lumbar Puncture

To collect sample of fluid lumbar puncture is done between 3rd and 4th lumbar vertebra. A needle of 1 mm bore is inserted between 3rd and 4th lumbar vertebra into subarachnoid space with subject, lying on the side.

It is performed for:

1. Dignostic purposes
2. To relieve raised intracranial pressure, e.g. in meningitis.
3. Introduction of drugs, e.g. spinal anesthetics. Spinal cord ends at the lower border of 1st lumbar vertebra therefore, injury to spinal cord is avoided when we do lumbar puncture between 3rd and 4th lumbar verterbra.

CHAPTER

119

Learning and Memory

Memory: It is capability of recalling a thought at least once.

Learning: It is defined as a more or less permanent modification of response that occurs as a result of practice, experience or observation.

1. In this context habituation is a form of learning.
2. It is studied by testing input (i.e. stimulus) and output (i.e. response) relations.
3. Both are complex.
4. Usually, output falling into the category of behavior.
5. Stimulus leads to response and the subject learns because of experience.
6. Reward and punishment are crucial ingredients of learning and conditioned reflexes play important part.

SITES OF LEARNING

Learning occurs in invertebrate animals that have no cerebral cortex. It also occurs at subcortical and spinal level in mammals. But more advanced types of learning are largely cortical phenomenon. Brainstem is also involved in this process.

Some types of learning have been shown to produce structural changes in the cerebral cortex. For example, rats exposed to visually complex environments and trained to perform various tasks have thicker and heavier cerebral cortices than control rats exposed to monotonously uniform environments.

What happens? In the cortex during learning:

1. When a new sensory stimulus is first presented it produces:
   i. Diffuse electroencephalographic arousal, and
   ii. Prominent evoked responses in many parts of the brain, and
   iii. Behaviorally the human or animal becomes alert—Povlov called it *orienting reflex* (or what is it? type of response).
2. If the stimulus is neither pleasurable nor noxious it evokes less electrical response when repeated and EEG and other changes eventually cease. The animal becomes habituated to stimulus and ignores it. Now, if this stimulus is stopped or changed it will produce arousal.
3. If the stimulus is paired with pleasant or unpleasant experience it will produce :
   i. Electroencephalographic and behavioral arousal, and
   ii. Widespread evoked potentials.

This is how reward and punishment are crucial ingredients of learning and conditioned reflexes are important in learning process. Conditioned refelexes are difficult to form unless the unconditioned stimulus is associated with pleasant or unpleasant affect.

INTERCORTICAL TRANSFER OF LEARNING

If a cat or monkey is conditioned to respond to a visual stimulus with one eye covered and then tested with the blind fold transferred to the other eye it performs the conditioned response. It will occur even if the optic chiasma is cut making the visual input from each eye go only to ipsilateral cortex. If in addition to optic chiasma the anterior and posterior commissures and corpus callosum are sectioned (split brain animal)—no transfer of learning occurs. This demonstrates that commissures play a role in transfer of learning to opposite side.

Ultimately, learning takes place by forming a memory and storing it and the sequence is → conditioning → learning → memory.

MEMORY

It is defined as capability of recalling a thought at least once.

A variety of hypothesis have been advanced recently to explain how individually acquired information may be stored by the brain. The postulated neural correlate of memory is called the memory trace. The laying down of memory trace occurs in minutes during which the memory is known as short-term memory. After this somewhat labile formative period the memory is stored as long-term memory.

1. There is no exclusive site for storing memory because removal of specific parts of brain do not remove specific memory.
2. In discussing conscious memory in humans, it is also important to distinguish between recent and remote memories.
3. Three mechanisms are actually involved:
   - i. One mediating immediate recall of the events of the moment.
   - ii. One mediating memories of recent events that occurred seconds to hours or days before.

   ˇ *Recent*
4. Recent memory is impaired by various neurologic diseases and injuries, and
   - i. One mediating memories of the remote past. Remote memories persist in presence of severe brain damage.
5. The second mechanism is responsible for Consolidation of a memory trace (a process that eventually encodes the memory in a remarkably resistant form).
6. The animal builds a strong memory trace for sensations that are either rewarding or punishing because it causes:
   - i. Strong evoked potential
   - ii. Conditioned reflex, and
   - iii. Strong memory trace.
     - a. But for stimuli that are indifferent the animal develops complete habituation.

Short-term Memory

1. It is a limited capacity storage process, which serves as initial depository of information.
2. Generally as new items enter the older ones are replaced, e.g. if a person looks up a second telephone number the first is lost.
3. Information that has entered short-term memory:
   - i. May be forgotten
   - ii. Recycled by actively rehearsing information or

iii. Transferred to a more durable storage mode.

4. The most important feature of short-term, memory is that the information is instantaneously available.
5. One theory suggests that the memory trace during early phases of learning is a reverberating neural circuit in which electrical activity passes around and around in closed neuronal loopes (Fig. 119.1).
6. The activity once started in such loops could be maintained to keep the memory of the input for sometime.
7. Then as the reverberating circuit fatigues or the new signals interfere with the reverberations the short-terms memory fades away.
8. **Evidence**
   i. Conditions such as coma, deep anesthesia, electroconvulsive shock and insufficient blood supply to the brain, interfere with electrical activity of the brain and also interfere with retention of recently aquired information. These same states do not interfere with long-term memory.
   ii. When a man becomes unconscious from a blow on the head he cannot remember anything that happened for about 30 minutes before he was hit. This phenomenon is called *retrograde amnesia*. The loss of consciousness in no way interferes with memories of experiences that were learnt before the period of amnesia.

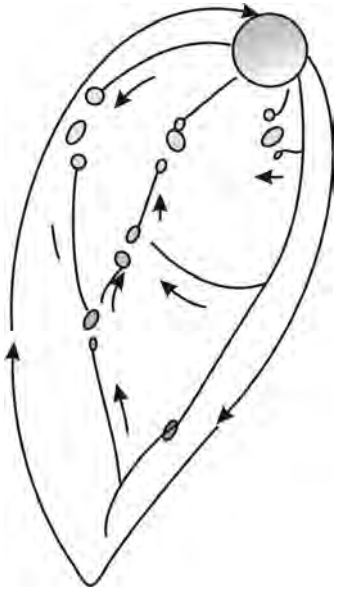


Fig. 119.1: Memory trace

Long-term Memory

Means the ability of the nervous system to recall thoughts long after initial elicitation of thought is over.

Two terms are used:

1. Secondary memory (recent memory) with moderately strong memory trace.
2. Tertiary memory—well integrated in the mind lasts for lifetime, e.g. name, numbers 1 to 10 alphabets, etc.
   i. Long-term memory does not depend on continued activity of nervous system because the brain can be totally inactivated by cooling, general anesthesia, hypoxia or ischemia, yet the memories that are previously stored are still retained when the brain becomes active again.
   ii. They may be changed or suppressed by other experiences but memories do not decay with time.
   iii. Removing parts of brain does not remove specific memories and the fact that these memories have stability and durability suggest that memory is stored in widespread chemical form or memory trace is an alteration in structure of some elements of brain.

iv. Retrieval of items from short-term memory seems to be much faster than retrieval from long-term memory, perhaps because the stores in long-term memory are much larger.
v. Evidence suggests the involvement of hippocampus and its connections in encoding mechanism for translating short-term memory into long-term memory and without the hippocampus consolidation of long-term memory does not take place especially for verbal information.

Different theories have been offered to explain the synaptic changes that cause long-term memory.

1. Morphological
2. Molecular.

Morphological

Fixations of memories in the brain results from:

1. Anatomical changes in the synapses. Such as size of the terminal which cause permanent or semi-permanent increase in the degree of facilitation of specific neuronal circuit. Thus, more often the circuit (memory trace) is used; the signals pass through the circuit with more ease. This explains the memory becomes deeply fixed the more often they are recalled or more often the person repeats the experience.
2. Physical or chemical change in presynaptic terminal or postsynaptic membrane.
   i. When the memory terminal is stimulated repeatedly without stimulating the sensitizing terminal, signal transmission becomes less and less intense until transmission almost ceases—this is known as habituation.
   ii. If noxious stimulus excites the sensitizing terminal at the same time that the memory terminal is stimulated, there is ease of transmission and transmission becomes strong for hours, days and weeks even without further stimulation of the sensitizing terminal. Thus, noxious stimulus causes the memory pathway to become facilitated for weeks thereafter (Fig. 119.2).
   iii. In habituation, there is closure of calcium channels.
   iv. In sensitization, excess cyclic AMP is formed inside the memory terminal, this opens more calcium channels.

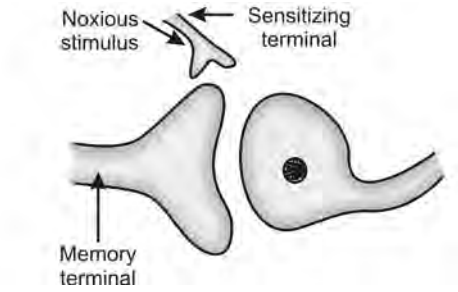


Fig. 119.2: Memory terminal and sensitizing terminal

Molecular

1. DNA and RNA can act as codes to control reproduction, which in itself is a type of memory from one generation to the other.
2. These substances once formed in the cell tend to persist for the lifetime of the cell. These facts have led to the theory that nucleic acids might be involved in the memory changes in neurons that could last for the life-time of the persons.
3. Biochemical studies have shown an increase in RNA in some active neurons.

So, some actual

- Anatomical
- Physical
- Chemical

changes occur in synaptic knob or in post-synaptic neurons

These changes permanently facilitate transmission of impulse at the synapse. All these synapses are thus, facilitated in a thought circuit; this circuit can be re-excited by anyone

of diverse incoming signals at later dates thereby causing memory.

The overall facilitated circuit is called a *memory trace.*

Consolidation of long-term memory: If memory is to last in the brain so that it can be recalled days later it must be consolidated, i.e. synapses must become permanently facilitated. This process requires 5-10 minutes for minimal consolidation and an hour of more for maximal consolidation.

1. Therefore, rehearsal accelerates the degree of transfer of short-term memory into long-term memory and also causes consolidation.
2. During the process of consolidation, new memories are not stored randomly in the brain but are stored in direct association with other memories of the same type.
3. Rehearsal also plays an important role in changing a weak type of trace of long-term memory (called secondary memory) into the strong trace type (called tertiary memory).

   The memory finally becomes so deeply fixed in the brain that it can be recalled within a fraction of a second and it will also last for lifetime. Both are the characteristics of long-term, tertiary memory.

Drugs that Facilitate Memory

A variety of CNS stimulants have been shown to improve learning in animals; when administered immediately before and after learning session. These include—caffeine, physostigmine, amphetamine, nicotine, convulsants like strychnine, picrotoxin, metrazol.

The brain has a natural tendency to rehearse information that catches minds attention. Therefore, person can remember information that is studied in details and in wide-awake state than in mental fatigue state.

Some Important Differences

Short-term memory

1. Cerebral cortex is involved
2. Depends on continued activity of nervous system
3. Retrieved faster
4. Fades with time.

Long- term memory

1. Limbic system is involved
2. Does not depend on continued activity of NS
3. Not retrieved fast
4. Does not fade with time.

CHAPTER

120

The Limbic System

The name limbic system was given in 1958 by Maclean to part of rhinencephalon to denote it's major function emotional exteriorization because only a fraction of rhinencephalon is engaged in olfactory appreciation.

The term limbic means border and it was used by Broca to denote this region.

Emotions have both mental and physical components.

They involve:

1. Cognition—awareness of sensation and its cause;
   Affect—feeling it;
   Conation—Urge to take action; and
2. Physical changes such as:
   i. Hypertension
   ii. Tachycardia
   iii. Sweating

For example, I hear noise, recognize as that of an exploding bomb (cognition). I feel frightened (affect) and I want to take shelter (conation).

Physiologists have been concerned for sometime with the physical manifestations of emotional state, while psychologists have been concerned with emotions themselves. Their interests merge in hypothalamus and limbic system, because these parts of the brain are now known to be intimately concerned with (a) emotional expression, and (b) genesis of emotion.

ANATOMICAL CONSIDERATIONS

Each limbic lobe consist of: (a) a rim of cortical tissue around the hilus of the cerebral hemisphere, (b) a group of associated deep structures—the amygdala, the hippocampus and septal nuclei, (c) hypothalamus is one of the central elements of the system, surrounding it are the other subcortical structures of the system.

Rim: Orbitofrontal area extending in front and above corpus callosum to cingulate gyrus and passing behind corpus callosum and downward to hippocampal gyrus, piriform area and uncus (Fig. 120.1).

Histology

The limbic cortex is phylogenetically the oldest part of cerebral cortex (Fig. 120.2). Histologically, it is made up of a primitive type of cortical tissue called *allocortex* surrounding the hillus of the hemisphere and a second ring of transitional type of cortex called juxta-allocortex between the allocortex and the rest of the cerebral hemisphere. The cortical tissue of the rest of the non-limbic portion of the

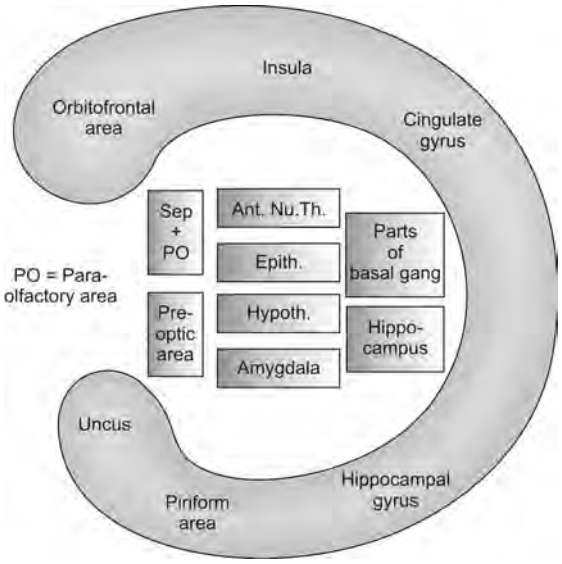


Fig. 120.1: Limbic system

hemisphere is called neocortex. The neocortex is most highly developed and is characteristically 6 layered.

Allocortex = Paleocortex.

Afferent and Efferent Connection

Major connection—(Papez circuit)

– and have extensive functional connection with hypothalamus.

Fornix connects *Hippocampus to*
|
Mammillary bodies
Mammillothalamic tract |
Anterior nuclei of thalamus
|
Cingulate cortex
|
Hippocampus

This circuit was originally described by Papez, and is called as *Papez Circuit (Fig. 120.3).*

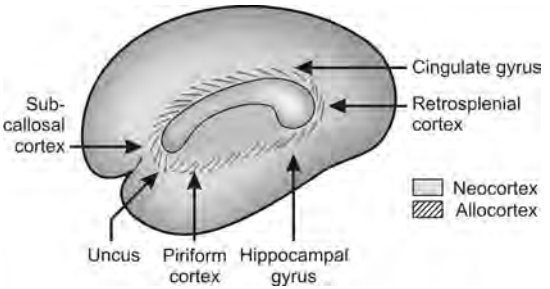


Fig. 120.2: Limbic cortex

Correlation between Structure and Function

One characteristic of the limbic system is the paucity of connection between it and the neocortex.

There are fibers from frontal lobe to adjacent limbic structures and probably some indirect connection via thalamus.

From functional point of view:

1. The neocortical activity does modify emotional behavior and vice versa.
2. However, the emotion cannot be turned on and off at will.
3. Limbic circuits show prolonged after discharge following stimulation. Therefore, emotional responses are generally prolonged, and outlast the stimuli that intiate them.
4. Regulate visceral and vascular functions through hypothalamus.

LIMBIC FUNCTIONS

Experimental study shows that limbic functions are:

1. Olfaction
2. Feeding behavior
3. Sexual behavior
4. Emotions of rage and fear and both sensory and motor aspects of emotions.
5. Motivation
6. Memory.

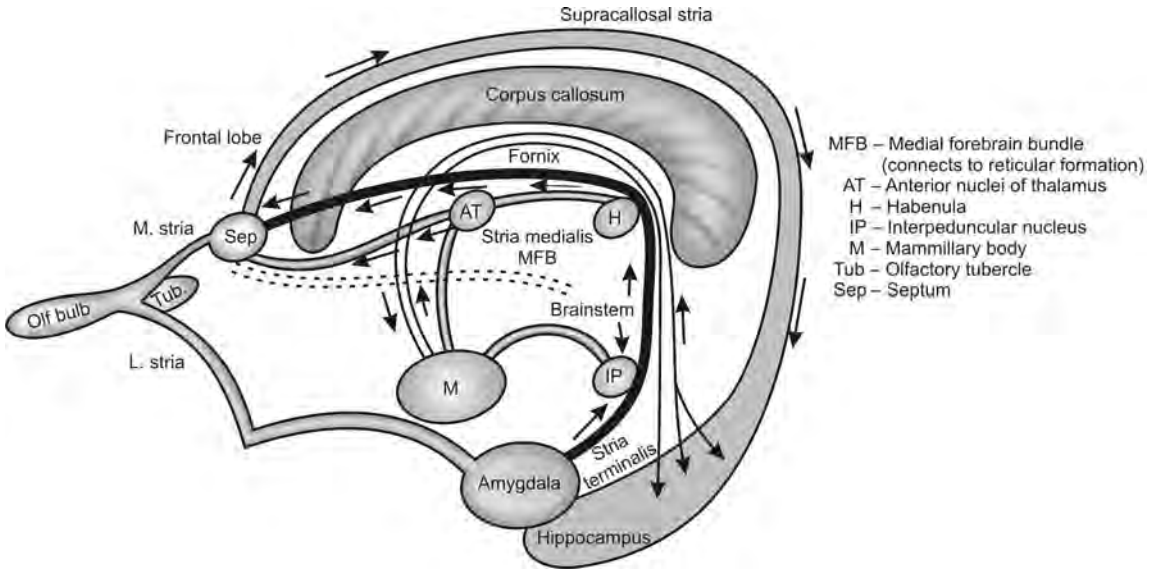


Fig. 120.3: Papez circuit

1. *Olfaction:* A small part of limbic system is concerned with olfaction. In past limbic system was called rhinencephalon (meaning nose brain) because in those days it was believed that the chief function of some structures like hippocampus is that it is the highest area for olfaction.
2. *Autonomic responses and feeding behavior:*
   i. Limbic stimulation produces the autonomic effects—particularly changes in blood pressure and respiration. These responses are part of emotional and behavioral responses.
   ii. Stimulation of the amygdaloid nuclei causes movements such as chewing and licking and other activities related to feeding. Lesions of amygdala cause moderate hyperphagia, with indiscriminate ingestion of all kinds of food. This type of omniphagia has a relation with hypothalamic mechanism regulating appetite.

   Area associated with hunger—lateral hypothalamic area and center that opposes desire for food called satiety center is in ventromedial nucleus.
3. *Sexual behavior:* Behavior and emotions are closely related but are not identical terms. Emotions often culminate in behavioral pattern. Sexual behavior is the result of sex desire.
   i. Mating is a basic but complex phenomenon in which many parts of the nervous system are involved.
   ii. Copulation itself is made up of series of reflexes integrated in spinal centers and lower brainstem centers.
   iii. But the behavioral component, i.e.
      a. Urge to copulate, and
      b. Coordinate sequence of events in male and female that lead to pregnancy are regulated to a large extent in limbic system and hypothalamus.

iv. Learning plays a part in development of mating behavior particularly in primates and humans.
But in lower animals successful mating can occur with no previous sexual experience.
v. Therefore, the basic responses are innate and present in all mammals. But in human, sexual functions have become extensively encephalized and conditioned by social and psychic factors.

Sexual behavior shows distinctive patterns in male and female, at least in subhuman mammals. Usually in the subhuman mammals, the adult male is prepared to charge a female at anytime but the female is prepared to accept male only at specific periods.

These female animals become receptive only when they are in estrus and sometimes at the time of estrus they secrete chemical compounds called pheromones, which have a strong odor, which whets up the sexual hunger of male of its own species. Olfactory nerves are connected to limbic system particularly to amygdala. Female sexual activity is thus cyclic whereas that of male is continuous.

But human female is prepared to receive their sex partners at anytime.

i. What is the role of sex hormones in development of sex desire?
   i. In subprimate mammals and submammals, rise of estrogen concentration in the body does stimulate sex drive. Therefore, female becomes receptive only during estrus. Role of progesterone may be inhibition of sex drive.
   ii. Androgen causes stimulation of sex drive in males, castration in adult male results in lack of sex drive.
   iii. Hormones become less and less dominant, higher is the evolutionary scale, because encephalization, psychological and social aspects begin to play more and more dominant role.

2. *Nervous system:* Also plays a very dominant role in development of sex drive.
   i. In male animals, removal of neocortex generally inhibit sex behavior. Partial cortical ablation (especially the frontal lobes) produces some inhibition.
      a. In cats and monkey with bilateral limbic lesion localized to piriform cortex overlying amygadala develop a marked intensification of sexual activity.
      b. Hypothalamus is also involved in control of sexual activity in males. In intact rats appropriately placed anterior hypothalamic lesions abolish interest in sex.
      c. In human beings (i.e. males) hypersexuality is reported with bilateral lesion in or near the amygdaloid nuclei.
      d. In female, amygdaloid and the periamygdaloid lesions do not produce hypersexuality.
      e. Anterior hypothalamic lesion abolish behavioral heat without affecting regular pituitary ovarian cycle.
      f. Removal of neocortex and the limbic cortex in females abolish active seeking out of male during estrus, but other aspects of heat are unaffected.

It appears, atleast in males there are at least two opposing influences. The neocortex causes stimulation of sex drive and piriform cortex, which overlies amygdala causes inhibition of sex desire.

Maternal Behavior

Maternal behavior is depressed by lesions of the cingulate and retrospinal portion of the limbic cortex in animals. Prolactin from anterior pituitary may facilitate its development. Prolactin is secreted in large amounts during lactation.

Fear and rage: These two emotions are very closely related when an animal is threatened, it usually attempts to flee. If cornered, an animal fights. Thus, fear and rage reactions are probably related instinctual protective responses to threats in the environment.

The external manifestations of fear, fleeing or avoidance reaction in animals are: autonomic responses, such as sweating, pupillary dilatation, cowering and turning head from side-to-side to seek escape.

The external manifestations of rage, fighting or attack reaction in animals are—e.g. in cats—hissing, spitting, piloerection, pupillary dilatation and well directed biting, chewing. Both reactions are sometimes mixed and can be produced by hypothalamic stimulation.

Fear

1. Stimulation of the hypothalamus and amygdaloid nuclei in conscious animals produce fear reactions.
2. When the amygdalae are destroyed, fear reactions, its autonomic and endocrine manifestations are absent. Dramatic example is reaction of monkeys to snakes. Monkeys are normally terrified by snakes. After bilateral temporal lobectomy monkeys approach snakes without fear, pick them up and even eat them.

Rage and Placidity

Most humans and animals maintain a balance between rage and its opposite emotional aspect (placidity).

Major irritation makes normal individuals to lose their temper, but minor stimuli are ignored.

1. i. Stimulation of some parts of amygdala in cats—produce rage.
   ii. Rage responses to minor stimuli are observed after:
      a. Removal of the neocortex.
      b. In animals with (ventromedial hypothalamic nuclei and septal nuclei) lesion and intact neocortex.
2. Bilateral destruction of the amygdaloid nuclei results in abnormal placidity—in monkeys, cats and dogs.
3. The placidity produced by amygdaloid lesions in animals is converted into rage by subsequent destruction of ventromedial nuclei of hypothalamus.
4. Gonadal hormones appear to affect aggressive behavior. In animals, aggression is decreased by castration and increased by androgen.

Therefore, neocortex, amygdaloid nuclei, ventromedial nuclei of hypothalamus play, important role in rage.

Sham rage: Removal of brain, rostral to thalamus causes violent rage reaction (shown by Goltz and Ewald in 1896). A cat, which is operated like this, assumes an attacking posture on slightest provocation, i.e. it hisses, growls, extends tail and spine and exposes teeth (Halloween cat). It was erroneously believed that, in such a Halloween cat, only motor manifestations were present and sensory (e.g, affect, conation) were absent.

(That is, in mind the cat was not angry, only it behaved as an angry cat). Therefore, they called this condition "Sham rage" (sham = false). Later on it was proved that the sensory aspects of emotion are also present in this so-called "Sham rage".

Significance and Clinical Correlates

There are two intimately related mechanisms in the hypothalamus and limbic system:

1. One promoting placidity
2. Other promoting rage.

At any given instance, the resultant of these two opposing influences determine the outcome.

- Some lesions produce a state in which the most traumatic and anger provoking stimuli fail to ruffle placidity.
- Many times in patients of brain damage — rage attacks in response to trivial stimuli are produced (e.g. as complication of pituitary surgery when there is more damage to the base of the brain).
- Number of diseases of nervous system especially epidemic influenza and encephalitis destroy neurons of limbic system and hypothalamus also produce rage attacks in response to trivial stimuli.
- Stimulation of the amygdaloid nuclei and parts of hypothalamus in conscious human produces sensation of anger and fear.

Motivation: By proper surgical procedure, an electrode is introduced and kept chronically implanted in selected areas of limbic system of the brain of an animal. The animal is allowed to recover and lead a normal life in the cage which has a pedal or bar which can be pressed by the animal sooner or later accidentally. When the bar is pressed, the animal receives a stimulus in the area where the electrode is implanted, because bar pressing completes the circuit. It will produce a feeling, which is either pleasant or unpleasant. Areas of brain which on stimulation produce pleasant sensations are called reward areas and grief (or unpleasant sensation) producing areas are called punishment areas (Fig. 120.4).

If the implanted electrode is in reward area, then the animal will keep on pressing the bar again and again, on the other hand, if the electrode is in punishment area, the animal will avoid the bar. The reward areas are much more extensive than punishment or avoidance areas.

Reward areas: Medial band of tissue passing from the amygdaloid nuclei through hypothalamus to the midbrain tegmentum.

Areas with highest bar pressing: Points in tegmentum, posterior hypothalamus and septal nuclei.

Avoidance area (Punishment areas):

- Lateral portion of posterior hypothalamus
- Dorsal midbrain
- Entorhinal cortex.

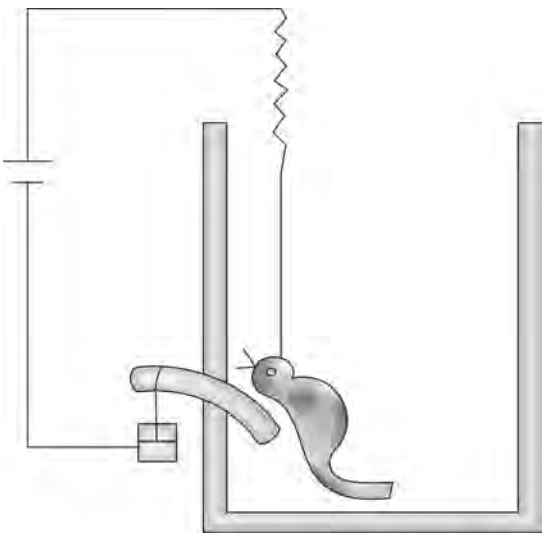


Fig. 120.4: Experiment for reward and punishment areas

In humans, such experiments are carried out in selected cases such as schizophrenics, epileptics and patients with visceral malignancies and intractable pain. When electrodes are in reward areas, they reported relaxed feeling; relief of tension and some even felt joy or ectasy.

- When electrodes are in avoidance areas—patients reported sensation ranging from vague fear to terror.

6. *Memory:* The hippocampus is concerned with memory. Destructive lesions of the hippocampus cause loss of recent memory.

CHAPTER

121

Hypothalamus and Emotion

HYPOTHALAMUS

It is situated below thalamus. Consists of large number of nuclei, having important functions, which are strangely not related to each other. Hypothalamus extends from preoptic area to caudal part of mammillary bodies. Laterally hypothalamus extends up to internal capsule. Hypothalamus forms the floor of 3rd ventricle; in addition it also forms the lower parts of the lateral walls of 3rd ventricle.

The hypothalamus consists of masses of gray matter called nuclei. For descriptive purposes, the nuclei are grouped in three groups (Fig. 121.1).

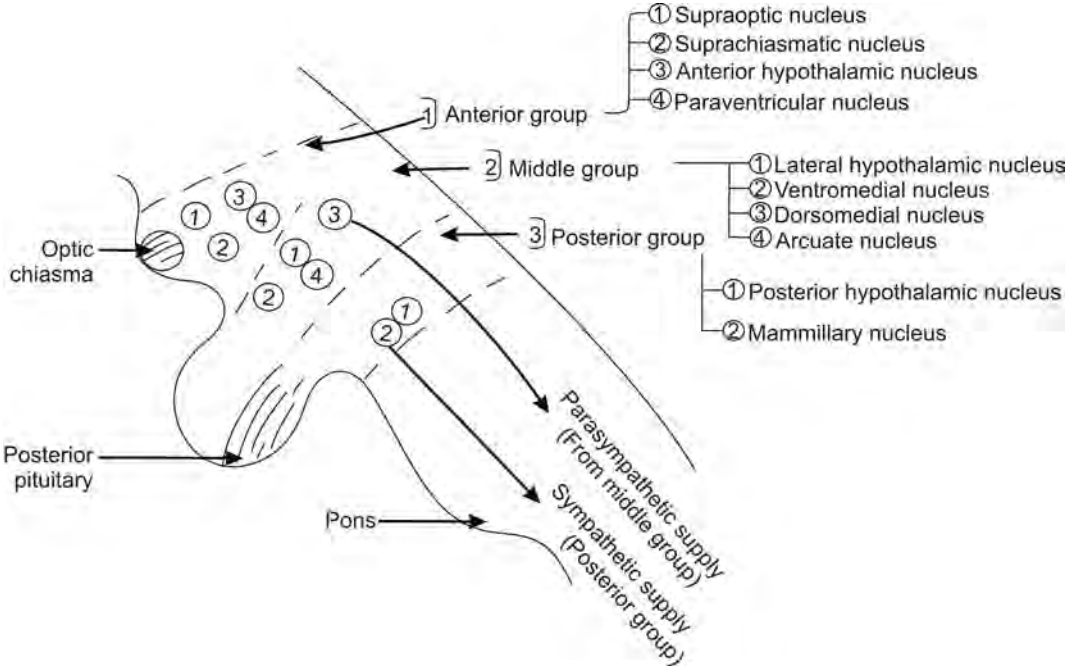


Fig. 121.1: Hypothalamic nuclei

Total Nuclei 10:

1. Anterior group of nuclei:
   i. Supraoptic nucleus
   ii. Suprachiasmatic nucleus
   iii. Anterior hypothalamic nucleus
   iv. Paraventricular nucleus.
2. Middle group of nuclei:
   i. Lateral hypothalamic nucleus
   ii. Dorsomedial nucleus
   iii. Ventromedial nucleus
   iv. Arcuate nucleus.
3. Posterior group of nuclei:
   i. Posterior hypothalamic nucleus
   ii. Mammillary nuclei.

From the region of median eminence of the hypothalamus, hangs the pituitary gland by its stalk. Capillaries of hypothalamus are collected into arteries, which run through the stalk and again breakdown into capillaries in the anterior pituitary, thus forming portal circulation. Blood from hypothalamus via these vessels goes to supply the anterior pituitary, carrying the various hypothalamic-releasing hormones.

Connections (Fig. 121.2)

Afferents

1. From limbic system:
   i. From Hippocampus, and
   ii. Amygdala.

   Limbic system is concerned with various aspects of emotion and behavior. Thus, hypothalamus is related to physiology of emotion and behavior.
2. From cortex: Particularly from:
   i. Area 6 and
   ii. Prefrontal area.

   These fibers enter the hypothalamus directly. Whereas many other fibers from cortex enter the hypothalamus via thalamus.
3. From olfactory and paraolfactory area: Olfactory tract is connected to limbic system also. Thus, the sense of olfaction, emotion and behavior and hypothalamus are linked up.

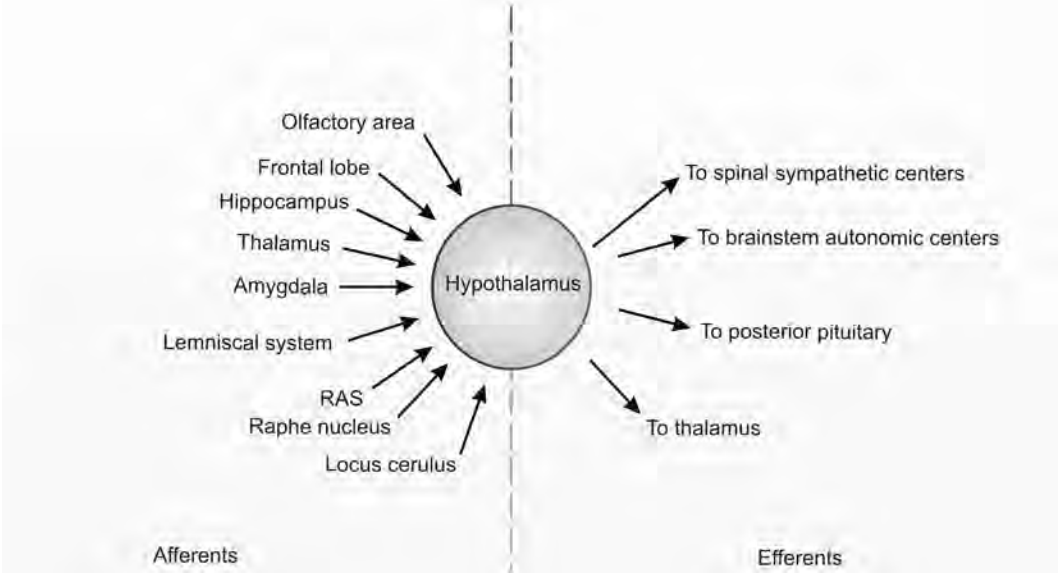


Fig. 121.2: Afferent and efferent connections of hypothalamus

4. Collaterals from the lemniscal system and fibers from the reticular activating system (RAS). Fiber which come from RAS are concerned with alertness. Collaterals from the lemniscal system keep the hypothalamus informed about the somatic sensations.
5. From the corpus striatum.
6. From thalamus.
7. From brainstem—from the:
   i. Raphe nucleus (Serotonergic neurons)
   ii. Locus cerulus (Noradrenergic neurons)
   iii. Medulla.

Efferents

1. *To brainstem and spinal cord:* Fibers from hypothalamus control the brainstem autonomic centers, particularly vasomotor center.
   i. Sympathetic supply from posterior group of nuclei.
   ii. Parasympathetic supply from middle group of nuclei.
2. Fibers from supraoptic and paraventricular nuclei form the hypothalamo-hypophyseal tract to end in posterior pituitary.
3. To thalamus
4. To midbrain.

Functions

Through its various connections with cortical, subcortical and brainstem centers and as it is an integral part of limbic system, it is concerned with homeostasis of the body.

1. It regulates autonomic activity.
2. It is center for emotions.
3. Many important centers are located in hypothalamus, which actively govern day to day activity.

Regulation of Water Balance

It regulates water balance of the body. Osmoreceptors situated in hypothalamus are stimulated by increased osmotic pressure. When osmoreceptors are stimulated, they will initiate two mechanisms—(a) ADH (antidiuretic hormone mechanism), (b) Drinking mechanism.

ADH secretion: It is increased by supraoptic and paraventricular neurons, which will prevent water loss through urine, i.e. there will be increased absorption of water from renal tubules.

Drinking: Reduced ECF leads to secretion of renin, which in turn leads to formation of angiotensin II. This acts on the subformical region where receptors are located which will stimulate the neural centers for thirst (Fig. 121.3).

Formation of Oxytocin and Vasopressin

From supraoptic and paraventricular nuclei, two hormones, oxytocin and vasopressin (ADH) are secreted. These hormones pass along the nerve fibers to posterior pituitary, bound with neurophysins, via hypothalamo-hypophyseal tract.

Vasopressin (ADH): Acts on renal tubules, attaches to external surface of sensitive renal tubule (i.e. distal tubules and collecting ducts) and stimulates adenyl cyclase mechanism, causing formation of cyclic AMP, in the tubular cells. Cyclic AMP increases permeability of luminal side of the tubular cells, for absorption of water. Cutting of the above tract will produce lack of ADH, therefore less absorption of water and large amount of urine is passed (Diabetes Insipidus).
Oxytocin: It is released in response to various stimuli:

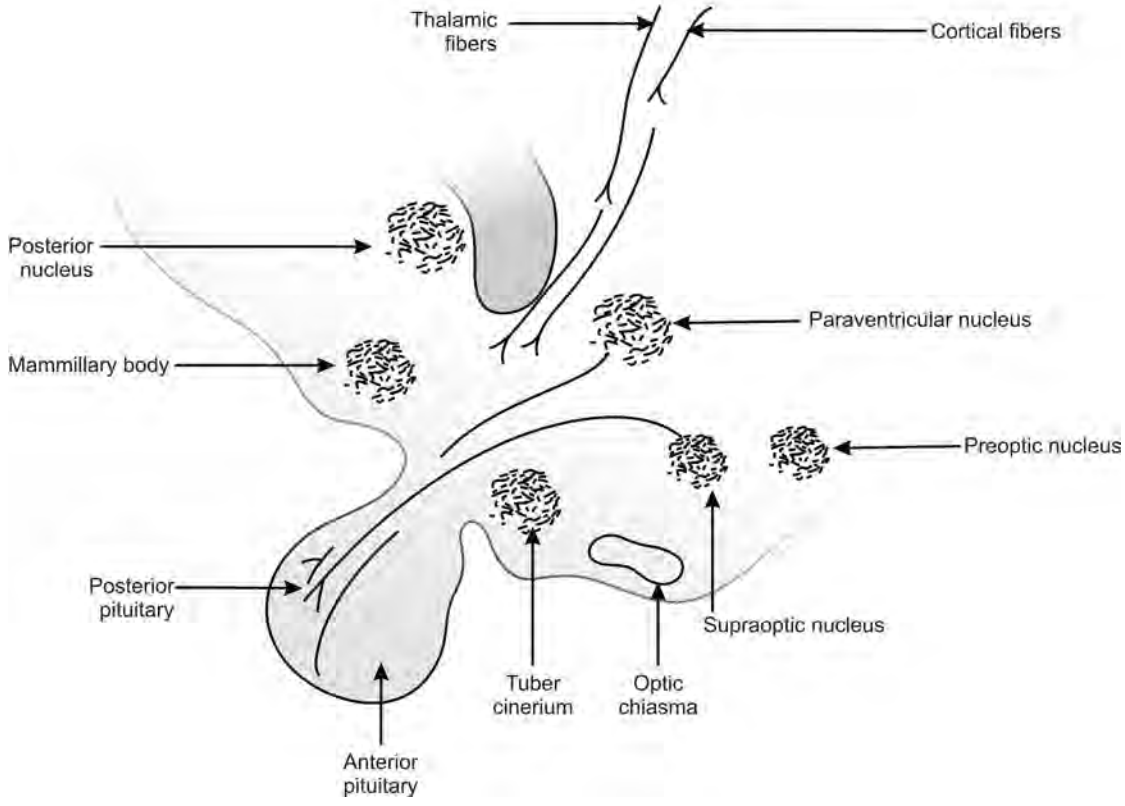


Fig. 121.3: Hypothalamus and pituitary gland showing various hypothalamic nuclei

i. Stretching of cervix during parturition
ii. Coitus
iii. Suckling.

When released, it causes contraction of uterine smooth muscle and contraction of myoepithelial cells.

Oxytocin: When released in response to suckling of breast causes milk ejection in lactating animals and women by contraction of myoepithelial cells surrounding the alveoli of mammary gland. This is known as milk ejection reflex (Fig. 121.4).

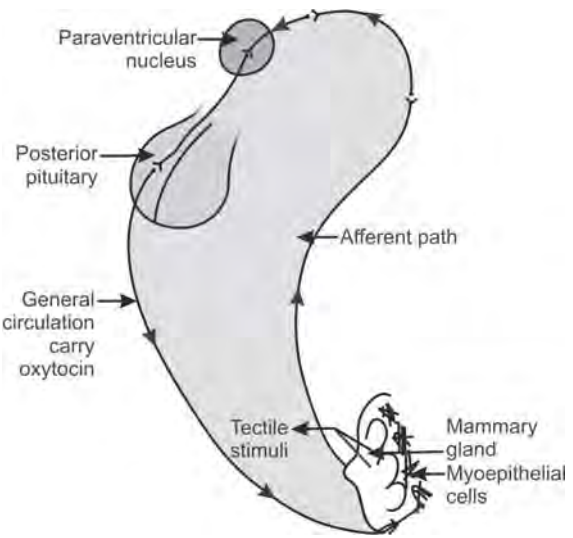


Fig. 121.4: Milk ejection reflex

Controls: Secretion of Anterior Pituitary

Hormones by various releasing hormones and some inhibiting hormones, e.g. CRH, GnRH,

TRH, GHRH, GHIH and PIH. Anterior pituitary in turn controls many different endocrine glands which control metabolism and reproduction. Anterior pituitary also controls growth.

Concerned with Sleep

Experimental studies show:

1. Posterior hypothalamic damage—produces prolonged sleep.
2. Dorsal hypothalamic stimulation—causes sleep.

Therefore, in posterior hypothalamus waking center is situated and in dorsal hypothalamus sleeping center is situated. This is the conclusion of experiments.

1. Slow stimulation producing sleep (Stimulation of dorsal hypothalamus) is due to stimulation of the diffuse nervous pathways passing through it rather than stimulation of hypothalamus directly.
2. Damage to posterior hypothalamus interferes with fibers from RAS to cerebral cortex and thalamus leading to prolonged sleep.

   Therefore, role of hypothalamus in producing sleep is questionable.

Concerned with Regulation of Body Temperature

In homeothermic animals, a number of reflexes are integrated in the hypothalamus to maintain the body temperature, inspite of variation in environmental temperature. Hypothalamus acts as a thermostat.

The hypothalamus has two centers for heat regulation:

In increased environmental temperature—Anteriorly located heat loss centers are activated and they will produce cutaneous vasodilatation and sweating in man and panting in dogs and cats.

- In cold surroundings, posteriorly located heat conservation and heat production centers are activated which will produce vasoconstriction, shivering, piloerection and increased production of catecholamines.

  The receptors are:

  1. Cutaneous
     - Ruffini's end organ for heat
     - Krause's bulb for cold.
  2. Hypothalamic receptors for both heat and cold.

     Failure of hypothalamic heat regulating mechanism results in heat stroke in hot environment.

Concerned with Hunger, Feeding, Satiety and Thirst

Hypothalamus is concerned with regulation of the amount of food ingested.

In ventromedial nucleus is situated satiety center—because bilaterals lesion of ventromedial nucleus produces obesity.

In lateral nucleus is situated feeding center because bilateral lesion of most lateral parts of hypothalamus leads to complete cessation of eating (Anorexia).

In hypothalamus, small areas are found which on electrical stimulation cause polydipsia and lesion of these areas cause hypodipsia.

It serves as a reflex center for emotional expression:

Emotional behavior has control from hypothalamus

Emotional experience } Two things are related to each other
Emotional expression }

Emotional experience—requires a human subject.

Emotional expression—can be studied in experimental animal.

1. A fear, flight, fleeing or avoidance reaction is seen when animal is exposed to threatening situation.
2. A rage, or aggressive reaction or fighting attack is seen when the animal is in anger.

Both reactions are seen on stimulation of certain areas of hypothalamus. Cardiovascular changes as in a situation of stress are seen in both the conditions.

i. An area extending through lateral hypothalamus to central gray matter of midbrain when stimulated causes rage reactions.
ii. Lesion of lateral hypothalamus and rostral midbrain abolishes rage.

Cerebral cortex exerts inhibitory control over emotional behavior and sympathetic effect.

Androgen in male potentiates the rage reaction.

EMOTION

Man is body and mind or psychobiologic whole. Therefore, emotions play important role in his physiology.

Changes in emotion: Emotion has mental and physical side. Behavioral changes are also seen.

1. Mental side—includes:
   - Cognition
   - Affect
   - Conation.
2. Physical changes: In viscera and skeletal muscles are coordinated activity of both autonomic and somatic nervous system.
3. Behavioral changes:
   Somatic:
   - Smiling
   - Laughing
   - Crying
   - Screaming
   - Running
   - Facial expression of distortion or delight.

   Fear is accompanied by:
   - Tachycardia
   - Tachypnea
   - Vasoconstriction of skin
   - Sweating (cold sweat)
   - Piloerection
   - Pupillary dilatation
   - Dryness of mouth
   - Muscular tremors.

   Thus, both sympathetic and somatic activity takes place.

   Grief is accompanied by:
   - Tears
   - Excess nasal secretion
   - Skin pallor
   - Muscle tone is reduced
   - Movements are slow and feeble.

   Again, both somatic and autonomic functions are disturbed.

   Emotional outbursts are always associated with a variety of autonomic responses, e.g. increase or decrease of BP and heart rate.
   - Pallor or flushing
   - Fainting.

   Complex patterns of emotional exteriorization are achieved, the brain component responsible is, prefrontal—hypothalamic—thalamic complex.

   There is no doubt that the mental and viscerosomatic sides of an emotion can be dissociated, e.g. a patient with vascular lesion of the internal capsule may manifest viscerosomatic changes which ordinarily accompany emotions but in this case the affect is lacking. He feels nothing.

CHAPTER

122 Reticular Formation and Reticular Activating System

There are diffuse poorly defined groups of cells with fibers (surrounding the central canal of brain) extending from medulla to thalamus, which form delicate interlacement (the reticulum) and is called formatio reticularis or reticular formation. Located within it are centers that regulate respiration, blood pressure, heart rate and other vegetative functions.

The reticular formation includes the organization of cell masses in:

1. Medulla oblongata
2. Pons
3. Tegmentum of midbrain
4. Hypothalamus
5. Subthalamus, and
6. Some thalamic nuclei.

And includes all the cells and their various connections, except:

1. Cranial nerve nuclei
2. Lemniscal relay nuclei, and
3. Relay nuclei of the cerebellum.

Reticular formation is organized into two divisions:

1. Ascending reticular formation OR ascending reticular activating system (ARAS) (Fig. 122.1).
2. Descending reticular system.

Reticular activating system constitutes that portion of the reticular system, which by their activity maintains the wakeful state and control over the activities of the brain.

It is multineuronal and polysynaptic pathway and is slow conductive system compared to primary sensory pathway.

CONNECTIONS

Afferent

1. The collaterals from different ascending sensory pathways including:
   i. Optic
   ii. Auditory
   iii. Gustatory
   iv. Olfactory
   v. Labyrinthine

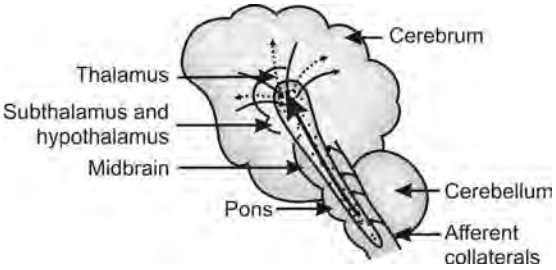


Fig. 122.1: Ascending reticular activating system in brainstem (ARAS)

vi. Trigemninal and spinal system carrying
   a. Pain
   b. Touch
   c. Temperature
   d. Muscle sense
   e. Joint sense
   f. Pressure
   g. Vibration
   h. Visceral sense, etc.

Reach the reticular formation in the brainstem and stimulate the cells of the reticular formation nonspecifically, that means a particular specific sensation carried by a specific path fires off these cells which in turn give rise to a response, different in nature from the sensation carried by the same path, e.g. the auditory fibers carrying auditory impulses fire off these cells whose response is different from the sensation of audition, that is non-specific response.

The non-specific response is due to:

1. Complexity of neuronal net, and
2. Degree of convergence

These two factors abolish the modality specificity.

The system is therefore nonspecific:

2. Afferent fibers from
   i. Basal ganglia
   ii. Cerebellum
   iii. Thalamus
   iv. Rhiencephalon
   v. Cerebral cortex
      a. Only from Sensory motor area
      b. Ocular
      c. Orbital
      d. Superior temporal
      e. Posterior parietal cortex, and
      f. Cingulate gyrus.

Stimulation of RAS causes diffuse stimulation of cortex—desynchronizing EEG. Thus, it receives fibers from different afferent system carrying:

1. Cutaneous
2. Deep
3. Somatic
4. Autonomic
5. Proprioceptive
6. Special sense and projects into all parts of CNS (Fig. 122.1).

THE MAIN FUNCTION

The reticular activating system is mainly concerned in maintaining *conscious alert state*, which is very essential for perception of various other sensations. When inhibited, the facilitation for evoked—potentials to cortical areas, goes off and sleep occurs.

There is inhibitory system, which cuts off the inputs to this facilitatory ascending activating system:

1. Diencephalic inhibitory system
2. Medullary inhibitory system.
3. Basal forebrain inhibitory zone.
   i. *Diencephalic inhibitory system:* Stimulation of posterior hypothalamus and adjoining intralaminar and anterior thalamic nuclei with a slow (8/sec) frequency produces sleep. Faster rate produces arousal.
   ii. *Medullary inhibitory system:* Stimulation of medullary region at the level of tractus solitarius produces sleep when frequency is slow but when frequency of stimulation is high —arousal by affecting pathways to thalamus.
   iii. *Basal forebrain inhibitory zone:* Suprachiasmatic area, preoptic area and diagonal band of brain.

When stimulated either with fast or slow frequency current produces sleep and synchronizing EEG pattern.

These inhibitory areas send their impulses through descending pathways to the ascending reticular system and inhibit them, thus transforming arousal or alert response to sleep or somnolence.

Efferent Connections

The efferent fibers pass from reticular formation in two different directions.

1. *Cephalic projection:* Pass into all areas of cerebral cortex (neocortex) of both sides. In doing so most of the fibers bypass thalamus and pass directly into cortex, some fibers relay into reticular nuclei of thalamus and from these, efferent fibers project into cerebral cortex. These fibers form ascending reticular activating system or ascending reticular formation.
2. *Spinal projection:* The other group passes caudally into spinal cord and form multisynaptic descending pathway organized into lateral and medial reticulospinal tracts, both of which contain both crossed and uncrossed fibers. The medial reticulospinal tract descends through anterior funiculus of spinal cord whereas the lateral reticulospinal tract descends through lateral funiculus.

Factors Affecting

Reticular formation is influenced by:

1. Sensory tracts
2. Drugs—adrenaline, acetylcholine, barabiturates, anesthetics, tranquilizers, etc.
3. Chemical changes of blood, e.g. alteration of CO_2 content.
4. Certain hormonal changes.
5. Sympathomimetic agents, e.g. adrenaline, noradrenaline, amphetamine.
6. Sympathetic stimulation.
   Produces arousal or alert reaction due to lowering of threshold of brainstem reticular formation.
7. Stress: Which leads to increased secretion of catecholamines from adrenal medulla, also hightens alert attentive behavior.
8. General anesthetics depress RAS and produces unconsciousness, barbiturates also act in the same way.
9. Increased arterial pressure increases RAS activity.

Clinical Significance

1. Tumors or vascular lesions affecting RAS produces coma.
2. In sleeping sickness the lesion is in RAS. Posterior hypothalamus and upper part of midbrain are the areas, where small lesions grossly interferes the activities of RAS.
3. Concussion following head injury also depresses RAS.

FUNCTIONS OF RETICULAR FORMATION

If the cerebral cortex is the Commander-in-Chief in commanding the whole nervous system, the reticular formation is taken as next in command.

A Summary of Activity

1. Activity of RAS maintains the conscious alert state, which is essential for perception of all other sensations.

   Lesions affecting ascending reticular activating system leads to coma. Concussion of brain depresses RAS and produces coma. Anesthetic agents and hypnotics depress RAS by producing synaptic block.

   Therefore, it serves as *center for wakefulness.*
2. Integrity of RAS is necessary for the generation and transmission of sensory impulse because it forms a background for reception of sensory impulse by cerebral cortex. It prepares the cortex for such perception.

3. It is concerned with regulation of viscerovascular system that is regulation of heart rate, respiration, blood pressure and other organic activity. It also regulates gastrointestinal and metabolic activities.
4. It plays important role in adjustment of endocrine secretion and function.
5. It has regulatory influence on the formation of conditioned reflexes and development of learning process.
6. It is organized into nuclear groups (centers) responsible for feeding, thirst, and satiety.

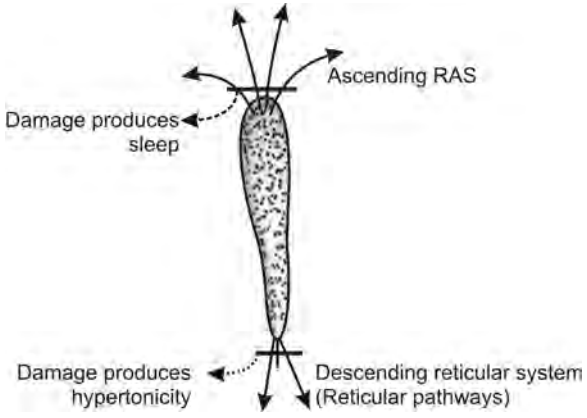


Fig. 122.2: Effects of damage to reticular system

7. It is higher center for autonomic nervous system.
8. It is concerned with emotional behavior, sexual emotions, etc.
9. In reticular formation, some of the centers for autonomic reflexes and somatovisceral reflexes are present.
10. By its balancing action through facilitatory and inhibitory pathways on motoneurons, it regulates tone and posture and gives stable background for suitable execution of smooth, intricate, delicate and purposeful movement. It is responsible for postural reflexes and righting reactions. Plays a role in phasic movement. But there is higher control from brain.
11. It represents higher center for temperature regulation.
12. It is also higher center for glucostatic mechanism.
13. Controls sleep.
14. If the activating system is damaged, the subject is plunged into deep sleep. If the descending inhibitory path is damaged, hypertonicity is observed (Fig. 122.2).

CHAPTER

123

Electroencephalogram (EEG)

There are two types of electrical activities in cerebral cortex:

1. *Spontaneous:* Recorded from cortex without any stimulus being applied.
2. *Evoked:* Occurs in cortex after application of stimulus to a sense organ or nervous pathway.

By placing two electrodes on the scalp and leading via suitable amplifiers to a cathode ray oscillograph or ink writing device or an electronic recorder of suitable type (Fig. 123.1), a record is obtained of the electrical activity of the cerebrum—known as *electroencephalogram.* A similar record may be obtained by placing electrodes directly on the exposed surface of the cerebral hemisphere —known as *electrocorticogram.*

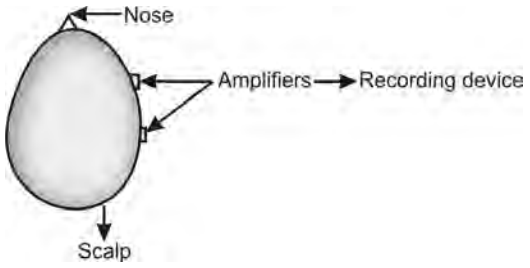


Fig. 123.1: Principle of electroencephalograph

The machine with which it is recorded is known as *electroencephalograph* and the technique is known as *electroencephalography.* The term was introduced first by Hans Berger, a German neurologist. He observed the presence of significant bioelectric activity in human brain. In 1929, Berger recorded potential by placing electrodes on the scalp of human beings. He also recorded changes in electrical potentials by placing minute electrodes on the surface or within the substance of the cerebral cortex in animals—*electrocorticogram.* However, the great expectations of Berger were not fully realized and Berger ended as a much-frustrated man.

To detect the brain cell electrical activity highly intricate electronic amplifying systems are necessary to potentiate minute currents into recordable intensity.

Electroencephalographic records may be bipolar or unipolar. Bipolar record is the record of potential fluctuations between two cortical electrodes.

Whereas unipolar record is the record of potential difference between a cortical electrode and an indifferent electrode having zero potential placed on some part of the body (Fig. 123.2).

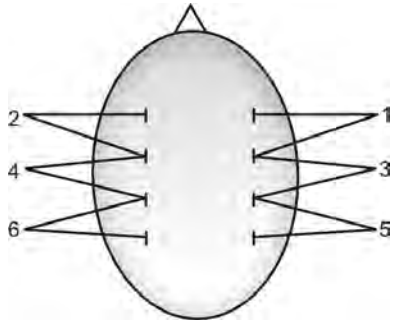


Fig. 123.2: Position of electrodes

ORIGIN OF BRAIN WAVES OR NEUROPHYSIOLOGICAL BASIS OF EEG

1. Evidence tells us that slow rhythmic waves are not formed by summation of individual spikes. They are not action potentials, they are local potentials.
2. By recording from the brain at different depths it has been shown that the waves originate in gray matter, rather than white matter and the nuclear masses of thalamus make an important contribution to the EEG record. The thalamocortical loop keeps the constant electrical activity. If an area of cortex is isolated from its cortical connection its activity persists until undercutting destroys its thalamic connections.
3. EEG waves are the results of summated potentials of the dendrites of gray matter of the superficial layer of cerebral cortex and it is due to current flow in the fluctuating dipoles formed on the: (i) dendrites of the cortical cells, and (ii) cell bodies, i.e. dipole is formed between (i) and (ii).
4. Cortical dendrites are densely packed units placed in superficial layers of the cortex. They are not the processes for conduction and do not propogate action potentials. Action potentials are propogated through axonic terminals. Many of these cortical neurons are alined vertically in the cortex with dendrites lying parallel. On the dendrites are the synaptic knobs, some of which are excitatory and others inhibitory. When the excitatory axodendritic synapses are activated current flow into and out in between the cell body and axodendritic endings, causing wave like potential fluctuation in the volume conductor when many neurons are activated synchronously, quite a large change in potential may be recorded. Thus, EEG is the potential fluctuation in volume conductor. Thus, the dipole formed in between the dendrites and the cell bodies fluctuates constantly due to the excitatory and inhibitory axodendritic synapses (Fig. 123.3).

Mechanism of Desynchronization and Synchronization

1. The definite pattern of rhythm is due to synchronized activity of the many dendritic units.
2. When the synchronized activities of many dendritic units are disturbed by incoming different sensory impulses the synchronized pattern of rhythm no longer persists and is replaced by disynchronized pattern of irregular low voltage activity.

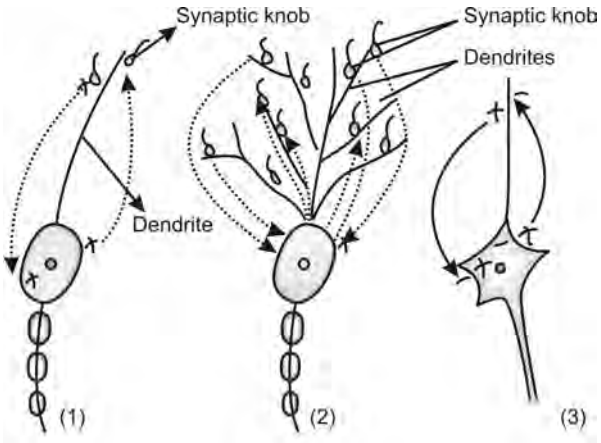


Fig. 123.3: Current flows in diapole from +ve to –ve

For genesis of *synchronized wave pattern* two factors are responsible:

1. Synchronizing effects of two parallel fibers, and
2. Influences of impulses from thalamus and brainstem.

The characteristics of α waves indicate that the activities of many dendritic units are synchronized.

Desynchonization of EEG pattern with irregular low voltage activity can be produced by:

i. Stimulating specific sensory input up to the level of midbrain.
ii. High frequency stimulation of reticular formation in the midbrain tegmentum.
iii. Stimulation of nonspecific projection nuclei of the thalamus.

Nature of Brain Waves

From the human cerebral cortex 3 principal kinds of waves or rhythm may be detected which go by common name Berger rhythm after Hans Berger.

1. *The alpha (α) rhythm:* If an EEG record is taken in a normal subject (Fig. 123.4).
   i. Who refrains from mental activity, and
   ii. Who keeps his eyes closed.

   The usual pattern of electrical activity consist of a sequence of waves which recur at a frequency 8-12 cycles/sec (Hz) and voltage of 10-100 microvolts (average amplitude 50 microvolts). These are α waves which occur in spindles or bursts that is they gradually build up and recede. Their average amplitude is 50 microvolts but it varies from cycle-to-cycle.

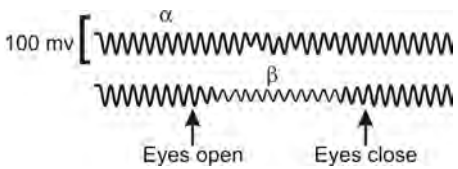


Fig. 123.4: α and β waves

   a. If the eyes are opened or subject—indulges in mental arithmetic or other purposive activity the large α-waves disappear (= α block). It is also known as desynchronization or arousal or alert response, the record shows small irregular oscillations.
   b. α-wave is pattern of inactivity, such activity is highly characteristic for any given individual.
   c. It can be recorded most easily from the occipital and parieto-occipital region of the head of the person in absolute physical and mental rest and eyes closed.
2. *Beta (β) rhythm:* It is faster. Frequency ranges between 18-35 cycles/sec or maximum 60 cycles/sec.

   Two types: β I—frequency double that of alpha.

   β II—found during tension or intense activation of CNS.

   Amplitude
   i. 5-10 microvolts.
   ii. Found in parietal and frontal precentral region of head.
3. Delta (δ) rhythm (Fig. 123.5)
   i. Largest waves
   ii. Appear during sleep (deep)
   iii. Amplitude 100 microvolts (20-200) range
   iv. Extremely slow—3 to 5 (or 6) cycles/sec.

   They are high voltage slow waves found in:
   i. Deep sleep
   ii. Brain tumor
   iii. Hypoglycemia
   iv. Overbreathing.
4. Theta θ rhythm: In children between age:
   i. 2-5 years theta waves are prominent
   ii. Low amplitude 10-20 microvolts
   iii. Frequency 4-7 cycles per sec.
   iv. In children, it can be inhibited by visual attention or emotional augmentation.

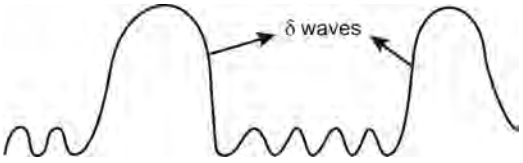


Fig. 123.5: Delta waves

Not present in normal adults. If present in adults, it indicates neoplasm.

γ waves: 40-50 cycles/sec. It is abnormal wave.

Note: In children, below the age of 1½ years slow EEG of low amplitude without any regular rhythm. α wave is not fully established before 12-13 years. Up to this age the predominant rhythm is of low amplitude and slow frequency.

Significance

EEG is extensively used as an aid to clinical diagnosis.

The objects of clinical recording are:

1. To determine the distribution of electrical activity over wide areas of the cortex.
2. To observe activity arising simultaneously in different areas of the brain.

To attain these objects, six simultaneous tracings are taken, many electrodes are placed on the scalp and are connected to the amplifiers in pairs (See Fig. 123.2).

i. The recordings obtained from corresponding areas of two cerebral hemisphere are remarkably similar in timings and shape under normal conditions.
ii. Lesion affecting one cerebral hemisphere affects the same side recording. So when recording, from two corresponding points in each cerebral hemisphere is compared a focal lesion can be detected.

α rhythm—appears:

1. When brain is not functioning very greatly.
2. Suggesting only wakefulness.
3. It is a wave of inattention as it disappears when visual attention is made.

β rhythm—appears:

1. When brain is showing intense activity, and
2. When alpha rhythm disappears.
   It is restricted to localized region.

δ wave—appears:

1. During sleep
2. During deep breathing
3. Hypoglycemia
4. Local delta wave production signifies neoplasm.

γ and θ and waves—are abnormal.

Sleep and EEG

As soon as a subject gets relaxed he feels drowsy and gradually falls asleep; pattern of EEG is replaced by slower and larger waves. In deep sleep there are often irregular delta waves having frequency less than 4/sec.

EEG pattern of deep sleep is sometimes replaced by low voltage and high frequency irregular waves along with eye movements. This type of sleep is known as paradoxical sleep and for associated movements of eyes it is also called rapid eye movement sleep (REM sleep).

Sleep having high voltage slow wave EEG pattern (Spindles) is called slow wave sleep or nonrapid eye movement sleep (NREM sleep). REM sleep occurs at about 90 minutes of sleep period.

EEG IN VARIOUS DISEASES

Changes in EEG have been noted in following diseases:

1. *Increased intracranial pressure:* Berger demonstrated slow δ waves of an ampli-

tude up to 100 microvolts and a frequency of 3 cycles per second in rise of intracranial pressure due to cerebral tumor, concussion, meningitis, etc.

2. *Cerebral tumors:* Presence of intracranial tumor may cause mechanical stress in neighboring parts of the brain, which in turn act as a source of delta wave activity. So tumor can be localized by EEG tracing.
3. *Epilepsy:* It is a disorder characterized by an abnormal and severe discharge of nervous energy from either part of the central nervous system (usually the cerebral cortex) or all of it. There are usually two types of epilepsy.

1. Generalized	Petitmal i. Myoclonic form single violent muscular jerk of head or arm lasts for few sec	Grandmal Generalized convulsions with abrupt loss of consciousness Lasts for 3 sec to 4 mt. Post seizure depression of entire nervous system.
2. Focal—psychomotor characterized by automatic movement, e.g. chewing, smacking of lips along with dreamy feeling of unreality – Due to disturbances in temporal lobe. – May cause attack of abnormal rage, short period of amnesia, a moment of inchorent speech sudden anxiety or fear or discomfort.	ii. Absence form 4 to 22 sec. Unconsciousness and several twitch like contractions of muscles usually in head region.	It is due to increased activity of midbrain part of RAS.

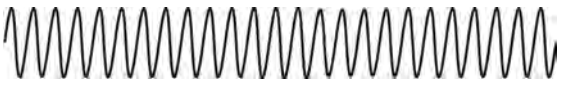


Fig. 123.6: Grandmal epilepsy (EEG pattern)

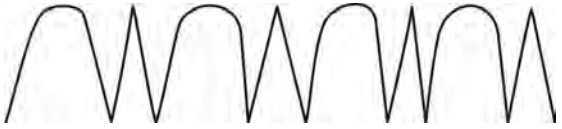


Fig. 123.7: Petimal epilepsy (EEG pattern)

Fig. 123.8: Psychomotor epilepsy (EEG pattern)

EEG Pattern

In grandmal: During attack 25-30/sec sharp spikes (increase in number of spikes preceeds grandmal) (Fig. 123.6).

In petitmal: Shows spike and dome pattern (just before attack large slow irregular waves) (Fig. 123.7).

In psychomotor: Low frequency or rectangular wave frequency 2-4 sec (Fig. 123.8).

CHAPTER

124

Sleep

Sleep is the important physiological function. Without repetition of sleep, healthy mental and bodily activity is impossible. Sleep and wakefulness together form basic rhythm of existence of all higher forms of life.

DEFINITION

With the present knowledge, the working definition of sleep is as follows:

Sleep is a temporary and rhythmical interruption of wakefulness induced by internal factors in which:

1. Consciousness of environmental features subsides to a minimum.
2. In which movement of the body is almost absent.
3. In which there is an increase in the threshold of reactivity.
4. In which there is light sleep and deep sleep (a rhythmical alteration of cycle) and phenomenon of dreaming.
5. In which there exists a builtin mechanism, which after a time produces phenomenon of arousal.

Simpler Definition

Sleep is a state of unconsciousness from which a person can be aroused by appropriate sensory or other stimuli.

Thus, by this definition, coma, anesthesia are not sleep.

Why Do We Sleep

Investigators have attempted to answer this question by sleep deprivation—continuous deprivation of sleep in young men for 205 hours—this is the longest study on record.

1. Initially subjects felt gradual onset of fatigue and gradual fall of mental capabilities.
2. Fatigue came and went in waves first, it was always worst in the night hours.
3. During first 2-3 days of deprivation of sleep, subject could show fairly good efficiency to perform various tasks, but this fell progressively.
4. On 5th day, things deteriorated at a rapid rate, subjects became very irritable, felt weakness of musculature, and hallucinations began. There occurred the onset of lapses in subjects (with their eyes open lapsed into a state of disorientation or nonresponsiveness to environment). Lapse would end as abruptly as it began. The subject's emotions became extremely labile.
5. After recovery, subjects showed no lasting effects.

In sleep, brain is not truly resting, on the contrary, it is hard at work and receiving more blood supply.

Thus, sleep is essential for:

1. Normal higher functions (e.g. learning, memory, judgement, etc.)
2. Normal motor functions, and
3. Emotional stability.

Duration of Sleep

Length of sleep rapidly decreases with age. Newborn child sleeps most of its time. It awakens at fairly regular intervals regardless of time of day or night, but the infant soon learns that the night is the time for sleep. By one year, a pattern of nightlong sleep plus a morning and afternoon nap is established. By 2 years, morning nap is given up. Then afternoon nap shrinks. After 5 years, night sleep itself shrinks until adult pattern is reached (5-10 hours). Adults need 5-10 hours of sleep, some persons sleep less, some more.

Sleep Concomitants

I. Most changes in sleep occur in CNS
   i. There is general decline of excitability.
   ii. Reflexes may vanish, e.g. knee jerk is not elicitable in deeper stages of sleep.
   iii. Muscle tone falls and muscles relax.
   iv. A very peculiar phenomenon, which occurs in normal adults only in deep sleep, is the appearance of Babinski's sign, i.e. great toe extension produced by scratching of sole of foot.
   (Babinski's sign is positive in newborn, upper motor neuron lesion, anesthesia and deep sleep. That this occurs in deep sleep indicates some kind of functional interruption of connections of cortex with lower segments of CNS. Thus, tremors of parkinsonism dramatically decline in sleep).

2. Energy metabolism of brain during sleep. Physiological sleep in man is associated with a slight but significant increase in:
   i. Cerebral blood flow
   ii. No change or slight fall in cerebral O_2 consumption
   iii. Arterial CO_2 tension is increased in sleeping subject and those about to sleep.
3. Blood pressure, heart rates and rectal temperature fall, respirations become slower but deeper.

Types of Sleep

1. Slow wave sleep or non rapid eye movement sleep (NREM sleep).
2. Paradoxical sleep or rapid eye movement sleep (REM sleep).

1. *NREM sleep:* Results due to decreased activity of reticular activating system and it is called slow wave sleep because brain waves are very slow. It is also called NREM sleep because there are no rotatary eye movements.
2. *REM sleep*: Results from abnormal channeling of signals in the brain even though brain activity may not be significantly depressed. This is called as *paradoxical sleep* or *desynchronized sleep.* It is also called REM sleep as rotatory eye movements are present.

Most of the sleep during each night is of slow wave variety. This is deep restful type of sleep. Short episodes of paradoxical sleep usually occur at intervals during each night.

Distribution of Sleep Stages (Fig. 124.1)

In a typical night of sleep, a young adult first enters NREM sleep, passes through stages I and II and spends 70-100 min in stages 3 and 4, sleep then lightens and a REM period follows. This cycle is repeated every 90 min

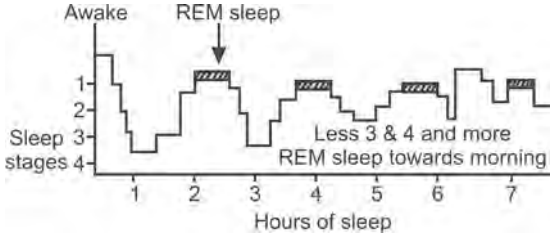


Fig. 124.1: Distribution of sleep stages

throughout night. The cycles are similar although there is less stages III and IV sleep and more REM sleep towards morning. Thus, there are 4-6 REM periods per night. At all ages REM sleep constitutes about 25% of total sleep (Fig. 124.1). Children have more stage 3 & 4 sleep than young adult, and old people have much less.

***Slow wave sleep*—**Different names are:

1. Deep restful sleep
2. Dreamless sleep
3. Delta wave sleep
4. Normal sleep
5. NREM sleep.

EEG changes in person who falls asleep—beginning with wakefulness and proceeds to deep slow wave sleep.

1. *Alert wakefulness:* Low voltage high frequency waves (Fig. 124.2).
2. *Quiet restfulness:* Predominance of alpha waves (Fig. 124.3).
3. *Light sleep:* Mainly theta or low voltage (low amplitude) waves but interspersed with spindles of alpha waves called sleep spindles that lasts for few seconds (Fig. 124.4) at a time.
4. *Deep slow wave sleep:* High voltage (high amplitude) delta waves occurring at a rate of 1-2 / Sec (Fig. 124.5).
5. *In paradoxical sleep:* Brain waves change to still different pattern approaching that of normal wakefulness.

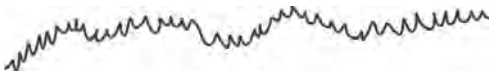


Fig. 124.2: EEG in alert wakefulness

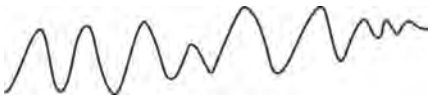


Fig. 124.3: EEG in quiet restfulness

Fig. 124.4: EEG in light sleep

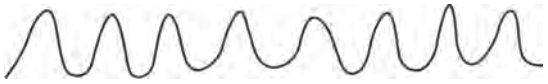


Fig. 124.5: EEG in deep slow wave sleep

Characteristic of Deep Slow Wave Sleep

Occurs 30 min to 1 hour after going to sleep.

1. This sleep is dreamless sleep.
2. Exceedingly restful.
3. Associated with decrease in peripheral vascular tone.
4. Decrease in most of the vegetative functions of the body.
5. BP falls by 10-30%, heart rate and respiratory rate also falls.

REM Sleep or Paradoxical Sleep (Fig. 124.6)

1. Imposed on slow wave sleep. Never occurs by itself.
2. Occurs in bouts of 5-10 min each, after about 90 min.

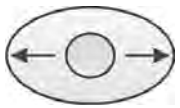


Fig. 124.6: Rapid eye movement

3. EEG shows low voltage fast (20-30 Hz) waves, EEG resembles waking state.
4. But individual is difficult to arouse. If awakened—tells about interrupted dream. Dreaming predominantly in REM sleep.
5. Muscle tone throughout the body is depressed. Muscular relaxation is profound. Therefore, cannot move during dream.
6. Limbs are flaccid—indicates strong inhibition of spinal projection from RAS.
7. Occasional muscular twitch or jerk.
8. Rapid horizontal eye movements are present.
9. Heart rate and respiratory rate irregular.

In summary, paradoxical sleep is a type of sleep in which brain is quite active, but the brain activity is not channeled in the proper direction for the person to be aware of his surroundings and, therefore awake.

BASIC THEORIES OF SLEEP AND WAKEFULNESS

Stimulation of RAS—Produces a State of Wakefulness but What Causes Sleep?

In deep slow wave sleep, transmission of signals from reticular activating system to cortex is greatly diminished.

Therefore, slow wave sleep probably results from decreased activity of RAS.

Paradoxical sleep: It is paradoxical because some areas of the cerebrum are quite active despite the state of sleep. Probably this type of sleep results, from curious mixture of activation of some brain regions while other regions are still suppressed.

Therefore, to understand wakefulness and sleep:

1. We must know what mechanisms activate RAS during wakefulness? and
2. What suppress this system during sleep?

Neuronal centers, transmitters and mechanism that cause wakefulness:

1. Stimulation of medial portion of reticular formation especially in mesencephalon and upper pons cause intense wakefulness.
2. Widespread stimulation of sensory nerves throughout the body cause wakefulness. These nerves transmit strong signals into mesencephalic portion of RAS.
3. Stimulation of most areas of cerebral cortex will also cause a high level of wakefulness. These areas also transmit strong signals into both mesencephalic and thalamic portions of RAS.
4. Stimulation of certain regions of hypothalamus, particularly lateral regions can also cause extreme degree of wakefulness. From here also, strong signals are transmitted to RAS.
5. *Locus cerulus:* It is collection of neurons, lies bilaterally beneath floor of IVth ventricle. It is part of reticular formation.

Nerve fibers from this are widely distributed to other portion of reticular formation and almost all areas of cerebrum.

Norepinephrine is secreted at these nerve endings. Norepinephrine plays important role in wakefulness process.

Dopamine and epinephrine also contribute to wakefulness, which are similar to norepinephrine, because neurons in the nearby regions in brainstem secrete these transmitters, and seem to be activated in many instances along with norepinephrine system.

Lesion in Wakefulness Areas

1. Lesion of mesencephalic portion of RAS or in fiber pathway leading up from this area if large enough will lead to coma.
2. Lesion in locus cerulus—will cause a type of sleep closely resembling natural sleep.

Neuronal Centers Transmitters and Mechanism that can Cause Sleep

Stimulation of several specific areas of the brain can produce sleep nearer to natural sleep.

1. Raphe nuclei in pons and medulla: They are thin sheet of neurons located in midline (medullary inhibitory system).
   Nerve fibers from these nuclei spread widely to:
   i. Reticular formation
   ii. Thalamus
   iii. Hypothalamus
   iv. Limbic cortex (most areas)
   v. To spinal cord terminating in posterior horn where they can inhibit incoming pain signals.

   Nerve fibers from raphe nuclei secretes serotonin. Therefore, it is assumed that serotonin is major transmitter substance associated with production of sleep.
2. Stimulation of other regions in diencephalon (Diencephalic inhibitory system), e.g. posterior hypothalamus and adjoining intralaminar nuclei—produce sleep.
3. Suprachiasmtic area—(Basal forebrain bundle)
   i. Stimulation produces sleep.

Effects of Lesion in Sleep Producing Centers

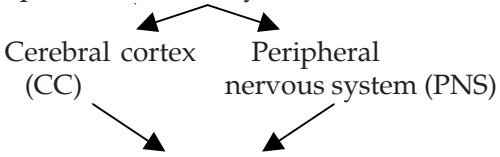
1. Discrete lesion in raphe nuclei, and
2. Discrete lesion in posterior hypothalamus
   Lead to high state of wakefulness. In both, RAS is released from inhibition.

Other Possible Transmitter Substances Related to Sleep

Small polypeptides of molecular weight less than 500 is found in CSF and blood of animals that have been kept awake for several days. When this substance is injected in ventricular system of an animal, it produces sleep of several hours.

CYCLE BETWEEN SLEEP AND WAKEFULNESS

1. Wakefulness and sleep occur cyclically:
   i. When RAS is rested and sleep centers are not activated, wakefulness centers begin spontaneous activity and it will excite:



   Cause—Positive feedback to RAS, which is still further acitivated and once wakefulness begins, its natural tendency is to sustain.
   ii. CC and peripheral nerves play important role in causing sleep-wakefulness rhythm.
2. Hours after brain remains activated, neurons within reticular activating system will fatigue or other factors might activate sleep center, so positive feedback cycle between:
   CC → RAS
   and PNS → RAS } will begin to fade

   As soon as few of the neurons in the RAS become inactive, this eliminates part of the feedback stimuli to other neurons. Therefore, these also become inactive. This process spreads rapidly leading to rapid transition from wakefulness to sleep.
3. During sleep neurons of RAS gradually become more and more excitable, because of prolonged rest and inhibitory neurons of sleep center becomes less excitable thus leading to new cycle of wakefulness.

This theory can explain rapid transition from sleep to wakefulness and wakefulness to sleep.

PHYSIOLOGICAL EFFECTS OF SLEEP

On CNS is important. Prolonged wakefulness causes malfunction of mind.

CHAPTER

125

Muscle Tone

MUSCLE TONE

Muscle tone and posture always go together as they are very much interrelated. Secondly, equilibrium also depends on muscle tone to a large extent.

1. By *posture* is meant the attitude taken by the body in different situations like standing and sitting.
2. A certain amount of muscular activity is necessary for maintenance of posture, but this has to be different from ordinary muscular contraction and relaxation for the simple reason that posture has to be maintained for long period of time and this should be achieved by minimum expenditure of energy.

Muscle tone is due to partial state of contraction of muscles. Distribution of tone in different postural muscles in different degrees results in a particular posture. Equilibrium means balancing the body in different postures and movements.

Basis of this phenomenon is stretch reflex or myotatic reflex.

Stretch Reflex

Stretch reflex is the basic reflex and in its simplest form means that the muscle contracts when it is stretched. The pull on the muscle acts as a stimulus for the receptors or end organs present in the muscle which are known as muscle spindles (Fig. 125.1).

Muscle spindle: Detailed structure:

1. Each muscle spindle consists of 4 to 6 intrafusal fibers.
2. A single intrafusal fiber has two striated polar sections (microtube) separated by a nuclear bag or nuclear chain. Two polar sections are innervated by floral spray type of afferents (Group II afferents). The nuclear bag or chain is innervated by a primary afferent ending known as annulospiral or group I A ending.
   In the spinal cord it is relayed over a single cell - α motoneuron or anterior horn cell. Discharge from α motoneuron results into muscular contraction (monosynaptic reflex).

Anterior horn cells are of two types:

i. α has greater diameter
ii. γ has small diameter.

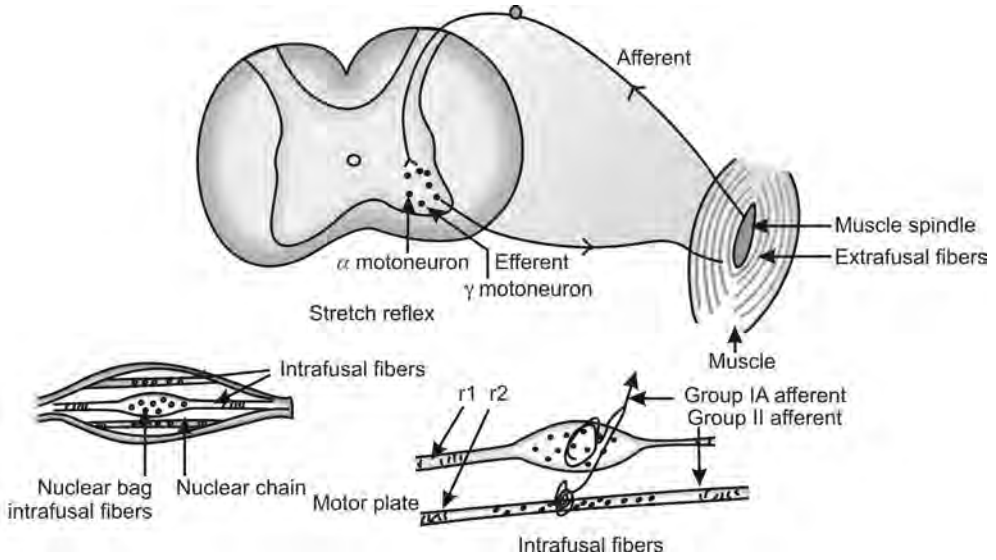


Fig. 125.1: Stretch reflex, muscle spindle—intrafusal fibers

(Therefore, nerve supply of muscle is bimodal).
— Nerve supply of muscle:

Efferent

1. α motoneurons supply nerve fibers to extrafusal fibers.
2. γ motoneurons supply nerve fibers to intrafusal fibers.
   γ 1 to microtube of nuclear bag fiber
   γ 2 to microtube of nuclear chain fiber.

Afferent

Group I A afferent comes from central area of nuclear bag and nuclear chain known as annulospiral nerve fiber.

1. Group II afferent arise from polar area of nuclear bag and nuclear chain fibers.
   Stretch reflex is normally present. It is a monosynaptic reflex and maintains tone and posture.
2. Intact reflex arc is essential. Lesion of any part of the arc results in loss of tone, e.g. Tabes dorsalis and anterior poliomyelitis.
   In Tabes dorsalis – Dorsal (Post.) horn cells are damaged.
   In anterior poliomyelitis – Ventral (Ant.) horn cells are damaged – which results in decrease of tone and wasting of muscles.
3. The tendon jerks like knee and ankle jerk are the functional examples of the stretch reflex and any condition, which enhances the stretch reflex increases the tendon jerks. Since, the knee jerk is brief and twitch like it is spoken of as the phasic reaction of the stretch reflex. Whereas, the sustained contraction resulting from continuous pull upon the tendon and which is concerned with the maintenance of posture is referred to as static or postural reaction of the stretch reflex.
4. The smooth and steady type of contraction characteristic of maintenance of posture results from the asynchronous nature of the impulses set up by numerous stretch receptors and the consequent

asynchronous reflex discharge through the motor neurons.
5. So, a stretch of continuous degree causes a steady maintained contraction.
6. So, these receptors do not show adaptation.
7. The reflex ceases when the stimulus is stopped. So, there is no after discharge.
8. The latent period is short less than 20 milli sec.
9. Stretch reflex is mostly obtained from antigravity muscles namely extensors which maintain erect posture of the body.
10. The center is the spinal cord, but when mediated by spinal cord alone it cannot maintain the muscles in a state of tone for an indefinite period. It requires re-enforcement from higher centers.

The Tone of Skeletal Muscles

1. The term tone or tonus was originally coined by Sherrington, has today a definite concept.
2. It denotes a steady reflex contraction of muscles concerned in maintaining the posture characteristic of a given species.
3. Response of muscle to stretch is contraction and maintenance of contraction is tone.

Cause

Tone is due to static reaction of stretch reflex, initiated by innumerable muscle spindles, distributed throughout the body but specially found in antigravity muscles.

In man: The antigravity muscles are:
1. Retractor of the neck
2. The extensors of back
3. The extensors of ankle joints
4. The extensors of knee joints and
5. The flexors of elbow due to erect posture in man.

When these muscles are completely relaxed as happens in unconscious person the body collapses and which is prevented in normal individual by continuous activity of stretch reflex.

Though the stretch reflex acting through the spinal cord is the primary factor in maintenance of tone in voluntary muscles, the impulses originating from the:
1. Labyrinth
2. Neck muscles
3. Cerebellum
4. Midbrain, and
5. Cerebrum.

Profoundly Influence the Spinal Centers

1. In the tonic contraction for the maintenance of posture, expenditure of energy is minimal and postures can be maintained for long periods at a time with no evidence of fatigue.
2. This economy of energy is achieved by asynchronous contraction of different groups of muscle fibers in relays, so that only a percent of muscle fibers are active at a given time.
3. The skeletal muscle fibers contain two types of muscle fibers – Red and White.

Red muscle fiber are—Smaller
1. Possess more prominent longitudinal striations
2. Contain more sarcoplasm
3. Contract more slowly
4. Fatigue less readily and are tetanized at a lower rate of stimulation.

The white fibers are:

Translucent with prominent cross strations, and are designed to execute rapid movements.

Most muscles contain both varieties though the proportions differ to a remarkable extent. The muscles charged with responsibility of

maintaining posture are mainly red in character.

Production of Tone

1. If muscle is stretched, because the muscle spindle is attached to endomysium, it is stretched.
2. Therefore, there is distortion of central equatorial area.
3. There is increased IA activity which stimulates anterior horn cells.
4. There is increased α (alfa) motoneuron discharge.
5. Muscle contracts.

Response of muscle to stretch is contraction and maintenance of contraction is tone.

6. Muscle is shortened, therefore, there is shortening of muscle spindle.
7. Therefore, IA activity die down.
8. Therefore α activity die down and
9. Muscle relaxes.

If useful purpose is to be served there should be sustained contraction. Sustained contraction (1) can be maintained by γ motoneuron activity, (2) which leads to contraction of intrafusal fibers, which contract only at the polar end, (3) so there is distortion of central area, (4) and generation of IA activity, (5) so that α motoneuron firing can continue.

Muscle tone is increased:

1. In increased γ activity
2. In increased IA activity
3. Increased activity of α motoneurons

Activity of α motoneuron is controlled by γ activity, therefore it is known as γ led or myotatic OR activity of α motoneuron may be independent which means not γ led or non-myotatic (Fig. 125.2).

From cerebral cortex to the lowest level of the medulla there are several areas, which give rise to facilitatory or inhibitory fibers.

These fibers following multisynaptic pathways culminate into extrapyramidal paths mentioned previously.

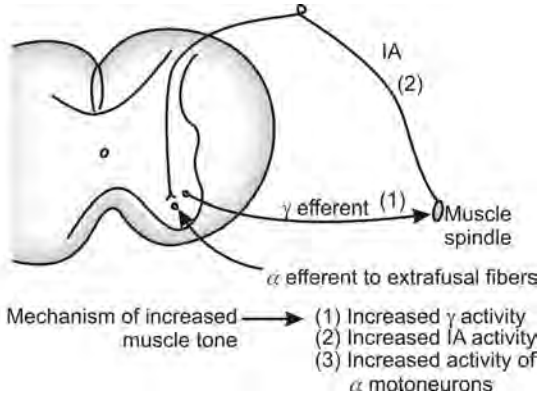


Fig. 125.2: Mechanism of increased muscle tone

In the diagram (Fig. 125.3) + sign indicates facilitatory area (= areas whose discharge causes increase of tone) and – ve sign indicates the inhibitory areas.

In the brainstem, there are two facilitatory areas in the pons, in addition to the vestibular nucleus, which is also facilitatory.

In the lower part of the medulla, there is an inhibitory center.

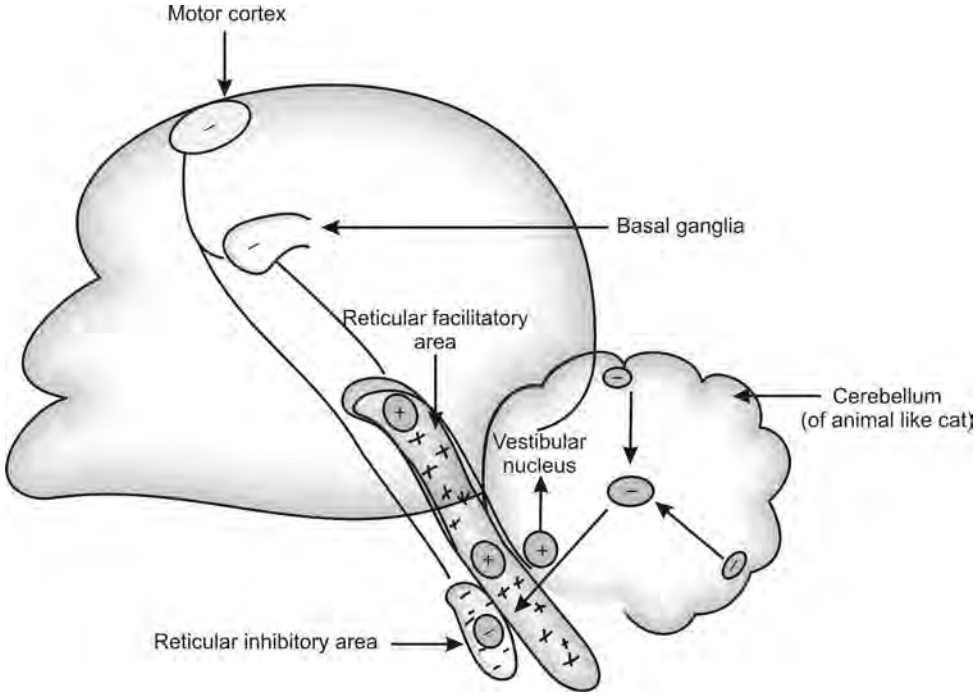
The facilitatory areas are intrinsically active, that is if freed from all other connections they will continue to discharge facilitatory impulses to the spinal center. They can be suppressed by inhibitory influences reaching them by other areas of brain.

On the other hand, the inhibitory area (of medulla) becomes active only when it receives impulses from the cerebral cortex or the cerebellum, when these connections are lost its inhibitory discharge disappears.

Cerebral cortex sends impulses to:

i. Medullary inhibitory center
ii. Basal ganglia and keeps them active.
iii. In addition, in animals like cat cerebellum also sends impulses to medullary inhibitory center and keeps it active.

The resultant of the opposing effects of inhibitory and facilitatory areas determines the



\+ Sign indicates facilitatory areas (= areas whose discharge causes increase of tone)
– Sign indicates the inhibitory areas

Fig. 125.3: Facilitatory and inhibitory areas

nature of supraspinal control and degree of tone. This resultant of opposing forces through extrapyramidal tracts reach α and γ motor neurons and influences them and thus influences the basic stretch reflex. Fibers from pyramidal tract also have influences.

DECEREBRATE RIGIDITY

CS Sherrington first in 1890s did the operation in experimental animals (cats) in which a transection is made in between superior and inferior colliculi. After this operation the animal develops what is called as decerebrate rigidity and animal is decerebrate animal (Fig. 125.4).

1. The limbs are hyperextended
2. Tail and head dorsiflexed
3. Extreme hyperextension of back.
4. Opisthotonos (back becomes concave).

The animal can be carefully balanced in standing position on its four legs but the slightest displacement causes the decerebrate animal to topple over. It has no righting reflexes.

Experiments have established that these facilitatory influences cause stimulation of the γ efferents and thus increase the tone.

Fig. 125.4: Decerebrate rigidity

Viewed in another way the decerebrate rigidity is due to release of the brain stem centers from the influences of cerebral cortex and basal ganglia. The decerebrate rigidity is example of release phenomenon.

Effects of Decerebellation

In a decerebrate cat (where the decerebration has been produced by Sherrington's intercollicular transection), the influence from the cerebellum continues to reach the medullary inhibitory center and it is active. If now the cerebellum is removed (decerebellation) the rigidity of decerebrate cat further increases.

If without producing Sherringtonian decerebration, simply the cerebellum is removed in the cat (or even cooled) as shown by Pollock and Davies in 1930s, a rigidity develops which apparently resemble Sherringtonian rigidity. A rigidity developed by cooling cerebellum is called ischemic rigidity.

From clinical case studies, it is clear that in human being, the influence of the cerebellum on the tone is quite different. Destruction of cerebellum due to diseases or injuries produces hypotonia (not hypertonia as in cat). This means that in man whole cerebellum facilitates the tone. In man, the middle lobe of cerebellum is well developed but in subhuman mammals (e.g. cats) the middle lobe of cerebellum is poorly developed. This is the difference in human beings and subhuman mammals.

Clinical Correlates

Theoretically, it might be said that a disease grossly injuring the upper part of the brain stem should produce a picture of decerebrate rigidity, but such cases do not survive and hence the clinical homologue of the decerebrate cat is not easy to find.

In hemiplegia, there is rigidity of extensor of the lower limb but in upper limb the rigidity affects the flexors because of erect posture in man the flexors of the upper limbs are the antigravity muscles.

CHAPTER

126

Posture

DEFINITION

It is a stance, e.g. standing, squatting. It is the adjustment of muscle tone for some purpose, e.g. standing erect. Hence, the basis of posture is muscle tone.

- The different factors and mechanisms, which help in maintaining posture can be summed up in postural reflexes.

Posture can be divided into two types:

1. Static posture, e.g. standing erect.
2. *Dynamic posture:* When body is moving for some coordinate work.

POSTURAL REFLEXES

Postural reflexes to maintain body in static posture are:

1. Static reflexes
   i. Local, e.g. positive supporting reaction
   ii. Segmental, e.g. crossed extensor reflex
   iii. General.
2. Statotonic or attitudinal reflexes.
3. *Righting reflexes:* Righting reflexes come into picture when there is already an upset in equilibrium and help in restoring the posture. Righting reflexes are really part of general static reaction. They help in bringing head in normal position and maintain body in definite relation to the head, which is characteristic of animal.

Postural reflexes for dynamic posture are:

Statokinetic reflexes.

STATIC POSTURE

That is mechanism for erect posture. This is understood to some extent by studying decerebrate rigidity (Fig. 126.1).

Section – I

1. Above thalamus
2. No change in muscle tone.

Section – II

1. Below thalamus
2. No change in muscle tone.

Section – III

1. Midcollicular section
2. Produces decerebrate rigidity.

Section – IV

1. Below vestibular nucleus
2. Above rigidity vanishes completely. Therefore, vestibulospinal and reticulo-

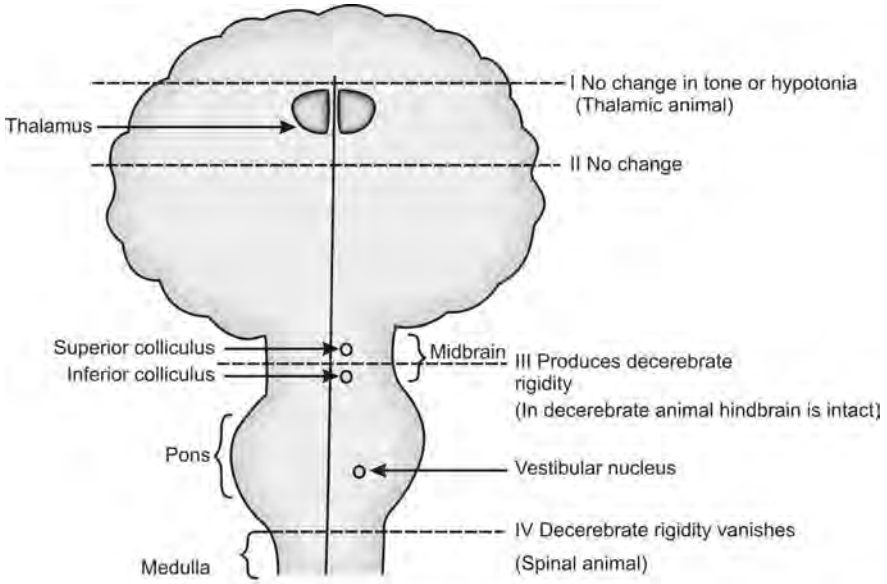


Fig. 126.1: Sections at I, II, III and IV levels

spinal tracts are responsible for decerebrate rigidity.

In decerebrate rigidity, all muscles of the body become rigid. Extensor muscles become more rigid than flexors (Fig. 126.2).

So that dog: Will assume extended head, back arched, tail extended and both hind and forelimbs extended. This animal can remain standing for hours in this posture, known as caricature of normal erect posture.

Reflexes Involved in Normal Erect Posture

1. *Stretch reflexes:* From antigravity muscles, i.e. extensors of the body produced due to gravitational effect on the body.

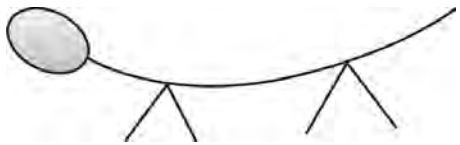


Fig. 126.2: Decerebrate animal

2. *Positive supporting reaction:* Means pressure over sole of foot will reflexely contract both flexors and extensors of knee joint. So that knee joint is firm and animal can stand erect.
   This is example of static reflex—local type.
3. *Visual reflexes:* Will also help for standing erect by adjusting different muscles of body.
4. *Different curvatures of spinal cord:* Are such that ultimately the gravity acts in perpendicular line, which will also contribute towards erect posture.

Statotonic or Attitudinal Reflexes

This is one example where reflexes are produced due to changes in the attitude of the body.

Therefore, the name attitudinal reflexes. They consist of:

a. Tonic labyrinthine, and
b. Tonic neck reflexes

] Acting on limbs ↓ Produce an attitude appropriate to head

Tonic Neck Reflexes

(Best studied after labyrinthectomy).

The tonic neck reflexes are set up by alterations in the position of the head in relation to the body—receptors are neck proprioceptors.

1. By ventroflexing the head, the forelimbs flex and hindbind limbs extend, as when we enter underneath the table (Fig. 126.3).
2. Dorsiflexion of head produce just the opposite-extension of forelimbs and flexion of hindlimbs, as when we come out from underneath the table (Fig. 126.4).
3. Pressing ventrally the lower part of cervical vertebral column will produce flexion of forelimbs and also hind limbs—as required while rolling under the table (Vertebro prominens reflex) (Fig. 126.5).

   Centers for (1), (2) and (3) in upper cervical region.
4. When head is rotated to various directions the jaw limbs extend to support the weight of the body and vertex limbs flex.

   Center for (4) in lower cervical region.

Tonic Labyrinthine Reflexes

(Receptors are Otolith organs). These reflexes are studied after section of dorsal roots of the 1st, 2nd, 3rd cervical roots or after immobilizing the head, neck and upper thorax in a plaster jacket to avoid neck reflexes.

- The reflexes are set up by alteration in the position of the head in relation to the original plane.

1. When the animal is placed on its back the tone is maximum of extensors of all limbs, when the head is inclined 45° upwards from horizontal plane (Fig. 126.6).
2. In prone position, the tone is reduced in all the limbs, maximum when the mouth is inclined downwards by 45° (Fig. 126.7).
3. By lateral inclination of the head, extensor tone on the side to which the head is turned is increased and tone is diminished on opposite side (Fig. 126.8).

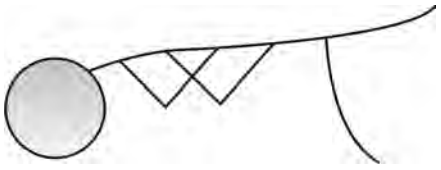


Fig. 126.3: Entering under the table (Forelimbs flex and hindlimbs extend by ventroflexing the head)

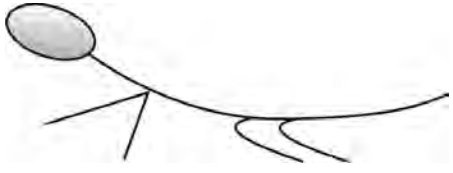


Fig. 126.4: Coming out from underneath the table (Extension of forelimbs and flexion of hindlimbs by dorsiflexion of head)

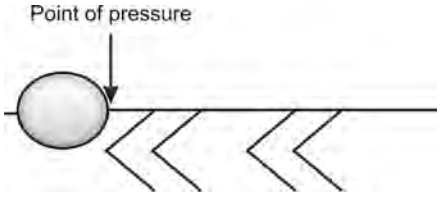


Fig. 126.5: Rolling under the table vertebro prominence reflex (Flexion of forelimbs and also hindlimbs)

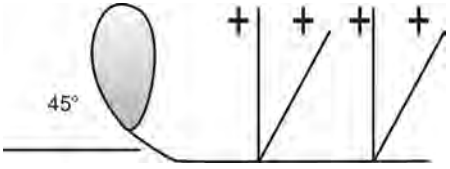


Fig. 126.6: Tonic labyrinthine reflex when animal is placed on it's back-tone in extensors of all limbs is maximum when head is inclined 45° upwards

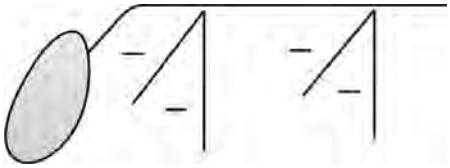


Fig. 126.7: Tonic labyrinthine reflex. In prone position, tone is reduced in all the limbs, maximum when mouth is inclined downwards by 45°

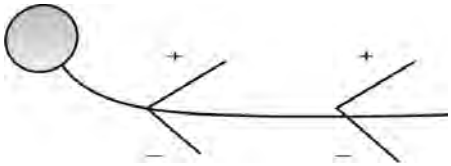


Fig. 126.8: Tonic labyrinthine reflex. Lateral inclination of head causes extensor tone to increase on same side limbs and tone is diminished on opposite side

RIGHTING REFLEXES

(For correcting the body).

This is very good example of postural reflexes where the position of body is corrected quickly when it is disturbed as, e.g. when cat is thrown out of 1st floor window, it will always land on its forelimb and hindlimbs after correcting the body with following postural reflexes.

1. *Head righting reflex:* Here the position of the head is corrected by:
   i. *Labyrinthine righting reflex:* When the animal falls into air from height the head is oriented the right way first due to labyrinthine reflexes acting on neck muscles. (Receptors otolith organ).
   ii. Optical or retinal righting reflex, i.e. by vision the position of head is corrected, not so important in lower animal where cortical development is poor. This is most important righting reflex in man.
2. *Neck righting reflexes acting on body:* Rotation of the head and twisting of neck muscles occur when head is righted reflexly and impulses are set up which reflexly rotate the thorax first, next abdomen and lastly pelvis and thus, reflexly bring the trunk in proper relationship with head (Receptors are neck proprioceptors).
3. *Body righting reflexes acting on head:* May right head also—when a man falls down, the asymmetric stimulation of skin receptors right the position of head.
4. *Body righting reflex acting upon the body:* Causes appropriate posture of limbs by proprioceptors of limb themselves.

Except optical righting reflexes the centers for righting reflexes is red nuclehus.

DYNAMIC POSTURE

It means adjustment of muscle tone while doing some daily coordinate movements. This is studied by studying different postural reflexes involved in different movements, e.g. postural reflexes for walking.

1. *Negative supporting reaction:* Withdrawal of pressure on sole will produce loose knee joint, as muscle tone vanishes. So that now leg is free to move forward for walking.
2. *Crossed extensor reflex:* Flexion of one limb will produce extension of opposite limb automatically, which is required while walking.

SUMMARY

It is impossible to separate postural adjustment from voluntary movement in any rigid way.

But postural reflexes: (a) maintain body in upright balanced position and also, (b) provide constant adjustments necessary to maintain stable posture for voluntary activity.

Adjustments

1. Static reflexes (involve sustained muscle contraction).
2. Dynamic reflexes (involve transient movement).

Both are integrated in CNS from spinal cord to cerebral cortex and are carried out largely through extrapyramidal pathways.

Major factor in postural control is variation in muscle tone by increasing excitability of motor neurons indirectly by γ efferent system.

Every movement begins from posture and ends in posture.

CHAPTER

127

Equilibrium

Following parts of brain are responsible for equilibrium of body—which means balancing the body while standing erect or walking, etc.

1. *Cerebellum:* Removal of cerebellum or disease of cerebellum produces loss of balance on the same side.
2. *Vestibular apparatus:* This is more important for birds and fishes for their locomotion. For human beings, we can have our equilibrium without it, if our, eyes are open.
3. Retinal and optical impulses are also important for equilibrium.

THE VESTIBULAR APPARATUS (LABYRINTH)

The vestibular apparatus is a complex sense organ, which is stimulated by: 1. gravity, and 2. rotational movements.

It plays important role in postural activity.

Anatomy (Fig. 127.1A)

Labyrinth consists of, (i) Auditory portion (Cochlea), (ii) Non-auditory portion.

The main parts of non-auditory portion are situated in a tunnel in petrous portion of temporal bone.

The vestibular apparatus consists of the three semicircular canals and the otolith organ (the saccule and utricle).

The semicircular canals are disposed off perpendicularly to each other. They are: (1) Lateral (Horizontal), (2) Superior (Anterior), (3) Posterior (Vertical).

The membranous canals contain endolymph and are enclosed in bony canals from which they are separated by the perilymph.

Each canal commences as a dilatation—ampulla. Containing a projecting ridge—the crista.

The canals open into the utricle by means of five apertures—one being common to the superior and posterior canal.

The utricle communicates with saccule and in turn is connected to the cochlear portion through canalis reuniens.

The proprioceptors of the labyrinth are the end organs found in semicircular canals and utricle and saccule.

The end organ present in semicircular canals is known as crista and is found in the ampulla of each semicircular canal.

A similar receptor known as macula is found in utricle and saccule. Both saccule and utricle contain a projecting ridge—Macula.

Crista and macula are the specific receptors of the vestibular apparatus and have similar structures.

Covering the ridge is a tall columnar epithelium (hair cells) giving attachment to

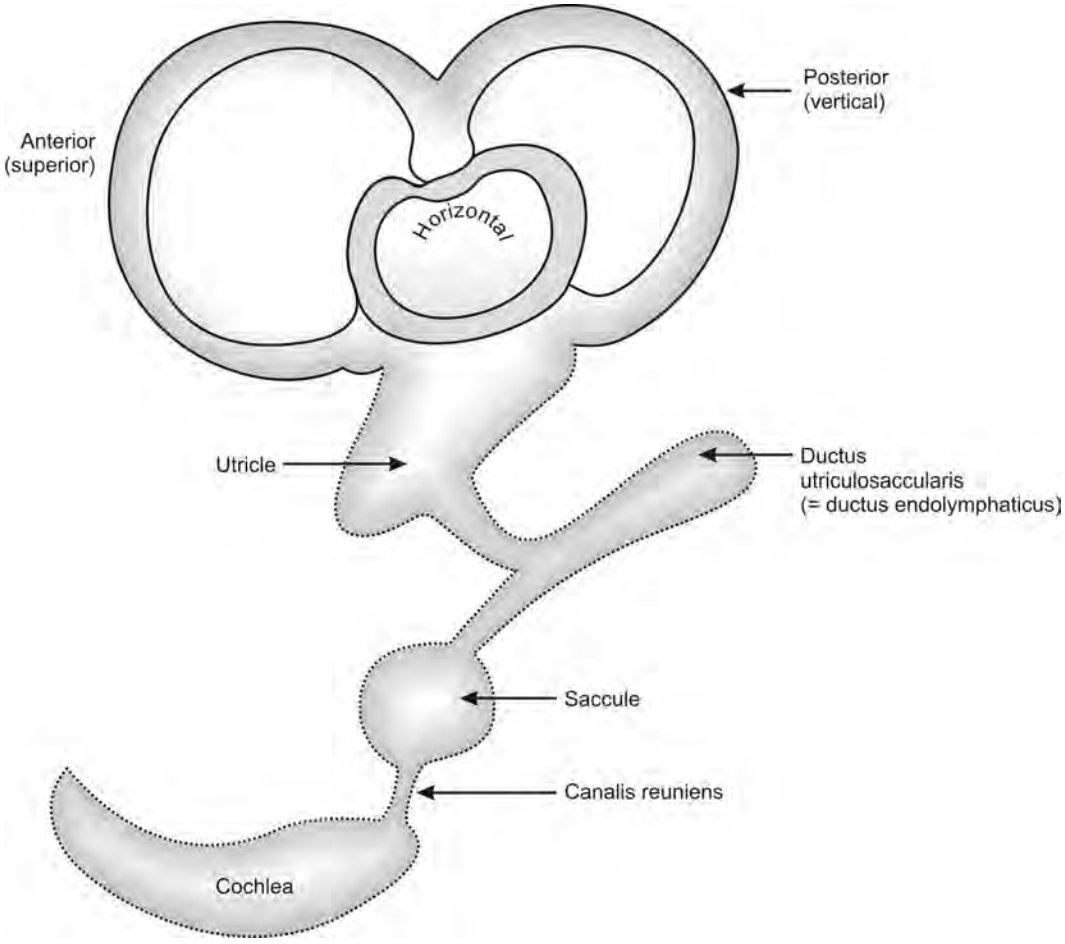


Fig. 127.1A: The vestibular apparatus (Labyrinth)

long stiff hairs which project into a firm gelatinous material—Cupula terminalis. Between the hair cells lie the fibers of origin of the vestibular division of VIII nerve.

Difference (Fig. 127.1B)

1. In case of ampullae, the covering material or cupula extends throughout its entire width and rises to the roof of the ampulla acting as a movable partition which divides the ampulla into two compartments.
2. In the saccule and utricle, the cupula contains many chalky particulars or microscopic crystals of calcium carbonates—otoconia, and hence the name otolith organ.

Utricle-macula lies in horizontal plane in floor. Saccule macula lies in lateral plane in walls.

In saccular macula, maximum stimulation occurs when head is tilted and gravity is acting on them (because macula is present in walls), e.g. right side—right tilting causes maximum stimulation and for left side—left tilting causes

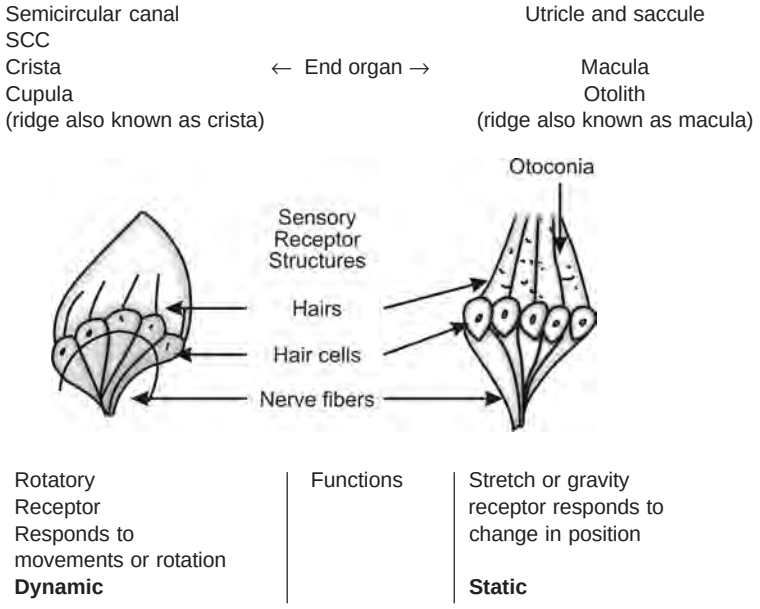


Fig. 127.1B: Crista and mucula

maximum stimulation. But in reality, hairs are in different direction. Therefore, differential stimulation of hair cells takes place. Therefore, different directions stimulate different hair cells.

So, different pattern is produced and therefore perception for different direction is possible.

In utricle-macula maximum stimulation occurs when head is upside down (because macula is present in the floor). The hair cells in utricle are also sensitive to linear acceleration. For example, when person runs, because otoconia are heavy they remain behind and person compensates by bending.

Connections of Labyrinth (Fig. 127.2)

1. Nerve fibers arise from the cristae and maculae and form the vestibular division of VIII nerve.
2. The cell bodies being situated at the vestibular ganglion (also called as Scarpa's ganglion), which lies close to the vestibular apparatus.
3. The central axons of the Scarpa's ganglion proceed towards brainstem.
4. They enter the brainstem and end in vestibular nucleus—1st relay.
5. Vestibular nuclei are situated in the pons.
6. Each vestibular nucleus has four subparts—Lateral (Deiters' nucleus), superior, medial and inferior vestibular nuclei. All these act as a single functional unit.
   i. Fibers from superior nucleus join the median longitudinal bundle of the same side—ends round III, IV, and VI nerve nuclei and integrate reflex movements of eyeballs.
   ii. Fibers from medial group are connected to opposite side.
   iii. Inferior group to both sides, cerebellum.
   iv. Lateral or Deiters' nucleus—gives rise to vestibulospinal tract (which controls muscle tone), which ends in anterior horn cells of spinal cord.

Thus, fibers from vestibular nucleus pass to:

i. Paleocerebellum or flocculonodular lobe of cerebellum of both sides via inferior peduncle.

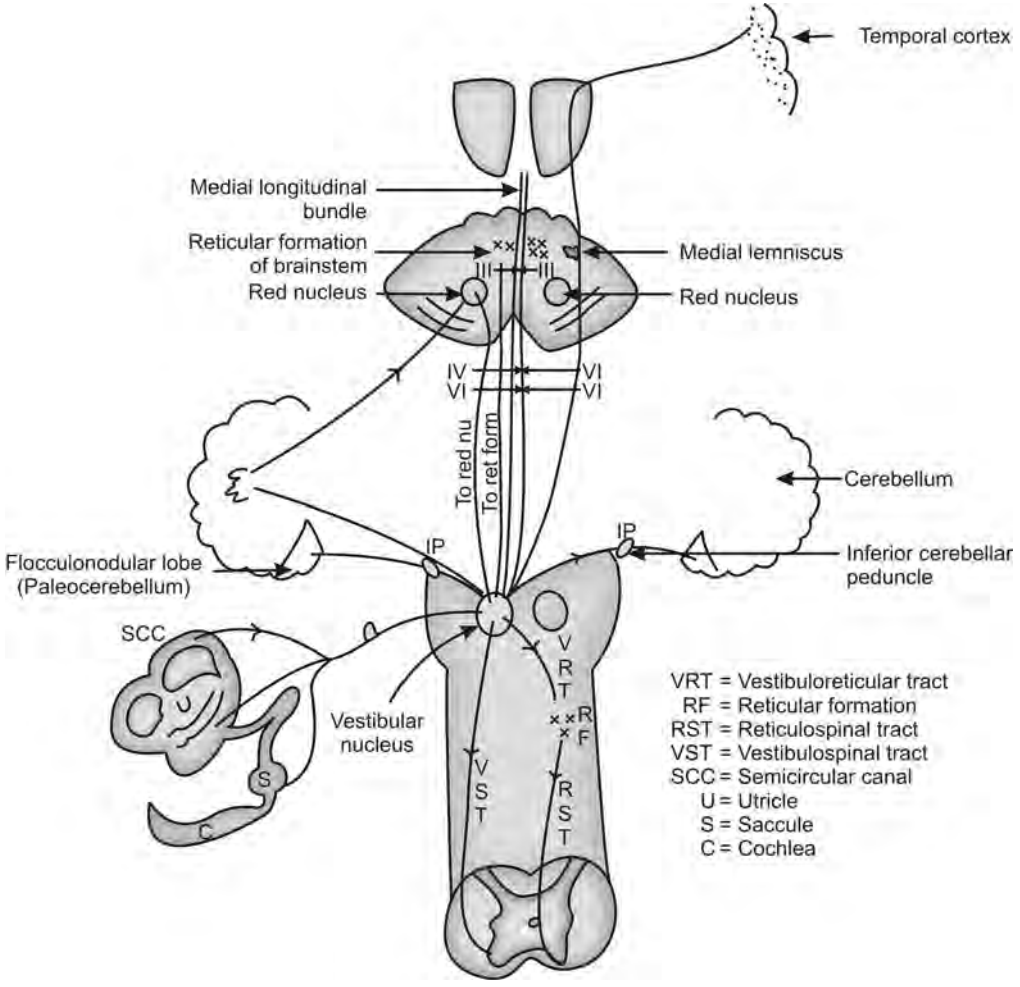


Fig. 127.2: Connections of labyrinth

ii. Directly and via cerebellum to red nucleus and nuclei of the reticular formation of brainstem.
iii. In median longitudinal bundle to the oculomotor nuclei of both sides.
iv. Via the medial lemniscus to opposite thalamus and thence to opposite temporal lobe.
v. Down in the vestibulospinal tracts to the ventral columns of spinal cord to end around ventral horn cells.
vi. To reticular formation from where begins the reticulospinal tract.

Mechanism

Semicircular canals are in three planes (Figs 127.4A and B):

1. Horizontal canal (lateral)—in coronal plane.
2. Anterior canal (superior)—directed up at 45° to sagittal plane.
3. Posterior canal (vertical) —directed down at 45° to coronal plane.
   i. Semicircular canals lie at 90° to each other.

Crista ampullaris has neuroepithelium of columnar cells (Fig. 127.3). Type I (flask shaped), Type II (Cylindrical) and supporting cells known as cells of Ritzius.

Orientation of kinocilia is in the same direction towards utricle, i.e. if utricle is to right, the kinocilia are to right, when the cilia move towards utricle there is maximum stimulation of nerve fibers.

Functions of SSC were first differentiated from utricle and saccule by Brewer in 1875. He stated that ampullar cristae are receptors for responses due to rotations, while maculae give rise to responses dependent upon: (1) Position of head in space, and (2) Upon the rectilinear motion or acceleration.

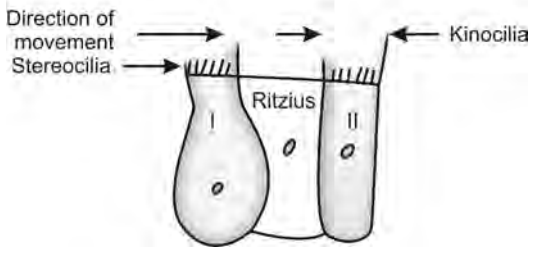


Fig. 127.3: Cells of neuroepithelium of crista ampullaris

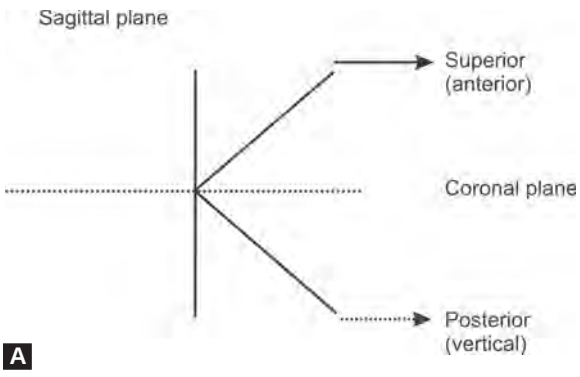
The crista of each ampulla is stimulated by rotation of the head in the plane of its canal and probably not at all or very slightly by rotation in any other plane.

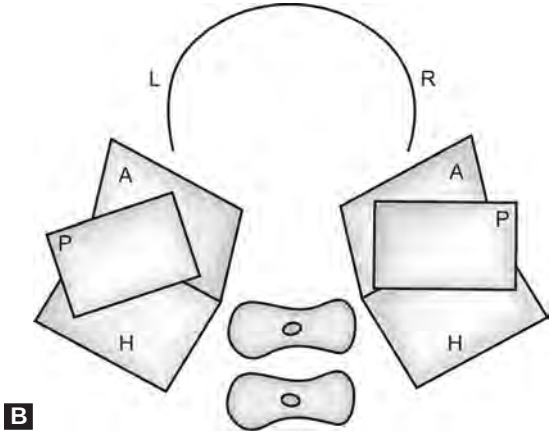
SSCs of two sides form the pairs (Fig. 127.4B) —Three:

i. Right anterior—Left posterior
ii. Left anterior—Right posterior
iii. Right horizontal—Left horizontal.

Each pair is lying in one plane. Therefore, 6 SSC behave as three functional pairs.

Normal stimulation of crista is caused by currents of displacements of the endolymph, which actually move the cupula. When person moves in rotation around an axis vertical to the particular plane, that particular functional unit comes into play, e.g. horizontal canal's cristae are stimulated maximum when person moves round himself. When head moves in one direction, the ampulla in that direction is leading ampulla and the ampulla behind is the trailing ampulla. The endolymph inside the SSC is not able to move as fast as bony labyrinth, therefore moves backward and hits trailing ampulla, causing maximum stimulation and the leading ampulla empties. Therefore, there is minimum stimulation of leading ampulla. After a while, the initial





Figs 127.4A and B: Plane of pairs of SSC

inertia is lost therefore now there is no stimulation. But when rotation stops because of inertia, endolymph does not stop. Therefore, hits leading ampulla causing maximum stimulation and empties trailing ampulla causing minimum stimulation (Fig. 127.5).

The cristae are very sensitive therefore even 1° movement is perceived and crista ampullaris of SCC is stimulated by angular velocity as well as angular acceleration, i.e. change of velocity.

Saccule

Macullae in the wall convey position of head because they are sensitive to gravity and are able to do so because of differential stimulation of macular hair cells.

Utricle

Maculla lie in the floor and they are sensitive to linear acceleration, e.g. when person runs because otoconia are heavier therefore remain behind. Therefore, person compensates by bending forward.

IMPORTANT DIFFERENCE BETWEEN AMPULLAR AND MACULAR RECEPTORS

There is qualitative difference:

Ampullar receptors: Convey the changing position of head, i.e. during movement like taking a turn while running.

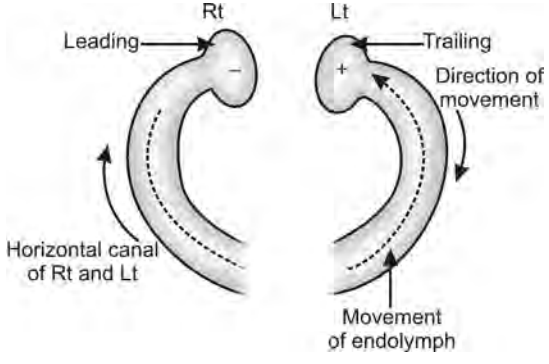


Fig. 127.5: Horizontal canal of Rt and Lt

This is known as predictive function of SSC.

Macular receptors (otolith organ): Convey the changed position of head, i.e. after the movement has taken place. Therefore, known as post facto function.

The role of labyrinth in motion sickness —Like:

1. Sea sickness
2. Air sickness, etc.

Motion sickness is a disorder, which is evoked, in susceptible persons and animals when they are subjected to movements, which have certain characteristics.

- Vestibular apparatus is essential for production of motion sickness.
- Only certain kinds of motion are capable of evoking motion sickness. Since, movement of the body at constant velocity regardless of direction or speed never evokes sickness. One essential feature of an effective motion is a repetitive change in velocity, in short, a series of accelerations. When exposed to such motion, the non-auditory labyrinth discharge a particular pattern of impulses to brain, and this bombardment should continue for some length of time if motion sickness is to develop. Motion sickness can be produced by either angular or linear acceleration. In angular acceleration, SCC are involved and nystagmus occurs, and when due to linear acceleration, utricular maculae are stimulated and no perceptible nystagmus occurs.
- In most cases, the sickness is due to motion of ships, aeroplanes and swings.
- When small angular accelerations are added to a motion, which has only a linear changes in velocity, its nauseating properties are augmented.

In a ship the most disturbing movement is so called—cork screw or wobble, in which large linear accelerations are combined with smaller angular changes in velocity.

CHAPTER

128

Autonomic Nervous System

Nerve fibers are of two major types: (i) somatic, and (ii) autonomic.

Afferent autonomic fibers bring information from the viscera and efferent autonomic fibers supply smooth muscles, cardiac muscles and exocrine glands, hence named as vegetative nervous system by Reil in 1807. The nomenclature of autonomic nervous system was given to this group of nerves by Langley. Gaskell named it as involuntary nervous system (because it is not under the control of volition or will).

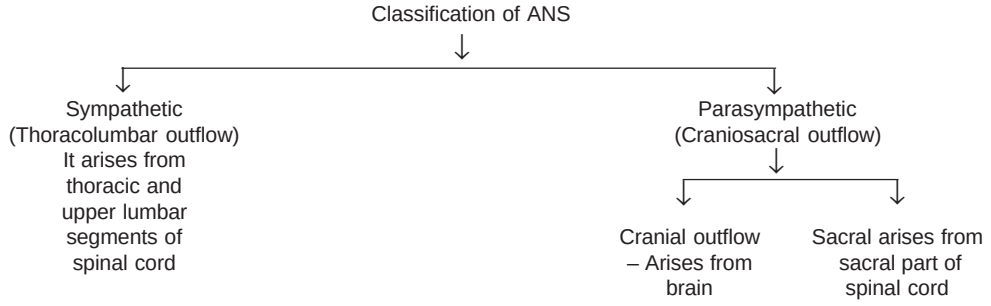
Autonomic nervous system is divided into two divisions: (i) Sympathetic, and (ii) Parasympathetic divisions. It was observed that injury produces tachycardia and as if tachycardia was occurring in sympathy to the injury or blood loss, this division was named as sympathetic.

The higher center for autonomic is cerebral cortex in the prefrontal lobe. From functional point of view hypothalamus is the center. Anterior goup of nuclei control the parasympathetic outlet and posterior group control the sympathetic. For sympathetic division vasomotor center is next higher center to lateral horn cells.

FUNCTIONAL ANATOMY

Sympathetic Division (Fig. 128.1)

From lateral horn cells of T1-L2 segments (sometimes L3) arise the preganglionic sympathetic fibers, which come out of the cord via the anterior horn along with anterior nerve root, leaves the anterior root to join sympathetic trunk. The preganglionic fibers are myelinated so they look white. The portion of the pregang-



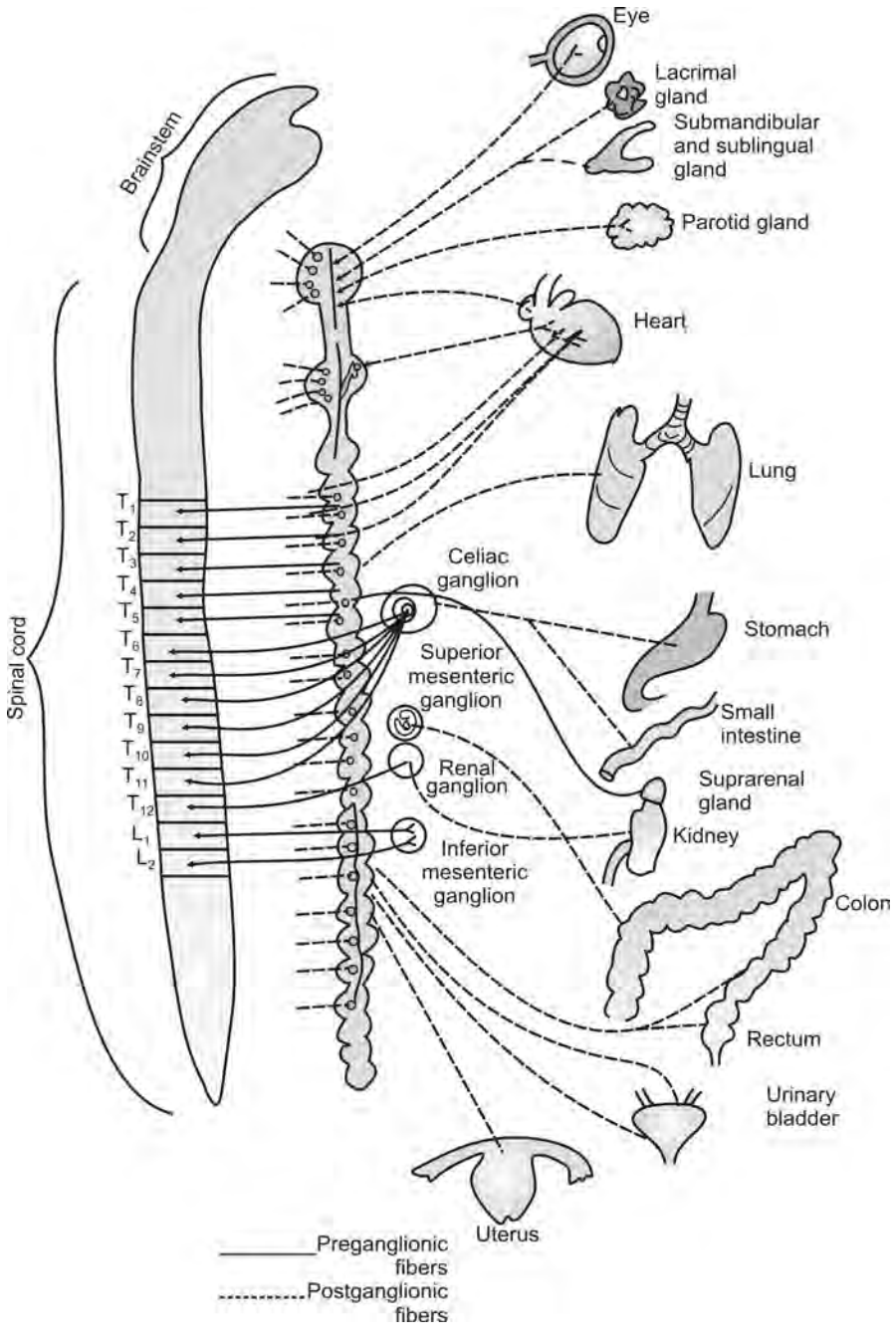


Fig. 128.1: Sympathetic nervous system

lionic fiber from the anterior root of the sympathetic trunk is called white ramus communicans (or pleural = rami communicantes).

After entering the sympathetic trunk, it can have one of the following fates:

1. The preganglionic fibers pass up or down the chain to establish connections with the postganglionic neurons situated above or below. A single white ramus may establish connection with even eight or nine other segments. Thus, magnifying and spreading a discrete central discharge. The postganglionic fibers pass through the gray rami communicantes to enter corresponding segmental nerve to effect sympathetic supply to the various organs. These postganglionic fibers are non-medullated they look grayish, so named as gray rami communicantes.
2. Some preganglionic fibers leave the sympathetic trunk still as preganglionic fibers, i.e. without synapsing, in splanchnic nerves and enter other ganglia, outside the sympathetic trunk, e.g. ciliac and other ganglia. These fibers supply the smooth muscles of blood vessels and glands of the abdominal and pelvic viscera. The case of the adrenal medulla is unique in that the preganglionic fibers of the splanchnic—directly innervate this gland so, whenever the sympathetic system is stimulated there is concomitant stimulation of adrenaline and noradrenaline secretion from adrenal medulla.

The structures innervated by postganglionic nerve fibers are:

i. The smooth muscle (e.g. of respiratory tract, vascular tree, gastrointestinal tract, etc.)
ii. The heart muscle
iii. The sweat glands
iv. The arrector pili muscles of the skin
v. Exocrine glands (e.g. salivary, pancreas, gastric glands, etc.).

The sympathetic ganglia are present in:

i. Sympathetic trunks, and
ii. Other places.

Sympathetic trunk is a chain of ganglia situated immediately lateral to the vertebral column extending from neck to coccyx. There are two sympathetic trunks one on either side of the vertebral column. Each trunk consists of 22 ganglia connected together by fibers. Although, lateral horns from where the sympathetic fibers arise extend only from T_1 to L_2 or L_3 because their fibers pass up or down, therefore, sympathetic trunk extends from neck to coccyx. Ganglia of cervical, lower lumbar and scaral segments lacking white rami receive their input by preganglionic fibers passing up or down.

The ganglia of the sympathetic trunk are also called *paravertebral ganglia.*

Stellate Ganglion

There are three cervical ganglia in the sympathetic trunk: (i) superior, (ii) middle, and (iii) inferior. The inferior cervical ganglion often fuse with the first thoracic ganglion and the resultant fused ganglion is called the stellate ganglion which is star shaped.

Sympathetic Ganglia Present in Other Places

1. Prevertebral ganglia also called as collateral ganglia are situated in relation to the abdominal aorta and its branches.

   Three collateral ganglia are well known:

   i. Celiac or solar—situated near origin of ciliac artery.
   ii. Superior mesenteric near origin of superior mesenteric artery.

iii. Inferior mesenteric ganglion near origin of inferior mesenteric artery. In man, usually in place of inferior ganglion a number of small scattered ganglia are present.

2. *Terminal ganglia:* They are situated near the bladder and rectum.

Splanchnic Nerves

There are three splanchnic nerves, the: (i) greater, (ii) lesser and the (iii) least.

The splanchnic nerves are formed by preganglionic sympathetic fibers, which have passed through the sympathetic trunk but have not relayed there. The fibers of the greater splanchnic nerve and lesser splanchnic nerve relay in the ciliac ganglion.

The fibers of least splanchnic nerve relay in renal ganglion.

The postganglionic fibers of these nerves supply the viscera and blood vessels within the abdomen.

THE PARASYMPATHETIC SYSTEM (FIG. 128.2)

Parasympathetic efferents arise from the brainstem as well as from sacral segments of the spinal cord and hence this system is called craniosacral outflow.

Cranial Outflow

1. The third (oculomotor) nerve arises from *Edinger-Westphal nucleus of the third nerve* situated in midbrain and relays in ciliary ganglion. The postganglion fibers travel through the short ciliary nerves and end in the ciliary body. Stimulation of these fibers produce constriction of pupil.
2. Superior salivary nucleus gives origin to the fibers of the VIIth nerve, is situated in lower part of pons. It gives fibers to lacrimal gland and submaxillary and sublingual salivary glands. The fibers to the lacrimal gland pass with the seventh nerve, the nervus intermedius of Wisburg and the greater superficial petrosal and the median nerves to reach sphenopalatine ganglion. Postganglionic fibers pass in the maxillary division of the fifth nerve to lacrimal gland. The axons to the submaxillary and sublingual glands pass in the facial nerve and enter respective ganglia through chorda tympani. Because of the contiguity of innervation between the lacrimal and salivary glands, often in lower animals there is a certain amount of lacrimation along with salivation. A typical example is the case of the crocodile tears, where the crocodile is forced to shed tears during the pleasant act of eating food.

   In man, fortunately the functional division is more exact, though lacrimation takes place when hot food is placed in the mouth.
3. The supply to the parotid gland is from the inferior salivary nucleus, which passes via the tympanic branch of IXth to the lesser superficial petrosal nerve to reach otic ganglion. From there through the auriculotemporal branch of the Vth nerve to the parotid gland. When parasympathetic supply to these glands is stimulated, it produces vasoconstriction and secretion.
4. Vagus arising from dorsal nucleus of the vagus situated in medulla, takes wandering course. Hence, named as *vagus or vagabond nerve.* A vagabond by definition is a purposeless loafer. But vagus has important role in the organization of the parasympathetic system. The ganglia for vagal efferents are situated close to their target organs.

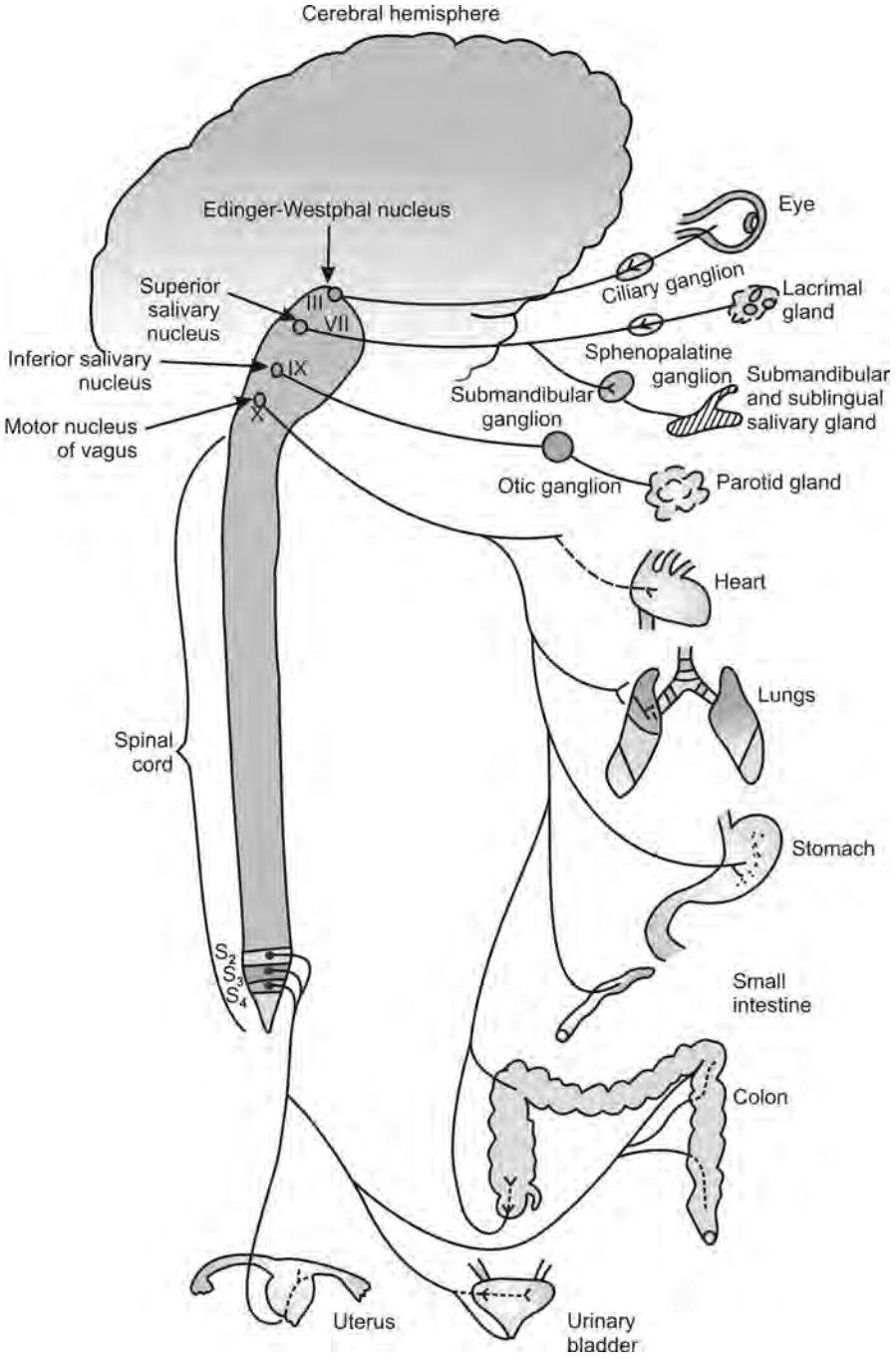


Fig. 128.2: Parasympathetic system

It gives fibers to cardiac plexus.

It also gives fibers to the great vessels and is parasympathetic supplier of vessels in the trunk and upper extremity.

It supplies larynx through recurrent laryngeal nerve.

It gives parasympathetic innervation to trachea, bronchi, bronchioles and the entire respiratory tract.

It supplies the whole of thoracic and abdominal viscera.

In digestive system, it supplies the esophagus, the stomach, the duodenum, the small intestine and large intestine up to splenic flexure and is main secretomotor to gastrointestinal tract.

It also supplies the liver, the gallbladder and pancreas.

The spleen, kidney also receive parasympathetic supply from vagus. (Cranial nerves IIIrd, VIIth, IXth and Xth contain parasympathetic fibers but also contain somatic afferent and efferent fibers).

Sacral Outflow

From the lateral regions of sacral segments of the spinal cord (IInd, IIIrd and IVth sacral segments) parasympathetic fibers come out to form pelvic splanchnic nerves. As their stimulation causes erection of penis, they are also called nervi erigentis (single = nervus erigens). The fibers from these nerves reach the ganglia situated in the walls of the organs innervated. The postganglionic fibers supply uterus, fallopian tubes, testes, sigmoid colon, rectum and bladder. Stimulation of these nerves causes contraction of the bladder and lower colon (Therefore, cannon has called this nerve as nerve of emptying).

Afferent nerves of the ANS: Visceral afferents may belong either to sympathetic or parasympathetic.

Sympathetic Afferents

Afferent fibers from viscera have their cell body in dorsal root ganglion. The axon from dorsal root ganglion (or posterior root ganglion) enter the posterior root. These fibers may form:

- Afferent limb of autonomic reflex arc or they may be the first order neuron carrying visceral sensations like pain of abdominal viscera. Then later order neuron for pain sensation travel along with spinothalamic tract to end in the thalamus—further relay occurs to sensory cortex. The path of abdominal visceral pain is similar to that of somatic pain.

PARASYMPATHETIC AFFERENTS

Cranial Parasympathetic Afferent

Fibers carried from periphery via the VIIth, IXth and Xth cranial nerves. Their cells bodies being situated at their corresponding ganglia. The central processes from the ganglia end in nucleus of tractus solitarius (Nuclues of tractus solitarius also receives fibers from many other structures like baroreceptors and chemoreceptors and olfactory and taste sensations).

The nucleus of tractus solitarius in turn sends fibers to many areas of the brain like:

i. Higher brain centers, which control lateral horn cells of sympathetic system.
ii. The hypothalamus (which can control endocrines).
iii. To dorsal motor nucleus of vagus which controls heart, bronchi, GIT.
iv. To selected parts of limbic system (which controls the emotion).

Pelvic Parasympathetic Afferents

Bring information from bladder, rectum and genitalia. These afferents mainly serve as afferent limbs of local reflexes.

EFFECTS OF AUTONOMIC STIMULATION

Sympathetic

1. *Cardiovascular System:*
   i. Heart—sympathetic stimulation causes:
      a. +ve chronotropic (increased rate)
      b. +ve inotropic (increased force)
      c. +ve dromotropic (increased contractility)
      d. +ve bathmotropic (increased excitability).

   Excess stimulation may lead to ventricular fibrillation and death.
2. *Blood vessels:* Target tissue is smooth muscles of the blood vessels. Sympa-thetic stimulation causes:
   i. Vasoconstriction of cutaneous and splanchnic arterioles and vasodilatation of coronary and skeletal blood vessels.
   ii. Venoconstriction.

   As a result, there is redistribution of blood. Skin and abdominal viscera get less blood and skeletal muscles and heart gets more blood.
   iii. Blood pressure rises as a result of sympathetic stimulation. Systolic, diastolic and mean blood pressures rise.
3. *Respiratory system:* Sympathetic stimulation causes bronchodilation, due to relaxation of bronchial muscles and tachypnea. Net result is increased ventilation.
4. *Digestive system:* Sphincters constrict and peristalsis is inhibited along with relaxation of gut. Therefore, there is holding up of contents of gut.
5. *Genitourinary system:* Relaxation of detrusor and spasm of sphincter leading to retention of urine results.

   In male, sympathetic stimulation causes ejaculation of semen. In female, effect on uterus is variable depending on presence or absence of pregnancy.
6. *Nervous system:* Mind becomes alert and there is loss of sleep.
7. *Eye:*
   i. Pupillary dilatation—due to contraction of dilator pupillae.
   ii. Retraction of eyelids.
8. *Adrenal medulla:* Sympathetic stimulation – causes secretion of adrenaline and noradrenaline from adrenal medulla.
9. *Skin and body temperature:*
   i. *Cutaneous vasoconstriction:* Leading to pallor.
   ii. *Piloerection:* Hairs stand on end due to contraction of arrectores pilorum muscle situated at the base of hair follicle. (i) and (ii) lead to elevation of core temperature of the body. Thus, sympathetic stimulation helps when we are exposed to cold.
   iii. Sympathetic stimulation also leads to sweating.

Metabolic

1. *Carbohydrate metabolism:* Sympathetic stimulation leads to glycogenolysis, therefore, hyperglycemia and glycosuria.
2. *Fat:* There is lipolysis of adipose tissue leading to rise of FFA. Catabolism of brown fat takes place.

Effects of Parasympathetic Stimulation

Effects of parasympathetic stimulation are opposite to those of sympathetic stimulation.

On heart: Parasympathetic stimulation causes bradycardia and fall of cardiac output.

On GIT: Effects are increased secretion of salivary glands, glands of stomach and pancreas and increased motility. These two

effects increase the formation of digestive juices and increased movements.

On blood vessels: No major action.

FUNCTIONS OF AUTONOMIC NERVOUS SYSTEM

The autonomic system is designed for continuous neurovegetative action and control of internal viscera and its functions.

Sympathetic system is designed for quick immediate and massive action and along with adrenal medullary stimulation initiates reactions in conditions of stress. Thus, sympathetico-adrenal stimulation is a part of alarm reaction and is a protective mechanism which is set in motion in conditions of fight, flight and fright when one is exposed to danger. Sympathetic system has short preganglionic fibers because they synapse with paravertebral ganglia and each fiber synapses with large number of ganglia, thus massive action can take place by single stimulus. The postganglionic fibers are very long so that action is far reaching and widespread and single stimulus can initiate widespread chain reactions.

Therefore, its action is compared to action of sten gun by Cannon.

In contrast, parasympathetic system has long preganglionic fibers, e.g. vagus and each ganglion has connections with only a limited number of postganglionic fibers so that action is individualized and descrete. In fact, many ganglia are almost on the target organ thus, limiting the action locally. This action has been called sniping action by Cannon.

The sympathetic system is called into play only in conditions of stress or emergency. Normally such instances are few. On the other hand, the moment-to-moment activity of parasympathetic is highly essential for carrying out innumerable metabolic functions of cells and to keep important organs like heart and lungs functioning. Thus, in normal palcid environment the parasympathetic system has an upper hand.

Tonic Action

Autonomic nerves exert a tonic action on their target organs, e.g. injection of atropine increases the heart rate because it nullifies tonic action of vagus on heart and another example is injection of phenoxybenzamine which nullifies effects of sympathetic, causes fall of blood pressure. This therefore, proves the existence of tonic sympathetic activity.

CHEMICAL TRANSMITTER IN AUTONOMIC NERVOUS SYSTEM (ANS)

Otto Loewi demonstrated vagus stuff at the vagal nerve endings, which now we know, is acetylcholine.

Acetylcholine is the chemical transmitter at the preganglionic level of both sympathetic and parasympathetic nerve ending. It also acts as a transmitter in postganglionic nerve endings of parasympathetic system. The overacitivity of acetylcholine at all these sites is prevented by cholinesterase, which neutralizes acetylcholine.

At postganglionic nerve terminals of sympathetic system noradrenaline is secreted, which acts as a chemical transmitter. Also at certain postganglionic fibers of sympathetic division acetylcholine is secreted, which acts as chemical transmitter and these fibers are named as cholinergic, e.g. sweat glands which receive cholinergic sympathetic fibers (Fig. 128.3).

Acetylcholine

It is liberated at:

1. Postganglionic parasympathetic nerve endings.
2. Preganglionic nerve endings of both parasympathetic and sympathetic.

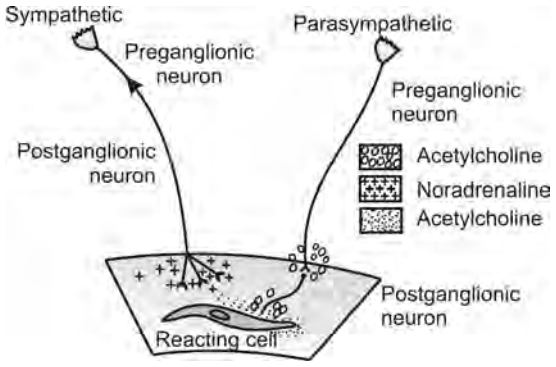


Fig. 128.3: Mode of action of autonomic nerves

3. Postganglionic sympathetic nerve endings supplying sweat glands and some arterioles of skeletal muscles (cholinergic sympathetic nerves).
4. Preganglionic sympathetic nerves terminating on adrenal medullary cells.
5. Acetylcholine is also chemical transmitter at neuromuscular junction.
6. Various synapses in brain and spinal cord (e.g. Renshaw cell transmission is cholinergic).

Synthesis

It is synthesized in the neuron from choline and Acetyl CoA. Synthesis requires the enzyme choline acetylase. Acetylcholine thus, synthesized travels down by the axonal flow to the terminal part of the axon where it is stored in vesicles.

When action potential travels down the nerve fiber and reaches the terminal part, the vesicles ruptures to release acetylcholine, which reacts with receptors on postsynaptic membrane or effector cell or skeletal muscle fiber as the case may be and depolarizes it.

Destruction

Acetylcholine is hydrolyzed by cholinesterase and its activity is decreased. Acetylcholinesterase is found where Acetylcholine is naturally secreted, e.g. neuromuscular junction, synapses, ganglion. This is known as true cholinesterase. Pseudocholinesterase is found in plasma and liver.

Drugs: Which enhance activity of acetylcholine or antagonize its activity are known, e.g. atropine antagonizes acetylcholine.

Noradrenaline

Noradrenaline is also called as norephinephrine. Noradrenaline is released at postganglionic sympathetic nerve endings. Therefore, they are noradrenergic nerve endings. Where as adrenaline is synthesized by adrenaline medullary cells (However, some neurons of brain can synthesize adrenaline, they are adrenergic neurons). Noradrenaline and adrenaline together are known as catecholamines.

Synthesis—From L. Tyrosine (amino acid)
↓ Enzyme tyrosine hydroxylase
L ↓ DOPA (dihydroxyphenylalanine)
↓ Enzyme DOPA decorboxylase dompaine
↓ Enzyme Dopamine hydroxylase
Noradrenaline

Removal and Inactivation of Catecholamines: By Two Uptake (Fig. 128.4)

Processes: Uptake 1 (neuronal) free noradrenaline is taken up into presynaptic noradrenergic nerve terminal by the process known as uptake 1 by active transport into cytoplasm of neuron and acted upon by enzyme monoamine oxidase (MAO). It accounts

for 85% of released noradrenaline. MAO is present in mitochondria.

Uptake 2 (extraneuronal): Less important than uptake 1 for removing noradrenaline because it accounts for only 15% of the released, noradrenaline.

It is mediated by postsynaptic cell, i.e. target cell, e.g. cardiac cells or smooth muscle cells. After uptake 2 the noradrenaline is metabolized intracellulary and inactivated by two enzymes. MAO and COMT (Catechol- o - methyl transferase). Both these enzymes are also present in liver, which inactivate circulating catecholamines secreted by adrenal medulla. The chief end product is VMA (3 methoxy-4 hydroxy Mandelic acid), which is excreted in urine.

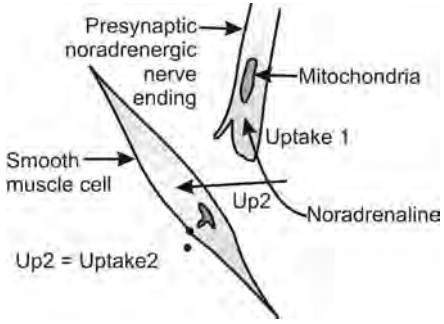


Fig. 128.4: Removal and inactivation of catecholamines

Drugs are known which block uptake 1—and therefore, prolong the action of sympathetic stimulation, e.g. amphetamine.

- Drugs like guanethidine (used in treatment of hypertension) block release of noradrenaline.

Sympathetic stimulation in intact animal or man causes stimulation of adrenal medulla also which secretes noradrenaline as well as adrenaline and both are released into blood. Thus, effects of sympathetic stimulation leads to noradrenaline secretion (from noradrenergic nerve endings and adrenal medulla) and adrenaline secretion (from adrenal medulla) and the effects are due to combination of activities of adrenaline and noradrenaline both.

RECEPTORS (TABLE 128.1)

Ahlquist in 1948, showed the presence of receptors in target cells of autonomic nervous system.

Table 128.1: Adrenergic and noradrenergic receptor sites

Receptors	*Important sites*	*Effects of stimulation of receptor*
α	1. Smooth muscles of arterioles particularly of skin and abdomen viscera	1. Vasoconstriction
	2. Pilomotor muscles sweat, glands of skin.	2. Horripilation, sweating
	3. Dilator pupillae	3. Pupillary dilatation
	4. GI tract smooth muscle	4. Inhibition of peristalsis and spasm of sphincters
	5. Sphincters of urinary bladder	5. Urinary retention
	6. Presynaptic nerve ending α2	6. Inhibition of NA release
β1	Heart	1. + ve chronotropic and inotropic action
		2. Lipolysis, rise of FFA
β 2	Bronchi; Smooth muscle	1. Bronchodilation
	Arterioles of skeletal muscle	2. Vasodilation of these vessels
	Liver	3. Glycogenolysis
	GI tract	4. Peristalsis inhibition
	Coronary arteries	5. Vasodilation

There are two types of receptors: (i) α, (ii) β.

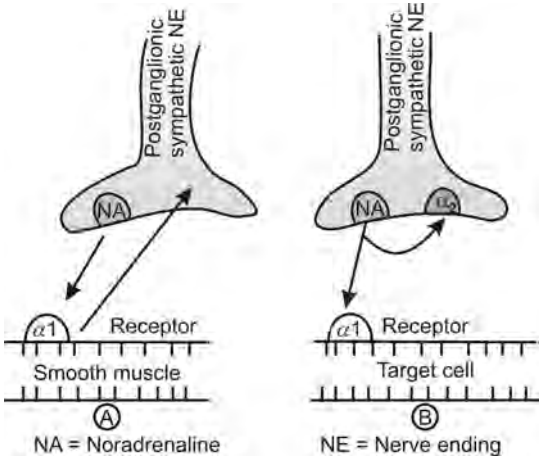
They have subclasses—α1 and α2 and β1 and β2.

Noradrenaline has high affinity for α receptors and moderate or low affinity for β1 receptors, whereas adrenaline has moderate affinity for α receptors, high affinity for β1 receptors and moderate affinity for β2 receptors.

Many drugs have selective action, some of them cause stimulation of receptors and some cause inhibition.

Now it is shown that some types of receptors are also present on postganglionic sympathetic nerve fiber on its terminal part notably α2.

In normal course of events noradrenaline released from noradrenergic nerve fiber excites α1 receptor of the target cell as usual, but in addition it binds with α2 receptor, situated at the terminal part of the postganglionic nerve fiber. This mechanism operates to prevent excessive NA release (Fig. 128.5).



A. Uptake 1 for removal of noradrenaline
B. α2 receptor and sympathetic inhibition

Fig. 128.5: Uptake 1, α2 receptor and sympathetic inhibition

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